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The use of enzymes to isolate cellulose nanomaterials: A systematic map review

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A R T I C L E I N F O

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A B S T R A C T

In the shift towards sustainable development, there is increasing interest in the isolation of cellulose nanomaterials using enzyme-mediated strategies that are more environmentally friendly. The principles of systematic mapping were used here to conduct a literature review covering the most recent research on cellulose nanomaterials whose production processes included the use of enzymes, identifying trends and gaps in the literature. The results evidenced a significant increase in the publications related to nanocellulose production using enzymes, especially in the last eight years (2013–2021). The feedstocks most used were derived from hardwoods and agro-industrial residues. The commonest enzymes employed were commercial cellulase and endoglucanase rich preparations. Importantly, there is still no commercially available enzymatic preparation specifically designed for nanocellulose production. Moreover, this systematic mapping showed that nanocelluloses have frequently been used in film preparation and as reinforcement agents. These data should assist researchers in future studies, while synthesizing information relevant to decision-making.

1. Introduction

The development and use of renewable and sustainable materials have become increasingly important in the shift away from materials based on non-renewable sources. Cellulose, the most widespread biopolymer on Earth, is a potential feedstock for producing commodities, specialty chemicals, and high value-added products (Fiorentino, Ripa & Ulgiati, 2017). Moreover, by applying suitable chemical, mechanical, and/or biochemical treatments, it is possible to produce cellulose nanomaterials, known as nanocellulose. These nanomaterials can be isolated from any naturally occurring sources of cellulose, opening routes to the production of cellulose-based materials with novel functions and applications in various fields (Abitbol et al., 2016; Dufresne, 2019; Thakur, Guleria, Kumar, Sharma & Singh, 2021). Nanocellulose combines important properties of cellulose, such as stiffness, high strength, hydrophilicity, and wide chemical-modification capacity, together with specific features of nanoscale materials, which are mainly associated with the large specific surface area (Klemm et al., 2011). In addition to their excellent mechanical properties and good biocompatibility, cellulose nanomaterials have low thermal expansion coefficient, low density, and interesting optical properties (Moon, Martini, Nairn, Simonsen & Youngblood, 2011; Phanthong et al., 2018). Due to these remarkable properties, there is increasing interest for uses of nanocellulose in composites (Dufresne, 2018; Liu, Liu, Yao & Wu, 2010; Soni, Schilling & Mahmoud, 2016), packaging (Leite et al., 2021; Li, Mascheroni & Piergiovanni, 2015; Sun, Peng, Duan, Xu & Li, 2015), coatings (Aulin, Gällstedt & Lindström, 2010; Kaboorani, Auclair, Riedl & Landry, 2016), medical applications (Klemm et al., 2020; Liu, Qamar, Qamar, Basharat & Bilal, 2021; Owoyokun, Berumen, Luévanos, Cantú & Ceniceros, 2020; Pandey, 2021; Squinca et al., 2021; Wei, Wu, Li, Yu & Ding, 2021), cosmetics (Moon, Schueneman & Simonsen, 2016), electronic devices (Hsieh, Kim, Nogi & Suganuma, 2013; Huang et al., 2013; Wang et al., 2015; Yuen, Walper, Melde, Daniele & Stenger, 2017), and sensors (Teodoro et al., 2021), among other uses (Dufresne, 2019; Norrrahim et al., 2021; Shatkin, Wegner, Bilek & Cowie, 2014; Thomas et al., 2018).

The continuous expansion of the market for nanocelluloses is due to their broad applicability and differentiated properties. The first pilot-scale plant for the production of nanocellulose was inaugurated in 2011 by Innventia in Sweden (Paperage, 2011). There is now an increasing number of organizations engaged in nanocellulose production, with capacities ranging from 560 kg to 1 ton per year (dry basis)

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(Miller, 2017; Vanderfleet & Cranston, 2021). The nanocellulose market has huge future potential, with estimates indicating that the market size could reach USD 418.2 million by 2026, at a compound annual growth rate (CAGR) of approximately 21.4% from 2020 to 2026, according to a report published by Global Market Insights Inc. (2020). The increased industrial interest in the nanocellulose field is also shown by the rapid increase in nanocellulose patents since 2010, especially from 2015 to 2017, which suggests an increasing trend that is likely to continue in the coming years (Charreau, Cavallo & Foresti, 2020). The growing demand for sustainable products, especially in the packaging, food, and beverage industries, together with the search for improved properties of current nanocellulose-based materials and the development of new applications, are driving forces for research in academia and industry (Markets & Markets, 2020). The nanocellulose market is undeniably increasing and will further expand as the production processes become cheaper (Dhali, Ghasemlou, Daver, Cass & Adhikari, 2021).

According to the International Organization for Standardization (ISO, 2017), cellulose nanomaterials are materials constituted predominantly of cellulose, with any external dimension or internal structure on the nanoscale. Materials mostly composed of cellulose, with surface structure on the nanoscale, are also considered to be cellulose nanomaterials, including cellulose nanocrystals (CNCs) and cellulose nanofibrils (CNFs). Cellulose nanocrystals are needle-like structures characterized by their high crystallinity, with cross-sections ranging from 3 to 50 nm, lengths from 100 nm to several micrometers, and aspect ratios between 5 and 50 (ISO, 2017). Although acid hydrolysis (mainly with HCl or H_2SO_4) is the most common method used for CNCs production, there is a growing interest in enzymatic hydrolysis, which offers several operational advantages. These include no requirement for corrosion-resistant equipment, the use of milder operating conditions, environmentally friendly characteristics, and minimization of the formation of undesirable byproducts, due to the greater specificity of biocatalysts (Ribeiro, Pohlmann, Calado, Bojorge & Pereira Jr, 2019). Furthermore, it has been reported that enzymatic hydrolysis may be used to produce CNCs with different morphologies (Tong, Shen, Chen, Jia & Roux, 2020), as well as to increase the CNCs yield when combined with acid hydrolysis (Tang et al., 2015).

Cellulose nanofibrils are elongated structures formed by alternating regions of amorphous and crystalline cellulose chains, with cross-sections ranging from 3 to 100 nm, and lengths up to 100 μm. The terms nanofibrillated cellulose, nanofibrillar cellulose, microfibrillated cellulose, microfibrillar cellulose, cellulose microfibril, and cellulose nanofiber have been used to describe cellulose nanofibrils typically produced by mechanical treatment of plant materials, often combined with chemical or enzymatic pretreatment steps (ISO, 2017). Besides cellulose nanofibrils isolated from plant cellulose sources according to a top-down approach, this category includes bacterial nanocellulose (BNC), also called bacterial cellulose, which is obtained by means of a bottom-up approach involving extracellular synthesis by bacteria during the fermentation of glucose or other carbohydrate feedstocks. The diameter of BNC ranges between 20 and 100 nm, with arrangements of different types of nanofiber networks (Klemm et al., 2011). CNFs are commonly produced by mechanical processes including high-pressure homogenization, ultrafine grinding, and ultrasonication (Nechyporchuk, Belgacem & Bras, 2016). To reduce the energy consumption and enhance the degree of fibrillation caused by the mechanical disintegration, pretreatments such as TEMPO-mediated oxidation, carboxymethylation, and enzymatic hydrolysis have been used (Jonasson, Bünder, Niittylä & Oksman, 2020; Jonoobi et al., 2015; Nechyporchuk et al., 2016). Enzymatic hydrolysis reduces the energy needed during mechanical processes, since enzymes improve the accessibility, hydration, and swelling of cellulose (Fritz et al., 2015). Studies have shown improvement in the size uniformity of CNFs, as well as higher yields, when enzymes were associated with mechanical treatments (Wang et al., 2016; Zhang, Wu, Yang, Song & Xu, 2020). Hence, the use of enzymes could contribute to improving the economic feasibility of large-scale production of cellulose nanomaterials (Ramos et al., 2020).

Several review articles have been published regarding the production of nanocelluloses, their properties and applications (Dhali et al., 2021; Dufresne, 2019; Kargarzadeh et al., 2017, 2018; Klemm et al., 2020; Mokhena & John, 2020; Moohan et al., 2020; Park, Choi, Oh & Hwang, 2019; Shojaeiarani, Bajwa & Shirzadifar, 2019; Thakur et al., 2021; Thomas et al., 2018; Trache et al., 2020). On the other hand, there are a limited number of review papers that have specifically addressed the enzymatic route to isolate cellulose nanomaterials (Afrin & Karim, 2017; Arantes et al., 2020; Michelin et al., 2020; Ramos et al., 2020; Ribeiro et al., 2019). These papers have reported on the structural aspects of cellulosic biomass as well as on the enzyme interactions and their action mechanism, mostly aiming to provide a better understanding of the enzymatic hydrolysis in the production and functionalization of cellulose nanomaterials. The main properties of the cellulose nanomaterials and their possible applications have been also addressed. Despite the valuable information already available in the literature, a more systematic and quantitative approach would be important in order to find gaps and guide future studies towards expanding the use of this technology and promoting novel applications for enzyme-mediated nanocellulose.

Systematic map (SM) is a rigorous, repeatable and transparent form of evidence synthesis that has been used to collate, describe and catalog available evidence (e.g. primary, secondary, theoretical, economic) relating to a topic or question of interest. This synthesis methodology aims to be comprehensive and should be undertaken according to a peer-reviewed protocol previously established. Along with detailed descriptive information, SMs provides searchable databases of studies being used to describe the state of knowledge, and identify knowledge gaps, unknown trends, and research clusters (Haddaway, Bernes, Jonsson & Hedlund, 2016; James, Randall & Haddaway, 2016). Whereas traditional literature reviews are potentially susceptible to some biases, such as, selection, publication and detection biases, and risks of missing important evidence, systematic mapping aims to reduce these biases, increase reliability and provide a readily usable resource for researchers and decision-makers when looking for evidence by retrieving all relevant publications of the targeted topic. Moreover, the detailed descriptive information regarding the protocol used in SMs facilitates follow-up studies (Haddaway et al., 2016 and Petersen, Vakkalanka & Kuzniarz, 2015). Hence, it is of great interest to apply the systematic mapping methodology search and evaluate primary studies related to cellulose nanomaterials, especially those that were isolated using enzymatic hydrolysis.

The objective of the systematic map presented here is to describe the current state of knowledge regarding cellulose nanomaterials whose production processes include the use of enzymes, identifying trends and gaps in the literature, as well as the most studied applications of these nanomaterials. This systematic mapping was performed as an attempt to present quantitative data identifying the feedstocks and enzymes most used in the isolation of nanocellulose using enzymatic hydrolysis, together with the main applications of these nanomaterials, based on carefully identifying and analyzing studies from the literature. This work assists in identifying recent advances and the main gaps, guiding researchers to conduct future studies on the isolation of cellulose nanomaterials using the enzymatic route.

2. Methodology

The systematic map was elaborated in five sequential steps, according to the criteria issued by the Collaboration for Environmental Evidence (CEE) Systematic Review Guidelines (Collaboration for Environmental Evidence, 2018). The steps can be briefly described as follows:

Step 1: Setting the scope, research questions, and selection criteria

Since the SM collates, describes, and catalogs available studies relating to a topic of interest, instead of answering a specific question as does a systematic review (Bates, Clapton & Coren, 2007), the research questions (RQ) can be more open-framed than those used in systematic reviews (James et al., 2016). These questions are important elements of the research and are formulated to reflect the goals of the work. In this study, the following research questions were used:

RQ1: What are the main roles of enzymes in the production of cellulose nanomaterials?

RQ2: What are the most common applications for nanocellulose obtained using enzymes?

Step 2: Conducting the search

Search strings were formulated following a five-step guideline: 1) definition of the major keywords, considering the research questions and keywords of the area; 2) identification of alternative words, synonyms, or related terms for the major keywords; 3) verification of the presence of the major keywords in relevant articles related to the topic; 4) association of the synonyms, alternative words, or terms related to the main keywords using the Boolean operator "OR"; and 5) association of the major terms using the Boolean operator "AND" (Kitchenham, Brereton & Budgen, 2010, 2011; Wohlin et al., 2012). The major keywords "cellulose nanomaterials" and "enzymatic hydrolysis", together with their synonyms and related words based on the literature (Charreau et al., 2020; Dufresne, 2019; Jonoobi et al., 2015; Kargarzadeh et al., 2018, 2017; Mariano, El Kissi & Dufresne, 2014; Pennells, Godwin, Amiralian & Martin, 2020; Phanthong et al., 2018; Shojaeiarani et al., 2019; Trache et al., 2020) are presented in Figure S1 (Supplementary Material). It is important to highlight that this work is limited to cellulose nanomaterials derived from plants and the use of top-down strategies, so bacterial cellulose is not included. The Web of Science, Scopus, and Engineering Village databases were used to search for relevant literature and data. Searches in the selected databases were performed in April of 2021 and they were restricted to articles published between 2000 and 2021.

Step 3: Study selection

The studies were selected in three steps: preliminary selection, primary selection, and final selection. A total of 2073 articles were retrieved from the selected databases and combined in a single Mendeley library file to be subjected to the selection steps. The duplicates (1042 articles) were removed using an automatic function in Mendeley. In order to ensure that unrelated articles were not unwittingly included in this study, the selection process was conducted by first analyzing the titles and abstracts (primary selection), and then full reading (final selection), considering the following inclusion (IC) and exclusion criteria (EC): (**IC1**) The article was published online during the period from January 2000 to March 2021; (**IC2**) The article describes a primary study (review articles and conference abstracts were not considered in this systematic mapping); (**IC3**) The study is related to nanocellulose isolated by the enzymatic route; (**EC1**) The study is not written in English; (**EC2**) The study is not accessible in full-text format; (**EC3**) The study is a duplicate of other studies; (**EC4**) Data regarding the properties and characteristics of nanocellulose are not well presented; (**EC5**) The study was published in a journal whose impact factor is lower than 1.5.

A total of 262 articles were then subjected to full-text analysis, resulting in a population of 200 primary studies being selected for inclusion in this study. Fig. 1 summarizes the numbers of articles included and/or excluded at each step of the selection process.

Considering the likelihood of subjective decisions at the selection step (Collaboration for Environmental Evidence, 2018), a sample of 1661 articles was analyzed by a second reviewer. The selected articles were compared using the Kappa test of agreement to ensure the repeatability of the process and avoid reviewer bias (Cohen, 1960). A Kappa score of 0.922 (95% lower/upper confidence limit) was obtained. In order to demonstrate the transparency of the screening process, a list

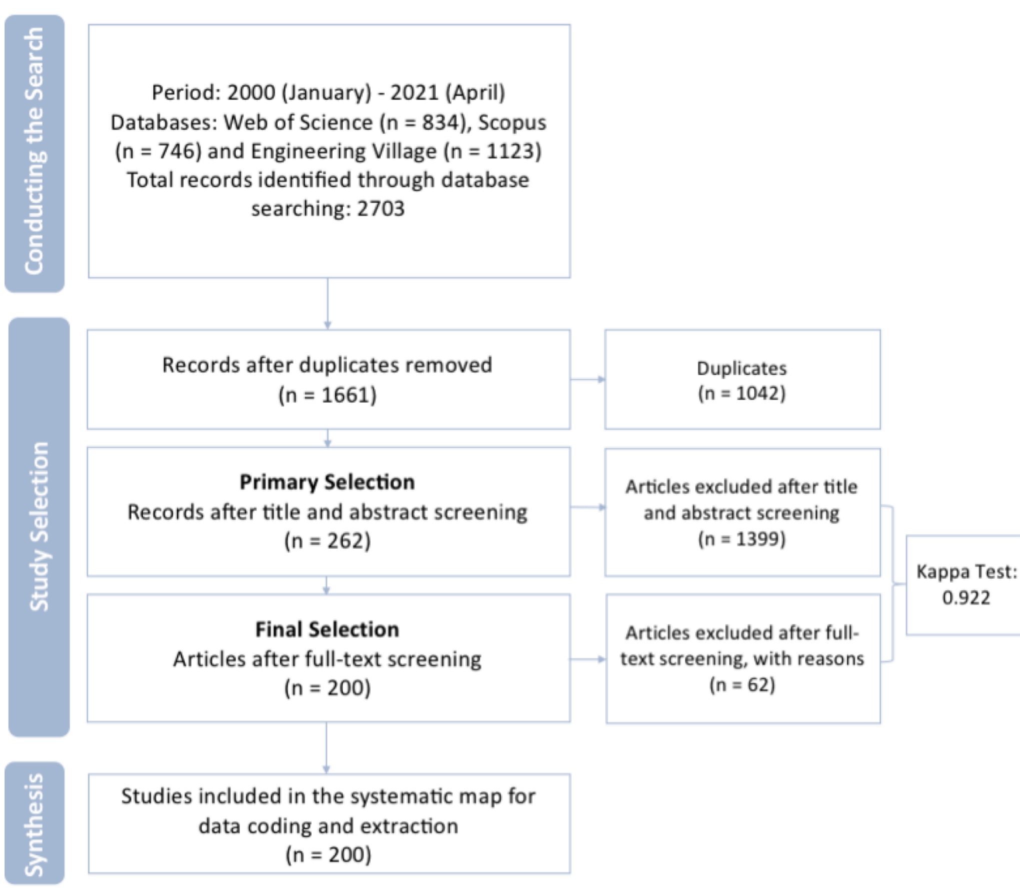

Fig. 1. Number of articles after each selection step. Adapted from Haddaway, Macura, Whaley & Pullin, 2017.

of articles excluded after the final selection based on full-text analysis, along with reasons for the exclusion, are presented in the Supplementary Material.

Step 4: Data coding and data extraction

Coding is the process of assigning categories to each study for a suite of variables that describe the study setting and design (Bates et al., 2007). This usually involves combining metadata and generic information (including author, title, year of publication, publication type, data source type, and data type) with topic-specific elements (such as interventions, populations, length of the study, and sampling strategy) describing the study setting (James et al., 2016). Here, the articles that met the selection criteria ($n = 200$) were subjected to data coding and synthesis of the results.

Besides retrieving the metadata, the main objectives, results, and highlights of the studies were also extracted from the articles.

Step 5: Data handling and describing the findings

The calculations were performed using MS Excel (v. 2016), while OriginPro software (v. 8.5) was used to construct the graphs. Terms were assigned to provide a "fingerprint" of each article, considering its information content (main objectives, results, and highlights), in order to answer the research questions and to explore the hot topics of cellulose nanomaterials production using enzymes. This procedure was assisted by the use of network maps drawn using VOSviewer software (v. 1.16.15). The text mining functions were used to construct and visualize co-occurrences of the terms, enabling the identification of trends across the literature included. VOSviewer is a software tool specifically designed for the analysis of bibliometric data (Gonçalves et al., 2019; Van Eck & Waltman, 2010).

3. Results and discussion

This section provides a brief overview of NCs production and the quantitative results obtained from the analysis of the 200 articles selected according to the methodology presented above.

3.1. The use of enzymes to produce cellulose nanomaterials

The interest in obtaining cellulose nanomaterials by means of enzymatic hydrolysis has increased, mainly because unlike acid hydrolysis and chemical treatment, it does not generate toxic residues, it is carried out under milder conditions of temperature and pressure, and the enzymes have high specificity for the substrate. However, the high cost of these biocatalysts is still a major challenge that needs to be overcome. Hence, considering the various advantages, especially related to process sustainability, the development of enzymes at a competitive production cost is important for improving the economic viability of nanocellulose production by enzymatic hydrolysis (Arantes et al., 2020; Michelin et al., 2020). Furthermore, relatively low yields and long reaction times have been reported, which need to be addressed since they suggest that the development of these processes is still at an early stage and needs to be addressed (Rosales-Calderon, Perira & Arantes, 2021).

With the aim of guiding future research in this field, a total of 2703 articles related to nanocellulose production processes using enzymes were retrieved and processed, following the methodology described previously. The screening process resulted in an evidence map of 200 primary studies (Fig. 1) and the annual distribution of them is shown in Figure S2 (Supporting Material).

Considering the period chosen to conduct this systematic map, the production of cellulose nanomaterials using enzymes was first reported by Hayashi, Kondo and Ishihara (2005) in an investigation of the selective enzymatic hydrolysis of microcrystalline cellulose using an enzyme sample rich in cellobiohydrolase from a commercial cellulase preparation. This process resulted in the formation of short elements with average length of 350 nm and diameter of 10 nm. In 2006, Janardhnan and Sain (2006)) demonstrated that the treatment of kraft pulp with *Ophiostoma ulmi* facilitated fibrillation during the subsequent mechanical refining. This was attributed to the weakening of hydrogen bonds between the fibrils, without significant cellulose loss, which resulted in distinct microfibrils with a narrower diameter distribution, compared to those obtained from untreated fibers. In the following year, Henriksson, Henriksson, Berglund and Lindström (2007) and Paakko et al. (2007) evaluated the application of endoglucanase (Novozym 476) to improve the efficacy of mechanical treatment of cellulose to isolate microfibrillated cellulose, while Agblevor, Ibrahim and El-Zawawy (2007) explored the use of commercial cellulases to produce microcrystalline cellulose from cotton gin waste and corn cob. It was reported that the use of enzymatic hydrolysis, in combination with mechanical treatment, favored the formation of longer and highly entangled nanofibrils,with the high aspect ratio leading to stronger networks and gels (Henriksson et al., 2007; Paakko et al., 2007).

Subsequent studies evaluated the use of monocomponent enzymes and enzymatic complexes as auxiliary methods combined with mechanical and/or chemical treatments. The aims were to reduce energy consumption (mechanical refinement), lower the acid concentration, increase the yield, and improve the properties of the nanomaterial (considering thermal stability, size, and morphology). Enzymatic treatment has also been used as the main step of the process for obtaining nanomaterials. Furthermore, enzymatic hydrolysis provides a promising route for integrating the production of nanocellulose and biofuels from lignocellulosic materials, according to the biorefinery concept, as reported by Bondancia et al. (2017) and Squinca et al. (2020).

It can be seen from Figure S2 (Supporting Material) that no consistent growth in the number of publications was evident from 2000 to 2013. However, there was a significant increase between 2014 and 2021. These results were in agreement with Charreau et al. (2020), who reported a substantial increase from 2010 to 2017 in the number of patents referring to cellulose nanomaterials, including cellulose nanofibrils and nanocrystals, with especially high annual increases since 2015. The continuous increase in the number of studies and patent documents published every year highlights the growing interest shown by the scientific and industrial communities in the field of cellulosic nanomaterials. The trend shown in Fig. 2 indicates that this subject is in the early stages of development and that there is great potential for research into novel and more efficient production methods, as well as innovative future applications. Furthermore, the identification and use of cheaper renewable feedstocks could provide significant economic benefits for these processes (Mishra, Kharkar & Pethe, 2019).

3.2. Source materials for nanocellulose production

Cellulose can be derived from many sources, examples being hardwoods (eucalyptus, maple, birch, aspen, oak, and elm), softwoods (hemlock, yew, pine, juniper, and cedar), agricultural and forest residues (sugarcane bagasse and straw, garlic straw residues, mulberry fiber, and mengkuang leaves), municipal waste (organic and paper waste), animals (*Chordata*, tunicates, *Styela clava*, and *Halocynthia roretzi* Drasche), fungi, bacteria (*Acetobacter, Azotobacter, Aerobacter, Sarcina, Gluconacetobacter, Salmonella, Agrobacterium, Rhizobium, Alkaligenes, Pseudomonas*, and *Rhodobacter*), and algae (*Cladophora, Cystoseria myrica*, and *Posidonia oceanica*) (Trache et al., 2020). Vascular plants, which are the major industrial source of cellulose, have cell wall structures and compositions that vary according to plant species, tissue, and cell type (Lavanya, Kulkarni, Dixit, Raavi & Krishna, 2011; Siró & Plackett, 2010). Fig. 2 presents a hierarchical structure of plant material, at scales ranging from a hardwood tree to cellulose chains.

The primary constituents of plant cell walls are usually cellulose (20–50% on a dry weight basis), hemicellulose (15–35%), and lignin (10–30%), while minor components are proteins (3–10%), lipids (1–5%), soluble sugars (1–10%), and minerals (5–10%) (Pauly & Keegstra, 2008). A typical plant cell (Fig. 2) is organized into the middle lamella, the primary and secondary (outer, middle, and inner layers) walls, and the warty layer. The microfibrils of cellulose are aligned in

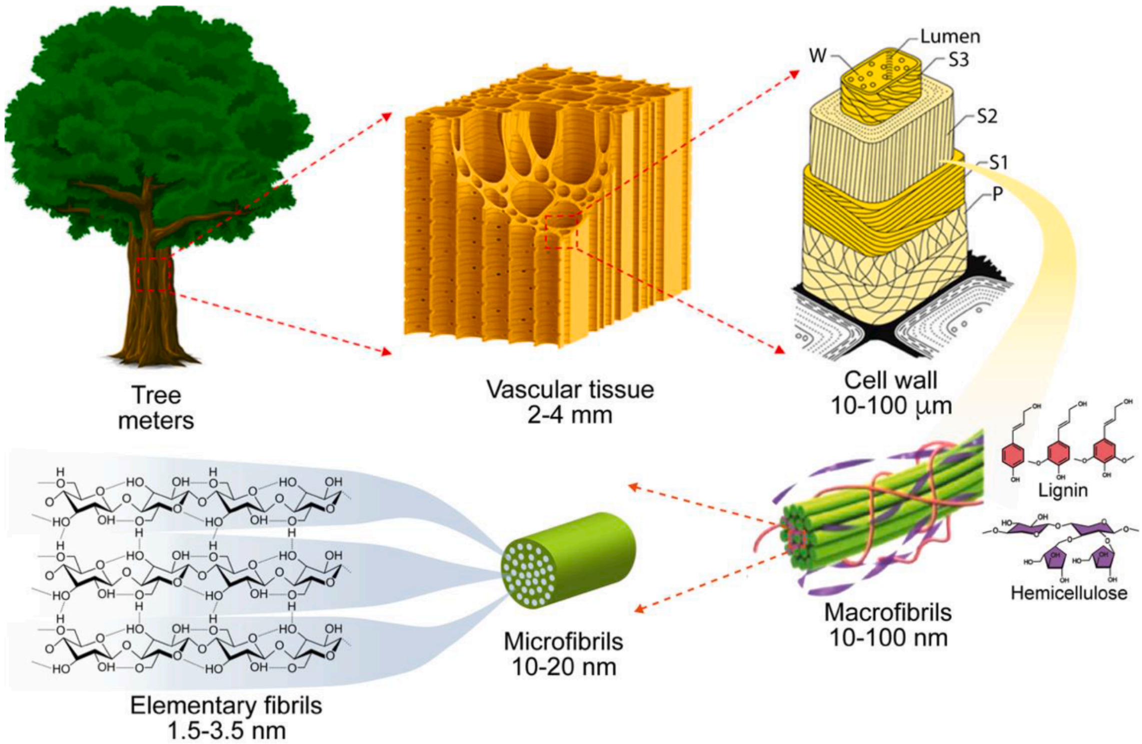

Fig. 2. Plant material hierarchical structure at scales from a hardwood tree to cellulose chains. Adapted from Chen and Hu (2018) with permission from American Chemical Society and Copyright 2022. The schematic illustrations of macrofibrils, microfibrils, and elementary fibrils were adapted from Jiang et al. (2018) with permission from John Wiley & Sons and Copyright 2022.

parallel and are densely packed in the secondary wall (Klemm, Philpp, Heinze, Heinze & Wagenknecht, 1998; Sjostrom, 1993).

Considering the articles selected for use in this systematic map, Fig. 3 presents the percentages of them reporting the use of enzymes for the production of a particular type of cellulose nanomaterial (cellulose nanofibrils, nanocrystals, microfibrils, or microcrystals), together with the percentages for the different feedstocks employed. A list of the feedstocks used in the selected studies and their occurrences can be found in the Supplementary Material (Table S3).

Cellulose nanofibrils (56.7%) were the commonest type of cellulose nanomaterial reported in the studies that used enzymes in the processes, followed by cellulose nanocrystals (29.3%), cellulose microfibrils (11.5%), and cellulose microcrystals (2.4%). The higher number of studies concerning cellulose nanofibrils could probably be explained by the fact that enzymatic hydrolysis has often been evaluated as an auxiliary step for mechanical treatments that typically generate this type of nanomaterial (Nechyporchuk et al., 2016). The majority of feedstocks used for the CNFs and CMFs were derived from hardwood (29.6% and 36.4% of occurrences, respectively), mainly consisting of bleached kraft pulp and northern bleached hardwood kraft pulp, while CNCs and CMCs have been often extracted from residues such as oat husks, sugar beet waste, sugarcane bagasse, and citrus bagasse, among others. The significant use of feedstock derived from hardwood was expected, since the pulp and paper industry is the most significant supplier of cellulose for the production of cellulose nanomaterials, providing delignified and bleached pulps (Klemm et al., 2018). As an example, Cebreiros, Seiler, Dalli, Lareo and Saddler (2021) obtained nanofibrillated cellulose from bleached eucalyptus kraft pulp using a combination of commercial enzyme cocktails (xylanase and swollenin). This enabled removal of more than 80% of the hemicellulose, achieving 61–97% yields of cellulose nanofibers with diameters ranging from 3 nm to 10 nm (Cebreiros et al., 2021). It should be noted that besides being environmentally friendly, the use of residues in processes to produce cellulose nanomaterials contributes to waste reduction, leading to higher profits due to the increased value of the industrial chain (Di Gruttola & Borello, 2021).

3.3. *Enzymes used in nanocellulose production*

The use of enzymes in the production of nanocellulose has most frequently been investigated as an additional step associated with mechanical treatments. However, enzymatic hydrolysis has also been evaluated as the main step in the process of nanocellulose isolation. Irrespective of their role in the overall process, carbohydrate-active enzymes, especially cellulases, are the biocatalysts most used in the top-down strategy to obtain nanocellulose from lignocellulosic materials.

Cellulases belong to the wider enzyme class of glycoside hydrolases, which cleave β−1,4-glucosidic bonds (Pandey, Kuila & Tuli, 2021). Cellulases are produced by a broad range of microorganisms, including fungi and bacteria, with those from the former group being most frequently used for industrial applications (Payne et al., 2015). The synergistic action of the cellulase enzymes with other auxiliary enzymes is essential for the hydrolysis of lignocellulose. Fig. 4 shows the major classes of cellulases, endo-1,4-β-D-glucanases (EG, EC 3.2.1.4), cellobiohydrolases (exo-1,4-β-D-glucanases, CBH, EC 3.2.1.91), and β-glycosidases (1,4-β-D-glycosidases, BG, EC 3.2.1.21) involved in hydrolyzing cellulose microfibrils present in the cell walls of plant-based materials.

EGs mainly hydrolyze the β−1,4 glycosidic bonds present in the amorphous regions of cellulose microfibrils, producing lower molar mass oligosaccharides (cellodextrins) and cellobiose, releasing the reducing and non-reducing chain ends. Due to their high specificity for acting at the disordered regions of cellulose, EGs can slightly increase the crystallinity of cellulose materials (Mansfield & Meder, 2003). The action of these enzymes decreases the degree of polymerization of cellulose (Cao & Tan, 2002), with CBH I acting on the reducing ends of the polysaccharide chains, while CBH II attacks the non-reducing ends of the chains, releasing glucose or cellobiose (a dimer of glucose) as major products. These enzymes can also act on microcrystalline cellulose

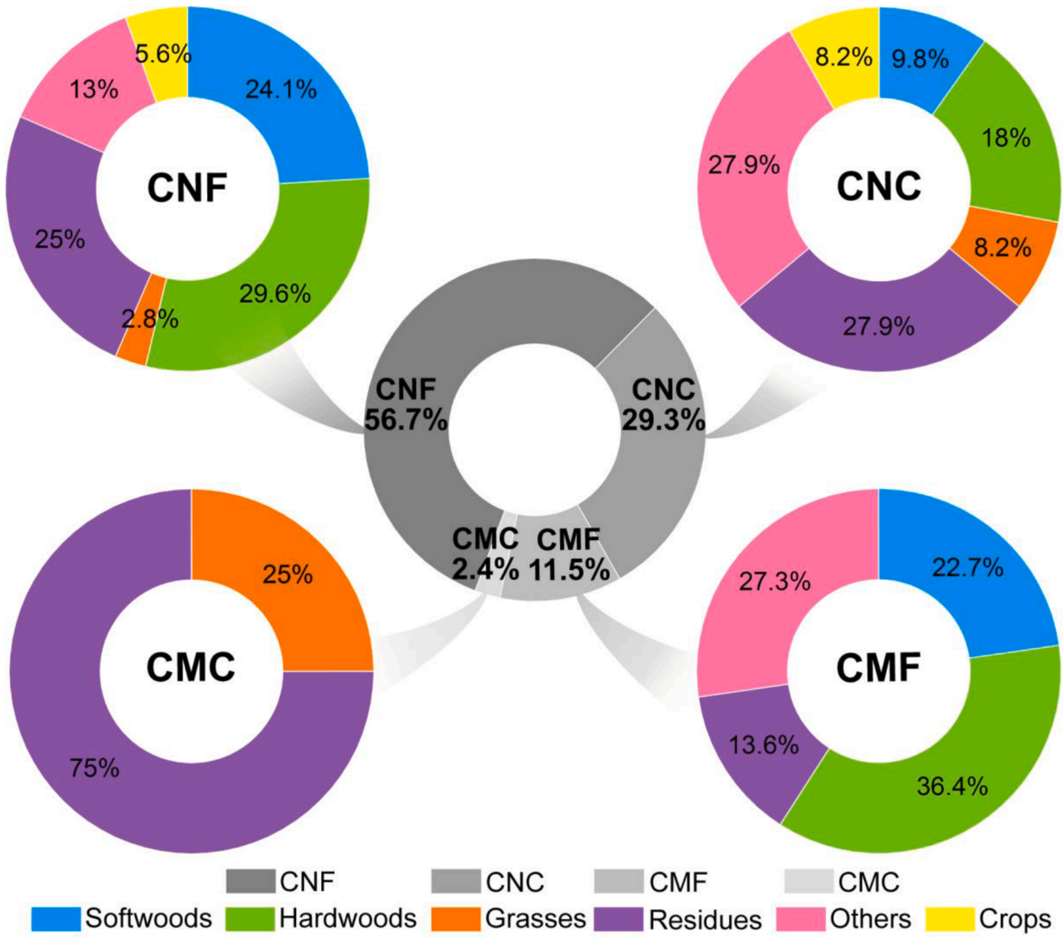

Fig. 3. Percentages of articles reporting the production of different types of cellulose nanomaterials (cellulose nanofibrils, nanocrystals, microfibrils, and microcrystals), and the proportions of the main feedstocks used in the enzymatic hydrolysis.

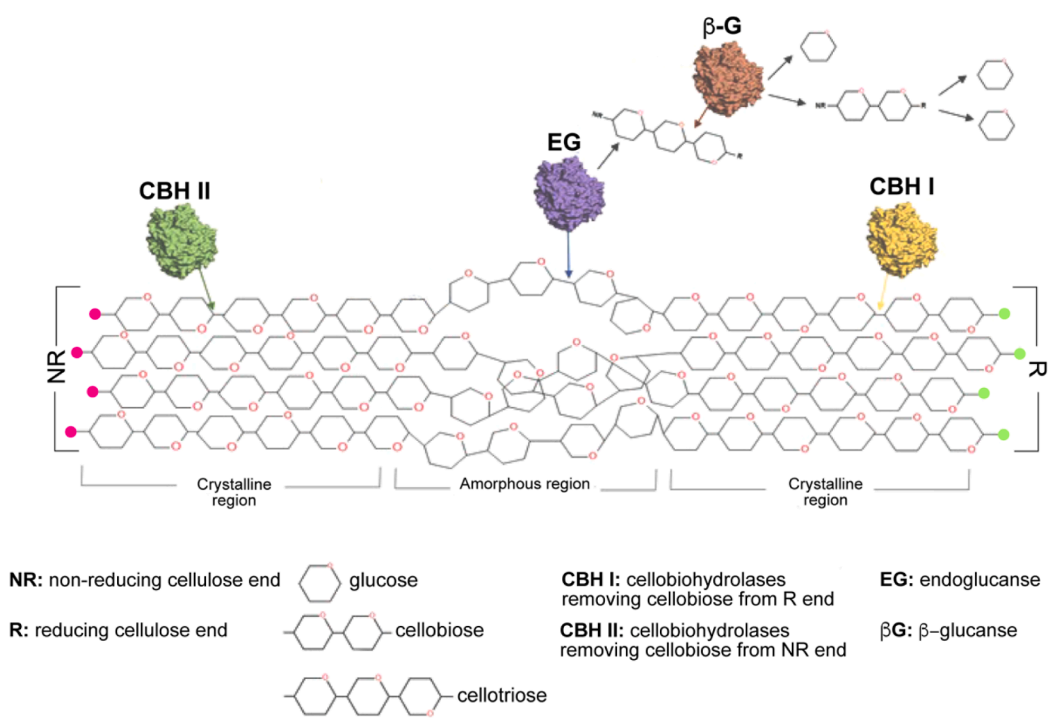

Fig. 4. Overall scheme of the enzymatic hydrolysis of cellulose, involving synergistic interactions of the major cellulases (endoglucanase, cellobiohydrolases, and β-glucosidase). Adapted from Andlar et al. (2018) with permission from John Wiley & Sons and Copyright 2022.

(Lynd, Weimer, Van Zyl & Isak, 2002). In general, cellobiohydrolases are processive enzymes, remaining bound to the cellulose until a minimum chain length is reached. The β-glycosidases act on cellobiose and cellodextrins, producing glucose (Kumar & Murthy, 2013).

In addition to cellulases, xylanases have also been extensively used in nanocellulose production, since lignocellulosic materials contain varying amounts of hemicellulose. Xylanases may also act synergistically with cellulases, increasing the swelling and porosity of the fibers, consequently enhancing the access of cellulases to cellulose (Bajaj & Mahajan, 2019; Song et al., 2016). Among several enzymes involved in depolymerization of the hemicellulose heterogeneous structure, endoxylanases (EXs) (EC 3.2.1.8) and exo-b-xylosidase (EC 3.2.1.37) are those most used in the isolation of nanocellulose. Endo-1,4-β-xylanases (1,4-β-D-xylan xylanohydrolase; EC 3.2.1.8) do not act randomly on the xylan backbone, instead cleaving selected glycosidic bonds, depending on the chain length, degree of branching, and the presence of substituents. Exo-b-xylosidase releases xylose from the non-reducing ends of xylo-oligosaccharides (Polizeli et al., 2005).

Lytic polysaccharide monooxygenases (LPMOs) are another class of enzymes that have been evaluated to assist NC production. LPMOs act on cellulose chains by oxidative cleavage of glycosidic bonds, generating oxidized chain ends in different positions, which increases the susceptibility of the substrate to the action of cellulases (Villares et al., 2017). Studies have reported the use of LPMOs in synergy with cellulases and/or xylanases to facilitate the deconstruction of cellulose fibers for producing CNFs (Hu, Tian, Renneckar & Saddler, 2018; Moreau et al., 2019; Valenzuela et al., 2019).

In order to evaluate the enzymes commonly used in enzymatic hydrolysis for nanocellulose isolation, the biocatalysts were divided into two main categories: (i) commercial enzymes, and (ii) non-commercial enzymes. It should be noted that the non-commercial category included enzymes from proprietary research formulations of private companies, heterologous expression in prokaryote or eukaryote host systems, and enzymatic extract production by microorganisms without genetic modification. The percentages of different commercial enzymes employed in enzymatic hydrolysis for the production of cellulose nanomaterials are displayed in Fig. 5. A list of the commercial enzymes and their occurrences is provided in Table S4 (Supplementary Material).

The majority of the selected articles (81.5%) reported the use of commercial enzymes, while less than a fifth of them (15.5%) described the use of non-commercial enzymes, and an even smaller number (3.0%) evaluated both types of enzymes. Studies have shown that cellulase enzymes such as endoglucanases, in combination with "amorphogenesis inducing" proteins such as xylanases, laccases, and LPMOs, are able to increase access to the cellulose and improve its nanofibrillation (Hu et al., 2018; Long, Tian, Hu, Wang & Saddler, 2017; Meesupthong et al., 2021; Valls et al., 2019). The use of LPMOs contributes to stabilizing the nanofibril suspension (zeta potential = ~60 mV), due to oxidative cleavage of the cellulose pulp, without compromising nanocellulose thermostability (Hu et al., 2018).

The use of alkaline treatments has been shown to improve enzymatic hydrolysis, since endoglucanase preferentially acts on disordered cellulose and the rate of cellulose II hydrolysis is faster, compared to cellulose I hydrolysis. Banvillet, Depres, Belgacem and Bras (2021) reported that this combination, followed by grinding, resulted in CNFs with rigid structures, diameters ranging from 10 to 20 nm, and lengths between 150 and 350 nm, which were suggested to be suitable for industrial production, due to a lower energy demand (Banvillet et al., 2021).

Blends of different classes of cellulases (denoted cellulases preparations in this study), such as Celluclast® 1.5 L, Cellic CTec2, Cellic CTec3, and cellulases from *Trichoderma reesei* ATCC 26,921, among others (Table S4, Supplementary Material), were the commercial products most used to isolate cellulose nanomaterials in the selected studies. The occurrences were 42.7% (CNFs), 51.4% (CNCs), 42.9% (CMFs), and 66.7% (CMCs). Monocomponent endoglucanase and enzyme

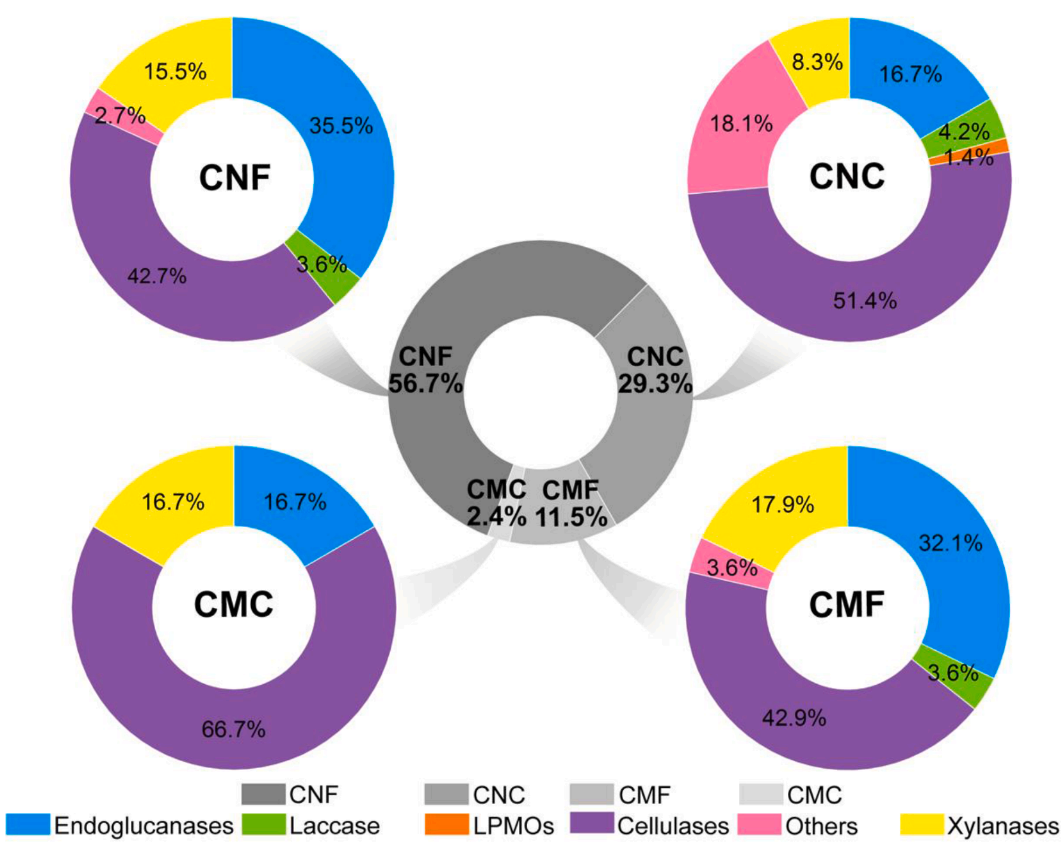

Fig. 5. Proportions of the main commercial enzymes used to isolate cellulose nanofibrils, nanocrystals, microfibrils, and microcrystals in the selected studies.

formulations rich in endoglucanase, such as Fibercare® R, Novozym 476, and Endoglucanase FR (Table S4, Supplementary Material), were also frequently used, representing 35.5, 16.7, 32.1, and 16.7% of the occurrences in articles reporting the production of CNFs, CNCs, CMFs, and CMCs, respectively. Endoglucanases from different sources (fungal and bacterial) and belonging to different glycosyl hydrolase families display distinct actions on substrates during hydrolysis, affecting isolation of the cellulose nanomaterials. The presence of a carbohydrate binding module, whose main role is to assist the enzyme in binding to cellulose, favors the release of nanoparticles (Siqueira, Dias & Arantes, 2019).

Although endoglucanases have been claimed to be more suitable for nanocellulose isolation, due to their selectivity towards the amorphous cellulose regions, cellulases preparations were the most used commercial enzymes. A possible reason for this was the lack of a commercial enzymatic preparation specifically designed for the production of cellulose nanomaterials. Therefore, research studies have had to use the cellulose-active enzymes available on the market, which were developed for other purposes, such as the complete hydrolysis of cellulose into soluble sugars (Arantes et al., 2020).

Fig. 6 shows the percentages of different non-commercial enzymes used in enzymatic hydrolysis for the production of cellulose nanomaterials. A list of the different non-commercial enzymes, together with their occurrences, is provided in Table S5 (Supplementary Material).

In contrast, endoglucanases were the most used non-commercial enzymes, representing 36.8, 35, and 100% of occurrences in the articles reporting the production of CNFs, CNCs, and CMCs, respectively. The main technique used was heterologous expression, which could be attributed to the possibility of producing and using different recombinant endoglucanases, in order to compare their hydrolytic activities and effects on the properties of the cellulose nanomaterials, providing a better understanding of the mechanisms involved in cellulose nanomaterial production using enzymes (Wang et al., 2016). Alonso-Lerma et al. (2020) reconstructed an ancestral endoglucanase from bacteria species and showed that this enzyme alone was able to generate chemically pure cellulose nanocrystals while preserving the native cellulose structure. These nanomaterials presented a maximum degradation temperature (T_{max}) of 356 °C and a crystallinity index (CrI) of 87.5% showing superior thermal stability and crystallinity compared to CNCs obtained by acidic treatment (T_{max}: 298 °C and CrI: 80.5%). Rossi et al. (2021) described the use of recombinant endoglucanase, in combination with xylanase and lytic polysaccharide monooxygenase, as a treatment of sugarcane bagasse which was performed before a relatively mild sonication step to enhance cellulose fibrillation. This procedure resulted in cellulose nanofibrils that were longer, with an average length of 1.3 ± 0.9 μm than those obtained using TEMPO oxidation (average value: 400 ± 200 nm) and slightly more thermostable showing a T_{max} of 315 °C.

As mentioned before, the use of enzymes in processes for the isolation of cellulose nanomaterials is at an early stage of development. Since no commercial enzymatic preparation has been fully developed for nanocellulose isolation, efforts are still required not only to produce enzymes with higher specificity and efficiency, but also to reduce their costs.

3.4. Trends and main applications for nanocelluloses whose production processes include an enzymatic hydrolysis step

Text mining tools were used in a qualitative and semi-quantitative approach to address the questions proposed initially. Network maps and the frequency of co-occurrence of assigned terms enabled elucidation of the current state-of-the-art and the hot-spots for research in the

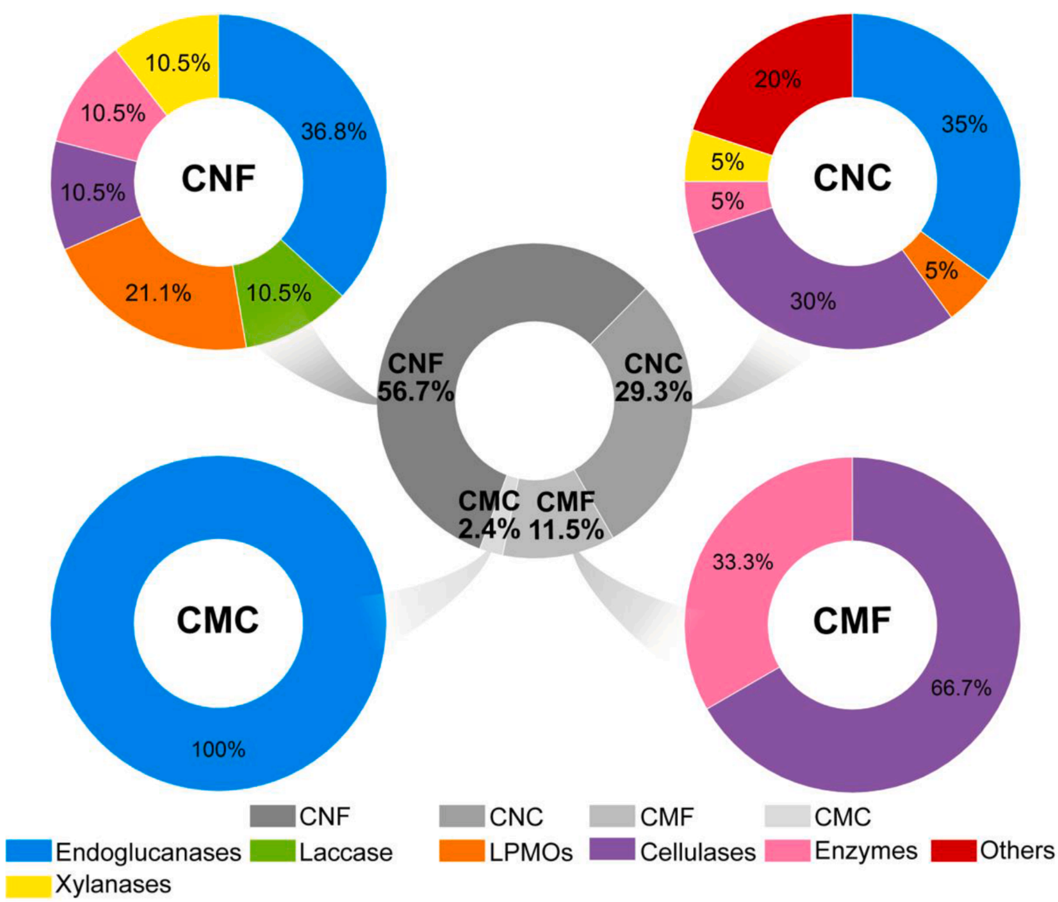

Fig. 6. Proportions of the main non-commercial enzymes used to isolate cellulose nanofibrils, nanocrystals, microfibrils, and microcrystals in the selected articles.

field of cellulose nanomaterials production using enzymes. Term co-occurrence is one of the analytical methods most used for bibliometric purposes. When the terms/keywords appear in one document, they are recorded as one co-occurrence. The more co-occurrences, the closer the relationships between the two words and the stronger the correlations (Gao, Huang & Zhang, 2019).

As mentioned previously, during the data handling step, terms were assigned to provide a "fingerprint" of each article. Fig. 7 shows the terms

(a)

Code	Description	Occurrences (%)
	Production process conditions	
M1	Comparison of different methods	2.5
M2	Comparison of different enzymes	4.1
M3	Comparison of different enzyme concentrations	9.1
M4	Comparison of different reaction times	5.9
M5	Comparison of different pretreatments	6.4
M6	Comparison of different feedstocks	4.1
M7	Comparison of different feedstock concentrations	1.1
M8	The conditions of reaction were optimized without design of experiments	2.3
M9	The conditions of reaction were optimized with design of experiments	2.1
M10	CNs were isolated using immobilized enzymes	0.2
M11	hydrolysis	0.2
M12	A life cycle assessment was performed	0.9
M13	CNs were produced within the biorefinery context	3.2
	Usage of enzymatic hydrolysis to	
P1	Facilitate cellulose nanofibrillation	4.3
P2	Control the CNs size	1.8
P3	Functionalize CNs	1.8
P4	Increase the crystallinity of CNs	0.5
P5	Increase the homogeneity of CNs	0.5
P6	Improve the CNs yield	0.2
P7	Synthesis of artificial CNs	0.5
	Evaluation of the enzymatic hydrolysis effects on	
P8	Thermal stability of cellulose nanomaterials	1.1
P9	Rheological behavior of CNs suspension	1.6

(b)

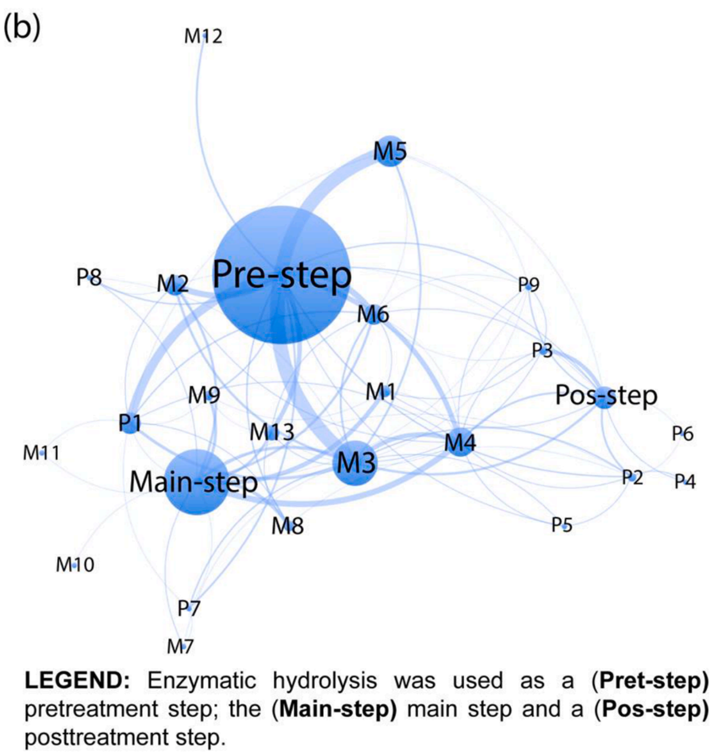

Fig. 7. Evaluation of the approaches, strategies, and reaction conditions for the use of enzymes in the cellulose nanomaterials production processes reported in the selected articles. A) Percentage occurrences and description of the selected terms. B) Network analysis of the terms.

and their occurrences related to the approaches, strategies, and reaction conditions for the use of enzymes in the cellulose nanomaterials production processes reported in the selected articles, together with a corresponding network map.

As shown in Fig. 7a, the highest number of occurrences was for the pretreatment step, followed by the main and post-treatment steps. Approximately 61.1% of the studies used enzymes in the pretreatment, while 28.8% used them in the main step, 9.1% used them in the post-treatment, and a small percentage evaluated the use of enzymes in both pretreatment and post-treatment. The use of enzymatic hydrolysis mainly as an auxiliary treatment was already expected, since conventional approaches for producing cellulose nanofibrils and nanocrystals are mechanical and chemical methods, respectively (Nechyporchuk et al., 2016).

The strongest interactions occurred between the pretreatment (Pre-step) and the terms represented by M2, M3, M4, and M5 (Fig. 7b). These associations suggested that in studies using enzymatic hydrolysis as a pretreatment, there were also comparative analyses considering other pretreatments and/or different reaction times, enzymes, feedstocks, and concentrations. Although the effects of different process variables on the properties of cellulose nanomaterials were broadly evaluated (~67.7% of the articles), less than 5% of the studies used experimental design methodologies for precise optimization of the enzymatic reaction conditions.

The studies that used enzymatic hydrolysis as the main step also compared the effects of different reaction conditions on the properties of the nanomaterials produced, as shown by the strong interactions between the main step (Main-step) and M3, M4, and M9. The production of cellulose nanomaterials within the biorefinery context was evaluated in about 7.6% of the articles, with the use of enzymes as a pretreatment (~4.5% of the publications) being more frequent than their use in the main step (~2.5%). Furthermore, life cycle assessments were only reported in articles (~2.0% of the publications) that assessed enzymatic hydrolysis as a pretreatment step. On the other hand, unusual and innovative approaches such as the use of immobilized enzymes (one publication), twin-screw extrusion with in situ enzymatic hydrolysis (one publication), and artificial synthesis of cellulose nanomaterials enabling the production of cellulose particles with a desired morphology in their pure form (two publications) were only evaluated in articles that investigated enzymatic hydrolysis as the main step of the production process.

Enzymatic hydrolysis has mostly been used to facilitate nanofibrillation of the cellulose (~9.6% of publications) (Banvillet et al., 2021; Bian, Li, Jiao, Yu & Dai, 2016; Cebreiros et al., 2021; Henriksson et al., 2007; Liu et al., 2019; Long et al., 2017; Perić, Putz & Paulik, 2020; Rossi et al., 2021; Valenzuela et al., 2019; Valls et al., 2019). Enzymes have also been used to control the nanoparticle size (~5.1% of publications) (Chen, Fan, Han, Li & Wang, 2017; Jang et al., 2020; Liu et al., 2020), increase the crystallinity (~1.0% of publications) (Jang et al., 2020; Laadila et al., 2020), and improve homogeneity (~1.0% of publications) (Y. Chen et al., 2017). Another important advantage of using enzymes is related to the production of cellulose nanomaterials with superior thermal properties, which can further expand their range of applications (Tao et al., 2019). For instance, Squinca et al. (2020) obtained cellulose nanocrystals by enzymatic hydrolysis with an initial thermal degradation temperature of 300.5 °C, which was higher than the values of 228.2 and 130.0 °C reported by Yu et al. (2012) and Tian et al. (2016), respectively, for nanocellulose isolated using sulfuric acid hydrolysis. However, enzymatic hydrolysis generally preserves the hydroxyl groups present on the surfaces of cellulose nanomaterials, compromising the stability of suspensions of these nanoparticles and hindering their dispersion in hydrophobic polymer matrices, due to their high hydrophilicity. Strategies to overcome this disadvantage include modifications of the hydroxyl groups present on the cellulose surface and the preparation of nanomaterials with considerable amounts of lignin or hemicellulose, for example by using laccase in TEMPO-mediated oxidation of cellulose nanomaterials (Jaušovec, Vogrinčič & Kokol, 2015; Jiang et al., 2020, 2021; X. Liu et al., 2019).

Considering the second research question, evaluation was made of articles that reported applications of the nanocelluloses obtained. Fig. 8 shows the terms related to the application of cellulose nanomaterials, together with the corresponding network map.

From Fig. 8a it can be observed that the most widely nanocellulose type used by the studies was CNFs (66.7% of the articles), followed by CNCs (~20.8%), CMFs (~11.1%), and CMCs (~1.4%). Overall, the most frequent applications of cellulose nano- and microparticles considered in the selected studies were preparation of films (17.7% of occurrences), reinforcement agent in nanocomposites (7.8%), reinforcement agent in paper sheets (5.0%), and preparation of nanocomposites (4.3%). These findings are in agreement with major uses of nanocelulose isolated from by other methods, as the cellulose properties at the nanoscale make them an attractive element for reinforcing different substrate such as pulp, paper and polymers matrix (Dufresne, 2019; Eriksen, Syverud & Gregersen, 2008; Sehaqui, Liu, Zhou & Berglund, 2010; Thomas et al., 2018). Moreover, the ability of cellulose nanomaterials, specially nanofibers, to form films via formation of fibrils network has been well documented in the literature justifying the high number of occurrences (Djafari Petroudy, Ghasemian, Resalati, Syverud & Chinga-Carrasco, 2015; Henriksson, Berglund, Isaksson, Lindström & Nishino, 2008; Mtibe et al., 2015).

It has been shown that the morphology and size of cellulose nanomaterials have significant effects on the mechanical properties and transparency of films fabricated with them (X. Li et al., 2020; Wang et al., 2016; Yang, Jiao, Liu, Deng & Dai, 2018, 2019). Qing et al., (2013) compared cellulose nanomaterials isolated by refining and microfluidization, in combination with enzymatic or 2,2,6,6-tetramethylpiperidine-1-oxyl pretreatment, considering their properties and the films prepared with them. The films produced with enzymatic pretreatment CNFs presented a tensile moduli around 14 GPa which was higher than the value achieved using TEMPO oxidized-CNFs (12.9 GPa), but relatively low tensile strength (around 120 MPa). The authors attributed the higher tensile moduli value to a higher crystallinity of the enzymatically pretreated CNFs (57%) compared with the TEMPO CNFs (34%), which was expected due to preferential hydrolysis of amorphous cellulose regions. Besides the films showed good transparency and the authors reported that CNFs enzymatic pretreated might provide a good potential as the reinforcing agent in composites. Tarrés et al. (2017) compared films produced with CNFs prepared by TEMPO-mediated oxidation and enzymatic hydrolysis in terms of tensile, thermal, optical and morphological properties. In agreement with the results found by Qing et al. (2013), those films prepared from enzymatically hydrolyzed CNF presented lower values of tensile strength (62.2 to 112.9 GPa) than those resulting from TEMPO-mediated oxidation (90.3 – 152.6 GPa), but similar level of stiffness at an equivalent tensile strength. Besides, TEMPO-oxidized CNF films presented superior transparency, but lower thermal degradation temperature (240 °C) compared to their enzymatically counterparts (285 °C) due to the presence of carboxylic groups. (Xu et al. (2021) demonstrated that post-treatment of using endoglucanase combined with homogenization improved the tensile strength and transparency of CNFs films from 132.3 MPa, 27.5% to 178.0 MPa, 61.7%, respectively.

More specifically, cellulose nanofibers have mostly been used in the preparation of films, as shown in Fig. 8b by the strongest interaction between CNF and A1, as well as by the greatest number of co-occurrences, being studied by 21 articles. In other words, 44.7% of the articles that evaluated the application of CNFs focused on preparing films with them. CNFs have also been studied as reinforcement agents in paper sheets (7 articles) and in nanocomposites (7 articles). Less frequent applications of CNFs included their use as reinforcement agents in films (5 articles) and hand-sheets (2 articles), nanofiller in nanocomposites (2 articles), and preparation of aerogels (2 articles) and foams (1 article).

(a)

Code	Description	Occurrences (%)
A1	Films preparation	17.7
A2	Reinforcement agent in nanocomposites	7.8
A3	Reinforcement agent in paper-sheets	5
A4	Nanocomposites preparation	4.3
A5	Reinforcement agent in films	2.8
A6	Reinforcement agent in hand-sheets	2.8
A7	Aerogels preparation	2.1
A8	Nanofiller in nanocomposites	2.1
A9	Reinforcement agent in foams	0.7
A10	Coating agent	0.7
A11	Foams preparation	0.7
A12	Nanofiller in hydrogels	0.7
A13	Metal ion removal	0.7
A14	Oxygen barrier agent	0.7
A15	Pickering emulsions preparation	0.7

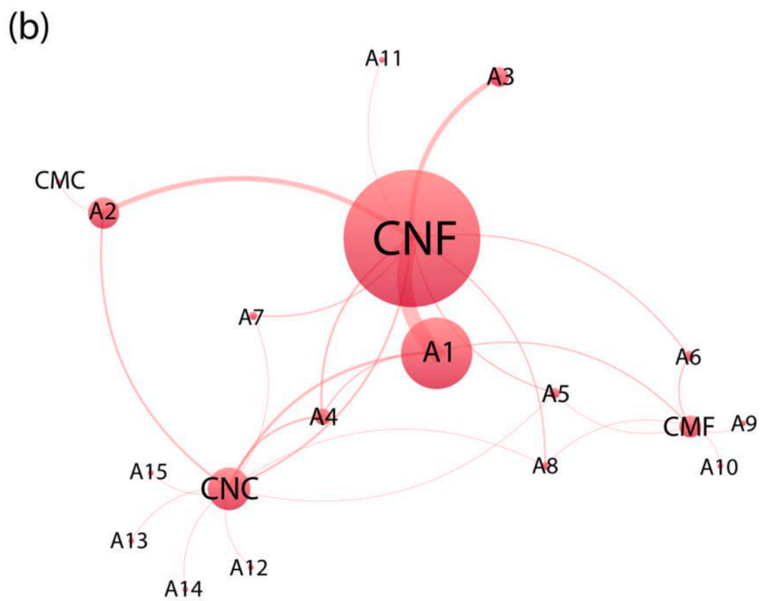

Fig. 8. Evaluation of the applications of cellulose nanomaterials obtained using enzymes in the processes, as reported in the selected articles. A) Percentage occurrences and description of the selected terms. B) Network analysis of the terms.

Cellulose nanocrystals were evaluated for the preparation of films (4 publications), nanocomposites (3 publications), and Pickering emulsions (1 publication). They were also used as a nanofiller of hydrogels (1 article), an oxygen barrier agent (1 article), and for metal ion removal (1 article). It should be noted that use of the nanocellulose in film preparation had the highest number of co-occurrences in both cases (CNFs and CNCs). However, cellulose nanofibrils are preferably used for the preparation of self-assembled films. This is because CNFs have a higher aspect ratio, greater flexibility, and propensity for entanglement, so they have a greater capacity to form networks, compared to CNCs (France et al., 2017). CMFs were mainly used for hand-sheet reinforcement and film preparation, while CMCs were employed for the reinforcement of nanocomposites.

Although there is a plethora of different nanocellulose applications, only slightly more than a third (34.8%) of the selected articles evaluated the applications of these nanomaterials, while none of them performed any study focused on the practical application of nanocellulose produced in the biorefinery context. This gap shows the need for future work focused on the application of cellulose nanomaterials whose production processes include the use of enzymes.

4. Limitations of the work

Reliable evidence reviews must include comprehensive search strategies among the main principles of their approaches, so that they can capture as much of the relevant scientific information as possible (Abdulla, Smith, Atherton & Idris, 2016). In this work, the publications were retrieved for the period from 2000 to 2021, using a search string composed of 65 terms, with 55 being “cellulose nanomaterial” synonyms and 8 being “enzymatic hydrolysis” synonyms. Therefore, it is acknowledged that some articles related to this theme may not have been found, given the existence of immense variety of terms to describe the nanocellulose types. However, it is believed that the findings of this study should make an important contribution to the field of cellulose nanomaterials, since the procedure adopted was according to the principles of a more rigorous review methodology that was recently introduced in the field of chemical engineering.

5. Final remarks and future perspective

Principles of systematic mapping were applied to studies of cellulose nanomaterials, reported during the last twenty years, where the production processes included the use of enzymes, in order to summarize the state-of-the-art and identify research opportunities in this subject area. This work was committed to systematically reviewing, developing, and promoting the evidence base for increasing the current knowledge on this topic. The following contributions can be highlighted:

- The results evidenced that during the period evaluated, there was a significant increase in the annual number of publications related to the production of nanocellulose using enzymes, especially between 2013 and 2021. This was aligned with the growing search for environmentally friendly and biodegradable materials, with industrial interest in this field enabling the installation of the first facilities for the production of nanocelluloses in commercial quantities.
- Although feedstocks derived from hardwoods were those most widely used, a large number of studies evaluated different residues as substrates for the production of cellulose nanomaterials. The interest in the use of plant-derived cellulose or residues enables the possibility of extracting nanocellulose from a wide variety of abundant sources of cellulose, which in turn ensures the low cost and renewability of the feedstocks.
- Cellulases were the commercial enzymes most studied in the articles related to nanocelluloses production, while heterologously expressed endoglucanases were mostly used in the studies employing non-commercial enzymes. Many efforts have been made to produce enzymes with high specificity and at competitive costs. However, there is currently no commercially available enzymatic preparation specifically designed for nanocellulose production. In addition, high costs of the available enzymes, long process times, and relatively low yields are still disadvantages of the enzymatic hydrolysis technology. These gaps indicate the need for research and development to obtain enzymes better suited to the production of cellulose nanomaterials, together with process optimization.
- The co-occurrence analysis of terms assigned to the articles showed that most of the studies evaluated different pretreatments and reaction conditions, varying the reaction duration, substrate type, and enzyme type and concentration. However, few studies used experimental design tools to optimize the reaction conditions.
- The co-occurrences among the terms related to the applications showed that the selected articles in this systematic map mostly evaluated the use of nanocelluloses for the preparation of films. It was also evident that the application of cellulose nanomaterials whose production process involves enzymes was not frequently investigated. Considering the advantages of using enzymes, such as operation under milder conditions of temperature and pH, no generation of harmful co-products, high selectivity, and the possibility of tuning the nanocellulose properties (such as nanoparticle size, uniformity, thermal stability, and crystallinity), the applications of enzyme-mediated nanocelluloses should be explored in greater depth.

In overall, this systematic mapping literature review highlights the main challenges regarding the exploitation of enzymes to isolate cellulose nanomaterials, and encourage further studies on the development of specifically designed enzymatic cocktails. Such studies will certainly enable the large-scale production of nanomaterials by enzymatic route and promote novel potential applications.

Supplementary material

Research string used to retrieve the articles.

Annual distribution of articles obtained after the second screening step.

List of the articles excluded during the final selection step, and the reasons for exclusion.

List of the articles included during the final selection.

List of the feedstocks, non-commercial enzymes, and commercial enzymes used for isolation of the cellulose nanomaterials in the selected studies, together with their occurrences.

Declaration of Competing Interest

The authors declare no competing financial interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.carpta.2022.100212.

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