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# Mechanochemical transformations of polysaccharides to value added products: a review with Green Chemistry evaluation

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Biopolymers, particularly polysaccharides, are a renewable feedstock with the potential to reduce reliance on petrochemicals and enable decarbonization and circularity efforts. Their sustainable chemical modification is essential to expand their use in the industry, yet this goal has proven hard to achieve because of their poor processability attributed to low solubility in most solvents. Mechanochemistry is a fast-emerging technique enabling the effective chemical transformation of materials in the solid state. It is effective for the chemical modification of biopolymers and composites with lower reagent, solvent and energy use compared to solution phase methods. Herein, we review recent progress in the development of mechanochemical methodologies for polysaccharide transformations, including depolymerization, nano-extraction, and chemical functionalization. We compare in detail the different techniques and their outcomes in terms of the functional properties of the final products, as well as the green metrics of each method based on reported parameters. Conclusions are then drawn to direct future research directions to expand the range of new functional biomaterials mechanochemistry that can be produced in a more sustainable manner.

## Green foundation

1. Recent advances in mechanochemistry have transformed polysaccharide valorization by enabling solvent-free or solvent-minimized reactions, significantly lowering reagent and energy use. Mechanochemical depolymerization, nano-extraction, and functionalization now achieve outcomes comparable or superior to traditional solution-phase methods. Innovations such as aging-assisted processes extend reactivity while maintaining polymer integrity, providing efficient access to new biopolymer architectures.
2. This research sits at the intersection of sustainable chemistry, materials science, and circular bioeconomy. Mechanochemical polysaccharide modification addresses global challenges in decarbonization, waste valorization, and plastic replacement by converting abundant biomass into high-value materials without reliance on petrochemicals. Its solvent-free nature and compatibility with insoluble substrates make it a model for sustainable process design. The field also demonstrates how physical energy inputs can replace hazardous reagents, aligning with the 12 Principles of Green Chemistry and inspiring innovation beyond biomass processing.
3. The full realization of the potential of this research requires that mechanochemical processes scaling is developed. Integrating real-time monitoring, and green metrics such as PMI and *E*-factor systematically will also further improve the field. Insights from this review highlight the need for systematic benchmarking of sustainability parameters, mechanistic understanding to guide rational process design and well as toxicity considerations. As green chemistry evolves toward circular and low-carbon manufacturing, these strategies will shape a new generation of functional biopolymers derived through energy-efficient, solvent-free transformations—cementing mechanochemistry as a cornerstone of sustainable materials science.

## 1. Introduction

Polymers are consistently ranked among the most important materials in modern civilization due to their wide range of

applications, stemming from the diversity of their functional groups and structures that define their physicochemical properties.<sup>1–3</sup> However, the mass production and widespread use of synthetic polymers have also introduced significant environmental challenges throughout their entire lifecycle. Many common synthetic polymers such as nylon,<sup>4,5</sup> polyolefin,<sup>6</sup> polystyrene,<sup>7</sup> polyester,<sup>8</sup> polyurethane,<sup>9</sup> Teflon,<sup>10</sup> and epoxy are all derived from petrochemicals,<sup>11</sup> which require extensive refining and processing of crude oil, resulting in substantial environmental impacts such as pollution, biodiversity loss, and climate change.<sup>12,13</sup> Synthetic polymers often lack biodegradability, leading to plastic waste persisting in the

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environment long after human consumption.<sup>14,15</sup> Disposal strategies such as incineration, further contribute to the release of toxic compounds and carbon dioxide in the atmosphere,<sup>16</sup> a primary driver of global warming and climate change,<sup>17,18</sup> while land-filling and release directly in the environment lead to water, soil and air pollution in the form of leached molecules, nano-, micro- and macro-plastics. This situation calls for urgent collective efforts from society to preserve our planet for future generations.<sup>19</sup>

Biopolymers have a crucial role in the process of decarbonization to reduce our reliance on petrochemical-derived synthetic polymers.<sup>20–22</sup> Unlike synthetic polymers, every biopolymer can be traced back to photosynthesis which converts carbon dioxide and water (H<sub>2</sub>O) into organic matter. The biochemical processes of living organisms then transform this simple organic matter into a diverse array of compounds that support life. It is important to stress that such schemes must be associated with sustainable land management, forestry and agricultural practices to truly yield environmental benefits and avoid unintended consequences such as biodiversity loss. Among the major classes of biopolymers polysaccharides are the most abundant,<sup>23</sup> with cellulose and chitin ranking first and second, respectively.<sup>21,24</sup>

Lignocellulosic and chitinous materials are widely available in biomass waste, such as sidestreams from the wood, agricultural, and food industries, making them ideal feedstocks for promoting a circular economy.<sup>21,25–27</sup> However, pristine polysaccharides often lack sufficient functionalities and properties that limit their ability to serve as substitutes for a broader range of synthetic polymers. For instance, most polysaccharides are hydrophilic, and are incompatible with many synthetic polymers that are hydrophobic, as well as with applications requiring water resistance.<sup>28–31</sup> On the other hand, plastics feature mechanical and durability properties allowing them to perform well in diverse conditions, which native lignocellulosic or chitinous materials cannot achieve.<sup>32</sup>

Several approaches have been developed to enable the use of polysaccharide and achieve desired properties. (1) Deconstruction typically proceeds through the depolymerization of polysaccharides into their monomers, followed by further treatments to access platform chemicals,<sup>33–35</sup> and eventually end products, including *de novo* polymers.<sup>36</sup> One prime example of the deconstructive strategy is the production of polylactic acid using lactic acid obtained from fermentation of starchy biomass,<sup>37,38</sup> and the synthesis of polyethylene furanoate (PEF) from sugars through furan dicarboxylic acid as a platform molecule.<sup>36</sup> Such strategies have been intensely researched and provide production pathways comparable to petrochemistry but suffer from the drawback of poor atom economy and the need for many reaction steps. (2) Nano-extraction involves the controlled and limited depolymerization of polysaccharides to produce nanoscale materials such as cellulose or chitin nanocrystals, nanofibers, or chitosan nanowhiskers,<sup>39,40</sup> typically through acidic or oxidative pathways.<sup>41–43</sup> These nanomaterials can be used directly or incorporated into composites<sup>44,45</sup> to create synergies between the properties of multiple materials or to enhance performance.<sup>46,47</sup> (3) Transformation strategies rely on maintaining most or all the biopolymer backbone, focusing

on its modification to achieve the desired properties. Chemical grafting of new functionalities onto these biopolymers gives access to robust materials, with modified solubility, chemical, optical, and mechanical properties.<sup>48,49</sup> Examples of transformation strategies include mass produced materials such as nitrocellulose and starch acetate.<sup>50,51</sup> Such transformations can also enable the combination of polysaccharide derivatives with other components to form biocomposites, creating synergies between the properties of multiple materials.<sup>52,53</sup> Transformation strategies have the potential to be more sustainable as they minimize steps to product, although accessing precise, high-performance properties in the targeted materials may be challenging.

All these strategies are of interest and need to be harnessed for a more sustainable future. However, their implementation requires careful consideration, guided by the 2025 Stockholm Declaration on Chemistry for the Future,<sup>54</sup> which emphasizes five pillars: (i) the sustainable and safe design of chemical products and processes, (ii) the reduction of risks, (iii) the integration of sustainability into education, (iv) ensuring data transparency, and (v) alignment with supportive policies. These strategies all face significant challenges: the most abundant lignocellulosic and chitinous polymers are insoluble in common solvents,<sup>55,56</sup> and extensive inter- and intramolecular hydrogen bonding networks within these polymers<sup>57</sup> reduce their chemical reactivity.<sup>58</sup> These properties naturally evolved in polysaccharides to act as an integral protective strategy for living organisms, making homogeneous solution-based and heterogeneous dispersion-based methods of polysaccharide modification ineffective unless harsh reaction conditions including high temperatures and extreme acidic or basic environments, along with large excess of reagents which are applied individually or together to promote the chemical reactions.<sup>59–62</sup>

In recent years, mechanochemistry has emerged as a successful strategy to overcome some or all these limitations in processing and functionalizing polysaccharides. Mechanochemistry is defined as the science of chemical reactions that is induced by the direct absorption of mechanical energy,<sup>63–65</sup> where the energy can be delivered either with grinding media typically in various types of ball mills through impact and shear,<sup>66,67</sup> or without grinding media, where acoustic waves introduces compression and shear. Examples of the latter include the conventional mortar and pestle,<sup>68</sup> extruders,<sup>69,70</sup> roller mills,<sup>71,72</sup> pan mills,<sup>73</sup> and the more recently developed resonant acoustic mixing (RAM).<sup>74,75</sup> Mechanochemistry is particularly well-suited for reactions involving insoluble substrates as reactivity is not reliant on the dissolution of reagents.<sup>76</sup> Additionally, the limited use of solvents and reagents allows for mechanochemistry to enhance the overall green metrics of polysaccharide modification such as the process mass intensity (PMI).<sup>77</sup> In the last 15 years, the use of mechanochemistry for the valorization of polysaccharides has exploded, with tremendous development in all three strategies: (1) deconstruction, (2) nano-extraction and (3) functionalization. In this context, accelerated aging, also simply referred to as aging has recently been established as an effective complement to mechanical activation. Rather than relying on high reagent loadings and prolonged milling, aging allows the reaction mixture, once activated, to rest under mild or ambient



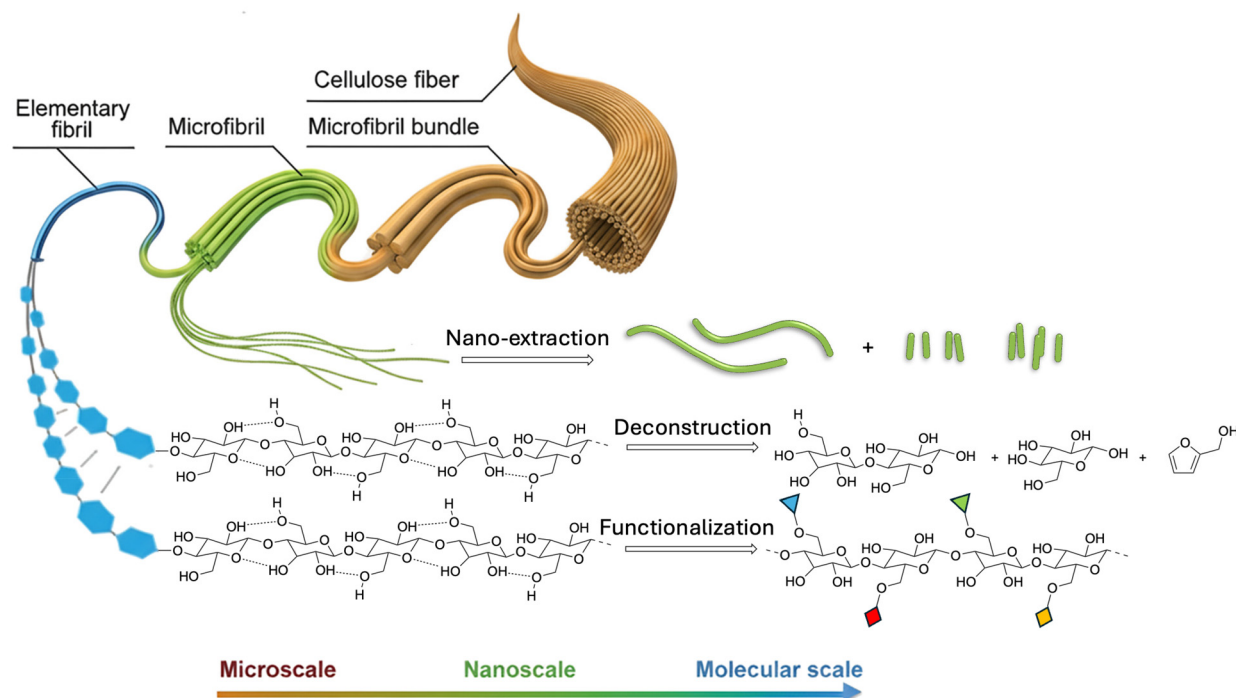
conditions. During this stationary period, reactions proceed through adsorption, penetration and diffusion, of substrates.<sup>78–83</sup> This approach has been successfully employed in a series of polysaccharide modification studies by our group<sup>84–88</sup> as well as by others.<sup>72,89–94</sup> In many cases, aging has been found to extend transformations while simultaneously reducing the energy consumption associated with mechanical treatment. Importantly, it also helps prevent unintended structural damage to polysaccharide substrates, offering an appealing unified strategy that promotes higher reaction efficiency than conventional solution phase synthesis while operating under milder conditions than purely mechanochemical methods.

In this review, we critically examine the methods of mechanochemical and aging processing for deconstruction, nano-extracting and functionalization of different polysaccharides, namely cellulose, starch, chitin and chitosan, including with the use of mechanoenzymology. We highlight the conditions of these mechanochemical transformations, the efficacy of the processes, and the performance of the resulting products in their applications. Furthermore, we identify key areas for further exploration, to ultimately enhance the overall green chemistry metrics and improve the feasibility and practicality of mechanochemical polysaccharide modifications for producing functional biopolymers as substitutes for conventional synthetic polymers. Considering the importance of this field, several reviews were published, covering part of the topics gathered here.<sup>95–98</sup> Kobayashi and coworkers described in 2024 reports on the mechanochemical depolymerization of polysaccharides with a focus on mechanistic considerations.<sup>99</sup> Kerton and coworker described in 2021 the use mechan-

ochemistry to valorize biomass, with examples from polysaccharides and biominerals.<sup>98</sup> These two reviews do not cover functionalization and nano-extraction strategies. In 2022, our review focused only on functionalization and nano-extraction with an important focus on the applications.<sup>100</sup> Since then, De Borggraeve and coworkers as well as Hernáiz and coworkers, they both highlighted the sustainability advantages of polysaccharide functionalization *via* mechanochemistry;<sup>101,102</sup> However, these works did not integrate green chemistry principles or apply quantitative metrics for process evaluation. We identify this as a gap in the field, underscoring the need for an extended discussion that systematically addresses the green aspects of all polysaccharide mechanochemical functionalization strategies within a single review, which had yet to be done. Specifically, in this critical review, we discuss the advantages of mechanochemistry and aging based methods as compared to liquid state transformations, the generality of these methods across polysaccharide reactivities as well as the selectivity of such methods for deconstruction, nano-extracting and functionalization, and finally toxicity considerations in such schemes.

## 2. Mechanochemical tools and aging strategies used in polysaccharide functionalization

Tools used in mechanochemistry and aging have been reviewed before and we point the reader to existing references for more



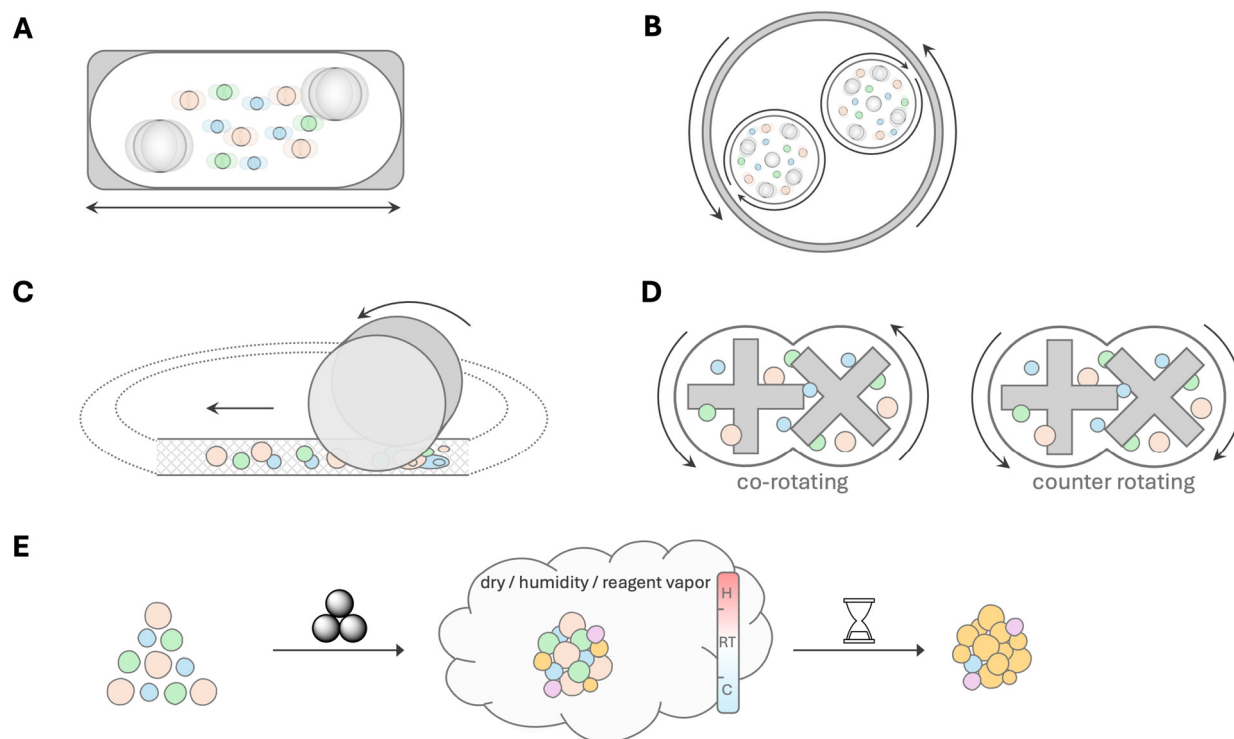
**Fig. 1** Visual representation of the three strategies presented in this review for the valorization of polysaccharides by mechanochemistry or aging-based methods. In this figure, cellulose from wood's structure is used as a model. Parts of the figure were adapted with permission from C. Chen, L. Hu, *Adv. Mater.*, 2021, **33**, 2002890. Copyright 2021, Wiley-VCH.



details (Fig. 2).<sup>66,103–107</sup> In this section we will focus on highlighting the equipment most used in the research covered in this review. Mechanical pretreatment is common in biomass processing, and many of the same tools have been adapted for mechanochemistry, particularly ball mills. Vibrational and planetary ball mills are most frequently employed. In ball-milling, the balls transfer energy to the material, with vibrational mills typically using one or two balls.<sup>105</sup> Key parameters including the number, size, mass, and material of the balls, as well as the size and material of the grinding jars determine ball movement, while milling frequency and duration define the total mechanical energy delivered. The addition of other grinding media or liquid additives for liquid-assisted grinding (LAG),<sup>108</sup> further defines the milling conditions in a mechanochemical treatment. Planetary milling combines two rotational motions: rotation of the jars around the planetary axis and simultaneous rotation around their own Z-axes, typically in the opposite direction.<sup>103</sup> This counter-rotation generates strong shear and impact forces between the balls and the vessel walls. Smaller balls in larger numbers are often employed to enhance mixing and activation. While similar to vibrational ball milling in relying on the ball and jar setup, the energy input in planetary milling is governed primarily by the rotational speed (rpm) and milling duration. Variations in the motion can tune milling intensity; for example, high-energy ball mills, a variant of planetary mills, generate stronger shear and impact forces by forcing multi-directional ball movement, making them particularly efficient for substrate comminution.<sup>109</sup>

Mechanochemical transformations may also be performed without balls as grinding media. In several examples discussed in this review, researchers have employed pan mills, where the material placed in the grinding chamber is crushed by heavy rollers.<sup>110</sup> Gear-like teeth on the roller surfaces provide both strong compression and shear, enabling mechanochemical transformations. Because pan-milling is not conducted in a sealed vessel, the total energy input is typically quantified by the number of cycles the material passes through the rollers rather than by continuous reaction time. Offering more process control, reactive extrusion has emerged as a versatile flow-based technique for mechanochemical synthesis.<sup>69</sup> One or two rotating metal screws, configured with alternating conveying and kneading blocks, apply strong shear and compressive forces to the substrate, initiating chemical transformations. What distinguishes reactive extrusion from other methods is its modularity: the arrangement of functional blocks can be customized to meet the requirements of a given reaction. In addition, precise temperature control is possible, as each barrel section can be independently heated, making the technique especially attractive for syntheses requiring simultaneous mechanical and thermal activation.

In several examples, aging, also known as accelerated aging, is used in conjunction with ball-milling. Aging is a diffusion-based technique in which a substrate mixture is left stationary at room temperature or under mild heating, in a dry atmosphere, high humidity, or in the presence of reagent vapors.<sup>78–83</sup> In many cases, this approach has proven highly



**Fig. 2** Schematic representation of the modes of mechanical action employed in mechanochemical processes: (A) vibrational ball mill, (B) planetary ball mill, (C) pan mill, and (D) twin-screw extruder a (E) combination of mechanochemical activation with subsequent aging.





effective in improving reaction efficiency in terms of reagent conversion rates, while reducing energy consumption compared to extended mechanical treatment.

### 3. Review of functionalization strategies, organized by substrates and reaction

#### 3.1. Cellulose

Cellulose is the most abundant biopolymer in the biosphere accounting for about 1.5 trillion tonnes available annually.<sup>21</sup> It is a linear biopolymer composed of D-glucose units linked by β-1,4 glycosidic bonds, which give cellulose its characteristic rigidity and strength. Found in the cell walls of plants and in the extracellular matrix of certain bacteria,<sup>42,111,112</sup> cellulose forms microfibrils with high crystallinity.<sup>113</sup> There is continuous growth of interest in the development of pathways to valorize cellulose by chemical modification.<sup>114,115</sup>

**3.1.1 Cellulose hydrolysis.** The hydrolysis reaction is a key mechanochemical modification of cellulose as it provides access to sugars and platform molecules. Hydrolysis of cellulose has historically been the seminal examples for the development of mechanochemistry in this field. Selected samples are presented in Table 1. Complete hydrolysis affords glucose,<sup>116</sup> a central feedstock for food and bio-based chemicals.<sup>117–119</sup>

Blair and Schüth laid foundation in the development of the method to hydrolyze cellulose by mechanochemistry through two distinct pathways. Blair and coworkers identified kaolinite, a phyllosilicate minerals, effective in solubilizing cellulose: milling microcrystalline cellulose (MCC) (1 g) with kaolinite (1 g) solubilized 84% cellulose, yielding glucose, fructose, and dehydration products including 5-hydroxymethylfurfural (HMF), levoglucosenone and levoglucosan.<sup>120</sup> With a similar strategy, Takagaki and coworkers screened 13 oxides; layered niobium molybdate (HNbMoO<sub>6</sub>) gave 72% water-soluble sugars after 24 h

milling (800 rpm).<sup>121</sup> This Brønsted acid facilitated chain insertion and random glycosidic bond cleavage.

The methodologies Schüth and coworkers developed involves impregnating cellulose with acids assisted by diethyl ether. They first tested impregnated cellulose with sulfuric acid (H<sub>2</sub>SO<sub>4</sub>), *p*-toluenesulfonic acid (*p*-TSA), or HCl before milling.<sup>122</sup> With 0.88 mmol g<sup>−1</sup> H<sub>2</sub>SO<sub>4</sub>, complete conversion to soluble oligomers with degree of polymerization (DP) over 3 was achieved in 2 h (800 rpm). At kilogram scale, a Simoloyer mill processed α-cellulose (1 kg) impregnated with H<sub>2</sub>SO<sub>4</sub> (0.8 mmol g<sup>−1</sup>). Milling at 527 rpm for 35 min produced 93% soluble products, mostly oligosaccharides. A saccharification step at 145 °C raised glucose yield to 65% with a total specific energy consumption for cellulose hydrolysis of 3450 kWh t<sup>−1</sup>.<sup>123</sup> Eliminating organic solvent, Yu and coworkers impregnated MCC in diluted H<sub>2</sub>SO<sub>4</sub> solution (0.5 mmol g<sup>−1</sup>) and removed excess water in the slurry prior to ball-milling (30 Hz, 60 min). The process yielded ~99% soluble oligomers, 14% with DP < 5. Subsequent hydrolysis (0.25 wt% H<sub>2</sub>SO<sub>4</sub>, 150 °C, 5 min) gave 91% glucose.<sup>124</sup>

Yan and coworkers developed a top-down mechanochemical approach to cellulose oligosaccharide surfactants *via* thermally-enhanced alcoholysis of MCC.<sup>125</sup> Milling MCC with concentrated H<sub>2</sub>SO<sub>4</sub> (1 wt%) and fatty alcohols (C<sub>6</sub>–C<sub>12</sub>) at 110 °C afforded >60% biomass conversion to fatty alcohol-grafted cellulose oligomers (DP ≈ 12), with predominant C1 substitution. The method was applicable to raw lignocellulosic feedstocks including wheat bran and poplar sawdust, albeit at lower conversion. The resulting water-soluble oligosaccharides exhibited low critical micelle concentrations (0.1–1 mmol L<sup>−1</sup>), comparable to commercial methyl ester sulfonate surfactants, highlighting their potential as sustainable bio-based alternatives.

Using a related one-pot mechanochemical protocol, the same group synthesized cellulose oligomeric glycosylamine surfactants by reacting crude cellulooligosaccharides with fatty amines (C<sub>8</sub>–C<sub>14</sub>).<sup>126</sup> Extended milling and heating at 120 °C afforded >50% conversion and degrees of functionalization up

**Table 1** Examples of mechanochemical hydrolysis of cellulose

Active reagent	Equipment	Conditions	Product	Yield	Ref.
Layered delaminated kaolinite (Al <sub>2</sub> Si <sub>2</sub> O <sub>7</sub> ·2H <sub>2</sub> O)	Mixer mill	3 h	Water-soluble sugars	84%	Blair and coworkers <sup>120</sup>
Layered niobium molybdate (HNbMoO <sub>6</sub> )	Planetary ball mill	800 rpm, 24 h	Water-soluble sugars	72%	Takagaki and coworkers <sup>121</sup>
Impregnated acid (H <sub>2</sub> SO <sub>4</sub> , HCl, or <i>p</i> -TSA)	Planetary ball mill	800 rpm, 2–5 h	Water-soluble sugars	80%	Schüth and coworkers <sup>122</sup>
Impregnated H <sub>2</sub> SO <sub>4</sub>	Simoloyer ball mill	527 rpm, 35 min	Glucose	65%	Rinaldi and coworkers <sup>123</sup>
Impregnated H <sub>2</sub> SO <sub>4</sub>	Vibrational ball mill	30 Hz, 60 min	Water-soluble sugars	99%	Yu and coworkers <sup>124</sup>
Fatty alcohol, H <sub>2</sub> SO <sub>4</sub> catalyst	Mechanochemical stirring	700 rpm, 30 min, 110 °C	Fatty alcohol-grafted cellulose oligomers	>60%	Yan and coworkers <sup>125</sup>
Fatty amine, H <sub>2</sub> SO <sub>4</sub> (pre-impregnated)	Mechanochemical stirring	700 rpm, 30–75 min, 120 °C	Cellulose oligomeric glycosylamine	>50%	Yan and coworkers <sup>126</sup>
Activated carbon	Planetary ball mill	60 rpm, 2 d	Glucose	88%	Fukuoka and coworkers <sup>127</sup>
Carbonaceous solid acid	Planetary ball mill	500 rpm, 4 h	Glucose	88%	Qi and coworkers <sup>128</sup>
Sulfonated carbon catalyst	Planetary ball mill	300 rpm, 18 h	Glucose	10%	Vogel and coworkers <sup>129</sup>
<i>T. longibrachiatum</i> cellulase	Vibrational ball mill	30 Hz, 5 min, 55 min aging, 12 cycles	Glucose	50%	Auclair and coworkers <sup>89</sup>
Al <sub>2</sub> (SO <sub>4</sub> ) <sub>3</sub>	Planetary ball mill	350 rpm, 4 h	HMF	44.6%	Qi and coworkers <sup>130</sup>



to 0.15. The glycosylamine derivatives showed surface activity comparable to the alcohol-grafted analogues with critical micelle concentrations slightly exceeding 1 mmol L<sup>-1</sup>, while the incorporation of amine functionalities imparted broad-spectrum antimicrobial activity, as demonstrated against *Escherichia coli* and *Bacillus subtilis*.

Fukuoka and coworkers pioneered the use of carbonaceous solid acid catalysts in mechanochemical pretreatment to selectively produce oligosaccharides and promote subsequent hydrothermal hydrolysis. In their study, MCC with alumina balls and activated carbon was milled (60 rpm, 2 d), then hydrothermally hydrolyzed in 0.012% hydrochloric acid (HCl) (20 min, 453 K), giving 98% conversion and 88% glucose yield.<sup>127</sup> Qi and coworkers achieved comparable results (88.0% glucose) with reduced mechanical treatment, by milling MCC with a carbonaceous solid acid catalyst (500 rpm, 4 h), followed by hydrothermal hydrolysis (200 °C, 1 h); without milling, yield dropped to 11.2%. Addition of 0.02 wt% HCl boosted glucose yield from 52.8% to 88.0%.<sup>128</sup> Vogel and coworkers milled MCC with sulfonated carbon catalyst (300 rpm, 18 h), then hydrolyzed at 165 °C under 20 bar with 1 mM ethylenediaminetetraacetic acid, reaching 27.2% conversion, with 17.4% oligosaccharides.<sup>129</sup>

Enzymatic routes under mechanochemical conditions have also been developed. Auclair and coworkers applied mechanoenzymatic reactive aging, or “RAGING” (5 min milling, 55 min aging, repeated 12 cycles) with cellulase and trace water, converting 50% MCC to glucose in 12 h.<sup>89</sup> This achieved > 20× throughput compared to conventional enzymatic digestion. Applied to raw biomass, 1.5 mmol glucose per g was obtained.

Other than glucose, the complete depolymerization of cellulose can yield aromatic by-products such as furfural and HMF, which are valuable lignocellulose-derived platform chemicals.<sup>120,123,129</sup> Qi and coworkers targeted HMF production by milling cellulose with a Lewis and Brønsted acid, Al<sub>2</sub>(SO<sub>4</sub>)<sub>3</sub> at 350 rpm, for 4 h, followed by hydrolysis in a water-γ-valerolactone biphasic solvent system (165 °C, 50 min), reaching 44.6% HMF yield.<sup>130</sup>

**3.1.2 Nanocellulose synthesis.** Nanocellulose is a family of cellulose-based materials with nanoscale dimensions,<sup>39</sup> with

applications as reinforcing materials,<sup>131</sup> fluidizing,<sup>132</sup> formulating or active ingredient<sup>133</sup> or as support for other functions.<sup>134</sup> They encompass cellulose nanofibers (CNFs), which typically have 5–10 nm in width and several hundreds of nm to several microns in length, as well as cellulose nanocrystals (CNCs), which typically are 5–10 nm in width and 100–250 nm in length. All these materials have high crystallinity index (CrI), a feature being critical in directing their synthesis. They are produced by the selective and controlled depolymerization of cellulose, either through acidic or oxidative pathways (Table 2). In general, these procedures rely on mechanical or chemical treatment or both. The seminal method to produce CNC relies on a purely chemical approach in the liquid phase, followed by sonication. For CNF synthesis, mechanical treatment is favored, with chemical assistance to add charges on the fibers to help in defibrillation. Recent development in the use of mechanochemistry blurs the lines between the use of mechanical and chemical means and offers integrated approaches to achieve conversions with improved yields, and better sustainability metrics.

Mechanochemical strategies for CNC production have recently been intensely researched. Lu and coworkers demonstrated ball-milling of bamboo pulp with phosphoric acid (H<sub>3</sub>PO<sub>4</sub>) followed by ultrasonication, yielding 77.4% CNCs with rod-like morphology (100–200 × 15–30 nm).<sup>135</sup> Similarly, Huang and coworkers applied milling with phosphotungstic acid (PTA) and hydrothermal hydrolysis, reaching 88.4% yield and a CrI of 79.6%, with enhanced thermal stability compared to the starting pulp (CrI 63.7%).<sup>136,137</sup>

Integration with natural deep eutectic solvents (NADES)<sup>138</sup> has also advanced the field. Bras and coworkers reported a one-step choline chloride (ChCl)/oxalic acid dihydrate (OAD) NADES process, achieving 65% yield *versus* 27% for citric acid monohydrate (CAM)-based NADES, with CNCs showing CrI of 92%, surface charge of 120 μmol g<sup>-1</sup>, and ~143 nm length.<sup>139</sup>

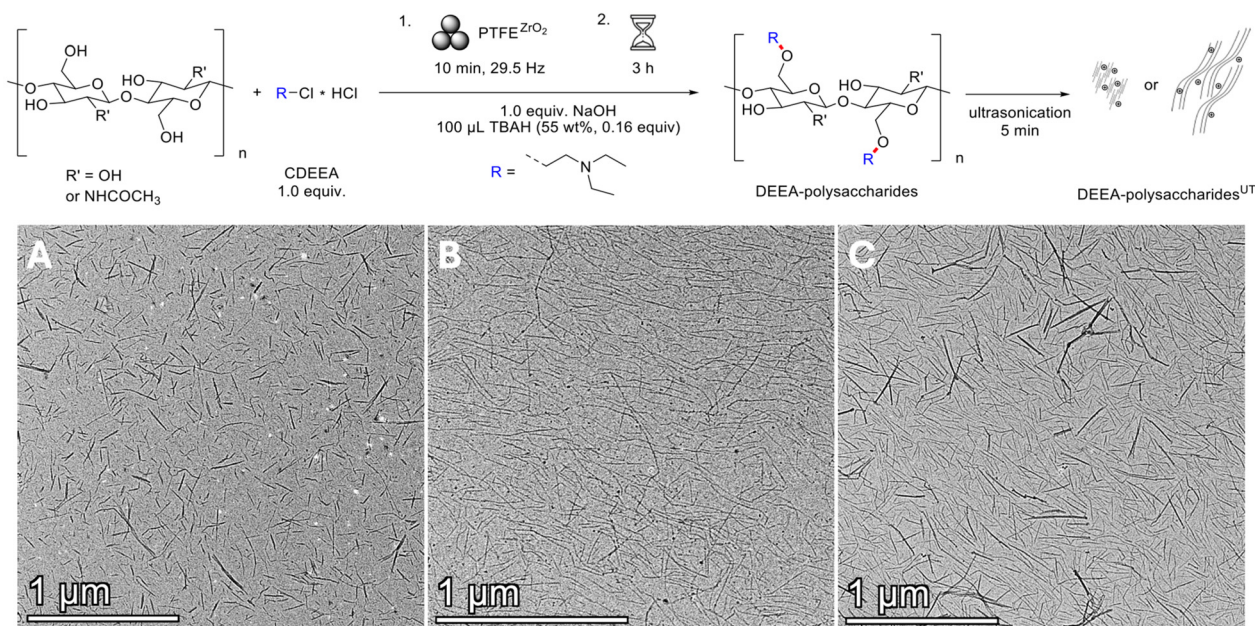
Another approach to the mineral acid-assisted production of CNC was demonstrated by Kontturi and coworkers where they observed the hydrolysis of CNFs on silicon dioxide by HCl gas, leading to CNC-like rods with lengths of 68 or 284 nm, depending on pressure.<sup>140</sup> In their work they demonstrated

**Table 2** Examples of mechanochemical cellulose nanocrystals synthesis

Substrate	Active reagent	Equipment	Condition	Yield	Characteristics	Ref.
Bamboo pulp	H <sub>3</sub> PO <sub>4</sub>	Stirring ball mill	400 rpm, 2.5 h	77.4%	Rod-like	Lu and coworkers <sup>135</sup>
Bamboo pulp	PTA	Planetary ball mill	—	88.4%	CrI = 80%	Huang and coworkers <sup>136</sup>
Fluffed cotton fiber	ChCl/OAD NADES	Vibrational ball mill	30 Hz, 1.5 h	65.0%	CrI = 92%	Bras and coworkers <sup>139</sup>
CNFs	HCl gas <sup>a</sup>	N/A	0.6 or 1.0 bar HCl gas for 30 min	N/A	CNC-like rods	Kontturi and coworkers <sup>140</sup>
MCC	APS	Mortar & pestle, shaker incubator	3 min mixing, 2 d HHSA	N/A	Carboxylated (DO = 20%)	Moore and coworkers <sup>88</sup>
MCC or Wood pulp	CDEEA·HCl, NaOH, TBAH	Vibrational ball mill	29.5 Hz, 10 min 3 h aging	63.7%	ζ-potential = + 68 mV	Moore and coworkers <sup>143</sup>
MCC	<i>T. longibrachiatum</i> cellulase	Roller mill	100 rpm, 48 h	49.3%	CrI = 77%	Su and coworkers <sup>146</sup>

<sup>a</sup> Process does not include mechanical treatment.



S<sub>N</sub>2-type aminoalkylation functionalization + ultrasonication

**Fig. 3** Mechanochemical and aging based synthesis of DEEA-MCC, DEEA-SBKP, and DEEA-chitin through S<sub>N</sub>2-type aminoalkylation of polysaccharide substrate with *in situ*-generated CDEEA electrophile, followed by ultrasonication defibrillation to produce cationic nanopolysaccharides DEEA-substrate<sup>UT</sup>; Figure: TEM images of defibrillated samples (A) DEEA-MCC<sup>UT</sup>, (B) DEEA-SBKP<sup>UT</sup>, (C) DEEA-chitin<sup>UT</sup>. Reproduced with permission from ref. 143. Copyright © 2025 Royal Society of Chemistry.

the power of aging to achieve CNC production with HCl gas, while completely avoiding mechanical damage the delicate nanocellulose.

Besides acidic routes, oxidative pathways have been important benchmarks for liquid state CNC synthesis. 2,2,6,6-Tetramethylpiperidine-1-oxylradical (TEMPO)-mediated oxidation<sup>42,141</sup> and ammonium persulfate (APS) oxidation<sup>142</sup> both promote CNF defibrillation by introducing anionic carboxyl groups to the cellulose substrate. Our group demonstrated mechanochemical high-humidity shaker aging (HHSA), producing CNCs ~220 × 5 nm with degree of oxidation (DO) = 0.20.<sup>88</sup> This work importantly combined a very short manual mixing (3 min) with aging to achieve high quality CNCs with limited energy input.

Our group recently proposed another strategy to help the defibrillation process with the introduction of cationic charges by mechanochemistry. Grafted cationic tertiary amine groups promoted defibrillation, producing CNFs and CNCs (Fig. 3).<sup>143</sup> Interestingly, CNFs (1.2 μm × 2 nm) were directly obtained from the mechanochemical and aging-based treatment of softwood bleached kraft pulp (SBKP) with 2-chloro-*N,N*-diethylethylamine hydrochloride (CDEEA-HCl), followed by short ultrasonication, hence by-passing complex defibrillation techniques.

Mechanoenzymatic methods are emerging,<sup>144–146</sup> as shown by Su and coworkers, who combined ball-milling with cellulase hydrolysis, affording 49.3% CNC yield, CrI 76.8%, and average length 457 nm.<sup>146</sup>

In the latter four examples,<sup>88,143</sup> aging played a key role in minimizing the milling step and serves as the primary reaction stage, offering a strategy for producing nanocellulose while

mitigating undesired degradation and amorphization of the cellulose crystallites.<sup>88,147,148</sup>

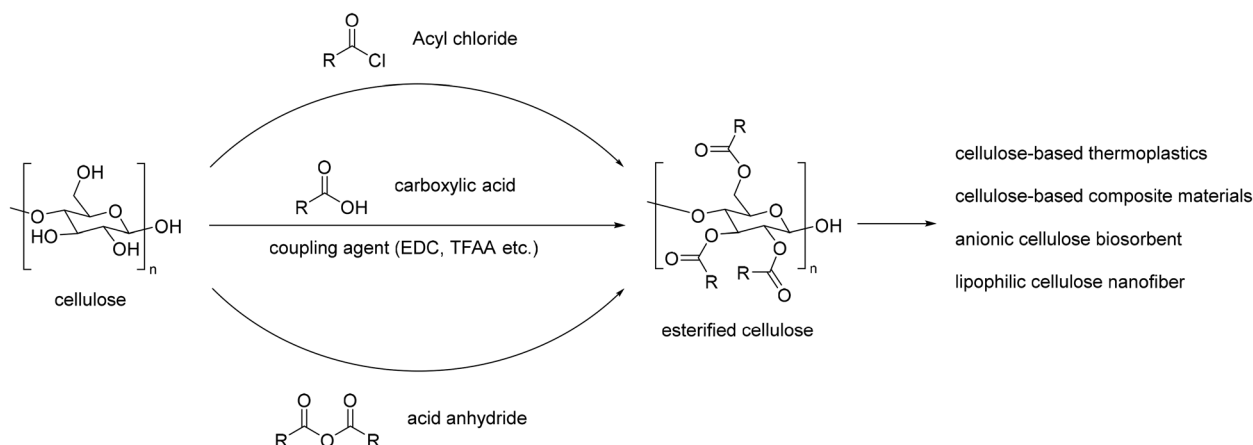
**3.1.3 Cellulose esterification.** After discussing hydrolysis and nano-extraction of cellulose, we explored the many functionalization reactions done on cellulose to achieve new physicochemical properties. Cellulose is rich in primary and secondary hydroxyl groups amenable to esterification. Typically, the acylation reaction proceeds with acid anhydrides, acyl chlorides, or carboxylic acid along coupling agents (Scheme 1) with examples presented in Table 3.

**3.1.3.1 Cellulose thermoplastic.** Andou and coworkers prepared cellulose oleate from MCC *via* mechanochemistry using a magnet mortar with oleic acid (OA) and 1-butyl-3-methylimidazolium acetate (BmimOAc).<sup>149</sup> Sulfonate esters were introduced with *p*-toluenesulfonyl chloride (TsCl), giving a maximum degree of substitution (DS) of 0.210 at 100 °C after 12 h, slightly decreasing to 0.204 after 24 h due to hydrolysis. CrI dropped modestly from 86.3% (MCC) to 80.8%, indicating limited amorphization.

Yang and coworkers reported thermoplastic cellulose oleate *via* two-stage planetary ball-milling (Fig. 4).<sup>150</sup> Regenerated cellulose, 6 equivalents (equiv) of OA, and 7.2 equiv. carbodiimide hydrochloride (EDC-HCl) were milled, followed by 4-dimethylaminopyridine (DMAP) addition to accelerate esterification. The process yielded pure cellulose oleate with DS 2.55, later moulded into transparent, flexible, hydrophobic films, offering an alternative to solvent-intensive acid-catalyzed acylation.<sup>151</sup> Expanding this strategy, Yang converted MCC into melt-processable cellulose stearate thermoplastics using







**Scheme 1** Mechanochemical cellulose esterification pathways and applications.

stearyl chloride and trifluoroacetic anhydride (TFAA) in a planetary ball mill.<sup>152</sup> Direct mechanochemical esterification required  $\sim 1/8^{\text{th}}$  the pyridine or TFAA compared to conventional heterogeneous methods.<sup>153,154</sup> Fatty acyl chlorides (C10–C18) produced fatty acid cellulose esters (FACEs) with DS 2.18–2.62, all processable by hot-pressing (160 °C, 10 MPa), though samples showed slight yellowing from pyridine.<sup>150,152</sup> To mitigate this, Yang later developed a TFAA-assisted milling method using carboxylic acids, yielding similar thermoplastic esters.<sup>155</sup>

**3.1.3.2 Cellulose composite.** Cellulose esterification has also been used as a method to produce composite materials (Table 3). Lu and coworkers prepared surface-acetylated cellulose powder (SACP) by pan-milling cellulose with acetic anhydride (1 : 4 ratio, 60 rpm, 2 cycles).<sup>156</sup> Milling disrupted H-bonding, exposed OH groups, and enabled acetylation.<sup>157,158</sup> The synthesized SACP was then compounded with natural rubber in a laboratory two-roll mill in the presence of zinc oxide (ZnO), stearic acid, *N*-cyclohexyl benzthiazyl sulphenamide (CBS) accelerator, and sulfur for vulcanization. When 30 parts per hundred resin SACP was compounded with natural rubber, the vulcanizate showed tensile strength of 14.5 MPa vs. 8.9 MPa for pristine cellulose, and elongation at break of 930% vs. 875%.

Hirotu and coworkers demonstrated the role of mechanochemistry in cellulose-polyolefin ester composites. Ball-milling cellulose with maleated polyethylene (MPE) followed by melt-mixing gave composites with 19.3–22.3% bonded MPE, compared to only 3.1% for melt-mixing alone.<sup>159,160</sup> This strong covalent ester linkage led to tensile elongation of 73% vs. 32% for untreated samples. Using maleic anhydride-grafted polypropylene (MAPP), mechanochemical treatment yielded 10.2 wt% bonded MAPP vs. 0.9 wt% for melt-mixing only, forming a core-shell structure with improved interfacial adhesion.<sup>160</sup>

Lu later applied pan-milling to produce polyvinyl alcohol (PVA)/cellulose composites using succinic anhydride (SA) as crosslinker.<sup>73,161</sup> The process consumed 61.6% SA and gave a tensile strength of 18 MPa and modulus of 66 MPa, compared to 14 MPa and 45 MPa for neat PVA.

Wu and coworkers addressed PP/cellulose incompatibility<sup>162,163</sup> by generating  $\beta$ -phase nucleating sites *via* mechanochemical

acylation.<sup>164–167</sup> SBKP was first milled to 71  $\mu\text{m}$  activated powders, which was then co-milled 120 min with mixed anhydride/pimelic acid/calcium carbonate ( $\text{CaCO}_3$ ), producing esterified cellulose that nucleated  $\beta$ -PP crystals (>50%).<sup>167</sup> The modified cellulose powders in PP (5% loading) yielded tensile strength of 43.2 MPa and elongation at break of 422%.

**3.1.3.3 Anionic cellulose.** Carboxylated cellulose is a staple in industrial use of cellulose.<sup>168</sup> Its negative charges<sup>169,170</sup> render it highly hydrophilic and has enabled applications such as high-performance films, biodegradable materials, and as a nanofiller in various composites, while its ability to bind toxic heavy metal ions is helpful in water decontamination.<sup>171,172</sup> Lu and coworkers reported a solvent-free mechanochemical method to carboxylated cellulose for use in  $\text{Pb}^{2+}$  removal.<sup>73</sup> Cellulose and SA (3 : 2) were milled at 60 rpm for 30 cycles, affording material with 2.70 mmol  $\text{g}^{-1}$  carboxylate groups, characterized by Fourier-transform infrared spectroscopy (FT-IR). In adsorption tests, it removed 421.8 mg  $\text{g}^{-1}$   $\text{Pb}^{2+}$  (84.4%) from a 500 mg  $\text{L}^{-1}$  solution, significantly higher than unmodified cellulose (26.4%).

Khaligh and coworkers used high-energy ball-milling (700 rpm, 4 h, 1 : 50 feed-to-ball ratio, 0.5 mm balls) for esterification of MCC with maleic anhydride.<sup>173</sup> The process achieved DS = 0.72, corresponding to 3.10 mmol  $\text{g}^{-1}$  carboxylates, with over 86% ring opening and grafting efficiency, confirmed by conductometric titration, back titration, and thermogravimetry-differential scanning calorimetry (TG-DSC). This efficient, additive-free method required only water for quenching and purification.

**3.1.3.4 Lipophilic cellulose.** Mechanochemical esterification is an effective method to functionalize already defibrillated CNFs. The efficacy of mechanochemical esterification of CNFs is dependent on multiple factors including, but not limited to, the surface area of dried CNFs, the carboxylic acid for the esterification reaction, and the energy input during ball-milling.<sup>71</sup> Wei and coworkers discovered that the addition of 10 wt% *tert*-butanol (TBA) to a 3.3 wt% aqueous slurries of CNFs prevented the collapse of CNFs during lyophilization and afforded CNFs with a significantly increased specific surface area of 23.47  $\text{m}^2 \text{g}^{-1}$  compared to 2.44  $\text{m}^2 \text{g}^{-1}$





Table 3 Examples of mechanochemical cellulose esterification and respective products

Substrate	Active reagent	Equipment	Condition	Product	Highest DS	Characteristics	Ref.
MCC	Oleic acid, TsCl	Magnet mortar	150 rpm, 13 h	Cellulose oleate	0.21	Thermoplastic	Andou and coworkers <sup>149</sup>
Regenerated cellulose	Oleic acid, EDC·HCl	Planetary ball mill	500 rpm, 2 h	Cellulose oleate	2.55	Thermoplastic	Yang and coworkers <sup>150</sup>
MCC	Fatty acyl chlorides, TFAA	Planetary ball mill	500 rpm, 4 h	FACES	2.32	Thermoplastic	Yang and coworkers <sup>152</sup>
MCC	Carboxylic acids, TFAA	Planetary ball mill	500 rpm, 4 h	Cellulose esters	2.9	Thermoplastic	Yang and coworkers <sup>155</sup>
SACP, NR	Acetic anhydride, stearic acid	Pan mill	60 rpm, 2 cycles	NR vulcanizates	—	Cellulose-filler reinforcement	Lu and coworkers <sup>156</sup>
Fibrous cellulose, MPE	Maleic anhydride	Planetary ball mill	250 rpm, 24 h	Cellulose/PE	—	Improved toughness and ductility	Hirotsu and coworkers <sup>159</sup>
Fibrous cellulose, MAPP	Maleic anhydride	Planetary ball mill	250 rpm, 8 h	Cellulose/pp	—	Core-shell structure	Hirotsu and coworkers <sup>160</sup>
Bleached hardwood pulp, PVA	SA	Pan mill	30 rpm, 20 cycles	Crosslinked PVA/cellulose	—	Improved toughness and ductility	Lu and coworkers <sup>161</sup>
SBKP, PP	Pimelic acid, acetic anhydride	Planetary ball mill	120 min	Cellulose/pp	—	Improved toughness and ductility	Wu and coworkers <sup>167</sup>
Cellulose fiber	SA	Pan mill	60 rpm, 30 cycles	Anionic cellulose	0.24	Biosorbent	Lu and coworkers <sup>73</sup>
MCC	Maleic anhydride	High energy ball mill	700 rpm, 4 h	Anionic cellulose	0.72	Unsaturated C=C group	Khaligh and coworkers <sup>73</sup>
CNF	Fatty acids	Rolling mill	350–400 rpm, 6 h	Lipophilic CNFs	0.46	Disperse in organic solvent	Wei and coworkers <sup>71</sup>

measured from the CNFs lyophilized in water only. The increased surface area significantly enhanced the DS in the mechanochemical esterification of CNF. This process involved milling one equiv. of granulated CNF with a low-speed rolling mill at 350–400 rpm for 6 h, along with two equiv. of acylimidazole intermediates. These intermediates were prepared by milling equal molar of fatty acids with carbonyldiimidazole. The addition of 10% TBA during lyophilization increased the DS in the optimized esterification reaction. Specifically, DS rose from 0.27 to 0.46 for hexanoic acid (C6), 0.11 to 0.25 for lauric acid (C12), 0.05 to 0.13 for OA, and 0.12 to 0.29 for stearic acid (C18). The esterified CNFs, with increased DS and higher surface area, demonstrated improved dispersion stability at 0.5 wt% in organic solvent as these CNFs remained well-dispersed after being resuspended in EtOH or chloroform by sonication.

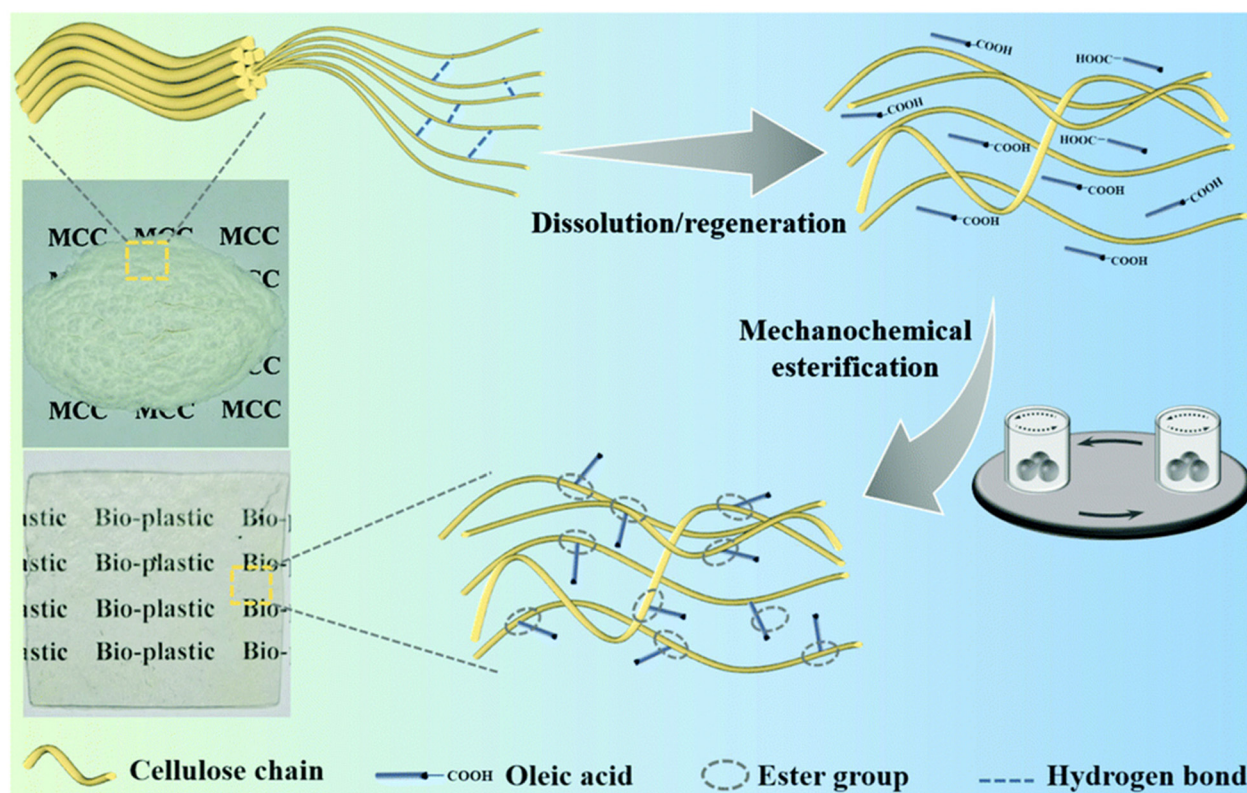
**3.1.4 Cellulose carbamation.** The urethane (carbamate) coupling reaction is an effective strategy for the surface modification of nanocellulose, wherein surface hydroxyl groups react with isocyanate species to form urethane linkages, thereby introducing new physicochemical properties to the polysaccharide material.<sup>174–177</sup> Bras and coworkers adapted their seminal surface carbamation of CNCs<sup>178</sup> to mechanochemistry by milling cotton fiber (0.75 g) with octadecyl isocyanate (1.37 g, 1 equiv.) at 30 Hz for 5–180 min.<sup>179</sup> Average bulk DS values were low (0.05–0.12), but XPS showed surface DS values 10–18× higher. CrI decreased moderately (60% → 50%), while fiber length dropped drastically ( $522 \pm 416 \mu\text{m}$  →  $20 \pm 11 \mu\text{m}$ ). Despite low conversion (<5%), the fibers gained remarkable hydrophobicity, with contact angle rising from <60° (unmodified) to 100° after 5 min, when surface DS was 1.25 and particle size remained large ( $339 \pm 375 \mu\text{m}$ ).

Chen and coworkers functionalized cellulose in lignin-containing bamboo powder (49.25% cellulose, 12.95% lignin, 21.44% hemicellulose) using 3,4-dichlorophenyl isocyanate.<sup>180</sup> One gram pretreated powder (0.49 g cellulose) was milled with 1.74 g isocyanate (3 equiv.) in 20 mL dimethyl sulfoxide (DMSO) at 300 rpm for 6 h, followed by 5 min ultrasonication. The process yielded thin CNFs with fiber width of  $2 \pm 1 \text{ nm}$  characterized by atomic force microscopy (AFM), with urethane formation confirmed by FT-IR. X-ray Diffraction (XRD) showed no crystallinity loss, and CNF films blocked >90% UV light while maintaining >80% transmittance. Ball-milling thus promoted carbamation, hydrophilization, and partial defibrillation to lignin-containing CNFs.

**3.1.5 Cellulose etherification.** Cellulose's primary –OH (C6) and two secondary –OH (C2, C3) possess moderate nucleophilicity for etherifying grafting reactions *via* nucleophilic substitution with small molecules<sup>181–183</sup> or other polymers.<sup>184–187</sup> With mechanochemistry, nucleophilic substitution can be performed either directly on pristine cellulose or as a secondary modification of already functionalized substrates.

Xiao and coworkers prepared carboxymethylated CNCs *via* mechanochemistry.<sup>188</sup> MCC (5 g, 1 equiv.) was first activated with sodium hydroxide (NaOH) (0.2 g, 0.16 equiv.) under argon and trace water, then ball-milled with agate beads at 600 rpm for 2 h. Sodium chloroacetate (0.2 g, 0.06 equiv.) was





**Fig. 4** Transparent thermoplastic cellulose oleate films produced from regenerated cellulose through mechanochemical esterification. Reprinted with permission from D.-F. Hou, M.-L. Li, C. Yan, L. Zhou, Z.-Y. Liu, W. Yang, M.-B. Yang, *Green Chem.*, 2021, 23(5), 2069–2078. Copyright © 2021 Royal Society of Chemistry.

added and the reaction mixture was milled 7 h, yielding DS = 0.99. However, titration suggested DS 720% above the theoretical maximum, highlighting the need for reliable characterization.  $\text{H}_2\text{O}$  addition (2 mL,  $\eta = 0.37 \mu\text{L mg}^{-1}$ ) enhanced hydration and reaction efficiency, giving nearly tripled DS compared to dry milling. Milling reduced particle size, promoted defibrillation into rods, and induced near-complete amorphization. Toxicological tests indicated low cytotoxicity, suggesting biocompatibility.

Kaabel and coworkers reported a two-step mechanochemical/aging approach to obtain C6-substituted aminated and carboxylic esterified CNCs.<sup>90</sup> Acid-hydrolyzed CNCs (200 mg, 1 equiv.) were tosylated with TsCl (360 mg, 1.5 equiv.) by ball-milling (25 Hz, 60 min) under LAG conditions (pyridine,  $\eta = 0.36 \mu\text{L mg}^{-1}$ ), yielding low DS = 0.11 to preserve crystallinity (CrI = 75%). Extended milling increased DS to 0.29 with 11 pt% CrI loss. Tosylated CNCs were then reacted with nucleophiles (0.708 mmol, 7.7 equiv.) *via* 5 min milling and 3 d aging at 55 °C, achieving near-quantitative substitution ( $\text{DS}_{\text{nuc}} \approx 0.10$ ). In the second milling stage the newly administrated nucleophiles react exclusively with the anhydrous glucose tosylate electrophile leaving the result repeating units untouched. In the second milling stage, the newly introduced nucleophiles react exclusively with the anhydroglucose tosylate electrophiles formed in the first step, leaving the remaining repeating units unaffected. This high mechanochemical selectivity not only

minimizes side-products and undesired derivatives but also calls for careful control of reagent loading to avoid unnecessary excess, in accordance with green chemistry principles. Transmission electron microscopy (TEM) showed rod-shaped CNCs with slight aggregation, attributed to both alkyl chain addition and mechanical treatment.

**3.1.6 Cellulose epoxide ring-opening.** The epoxide ring-opening reaction is a common strategy for functionalizing cellulose *via* an  $\text{S}_{\text{N}}2$  mechanism under alkaline conditions, yielding  $\beta$ -alkoxy alcohol structures. This approach is frequently employed with epichlorohydrin to produce cross-linked cellulose,<sup>189</sup> or with quaternary ammonium-containing epoxides such as (2,3-epoxypropyl) trimethylammonium chloride (EPTMAC) to obtain cationic cellulose.<sup>190</sup> However, this class of modification is often limited by its notoriously low efficiency and selectivity. A recent study by Kaabel and coworkers adapted the epoxide ring-opening functionalization of cellulose to a mechanochemical approach. In their work, 1 g of cellulose substrate (Whatman 1 filter paper) was first milled neatly (25 Hz, 5 min), followed by co-milling with a catalytic amount of NaOH (0.07 equiv.) and EPTMAC (20% water content, 0.43 equiv.) under LAG conditions using *i*-PrOH ( $\eta = 0.5 \mu\text{L mg}^{-1}$ ) for 30 min at 25 Hz.<sup>191</sup> The resulting mixture was then aged at 50 °C for 24 h, affording a moderate DS of 0.24 and converting 56% of the epoxide electrophile, significantly higher than the typical ~15% efficiency reported for solution-



phase methods,<sup>192</sup> while being far less wasteful with a drastically reduced  $\text{PMI}_{\text{reaction}}$  of 1.5. Kinetic studies of aging revealed a rapid increase in DS from 0.02 after milling to 0.21 after 6 h, plateauing at 0.24 after 12 h, indicating that aging served as the main reaction step. The process led to a reduction in fiber length from 0.037 mm to 0.021 mm, along with a minor decrease in CrI by 4 pt% to 48.6%, both attributed to the ball-milling step. The resulting cationic cellulose fibers ( $\zeta$ -potential =  $+34.5 \pm 2.5$  mV) were reprocessed into filter papers, which exhibited strong electrostatic binding with cowpea chlorotic mottle virus, efficiently removing virtually all viral particles from a  $50 \text{ mg L}^{-1}$  solution when filtered through five layers of the reconstructed cationic filter papers.

**3.1.7 Cellulose phosphorylation.** Kokol and coworkers demonstrated surface phosphorylation of CNCs under heterogeneous  $\text{H}_3\text{PO}_4$  or homogeneous  $\text{H}_3\text{PO}_4/\text{urea}$  conditions.<sup>193</sup> Inspired by this, our group developed a mechanochemical phosphorylation using phosphorus pentoxide ( $\text{P}_4\text{O}_{10}$ ) and urea, which circumvents the use of corrosive acids and energy-intensive drying.<sup>194</sup> Milling CNC with 1 equiv.  $\text{P}_4\text{O}_{10}$  and 10 equiv. urea at 30 Hz for 90 min yielded DS = 26%. Urea dis-

rupted inter- and intra-hydrogen bonds, enhancing reactivity. Phosphorylated CNC (P-CNC) showed improved char formation (inflection temperature =  $172^\circ\text{C}$ ,  $130.9^\circ\text{C}$  lower than pristine CNC) and 70% mass retention at  $500^\circ\text{C}$  vs. 96% loss for unmodified CNC.

Mechanochemical phosphorylation has also been applied to bulk cellulose. Laoutid and coworkers milled MCC (20 g) with  $\text{P}_4\text{O}_{10}$  (26 g, 0.75 equiv.) at 200 rpm for 1 h without urea, affording enough grafting efficiency (33% P, 4.15 wt%) to increase thermal degradation temperature.<sup>195</sup> Adding urea improves efficiency and lubrication. Su and coworkers milled MCC with  $\text{P}_4\text{O}_{10}$  and urea (1 : 0.5 : 5) at 650 rpm for 90 min, followed by 30 min aging at  $150^\circ\text{C}$ , producing anionic P-MCC defibrillated into P-CNCs ( $\sim 4 \text{ mmol g}^{-1}$  charge, 65% P grafted, CrI = 73.3%).<sup>91</sup> TEM showed uniform rod-shaped P-CNCs ( $254.9 \pm 27.3 \times 7.8 \pm 1.2 \text{ nm}$ ), showcasing the power of this method. This work was the only one to our knowledge providing a life cycle assessment (LCA) comparing a mechanochemical process with a solution phase one (Fig. 5). It revealed a > 10% reduction in five evaluated environmental impacts (global warming potential, primary energy demand, resource

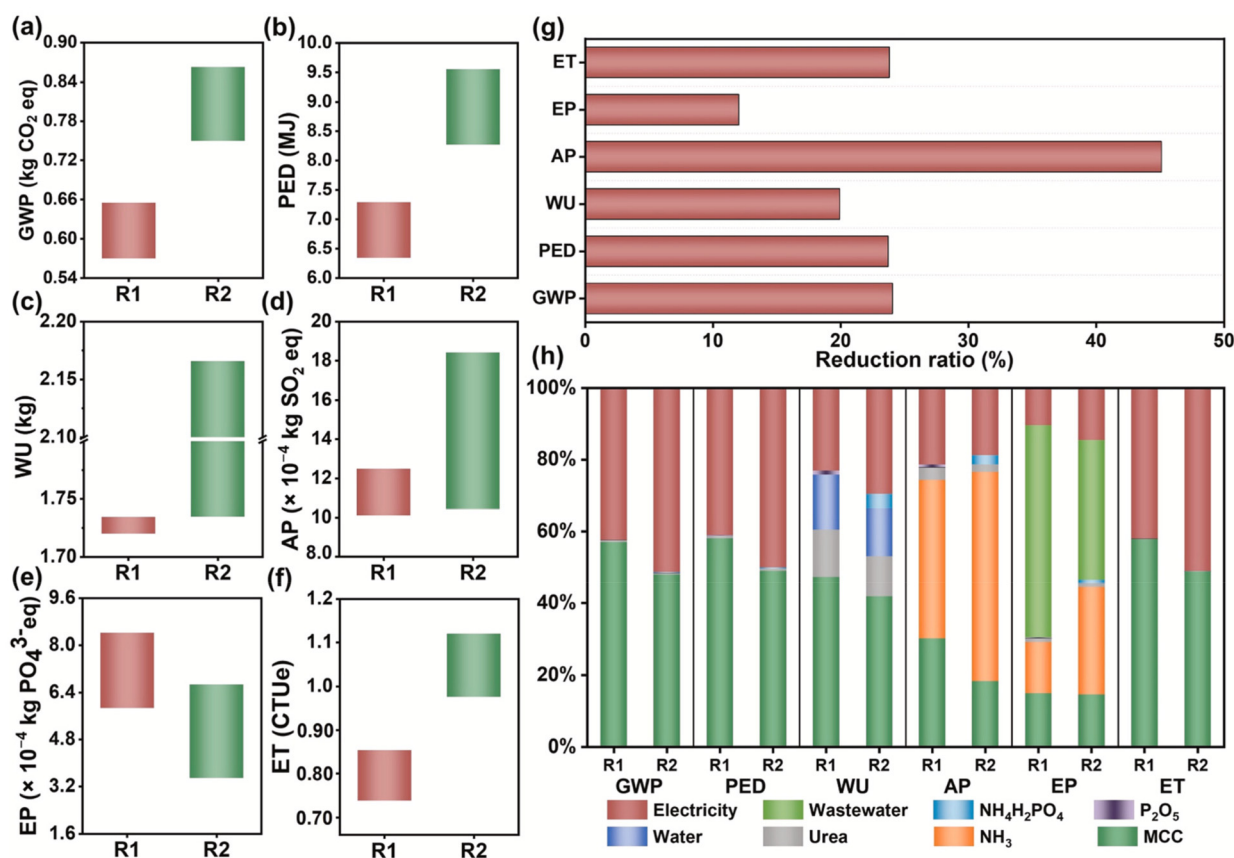


Fig. 5 LCA results of six selected environmental impact categories of two methods to access P-CNCs (R1: mechanochemical and aging-based phosphorylation, R2: heat soaking-assisted phosphorylation): (a) global warming potential (GWP); (b) primary energy demand (PED); (c) resource depletion water (WU); (d) acidification potential (AP); (e) eutrophication potential (EP); (f) ecotoxicity (ET). (g) Improvements of R1 compared with R2, where R1 corresponded to an MCC/ $\text{P}_2\text{O}_5$ /urea molar ratio of 1 : 0.25 : 2.5 and yielded P-CNCs with a charge content of  $3.499 \text{ mmol g}^{-1}$ , while R2 corresponded to an MCC/ $\text{NH}_4\text{H}_2\text{PO}_4$ /urea molar ratio of 1 : 0.6 : 2.4 and yielded P-CNCs with a charge content of  $2.664 \text{ mmol g}^{-1}$ . (h) Contributions of different listed substances in R1 and R2 for P-CNC production to the environmental impact categories. X. Gao, L. Zhang, M. Cui, W. Qi, H. L. Lam, R. Huang, R. Su, *Chem. Eng. J.*, 2025, 511 162260. Copyright © 2025 Elsevier B.V.





depletion water, acidification potential, and ecotoxicity) and 24.8% average reduction *versus* heat-assisted pre-phosphorylation, mainly by eliminating energy-intensive drying (electricity demand:  $0.579 \rightarrow 0.362 \text{ kWh g}^{-1}$ ).<sup>196</sup>

**3.1.8 Cellulose silylation.** Silylation is a versatile strategy to introduce substituted silyl groups to a substrate, where such transformation could occur on cellulose through either a  $S_N2$ -type reaction with silyl source such as *tert*-butyldimethylsilyl chloride,<sup>197</sup> or through the condensation of cellulose hydroxyl groups and the silanol groups of hydrolyzed silanes.<sup>198,199</sup> Other than surface modification, this approach was also employed in the chemical modification of bulk lignocellulosic material including wood hydrophobization.<sup>200</sup>

Even under mechanochemical conditions, the reaction with cellulose is usually performed in a  $H_2O/EtOH$  mixture medium, due to the necessity for silane hydrolysis to occur to introduce active silanol species. Jing and coworkers and Lee and coworkers conducted similar wet ball-milling reactions.<sup>201,202</sup>

Jing and coworkers prepared amine-functionalized silylated microfibrillated (MFC) with (3-aminopropyl)triethoxysilane (APTES) (2 g MFC, 0.2 equiv. APTES in 3 mL  $H_2O/100 \text{ mL EtOH}$ ) at 600 rpm for 24 h in a zirconia ( $ZrO_2$ ) planetary mill jar.<sup>201</sup> Quantitative efficiency was not reported, but vacuum-dried films showed high optical transparency ( $\sim 80\%$ ) and enhanced hydrophobicity (contact angle  $133.2 \pm 3.4^\circ$  vs. fully hydrophilic MFC). Lee and coworkers silylated MCC with trialkoxysilanes including methyltrimethoxysilane (MTMS), vinyltrimethoxysilane (VTMS),  $\gamma$ -glycidopropyltrimethoxysilane (GPTMS), and phenyltrimethoxysilane (PTMS) to introduce alkyl, vinyl, epoxy, or aromatic groups respectively.<sup>202</sup> One gram MCC was milled with 33 equiv. silane in  $H_2O/EtOH$  (17 g/13 g) in a  $ZrO_2$  planetary mill. Same as the other work, the reaction efficiency was not quantified with DS; Si–O–C bonds were confirmed qualitatively by FT-IR and scanning electron microscopy (SEM) coupled with energy dispersive X-ray spectroscopy (EDS) while XRD showed minor CrI loss. When used as fillers in silicone foams, silylated MCC greatly improved tensile strength (397 kPa),  $44.1\times$  and  $5.4\times$  higher than neat silicone foam and foam with pristine MCC, respectively.

**3.1.9 Cellulose copolymerization.** Mechanochemical activation of cellulose has been shown to favor weak bonding disruption to allow cellulose blending with other polymers such as PVA.<sup>203</sup> Beyond this physical activation, radical pathways are also accessible with mechanochemistry as cryomilling cotton can produce free cellulose mechanoradical for free radical-initiated reactions.<sup>204,205</sup>

Solala and coworkers studied this using styrene-modified cellulose: cotton linters were cryomilled with styrene and stainless steel balls, generating maximum radicals after 40 min.<sup>206</sup> In styrene's presence, electron paramagnetic resonance (EPR) intensity decreased while molecular weight ( $M_w$ ) was stabilized, attributed to low styrene binding. The process was judged inefficient for industry, though inert atmosphere might reduce oxygen side reactions.

Mechanistically, radicals arise from homogeneous scission of  $\beta$ -1,4-glycosidic bonds, as shown by Sakaguchi (Scheme 2).<sup>207</sup> Ohura and coworkers exploited this by synthe-

sizing a diblock copolymer: MCC (50 mg) and 2-hydroxyethyl methacrylate (pHEMA) (50 mg) were milled with 10 g alumina balls in vacuum for 6 h, where cellulose radicals initiated polymerization, yielding MCC-*block*-pHEMA (37 mol% pHEMA, DP = 69).<sup>208</sup> In contrast, heterogeneous scission produces mechano-ions. Sakaguchi and coworkers reported MCC milled with isobutyl vinyl ether (IBVE) in a vibrational glass mill (23 h, 77 K, vacuum), generating ionic yield of 0.692.<sup>209,210</sup> The resulting mechano-cations (MCC<sup>+</sup>) initiated cationic polymerization, forming MCC-*block*-PIBVE, where IBVE bonded to MCC<sup>+</sup> that produces new MCC mechano-cations and propagated PIBVE chains on the cellulose surface.<sup>211</sup>

### 3.2. Starch

Starch is an insoluble, semi-crystalline polysaccharide that serves as storage carbohydrate in some plants. Like cellulose, starch is also composed of D-glucose units. However, it simultaneously contains both linear amylose and highly branched amylopectin.<sup>212</sup> The most common application of starch is in the food and beverage sector where it is used as a thickening agent,<sup>213</sup> although it is also used as a feedstock in the chemical industry for bioplastics production or as a fermentation substrate for bioethanol.<sup>100,213–215</sup>

Traditional starch sources, such as potato and corn starch, can raise ethical concerns as they compete with food supplies. Researchers have turned to the by-products of protein extraction from legumes and pulses as sources for starch.<sup>215,216</sup> In our literature searches, the only types of mechanochemical modification of starch that involved the formation of new covalent bonds are esterification and etherification.

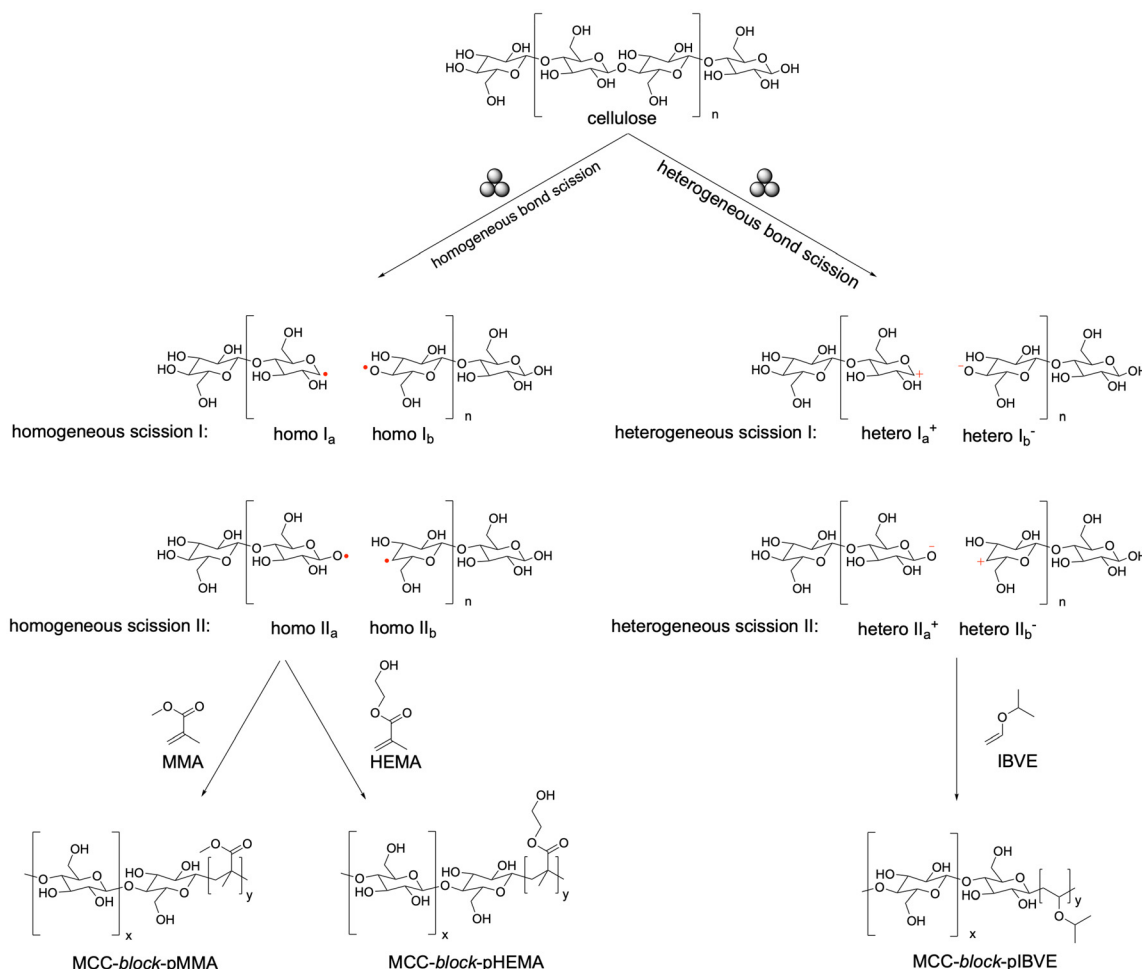
**3.2.1 Starch esterification.** Like cellulose, starch is rich in hydroxyl groups for chemical modification such as the esterification through acetylation reactions (Table 4). Dai and coworkers acetylated cassava starch using a rolling machine.<sup>72</sup> Native starch (40 wt% dispersion, pH 8.0–8.5, NaOH adjusted) was reacted with acetic anhydride at 30 Hz, 30 °C for up to 18 h, with additional aging. Products showed low DS (0.0140–0.0231) with no correlation to rolling time. Similarly, mung bean starch acetylation with a mortar grinder (20 rpm, 30 °C, 0–48 h, aged to 48 h) produced DS 0.0146–0.0259, also with no clear time-DS trend.<sup>92</sup>

Huang and coworkers developed ball-milling esterification using a stirring ball mill.<sup>217</sup> Cassava starch, lauric acid, and potassium carbonate ( $K_2CO_3$ ) catalyst yielded starch laurate (DS 0.0398) after 1 h milling at 60 °C, 375 rpm, with reduced crystallinity (measured by XRD) due to disrupted H-bonding (Scheme 3). Using octenyl succinic anhydride (OSA) and sodium carbonate ( $Na_2CO_3$ ) under similar conditions (90 min) produced OSA-starch (DS 0.0397), which was soluble in cold water up to 5.3 wt% with  $\sim 88\%$  transparency and enhanced emulsion stability ( $k < 2.0 \times 10^{-4}$ ).<sup>218</sup>

Zhao and coworkers explored the mechanochemical octenyl succinylation of starch using a planetary mill (450 rpm, agate jar and balls), where waxy rice starch was reacted with OSA in the presence of NaOH as a catalyst.<sup>219,220</sup> In their optimization, the highest reaction efficiency was obtained with 0.9 wt% NaOH relative to starch. Although increasing OSA loading led







**Scheme 2** Mechanochemical cellulose copolymerization through homogeneous bond scission and heterogeneous bond scission.

to a higher DS up to 0.032 at 9 wt% OSA, it simultaneously decreased the reaction efficiency from 75% at 3 wt% to 60% at 4 wt%. Under optimal conditions (0.9 wt% NaOH, 3 wt% OSA, 10 h milling), a DS of 0.017 and 60% reaction efficiency were achieved. Ball-milling reduced the CrI of OSA-starch from 18% to 4.12% after 10 h and rendered the samples fully amorphous after 30–50 h. The resulting OSA-starches exhibited high solubility (>20%) but relatively low viscosity and rigidity compared to conventionally prepared counterparts.

Hou, who previously contributed to several studies on mechanochemical cellulose esterification,<sup>150,152,155</sup> reported pyridine-catalyzed esterification of corn starch with lauroyl chloride.<sup>93</sup> Corn starch (0.324 g), lauroyl chloride (3.938 g, 9 equiv.), and pyridine (1.898 g, 12 equiv.) were milled at 500 rpm for 1 h, then aged 1 h at 110 °C, yielding DS 2.7. Claimed as more sustainable than *N,N*-dimethylacetamide (DMAc)/lithium chloride (LiCl) or pyridine solution (*E*-factors: 14.20, 5.21, vs. 2.05),<sup>221,222</sup> this assessment ignored EtOH used in purification, and the method left 70% unreacted lauroyl chloride as waste.

Gutiérrez and coworkers combined organocatalysis, flow mechanochemistry, and extrusion for salicylated starch.<sup>223</sup> Corn starch (140 g), glycerol (60 g), salicylic acid (4.0 g, 0.034

equiv.), and tartaric acid (4.35 g, 0.034 equiv.) were extruded (90–120 °C, 100 rpm, 15 g min<sup>-1</sup>). Titration reported DS 0.28 ± 0.06, exceeding the theoretical maximum (0.034), due to method overestimation. Solid-state cross-polarization/magic-angle spinning (CP-MAS) <sup>13</sup>C nuclear magnetic resonance spectroscopy (NMR) confirmed ester bonds. Films of salicylated starch showed 3% swelling in water, 0.099 MPa Young's modulus, 10% elongation, and slight antioxidant activity (6%), suggesting potential for food packaging.

**3.2.2 Starch etherification.** Similar to cellulose, starch can undergo etherification of its hydroxyl groups with chloroacetic acid under alkaline conditions to yield carboxymethyl starch,<sup>224,225</sup> which offers superior water-solubility and enhanced thickening properties compared to native starch.<sup>226–229</sup> The adaptation of this reaction to mechanochemistry was pioneered by Bhandari and Hanna, who investigated it using twin-screw extrusion (TSE).<sup>230,231</sup> In their work, sodium carboxymethyl starch with a DS of 1.54 was obtained when corn starch was kneaded (70 rpm, 80–85 °C) with 3.62 equiv. of sodium chloroacetate and 2.68 equiv. of NaOH in 50% EtOH/H<sub>2</sub>O ( $\eta = 0.13 \mu\text{L mg}^{-1}$ ). Despite the high DS, the overall reaction efficiency was moderate, with only 42% of



Table 4 Examples of mechanochemical starch esterification and respective products

Substrate	Active reagent	Equipment	Condition	Product	Highest DS	Characteristics	Ref.
Cassava starch	Acetic anhydride	Rolling machine	30 Hz, 18 h	Starch acetate	0.023	Improved solubility	Dai and coworkers <sup>72</sup>
Mung bean starch	Acetic anhydride	Mortar grinding machine	20 rpm, 48 h	Starch acetate	0.026	Improved solubility	Dai and coworkers <sup>92</sup>
Cassava starch	Lauric acid	Stirring ball mill	375 rpm, 1 h	Starch laurate	0.040	Improved hydrophobicity	Huang and coworkers <sup>217</sup>
Cassava starch	OSA	Stirring ball mill	375 rpm, 1.5 h	Starch octenyl succinate	0.040	High emulsion stability	Huang and coworkers <sup>218</sup>
Waxy rice starch	OSA	Planetary ball mill	450 rpm, 20 h	Starch octenyl succinate	0.032	High solubility, low viscosity	Zhao and coworkers <sup>219</sup>
Corn starch	Lauroyl chloride, pyridine	Planetary ball mill	500 rpm, 1 h 110 °C, 1 h	Starch laurate	2.7	Thermal processability, water resistance	Hou and coworkers <sup>93</sup>
Corn starch	Salicylic acid, tartaric acid, glycerol	Single-screw extruder	90 to 120 °C, 15 g min <sup>-1</sup> , 100 rpm	Salicylated starch	0.28 <sup>a</sup>	Thermal processability, antioxidant	Gutiérrez and coworkers <sup>223</sup>

<sup>a</sup> With overestimation, 8 times higher than stoichiometric maximum.

sodium chloroacetate converted into the final product. In another approach, Zhu and coworkers synthesized carboxymethyl starch in its acid form by ball-milling (450 rpm, 9 h, feed-to-ball ratio = 1 : 4) a premixed blend of corn starch and NaOH (1.6 equiv.) with monochloroacetic acid (0.8 equiv.) in the presence of a catalytic amount of tetrabutylammonium bromide (0.1 mol%) under LAG condition with isopropanol (i-PrOH) at  $\eta = 0.1 \text{ mL mg}^{-1}$ .<sup>232</sup> This method afforded carboxymethyl starch with a moderate DS = 0.631, where the DS increased steadily over the first 6 h of milling before plateauing. Although the process requires high energy input due to prolonged intense milling, it achieved notably high reaction efficiency, with 79% conversion of monochloroacetic acid to grafted carboxymethyl groups.

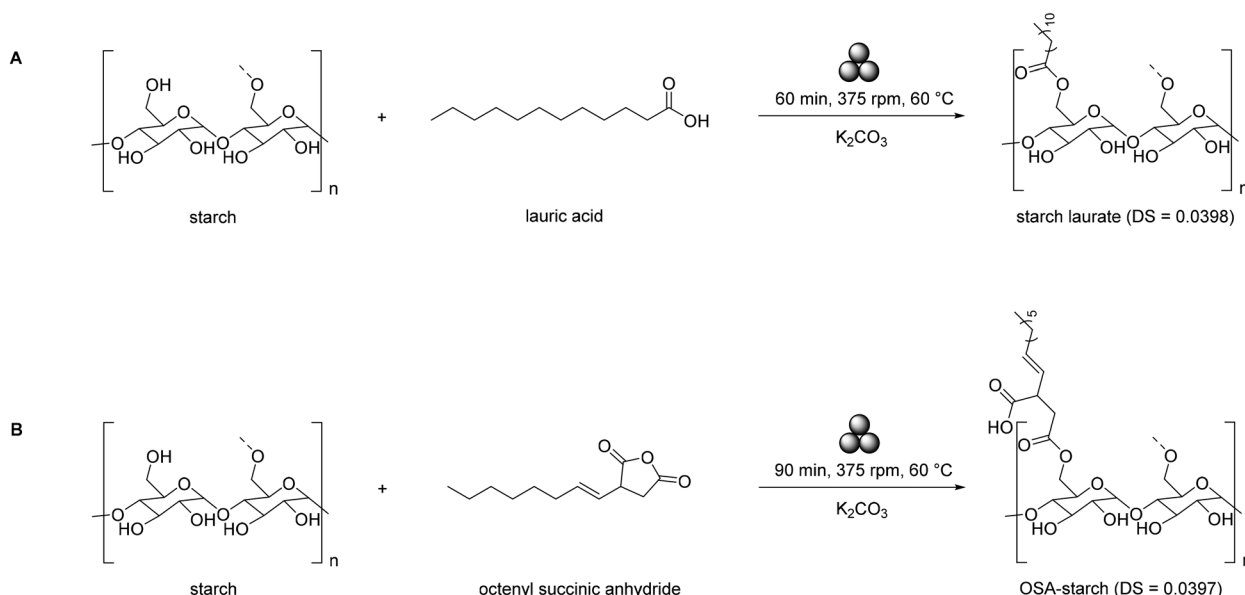
### 3.3. Chitin

Chitin, or poly(*N*-acetyl- $\beta$ -D-glucosamine) is one of the most abundant biopolymers second only to cellulose.<sup>24</sup> It is also the most abundant nitrogen-containing biopolymer widely found in the exoskeleton of arthropods and the cell walls of fungi and yeast.<sup>29</sup> Like cellulose, chitin also serves as a structural component in living organisms in the form of highly crystalline microfibrils.<sup>40</sup> Chitin can be depolymerized to form D-acetylglucosamine (GlcNAc) monomers or oligomers for applications in nutraceuticals, biomedical or fertilizers;<sup>233,234</sup> it can also be converted to nanofibers,<sup>235</sup> and nanocrystals for various uses.<sup>40,88,236,237</sup> Importantly, chitin featuring an amide functionality which can be deacetylated to yield chitosan, or poly( $\beta$ -D-glucosamine).<sup>238,239</sup> The nitrogen-containing nature of chitin and its derivatives makes them viable precursors for nitrogen-doped carbon materials capable of metal immobilization. Such materials have been prepared using mechanochemical techniques and applied in a range of contexts, including organic dye degradation,<sup>240</sup> bio-imaging,<sup>241,242</sup> and, more recently, cross-coupling catalysis.<sup>243</sup> While these developments represent an important advance in the valorization of chitinous waste, they do not involve intentional bond breaking or covalent bond formation within the polysaccharide backbone itself. In these systems, chitin and chitosan function primarily as structural supports or precursors rather than as chemically modified polysaccharides as defined by the three valorization strategies discussed in this review. Consequently, these applications are not covered in detail in the following sections. Readers are referred to a dedicated review from our group for a comprehensive discussion of mechanochemical transformations of biomass into functional material.<sup>100</sup>

**3.3.1 Chitin hydrolysis.** Like cellulose, chitin is susceptible to hydrolysis to produce oligosaccharides and GlcNAc monomers through bond breaking of the  $\beta$ -1,4-glycosidic linkages, a process explored with mechanochemistry (Table 5). All four major mechanochemical strategies developed for cellulose hydrolysis by milling with acidic minerals, acid impregnation, milling with carbonaceous solid acids, and mechanoenzymology have likewise been applied to chitin.

Kaolinite was applied by Kerton and coworkers for chitin amorphization/hydrolysis.<sup>244</sup> Milling  $\alpha$ -chitin (CrI = 91%) with





**Scheme 3** Mechanochemical starch esterification with (A) lauric acid and (B) octenyl succinic anhydride.

**Table 5** Examples of mechanochemical chitin hydrolysis

Substrate	Active reagent	Equipment	Condition	Product	Yield	Ref.
$\alpha$ -Chitin	Kaolinite	Mixer ball mill	1080 cycles	Chitin oligosaccharides	76%	Kerton and coworkers <sup>244</sup>
Chitin	Impregnated H <sub>2</sub> SO <sub>4</sub>	Planetary ball mill	500 rpm, 6 h	Chitin oligosaccharides	>99%	Fukuoka and coworkers <sup>245</sup>
Chitin	Air-oxidized activated carbon catalyst	Planetary ball mill	500 rpm, 48 h	Chitin oligosaccharides	66%	Fukuoka and coworkers <sup>249</sup>
Chitin, chitinous biomass	<i>Aspergillus niger</i> chitinase	Vibrational ball mill	30 Hz, 5 min, 12 h aging, 20 cycles	GlcNAc monomer	24%	Auclair and coworkers <sup>94</sup>

kaolinite (1080 cpm, 120 min) reduced CrI to 35% and increased solubilization (11.0% vs. 6.3% initially). Higher ball packing and longer milling (240 min) maximized soluble product yield to 76%. Matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-ToF) confirmed GlcNAc monomers and oligomers (DP 2–5).

Fukuoka and coworkers systematically studied mechanochemical chitin hydrolysis. Milling H<sub>2</sub>SO<sub>4</sub>-impregnated chitin (500 rpm, 6 h) achieved full conversion to water-soluble compounds, with 41.8% GlcNAc monomers/oligomers (DP < 5).<sup>245</sup> The small physisorbed water in chitin enabled acid-catalyzed hydrolysis without added solvent, while *N*-acetyl groups were fully retained, unlike in conventional heterogeneous hydrolysis.<sup>246</sup> Subsequent hydrolysis/methanolysis gave up to 53% GlcNAc and 70% 1-*O*-methyl-*N*-acetylglucosamine. Fukuoka's group also produced oligosaccharides using solid acid catalysts to avoid mineral acid by-products.<sup>245,247,248</sup>

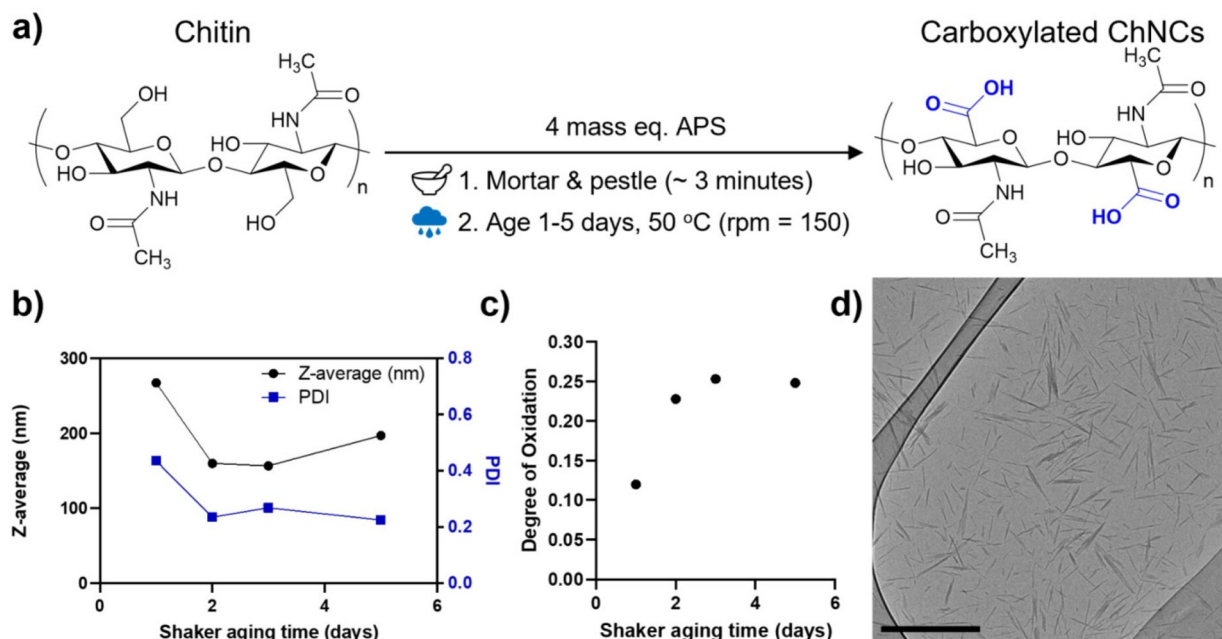
Kobayashi and coworkers introduced an oxidized carbon catalyst (AC-Air, 0.90 mmol g<sup>-1</sup> carboxyl, 0.84 mmol g<sup>-1</sup> phenolic).<sup>249</sup> Milling with AC-Air (48 h) solubilized 72 wt% chitin with 91% selectivity for oligosaccharides. Fukuoka's density functional theory (DFT) studies revealed that planetary milling

induced subnano Newton tensile/compressive forces that activated chitin glycosidic bonds.<sup>250</sup>

Mechanoenzymatic method has also been applied. Auclair and coworkers used RAgging (repeated 5 min milling at 30 Hz + 12 h aging, 20 cycles) with chitinase to convert 200 mg chitin to 47 mg GlcNAc and minor dimers/trimers.<sup>89,94</sup> When applied to acetic acid (AcOH)-washed shrimp (AcShrimp) and crab shells (AcCrab), yields improved (51 mg GlcNAc from AcShrimp, 49 mg from AcCrab, 10 cycles). This selective route offers a simple valorization pathway for chitinous biomass.

**3.3.2 Nanochitin synthesis.** Chitin nanocrystals (ChNCs) are an emerging polysaccharide-based nanomaterial for various value-added applications.<sup>27,251–253</sup> ChNCs can be produced in solution through acid hydrolysis using mineral acids such as HCl or H<sub>2</sub>SO<sub>4</sub>, or through oxidative hydrolysis by TEMPO or APS on the amorphous regions of chitin.<sup>142,254,255</sup> As mentioned briefly in nanocellulose synthesis, our group developed a HHSA method to produce highly crystalline polysaccharide nanocrystals (Fig. 6),<sup>88</sup> whereby the inevitable chitin amorphization in ball milling<sup>244</sup> was avoided by the use of short mixing in a mortar and pestle followed by aging at 50 °C and 98% relative humidity (RH) with gentle agitation.





**Fig. 6** (a) Scheme for shaker aging under humidity to make ChNCs. (b) Z-Average value (black dots and lines) and polydispersity index (blue dots and lines) (c) degree of oxidation (d) representative TEM image HHSA-synthesised carboxylated ChNCs. Reprinted with permission from T. Jin, T. Liu, F. Hajiali, M. Santos, Y. Liu, D. Kurdyla, S. Régnier, S. Hrapovic, E. Lam, A. Moores, *Angew. Chem., Int. Ed.*, 2022, **61**(42), e202207206. Copyright © 2022 Wiley-VCH GmbH.

The produced carboxylated ChNCs had expected morphology (average length of 173 nm and average width of 8 nm), a record high DO of 0.25 compared to previously reported solution phase methods,<sup>256</sup> with good crystallinity and excellent  $\zeta$ -potential.

We also extended our cationic tertiary-aminated CNF/CNC synthesis strategy to chitin.<sup>143</sup> Practical grade chitin was briefly ball-milled with CDEEA-HCl and NaOH under LAG conditions using TBAH solution for 10 min, followed by aging for 3 h. After purification, the resulting material was defibrillated by ultrasonication, yielding individualized ChNCs dispersed in water. In contrast to the anionic oxidized ChNCs obtained *via* the HHSA method, these ChNCs were highly cationic ( $\zeta$ -potential = +68 mV) and exhibited a higher aspect ratio (average length 425 nm, average width 2 nm). This morphology is likely attributable to the strong electrostatic repulsion from the high DS of 0.79. Notably, without requiring excess reagent, the process was remarkably efficient, achieving a low PMI<sub>reaction</sub> of 4.0.

**3.3.3 Chitin composite synthesis.** Given its biocompatibility and biodegradability, chitin has become one of the most exciting bio-based ingredient for composites.<sup>257–259</sup> Due to the insolubility of chitin in most conventional solvents, the dispersion of chitin in polymer matrix has been a major challenge for applications of chitin in polymer compositions.<sup>260,261</sup> Mechanochemistry provides a viable procedure for enhancing the dispersion of chitin particles in the polymer matrix to improve the quality of chitin composite products in solid-state.<sup>262</sup>

To construct flexible PVA/chitin films, solid-state shear milling ( $S^3M$ ) was used both to comminute chitin and disperse it into PVA (Fig. 7).<sup>263</sup> Ten cycles of neat  $S^3M$  reduced chitin particle size to 51.03  $\mu\text{m}$  and decreased CrI from 95.01% to 61.54%, improving processability. A second  $S^3M$  stage produced PVA/chitin composites with flat, smooth morphology confirmed by SEM, indicating good PVA-chitin compatibility. Films obtained by hot pressing showed hydrophilicity suitable for wet biological surfaces, unlike hydrophobic PVA.<sup>264</sup> Incorporation of 10 wt% chitin increased tensile strength to 23.25 MPa compared to 19.12 MPa for neat PVA, while maintaining flexibility and foldability.

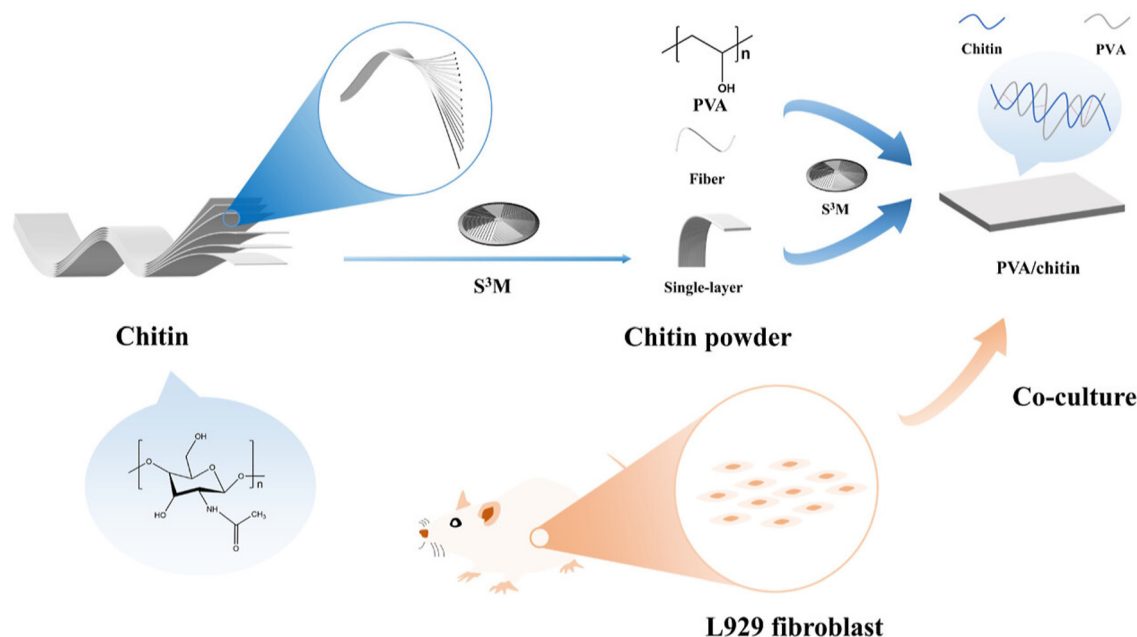
Lignin, an abundant biopolymer and pulp industry sidestream,<sup>256,265</sup> was mechanochemically combined with chitin by Bartczak and coworkers to prepare a chitin-lignin filler for polyurethane (PUR) composites.<sup>266</sup> Chitin and hydrogen peroxide ( $\text{H}_2\text{O}_2$ )-activated alkali lignin were ball milled at 600 rpm for 2 h in a planetary mill, yielding filler particles ~300 nm in size. During PUR foaming, the filler reacted with isocyanate groups *via* its hydroxyls, reinforcing the composite. Adding 10% filler extended rising time from 93 to 126 s, increased free rise density from 46.3 to 52.3  $\text{kg m}^{-3}$ , and raised tensile strength from 118 to 135 kPa due to chitin/lignin crosslinking with PUR chains.

### 3.4. Chitosan

Chitosan, obtained by deacetylating >50% of chitin's D-acetylglucosamine units,<sup>267</sup> contains protonatable primary amines that enable solubility below pH 6.0.<sup>268</sup> Dissolved chitosan







**Fig. 7** Schematic illustration of the mechanochemical process for the fabrication of chitin and PVA/chitin composite films with  $S^3M$  milling technology. Reprinted with permission from X. Ye, Z. Wang, Q. Wang, L. Zhu, L. Yang, D. Xu, *ACS Sustainable Chem. Eng.*, 2024, 12(11), 4497–4505. Copyright © 2024 American Chemical Society.

functions as a flocculant for water remediation,<sup>269</sup> and its amine-driven antimicrobial activity supports uses in nutraceutical,<sup>270</sup> biomedical,<sup>271,272</sup> coatings,<sup>273</sup> and packaging.<sup>274</sup> With ~8% nitrogen by  $M_w$ , it also serves as a slow-release fertilizer.<sup>275</sup> Unlike cellulose or chitin, even high- $M_w$  chitosan is water-soluble, making it one of the most studied polysaccharides for chemical modification.<sup>238,239</sup>

**3.4.1 Chitosan synthesis by deacetylation.** The transformation of chitin to chitosan is traditionally performed by treating chitin in hot alkaline solutions.<sup>276,277</sup> In recent years, mechanochemistry has been explored by different research groups as an alternative method for deacetylation (Table 6). Yan and coworkers produced low  $M_w$  chitosan directly from chitin by ball-milling with equimolar NaOH at 700 rpm (10 min  $\times$  8 cycles), yielding water-soluble chitosan with degree of deacetylation (DDA) 76.4%,  $M_w$  8.5 kDa, and polydispersity index (PDI) 1.1.<sup>278</sup> Milling amorphized chitin, enhancing deacetylation. Applied to shrimp shells (28.3 wt% chitin), 80 min milling recovered 20.9 wt% chitosan with comparable properties. Our group combined ball-milling and accelerated aging (50 °C, 98% RH, 6 d) to obtain high-DDA chitosan (95%) from amorphized chitin; omission of the amorphization step reduced DDA to 87%.<sup>84</sup> A modified protocol using ChNCs, mortar mixing (5 min), and aging produced rod-shaped chitosan nanocrystals (ChsNCs) with DDA 65.5% and CrI 36%, with PMI values of 170.0 (ChNC  $\rightarrow$  ChsNC) or 286.2 (chitin  $\rightarrow$  ChsNC). The relatively high crystallinity of ChsNCs enabled strong gel formation with alginate.<sup>85</sup> Usman and coworkers explored mortar grinding of mud crab chitin with NaOH, with the DDA increasing with chitin : NaOH ratio up to 4 : 1, reach-

ing 93.5%.<sup>279</sup> Unlike ball-milling, the softer method increased CrI from 61.3% to 68.3–75.3%.

**3.4.2 Chitosan hydrolysis.** DDA and  $M_w$  govern chitosan structure and properties.<sup>280–282</sup> Since base-catalyzed deacetylation of chitin makes simultaneous control of DDA and  $M_w$  difficult,<sup>278</sup> controlled hydrolysis of high- $M_w$  chitosan is key for optimized performance.<sup>269,283</sup> Our group developed a ball-milling/accelerated aging method with  $H_3PO_4$  to produce low  $M_w$ , narrow PDI chitosan.<sup>86</sup> High- $M_w$  chitosan was milled with 85%  $H_3PO_4$  in a vibrational mixer mill, then aged at 50 °C and 98% RH. Hydrolysis was tuned by varying acid equiv. (2 or 4), milling time (30–90 min), and aging time (0–48 h). Gel permeation chromatography (GPC) characterization showed low  $M_w$  products from 200 to 19.5 kDa and a narrowed PDI from 11.6 to 1.8. The process also improved sustainability, with a PMI of 805 *versus* 6826 for solution methods.<sup>284</sup>

**3.4.3 Chitosan N-functionalization.** The reactive primary amine groups of chitosan from the deacetylation of the *N*-acetyl groups of chitin enables opportunities for *N*-functionalization (Table 6). One advantage of chitosan over chitin is its improved solubility,<sup>56,285</sup> yet this property is restricted to acidic media.<sup>286</sup> Stevens and coworkers developed a mechanochemical route to *N*-sulfonated chitosan soluble at pH > 7.<sup>287</sup> Chitosan was milled with 0.2 equiv. 1,3-propane sultone (PrS) at 30 Hz for 20 min cycles until the desired DS was reached. After 3 cycles, DS = 51%; a 4th cycle only slightly increased it (53%), but purifying after 3 cycles and then milling gave DS = 78%. The *N*-sulfopropyl chitosan aggregated at pH 4–7 due to salt formation,<sup>288</sup> and showed an antipolyelectrolyte effect in acidic sodium chloride (NaCl) solution, with



Table 6 Examples of mechanochemical chitosan synthesis, N-functionalization, and oxidation

Substrate	Active reagent	Equipment	Condition	Product	Highest DS or DDA	Characteristics	Ref.
Chitin, shrimp shell	NaOH	Planetary ball mill	700 rpm, 80 min	Chitosan	DDA 76.4%	Low $M_w$	Yan and coworkers <sup>278</sup>
Shrimp chitin	NaOH	Vibrational ball mill	5 min, 3 d aging	Chitosan	DDA 95.0%	High $M_w$	Moore and coworkers <sup>84</sup>
ChNCs	NaOH	Mortar and pestle	Manual grinding, 6 d aging	ChNCs	DDA 65.5%	Moderate CrI Gels with alginate	Moore and coworkers <sup>85</sup>
Crab chitin	NaOH	Mortar and pestle	Manual grinding, 30 min	Chitosan	DDA 93.5%	High CrI	Usman and coworkers <sup>279</sup>
Chitosan	1,3-Propane sultone	Vibrational ball mill	30 Hz, 80 min	N-Sulfonated chitosan	DS 78.0%	water-soluble	Stevens and coworkers <sup>287</sup>
Prawn chitosan	Benzaldehyde derivatives	Shaker ball mill	700 cycles min <sup>-1</sup> , 10 min	Chitosan SBs	DS 79.5%	Aromatic	Hernawan and coworkers <sup>291</sup>
Chitosan	Aldehydes, NaBH <sub>4</sub>	Vibrational ball mill	29.5 Hz, 30 min, 2 stages, 3 d aging	N-Alkylated chitosan	DS 99.1%	Aldehyde species dependent	Moore and coworkers <sup>87</sup>
Low $M_w$ chitosan	Aldehydes, NaBH <sub>4</sub>	Vibrational ball mill	29.5 Hz, 30 min 29.5 Hz, 120 min	N-Alkylated chitosan	DS 64.4%	Thiophene $\pi$ - $\pi$ stacking	Stevens and coworkers <sup>296</sup>
Chitosan	CDMEA, NaOH	Vibrational ball mill, planetary ball mill	29.5 Hz, 30 min, 2 d aging; 300 rpm, 30 min, 2 d aging	N,O-Aminoalkylated chitosan	DS 1.67	High amine loading, CO <sub>2</sub> -switchable	Moore and coworkers <sup>299</sup>
Chitosan	H <sub>3</sub> PO <sub>3</sub> , paraformaldehyde	Planetary ball mill	780 rpm, 7 h	N-Phosphonated chitosan	DS 95.6%	Gypsum scale inhibition	Mady and coworkers <sup>303</sup>
Crab chitosan	Allyl bromide	Twin-screw extruder	-5 °C, several min	Allylchitosan	DS 50.0%	Photosensitive	Bardakova and coworkers <sup>304</sup>
Chitosan	Potassium persulfate	Planetary ball mill	225 rpm, 1 or 3 h	Oxidized chitosan	N/A	High adsorption capacity	Cagnetta and coworkers <sup>305</sup>

solubility (DS = 40%) increasing from 10% to >90% as NaCl rose from 0 to 400 mM. Compared to solution methods,<sup>289,290</sup> the process was efficient (reaction mass efficiency = 97.5%) and clean (PMI = 379.6).

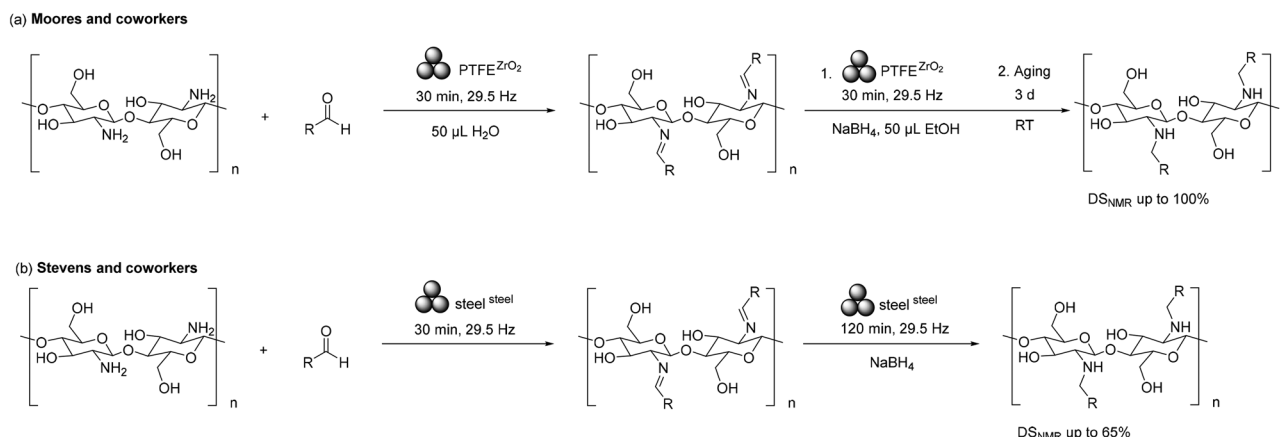
Hernawan and coworkers prepared air-stable chitosan Schiff bases (SBs) with benzaldehyde derivatives by solvent-free ball-milling.<sup>291</sup> Prawn chitosan and aldehydes (1 : 1) were milled in polytetrafluoroethylene (PTFE) jars at 700 cycles min<sup>-1</sup> for 10 min. DS depended on aldehyde: 34.3% (4-methoxybenzaldehyde), 79.5% (2-hydroxybenzaldehyde), and 5.5% (4-hydroxy-3-methoxybenzaldehyde). Like other SBs,<sup>291–293</sup> they were hydrolytically unstable in acidic solution,<sup>294,295</sup> limiting applications.

To overcome this, our group developed a two-step reductive alkylation *via* ball-milling and aging (Scheme 4).<sup>87</sup> Chitosan and aldehydes were first milled (30 min, 29.5 Hz, PTFE jar, with H<sub>2</sub>O) to form SBs, then reduced without purification by milling with sodium borohydride (NaBH<sub>4</sub>) under LAG condition with EtOH (30 min, 29.5 Hz), followed by 3 d aging. The method was found effective across 20 aldehydes with many afforded high DS, with products displaying altered solubility: bulky alkyl chains made chitosan hydrophobic, while reductive alkylation with 4-(dimethylamino)benzaldehyde introduced high-pK<sub>a</sub> amines, affording solubility up to pH 12. The approach was efficient with PMI = 36.

Independently, Stevens and coworkers developed similar protocols using low  $M_w$  chitosan.<sup>296</sup> One-step milling (500 mg chitosan + 1.0 equiv. aldehyde, 30 Hz, 30 min, stainless steel jar, 2 balls) produced chitosan SBs. For *N*-alkylated chitosan, NaBH<sub>4</sub> was added and the mixture milled for 2 h, giving 6 derivatives with DS up to 64.4% (<sup>1</sup>H NMR). Compared to our method, this was faster but with lower DS (*e.g.*, *N*-(furan-2-yl) methyl chitosan: 56% *vs.* 75%). *N*-(Thiophen-2-yl)methyl chitosan showed  $\pi$ - $\pi$  stacking, suggesting optoelectronic potential.<sup>297</sup> The authors also reported green metrics in this work including PMI<sub>reaction</sub> = 2.77, PMI<sub>isolation</sub> = 209, and reaction mass efficiency  $\approx$  100%.

Subsequently our group reported a one-pot S<sub>N</sub>2-type aminoalkylation of chitosan with tertiary amines for CO<sub>2</sub>-switchable applications.<sup>298,299</sup> Chitosan, 2-chloro-*N,N*-dimethylethylamine-hydrochloride (CDMEA-HCl), NaOH, and catalytic amount of TBAH solution were milled in a PTFE jar with a ZrO<sub>2</sub> ball on a vibrational mill for 30 min, followed by in-jar aging at room temperature for 2 d. The reactive CDMEA electrophile was generated *in situ* and reacted with C2 amine and C6 alcohol groups, producing DMEA-chitosan with up to 14.9% amine nitrogen (DS = 3.00), comparable to synthetic CO<sub>2</sub>-switchable poly(*N,N*-dimethylallylamine).<sup>300</sup> Unlike solvothermal synthesis, which only gave C6-O substitution,<sup>301</sup> the mechanochemical route avoided aqueous acid (which protonates C2 amines) and enabled full nucleophilicity. Aging reduced energy input to 1/6<sup>th</sup> (598 kJ g<sup>-1</sup>) compared to extended milling that affords same high DS. Scaling on a planetary ball mill to 10 g afforded DS = 1.60, 91% yield, and PMI<sub>reaction</sub> = 2.4. The product showed CO<sub>2</sub>-switchable properties in water for multiple cycles.<sup>302</sup>





**Scheme 4** Mechanochemical synthesis of *N*-alkylated chitosan through reductive amination via processes reported by (a) Moores and coworkers, (b) Stevens and coworkers.

Mady and coworkers synthesized phosphonated chitosan (P-chitosan) as a green oilfield scale inhibitor *via* the Moedritzer–Irani reaction under LAG condition.<sup>303</sup> Low  $M_w$  chitosan, phosphorous acid ( $\text{H}_3\text{PO}_3$ ) (3 equiv.), and paraformaldehyde (3 equiv.) were milled in a  $\text{ZrO}_2$  jar at 780 rpm for 7 h with  $\text{H}_2\text{O}$  ( $\eta = 0.26 \mu\text{L mg}^{-1}$ ). The water-soluble P-chitosan reached  $\text{DS} = 0.956$ . LAG improved mobility and diffusion of reactants, enhancing reaction efficiency. In antiscaling tests, P-chitosan matched or exceeded aminotrimethyl-enephosphonic acid and carboxymethyl inulin against gypsum, calcite, and heidrun calcite. It retained full activity after 1 week at  $130^\circ\text{C}$ , giving 100% inhibition at 2–100 ppm (gypsum) and 10–100 ppm (heidrun calcite).

Bardakova and coworkers produced photosensitive allylchitosan by TSE mechanochemistry.<sup>304</sup> Chitosan, allyl bromide, and NaOH were kneaded at  $-5^\circ\text{C}$ , affording allylchitosan with  $\text{DS}$  up to 50%. The material was structured into multilayer 3D scaffolds by vinyl photocrosslinking (325 nm, 15 mW). *In vivo* implantation in rats restored large tissue defects, demonstrating that mechanochemistry can produce biocompatible photosensitive chitosan derivatives with vinyl groups for mild, solvent-free scaffold fabrication.

**3.4.4 Chitosan oxidation.** Cagnetta and coworkers investigated solvent-free mechanochemical oxidation of chitosan for adsorbent applications.<sup>305</sup> Chitosan was milled with three solid oxidants: potassium persulfate ( $\text{K}_2\text{S}_2\text{O}_8$ ), sodium percarbonate ( $\text{Na}_2\text{CO}_3 \cdot 1.5\text{H}_2\text{O}_2$ ), and calcium peroxide ( $\text{CaO}_2$ ), in a planetary ball mill at 225 rpm for 1 or 3 h. CP-MAS  $^{13}\text{C}$  NMR spectroscopy and FT-IR tracked chemical changes. Sodium percarbonate induced oxidative deacetylation *via* hydroxyl radicals, while  $\text{CaO}_2$  caused only amorphization and chain cleavage. Only  $\text{K}_2\text{S}_2\text{O}_8$  effectively oxidized chitosan *via* sulfate radical oxidation, forming ketones at C2 and at the reducing ends of C4.<sup>306,307</sup> Adsorption tests with reactive red 2 showed the highest capacity of  $974 \text{ mg g}^{-1}$  for chitosan milled with 30 wt%  $\text{K}_2\text{S}_2\text{O}_8$  for 1 h. In a separate study, Penicillin G adsorption was evaluated using chitosan milled with 20 wt%  $\text{K}_2\text{S}_2\text{O}_8$

for 1 h, achieving a maximum adsorption capacity of  $1165 \text{ mg g}^{-1}$  at pH 5.<sup>308</sup>

### 3.5. Other polysaccharides

Beyond lignocellulose and chitinous biopolymers, other renewable polysaccharides such as pectin, alginate, and bacterial polysaccharides have been less explored in mechanochemical chemical modification, often serving as additives or coatings.<sup>309–311</sup> Mechanochemistry has been applied to study metal–polymer interactions in composite synthesis. For instance, Naimi-Jamal and coworkers employed ball-milling for a one-pot *in situ* synthesis of alginate-coated imidazole zinc-based metal–organic framework nanoparticles (ZIF-8@alginate NPs). Sodium alginate was co-milled with zinc acetate dihydrate and 2-methylimidazole in a stainless steel jar with two balls using a vibrational ball mill at 28 Hz for 1 h.<sup>309</sup> This produced spherical ZIF-8@alginate NPs (50–100 nm) with a surface area of  $476.18 \text{ m}^2 \text{ g}^{-1}$  and 9.9 nm pores characterized by Brunauer–Emmett–Teller (BET) analysis. FT-IR spectra indicated no new absorption bands, suggesting the coating arose from dynamic interactions, including hydrogen bonding and ionic interactions between zinc cations and alginate carboxylates.

Coordination chemistry is another strategy for polysaccharide-based composites. Luque and coworkers investigated fungal polysaccharides in enhancing zinc oxide (ZnO) NP biocompatibility.<sup>312</sup> Zinc nitrate hexahydrate and fungal polysaccharides (from *Abortiporus biennis*, *Lentinus tigrinus*, *Rigidororus microporus*, and *Ginkgo polypore*) were milled at 350 rpm for 30 min in a stainless steel jar with 18 balls using a Retsch-PM100 planetary mill. The resulting jelly-like nano-hybrids were oven-dried and calcined to remove unbound organics. Nitrogen adsorption showed BET surface areas of  $15\text{--}20 \text{ m}^2 \text{ g}^{-1}$ , pore diameters of 20–28 nm, and pore volumes of  $0.06\text{--}0.13 \text{ cm}^3 \text{ g}^{-1}$ . Diffuse reflectance infrared Fourier transform spectroscopy (DRIFT) confirmed Zn coordination with polysaccharide  $-\text{OH}$  and  $\text{C}=\text{O}$  groups, and XRD revealed high



crystallinity with a wurtzite structure and slightly reduced unit cell. Toxicological evaluation showed EC<sub>50</sub> values of 50 µg mL<sup>-1</sup> (A549 cells) and 100 µg mL<sup>-1</sup> (SH-SY5Y cells), higher than uncoated commercial ZnO powders, indicating improved biocompatibility.<sup>312–315</sup>

## 4. Critical discussion

### 4.1 Advantages of mechanochemistry and aging over liquid state transformations

To demonstrate the capability of mechanochemistry and aging in enhancing the green metrics of polysaccharide chemical modification, we highlight three representative examples chosen among the three pillars of this review: deconstruction, nano-extraction, and functionalization.

Conventional acid-catalyzed hydrolysis of cellulose with dilute H<sub>2</sub>SO<sub>4</sub> is typically performed at elevated temperatures above 170 °C,<sup>316</sup> well beyond the boiling point of water. This not only results in high energy consumption but also poses significant operational risks, as it requires pressurized equipment to handle the highly corrosive liquid. For example, Thompson and Grethlein reported hydrolysis of a 5 wt% water slurry of newsprint as a cellulose source under extreme conditions: 240 °C in a flow reactor with 1 wt% H<sub>2</sub>SO<sub>4</sub> (0.33 equiv.) present in the slurry.<sup>317</sup> These aggressive conditions enabled rapid hydrolysis, yielding ~50% glucose in only 0.22 min using a specially designed reactor. However, the authors identified the cellulose slurry concentration as the main bottleneck to process efficiency, since higher concentrations hindered flow and mixing.<sup>317</sup> More recently, Fierro and coworkers hydrolyzed cotton cellulose at a reduced temperature of 160 °C but with significantly higher H<sub>2</sub>SO<sub>4</sub> loading. Heating a 1.25 wt% cellulose suspension containing 5 wt% H<sub>2</sub>SO<sub>4</sub> (6.5 equiv.) yielded 20% glucose in 2 h. They concluded that the high crystallinity of cellulose with tightly associated polymeric chains necessitates harsh conditions combining elevated temperature with high acid loading.<sup>318</sup>

Ball-milling addresses both mixing and amorphization effectively, making cellulose hydrolysis less wasteful. In the three examples discussed, H<sub>2</sub>SO<sub>4</sub> loading was reduced to 0.14,<sup>122</sup> 0.08,<sup>319</sup> and 0.14<sup>123</sup> by impregnating cellulose prior to milling. In all cases, hydrolysis was completed within 2 h, or as short as 35 min using a Simoloyer ball mill at kilogram scale without heating. Near-quantitative conversion of cellulose to water-soluble glucose or low-DP oligomers was achieved without any subsequent hydrothermal treatment. Mechanochemistry thus enabled a ~50-fold reduction in acid consumption from Fierro's study for the same chemical transformation, meanwhile eliminating the hazardous hot corrosive acid solution under pressure, all within comparable time-scales. The solid-state nature of mechanochemistry also allows more elegant process design, enabling the replacement of conventional mineral acids with recyclable solid acids in other examples.<sup>120,121,127–129</sup> This not only simplifies the isolation and purification of hydrolyzed sugars but also opens opportu-

nities to design more benign acid catalysts, better aligning the process with safety-related green chemistry principles.

Mechanochemical techniques have shown a similar impact in reducing acid consumption in the synthesis of acid-hydrolyzed nanopolysaccharides,<sup>135,136</sup> selectively hydrolyzing the amorphous regions of native polysaccharides. Additionally, mechanochemistry has also proven influential in accessing oxidatively carboxylated nanopolysaccharides. Interestingly, TEMPO-mediated oxidation, the gold standard for the synthesis of CNF,<sup>320</sup> CNC, and ChNC<sup>254</sup> using TEMPO, sodium bromide, and sodium hypochlorite under maintained basic pH, has not been adapted to mechanochemical conditions. The HHSA technique developed by our group demonstrates that dynamic aging can enhance the green chemistry metrics from the solution phase APS pathway for producing carboxylated nanopolysaccharides, which conventionally requires refluxing native crystalline polysaccharides with 4 equiv. APS in aqueous solution at 60 °C for 16 h.<sup>88,321</sup> Although the APS loading in HHSA was not drastically reduced (3.5 equiv.), the oxidation was more effective, as indicated by fivefold higher DO values for ChNCs produced mechanochemically compared to the solution method (0.25 vs. 0.05).<sup>88</sup> In this example, the aging temperature (50 °C) was close to that of solvothermal condition, yet the solid-state mixing provided by mechanochemistry was pivotal in achieving ultra-high local APS concentrations during high-humidity aging with dynamic water adsorption, resulting in improved reaction efficiency. Equally important to this transformation, the aging process compensated for the mild mechanical treatment of manual grinding, avoiding the extensive amorphization typically caused by ball-milling. While amorphization can be beneficial for complete polysaccharide hydrolysis, it is undesirable in nano-extraction processes where preserving the native crystalline domains is essential. When evaluated with green chemistry metrics, by eliminating bulk solvent, the HHSA method generates less solvent waste, as reflected in its significantly improved PMI<sub>reaction</sub> of 12.5 compared to 203 for the solution phase process.

The advantages of mechanochemistry in functionalizing native polysaccharides can be divided into two main aspects. The first, though less relevant in hydrolysis and nano-extraction, lies in enabling new reactivity, selectivity, and compatibility by avoiding unwanted solvent effects that typically arise from dissolving the polysaccharide substrate to achieve mixability and processability. This benefit is particularly evident in the mechanochemical functionalization of chitosan, where the nucleophilicity of the C2 amine is fully expressed for a range of reactions discussed in this review, by avoiding the aqueous acidic environment required for its dissolution. We have observed such pattern in a few of our own works as well as other reports from other colleagues, such as the prevention of imine hydrolysis that facilitated chitosan reductive amination to introduce new functional groups, including those bearing acid-sensitive acetal protections;<sup>87,296</sup> and in the S<sub>N</sub>2-type *N*-aminoalkylation, which is otherwise inhibited in acidic media.<sup>299</sup>





The second advantage of mechanochemical polysaccharide functionalization is the high reaction efficiency and low waste generation observed across all three classes of modifications reviewed. A direct comparison can be drawn between transformations achievable by both solution phase and mechanochemical methods. For instance, the conventional synthesis of carboxymethyl starch involves reacting a 4 wt% starch suspension in a H<sub>2</sub>O/i-PrOH mixture (20 : 80 w/w) with 3.2 wt% NaOH and 1.7 equiv. monochloroacetic acid at 60 °C, yielding carboxymethyl starch with a DS of 0.53, corresponding to 31% conversion of the Williamson etherification agent.<sup>322</sup> Subsequent optimization by Tijssen and coworkers, adjusting the H<sub>2</sub>O/i-PrOH ratio to 10 : 90 w/w, did not significantly improve efficiency.<sup>323,324</sup> In contrast, the mechanochemical approach developed by Zhu and coworkers achieved a higher DS of 0.631 using less than half the amount of monochloroacetic acid (0.8 equiv.) and only a minimal amount of i-PrOH as a LAG additive rather than as a bulk solvent.<sup>232</sup> The mechanochemical method thus afforded a markedly higher 79% conversion rate and a nearly ideal PMI<sub>reaction</sub> of 1.55 compared to 21.98 for the conventional process, reflecting its greatly reduced solvent demand.

While the effect of aging in conjunction with mechanochemistry has not been systematically studied, it has been widely employed in a number of the studies featured in this review to reduce the extent of required mechanical treatment, as noted by several researchers.<sup>72,84–94,140,143,191,299,303</sup> The energy demand associated with the aging step varies considerably among these reports: some require heating at elevated temperatures, whereas others demonstrate that thermal input is not essential for achieving an effective aging process.<sup>87,143,299</sup> In such cases, the overall energy consumption can be viewed as proportionally reduced relative to the extent of mechanical treatment replaced by aging, in addition to preventing undesired degradation that mechanochemical techniques might otherwise induce.

We provide in Table 7 a qualitative comparison of mechanochemical/aging and solution-phase polysaccharide transform-

ations. This comparison is based on key CHEM-21 sustainability parameters and offers a quick overview of the sustainability benefits of the topic discussed.

#### 4.2 Mechanochemistry and aging as a tunable approach to polysaccharide depolymerization, nano-extraction and functionalization

In this review, we have demonstrated that mechanochemistry and aging-based approaches are now developing into a mature field. Interestingly, this review underscores the many similarities between the methods developed for cellulose, starch, chitin, and chitosan. For instance, the esterification reaction is often the model reaction developed in this space. Reaction conditions are remarkably similar among substrates such as common fatty acids<sup>71,149,150,217</sup> and acetic anhydride,<sup>72,92,156</sup> pointing to the generality of these methods. This applies as well to reactions such as the S<sub>N</sub>2 alkylation reaction, which functions in a fairly similar way with chitosan,<sup>299</sup> chitin, and cellulose.<sup>143</sup>

These methods can also be modulated to achieve the different targets of polysaccharide valorization, namely depolymerization, nano-extraction and functionalization, as illustrated in Fig. 1. Ball milling, especially if extended for one or several hours will lead to polysaccharide amorphization. This can assist with depolymerization and functionalization, as it can help expose and activate the polymer for reactivity. It may however interfere with nano-extraction, a method relying on the crystalline arrangement of the biopolymer to preserve its nanostructure. The use of aging can help mitigate this problem, as demonstrated by us and others.<sup>88,140</sup> It is also possible that functionalization and depolymerization can interfere with one another. No group has discussed this aspect so far, as common *M<sub>w</sub>* measurements methods, relying on standard-calibrated GPC, can not reliably measure the *M<sub>w</sub>* of functionalized polysaccharides yet. Future works should be geared to solving this challenge so as to further discuss the selectivity of these methods.

**Table 7** Qualitative comparison of mechanochemical/aging and solution-phase polysaccharide transformations according to key CHEM-21 sustainability parameters

Parameter (CHEM-21 dimension)	Mechanochemistry/Aging	Solution-phase techniques
Solvent	None or minimal (LAG; aging under solvent vapor) in reaction stage; often reduced in separation/purification	Bulk solvents typically required in reaction stage for dissolution/dispersion and heating
Reaction time	Minutes to hours of milling; aging allows conversion without continuous energy input, although over extended time (days)	Hours to days, often requiring prolonged heating or stirring
Energy	Mechanical energy activates substrates; reduced thermal input; aging decouples reaction progress from continuous energy supply	Thermal energy for heating, reflux, and solvent removal
Conversion	Often stoichiometric or near-stoichiometric; high local concentrations	Frequently large reagent excess to overcome solubility and diffusion limits
PMI <sub>reaction</sub>	Low to moderate; minimal solvent contribution	High, dominated by solvent mass
PMI <sub>workup</sub>	Low to moderate; simple (washing, drying); often no solvent-intensive purification	High, multi-step extraction, precipitation, filtration, and drying
E-Factor	Do not display difference when transformations occur through the same reaction pathway	
Atom economy	Favorable across solvent, waste, and energy metrics	Penalized by solvent intensity and waste generation
CHEM-21 overall assessment		



### 4.3 Toxicity considerations

Toxicity is a central aspect of green chemistry, reflected in both Principle 4, which calls for the design of safer chemicals, and Principle 3, which emphasizes the use of less hazardous synthetic methods.<sup>325</sup> Polysaccharides are inherently low in biotoxicity and have therefore found extensive use in biomedical and food applications for this reason.<sup>326,327</sup> However, chemical modification of these otherwise benign materials still demands the highest caution to minimize toxicity-related environmental impacts throughout the lifecycle of polysaccharide-derived products.<sup>328</sup>

Examples discussed in this review include reagents with recognized GHS health hazard classifications, such as persulfate oxidizers,<sup>142,305</sup> the electrophilic 1,3-propane sultone,<sup>287</sup> and the activating agents TFAA<sup>152</sup> and CDI.<sup>71</sup> Several other reagents are acutely toxic under GHS classification, including EDC·HCl and DMAP used in cellulose esterification;<sup>150</sup> furfural and NaBH<sub>4</sub> in chitosan reductive amination;<sup>87,296</sup> sodium chloroacetate,<sup>188</sup> CDMEA·HCl,<sup>300</sup> and CDEEA·HCl<sup>143</sup> as alkylating agents for cellulosic and chitinous polysaccharides; as well as allyl bromide employed in allylchitosan synthesis.<sup>304</sup>

Importantly, mechanochemical modification of polysaccharides, while sometimes still requiring these toxic reagents, can mitigate their overall toxicity-related environmental impacts by improving reaction efficiency and thereby reducing reagent quantities. Conversely, whenever mechanochemistry enables alternative synthetic pathways that avoid toxic substances, these routes should be prioritized. For instance, in many cases featured in this review, cellulose or starch esterification was accomplished efficiently using carboxylic acids, acid anhydrides, or acyl chlorides without employing activating agents.<sup>71,73,93,173</sup> Similarly, the elimination or minimization of solvent use in mechanochemical systems greatly reduces the risk of inhalation or dermal exposure to toxic organic solvents such as DMAc, commonly used with LiCl to solubilize starch for esterification.<sup>221</sup>

On the other hand, assessing the toxicity of functionalized polysaccharides is far more challenging. Many of these products are newly accessible only through mechanochemical synthesis, and their biological effects remain largely unknown. In general, molecules with molecular weights exceeding 700 g mol<sup>-1</sup> cannot readily penetrate cellular phospholipid bilayers and thus are unlikely to exhibit direct toxic effects.<sup>329</sup> Nevertheless, the biodegradability of functionalized polysaccharides may lead to the formation of oligomers (DP < 3) or monomers of sufficiently low molecular weight to pose potential risks.<sup>330,331</sup> Accordingly, evaluating the toxicity of such functionalized polysaccharides, as well as their metabolites, will require multidisciplinary collaborations, representing one of the most pressing current challenges in advancing green and sustainable polysaccharide chemistry.

### 4.4 Economic considerations and industrial relevance of mechanochemical polysaccharide transformations

Beyond environmental benefits, mechanochemistry has the potential to also deliver economic advantages for polysacchar-

ide valorization. While the cost of waste biomass-derived polysaccharides is low and competes favorably with virgin source,<sup>332</sup> other raw chemicals and auxiliaries used in the process have a large impact on the final price tag. Mechanochemistry reduces reliance on bulk solvents and minimizing reagent use and thus positively impacts marginal cost. This also decreases downstream separation and waste treatment expenses. Several examples in this review demonstrate low PMI values and high reaction efficiencies achieved without solvent-intensive processing,<sup>85–88,143,192,232,287,296,299</sup> suggesting favourable operating costs compared to conventional solution-phase methods.

Energy consumption is another crucial economic factor in the production of polysaccharide-based functional materials. While mechanical activation requires a significant initial energy investment, this can be offset by shortened treatment times with aging, eliminating the need for solvent heating, and reducing drying steps. Furthermore, aging-based strategies separate chemical conversion from continuous mechanical input, enabling reactions to occur under mild conditions with minimal additional energy. This is demonstrated by the life cycle assessment of mechanochemical cellulose phosphorylation,<sup>91</sup> which shows reduced electricity consumption and overall environmental impact compared to heat-assisted solution-phase processes, highlighting potential cost savings.

From an industrial perspective, mechanochemical platforms such as reactive extrusion and RAM are inherently scalable and compatible with continuous processing. These technologies are already widely used in the food,<sup>333</sup> polymer,<sup>334</sup> and materials industries,<sup>335</sup> lowering barriers to adoption for polysaccharide modification. Furthermore, the ability to process insoluble, heterogeneous biomass feedstocks without prior dissolution simplifies process design and reduces capital investment in tightly controlled solvent handling and corrosion-resistant equipment.

Nevertheless, economic challenges remain. Capital costs for specialized milling or extrusion equipment, wear on grinding media, and the need for careful process optimization to prevent over-milling are all important factors. The use of mechanical equipment by many industries, such as the mining,<sup>336</sup> forestry,<sup>337</sup> and food,<sup>338</sup> for applications for kg to ton scales, are offering opportunities for the commercialization of mechanochemical processes. Future studies performed on the scale up for the mechanochemical transformation of biomass will provide invaluable insights on the feasibility of such processes on scale, while clarifying questions on marginal and capital costs associated with them. Such work should combine techno-economic analysis with life cycle assessment will be crucial for quantitatively comparing mechanochemical routes to established industrial processes beyond lab scale techniques. Ultimately, the convergence of improved green metrics, scalable processing technologies, and reduced process complexity positions mechanochemistry as a promising and economically viable foundation for functional polysaccharide-based materials production as a sustainable alternative to fossil-based polymers.



## 5. Conclusion and future outlooks

Polysaccharides have received major interest as a feedstock for materials traditionally derived from petrochemical sources. Among abundantly available polysaccharides, cellulose has been studied the most and has been demonstrated as a sustainable feedstock for hydrolysis to produce sugars and nanocellulose, chemical modification to make thermoplastic, and composite formulation with other polymers. Mechanochemistry facilitates these transformations with the benefit of reduced solvent use to potentially lower the cost of polysaccharide-based material production, as well as improve the sustainability of such modification processes in reducing energy consumption, increasing reaction efficiency, and decreasing waste generation (PMI). This trend also applies to other polysaccharides such as chitin and chitosan.

However, the current studies also highlight some important knowledge gaps in this field of research: (1) many polysaccharides have not been extensively investigated as a substrate for modification compared to cellulose, starch, and chitin; (2) the scope of chemical transformations has largely been limited to esterification reactions; (3) the continued use of excess reagents, as opposed to catalytic amounts, for polysaccharide modification by mechanochemistry; (4) high energy input during mechanochemical process associated with high ball count-to-reactant (substrate) ratio and lengthy milling time; (5) insufficient study on the scalability of mechanochemical modifications beyond multigram scales; (6) insufficient use of green metrics to evaluate the processes under mechanochemical conditions; (7) the narrow focus on ball mills as the equipment; (8) lack of in-depth mechanistic study on the impact of mechanochemistry to polymer properties such as the  $M_w$  during chemical modification; (9) absence of toxicology investigations related to the degradation of chemically modified polysaccharides; and (10) inconsistency in quality of the biomass source and insufficient quantities to meet supply chain needs.

As further studies aim to address these gaps, it is anticipated that mechanochemical polysaccharide modification remains an emerging field of research with significant potential to access high performing, modified polysaccharides at scale to compete with petrochemical-derived materials.

## Author contributions

The manuscript was written through the contributions of all authors. All authors have given approval to the final version of the manuscript.

## Abbreviations

AC-Air	oxidized carbon catalyst
ACCrab	Acetic acid-washed crab shells
AcOH	Acetic acid
AcShrimp	Acetic acid-washed shrimp shells
AFM	Atomic force microscopy

APS	Ammonium persulfate
APTES	(3-Aminopropyl)triethoxysilane
BET	Brunauer–Emmett–Teller
BmimOAc	1-Butyl-3-methylimidazolium acetate
CAM	Citric acid monohydrate
CaO <sub>2</sub>	Calcium peroxide
CDEEA-HCl	2-Chloro- <i>N,N</i> -diethylethylamine hydrochloride
CDMEA-HCl	2-Chloro- <i>N,N</i> -dimethylethylamine-HCl
ChCl	Choline chloride
ChNC	Chitin nanocrystal
ChsNC	Chitosan nanocrystal
CNC	Cellulose nanocrystal
CNF	Cellulose nanofibre
CO <sub>2</sub>	Carbon dioxide
CP-MAS	Cross-polarization/magic-angle spinning
CrI	Crystallinity index
DDA	Degree of deacetylation
DFT	Density functional theory
DMAC	<i>N,N</i> -Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DMSO	Dimethyl sulfoxide
DO	Degree of oxidation
DRIFT	Diffuse reflectance infrared Fourier transform spectroscopy
DS	Degree of substitution
EDC-HCl	Carbodiimide hydrochloride
EDS	Dispersive X-ray spectroscopy
EPR	Electron paramagnetic resonance
EPTMAC	(2,3-Epoxypropyl) trimethylammonium chloride
EtOH	Ethanol
FACES	Fatty acid cellulose esters
FT-IR	Fourier-transform infrared spectroscopy
GlcNAc	D-Acetylglucosamine
GPC	Gel permeation chromatography
GPTMS	$\gamma$ -Glycidoxypolytrimethoxysilane
H <sub>2</sub> O	Water
H <sub>2</sub> O <sub>2</sub>	Hydrogen peroxide
H <sub>3</sub> PO <sub>3</sub>	Phosphorous acid
H <sub>3</sub> PO <sub>4</sub>	Phosphoric acid
HHSA	High-humidity shaker aging
HMF	5-Hydroxymethylfurfural
IBVE	Isobutyl vinyl ether
i-PrOH	Isopropanol
K <sub>2</sub> CO <sub>3</sub>	Potassium carbonate
K <sub>2</sub> S <sub>2</sub> O <sub>8</sub>	Potassium persulfate
LAG	Liquid-assisted grinding
LCA	Life cycle assessment
LiCl	Lithium chloride
MALDI-ToF	Matrix-assisted laser desorption ionization-time of flight mass spectrometry
MAPP	Maleic anhydride-grafted polypropylene
MCC	Microcrystalline cellulose
MCC <sup>+</sup>	Microcrystalline cellulose mechano-cations
MFC	Microfibrillated cellulose



MPE	Maleated polyethylene
MTMS	Methyltrimethoxysilane
$M_w$	Molecular weight
$\text{Na}_2\text{CO}_3$	Sodium carbonate
$\text{Na}_2\text{CO}_3 \cdot 1.5\text{H}_2\text{O}_2$	Sodium percarbonate
$\text{NaBH}_4$	Sodium borohydride
$\text{NaCl}$	Sodium chloride
NADES	Natural deep eutectic solvents
$\text{NaOH}$	Sodium hydroxide
NMR	Nuclear magnetic resonance spectroscopy
NPs	Nanoparticles
OA	Oleic acid
OAD	Oxalic acid dihydrate
OSA	Octenyl succinic anhydride
P-chitosan	Phosphonated chitosan
P-CNC	Phosphorylated CNC
$\text{P}_4\text{O}_{10}$	Phosphorus pentoxide
PDI	Polydispersity index
PEF	Polyethylene furanoate
pHEMA	2-Hydroxyethyl methacrylate
PMI	Process mass intensity
PrS	1,3-Propane sultone
PTA	Phosphotungstic acid
PTFE	Polytetrafluoroethylene
PTMS	Phenyltrimethoxysilane
PUR	Polyurethane
PVA	Polyvinyl alcohol
Raging	Reactive aging
RAM	Resonant acoustic mixing
RH	Relative humidity
$\text{S}^3\text{M}$	Solid-state shear milling
SA	Succinic anhydride
SACP	Surface-acetylated cellulose powder
SBs	Schiff bases
SEM	Scanning electron microscopy
TBA	<i>tert</i> -Butanol
TBAH	Tetrabutylammonium hydroxide
TEM	Transmission electron microscopy
TEMPO	2,2,6,6-Tetramethylpiperidine-1-oxylradical
TFAA	Trifluoroacetic anhydride
TG-DSC	Thermogravimetry-differential scanning calorimetry
TsCl	<i>p</i> -Toluenesulfonyl chloride
TSE	Twin screw extrusion
VTMS	Vinyltrimethoxysilane
XRD	X-ray diffraction
ZIF-8@alginate NPs	Zinc-based metal-organic framework nanoparticles
ZnO	Zinc oxide

## Conflicts of interest

There is no conflict to declare.

## Data availability

This article is a review and all its material are based on analysis of articles cited in the bibliography. There is no other data to report or share.

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