SURFACE-ENGINEERED NANOCELLULOSE FOR BIOMEDICAL APPLICATIONS: STRUCTURE–FUNCTION PERSPECTIVES

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Cellulose, an abundant and sustainable biopolymer, has emerged as a versatile platform for advanced biomedical nanomaterials. Nanocellulose is obtained through integrated pretreatment and mechanical processes, including chemical, enzymatic, and oxidation-based strategies that reduce energy consumption and enable controlled structural tuning. The three main forms – cellulose nanofibers (CNF), cellulose nanocrystals (CNC), and bacterial nanocellulose (BNC) – differ in morphology, crystallinity, and production routes, resulting in distinct physicochemical and biological properties.
A high density of surface hydroxyl groups allows extensive surface engineering through oxidation, grafting, crosslinking, and biofunctionalization. These modifications are central to tailoring structure–function relationships that govern biocompatibility, mechanical strength, drug loading capacity, and controlled release behaviour.
This review provides a focused structure–function perspective on surface-engineered nanocellulose for biomedical applications. Emphasis is placed on drug delivery systems, wound healing materials, tissue engineering scaffolds, antimicrobial platforms, and biosensing technologies. By correlating structural design with biological performance, this work highlights the expanding role of nanocellulose in next-generation biomedical innovations.

Keywords: nanocellulose, types, treatments, surface modifications, biomedical applications

INTRODUCTION

Cellulose is the most abundant renewable natural biopolymer on Earth, primarily occurring in plant cell walls and biosynthesized by specific bacteria and tunicates.[1,2] Cellulose is the main component of plant cell walls. It is the world's most prevalent organic compound due to its structural integrity. With 75 to 100 billion tonnes produced by photosynthesis per year, cellulose makes up around 40% of all organic matter on the planet.[3,4] Cellulose plays an important part in the human food chain in an indirect way. Veterinary meals, paper and wood, textiles and strands, pharmaceuticals, and beauty care goods are just a few of the industries that use this versatile polymer.[5]

Cellulosic materials with at least one dimension in the nanoscale range are referred to as nanocellulose. Nanocellulose can be made from a variety of lignocellulosic sources using a variety of processes. Nanocomposites made from renewable resources and reinforced with nanocellulose are currently a popular research topic. Nanocellulose's utility in hybrid composite materials, dispersions, foams, and films, as well as many other areas, have yielded promising results.[6] Due to its extraordinary physical features, distinctive surface chemistry, and good biological capabilities, nanocellulose, a unique and promising natural material derived from native cellulose, has received a lot of attention for its potential as a biomedical material.[7] The term "nanocellulose" refers to cellulose-based nanostructures, which have attracted much research attention in recent years due to their versatility in terms of physical properties, chemical modifications, and potential uses. There are three types of nanocellulose: cellulose nanofibers (CNFs), bacterial nanocellulose (BNC) and cellulose nanocrystals (CNCs).[8,9]

Cellulose is a linear homopolysaccharide composed of β-D-glucopyranose units linked

through β-(1→4) glycosidic bonds, forming extended polymer chains with a high degree of polymerization (typically 10,000–15,000 in native cellulose, as shown in Fig. 1). Each repeating unit contains three reactive hydroxyl groups that participate in extensive intra- and intermolecular hydrogen bonding, resulting in a highly ordered, crystalline microfibrillar structure.[10,11] The reaction potential of the hydroxyl group at position 6 is quite higher than that at position 2 and 3.[12] Due to its crystallinity and hydrogen bonding, cellulose is insoluble in most solvents.[13]

Cellulosic nanomaterials, in particular, have sparked enormous scientific interest due to their amazing mechanical, structural, chemical, and biological capabilities, as well as their high degree of biocompatibility, biodegradability, and bioavailability.[4] Nanocellulose is frequently used for the development of materials for drug delivery applications, in the form of nanoparticles, aerogels, tablets, and hydrogels. By using nanocellulose as a carrier for the drug formulation, it may be possible to regulate its release and focus on local drug administration, leading to a significant reduction in the drug quantity.[14] It allows for higher absorption and cell binding due to its high surface-to-volume ratio, enhancing the effectiveness of various delivery systems.[15] Nanocellulose has also been demonstrated to have a minimal toxicity risk when used as a carrier.[16] The areas for targeted drug release are determined by the hydrophobicity, surface charge, modification, and particle size of drug carriers.[17]

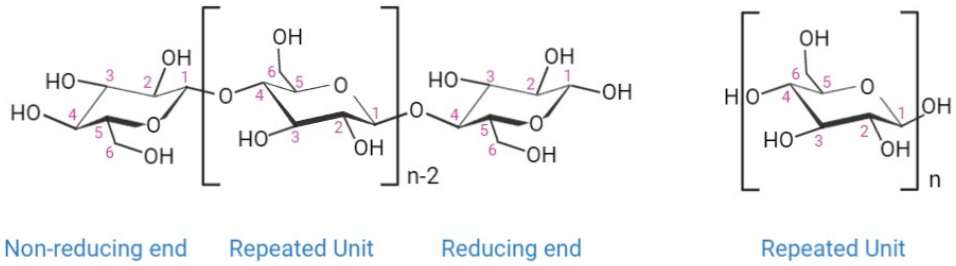

Figure 1: Chemical structure of cellulose

Types of nanocellulose

Figure 2 shows three types of nanocellulose, with the general morphological structure and alternative names of each class. These varied forms of nanocellulose have their individual significance in different areas like pharmaceuticals, textile, cosmetics, *etc*.

Cellulose nanofibers (CNF)

Cellulose nanofibers (CNF) are nanoscale fibrillar materials obtained by the mechanical and/or chemical disintegration of plant-derived cellulose fibres, with diameters of 20 to 60 nm and lengths of several micrometres. When compared to CNF made from secondary cell walls of natural fibres, CNF made from primary cell wall fibres is frequently larger and narrower.[18] Generally, these fibres have a high volume and huge surface area.[19,20] They are made up of crystalline and amorphous domains that alternate with one other.[21] Nanofibrillated cellulose (NFC) is typically made by mechanically delaminating wood pulp prior to and/or after enzymatic or chemical treatment.[22] A combination of chemical and mechanical treatments has been proven to be the most effective method due to the energy savings and improved fibrillation of cellulose fibres.[23]

Cellulose nanocrystals (CNCs)

CNC is less flexible than NFC because it lacks amorphous regions.[21] Acid hydrolysis is commonly used to isolate them from cellulose fibres.[24,25] The most widely used approach for producing CNCs is to hydrolyse cellulose with 60–64 weight percent H_2SO_4 at temperatures ranging from 45 to 60 °C.[26] A higher fraction of the amorphous areas is eliminated during acid hydrolysis, and CNC is considered to be more rigid than CNF, owing to its high crystallinity.[27,28]

The features and quality of the CNCs produced are influenced by the source material, along with hydrolysis environment, which includes type of acids, concentration, temperature, duration, and acid to cellulose ratio.[29]

Bacterial nanocellulose (BNC)

Bacterial nanocellulose (BNC) has the same molecular structure as cellulose generated from

plants, but unlike plant-derived nanocellulose, it is biosynthesized extracellularly by specific bacterial strains.[4] Bacteria that generate cellulose, such *Gluconacetobacter* species, mostly require aqueous culture conditions with a sugar supply.[30,31] This procedure might take from a few days to many weeks to complete, under static or stirred culture conditions.[32,36] By a biological process, these bacteria transform glucose to cellulose,[33] resulting in an ultra-pure cellulose network free from lignin and hemicelluloses. This intrinsic purity contributes to its high crystallinity, superior water-holding capacity, and excellent biocompatibility. By manipulation in bacterial culture conditions, the formation of controllable and desired microfibrils is possible.[34,35]

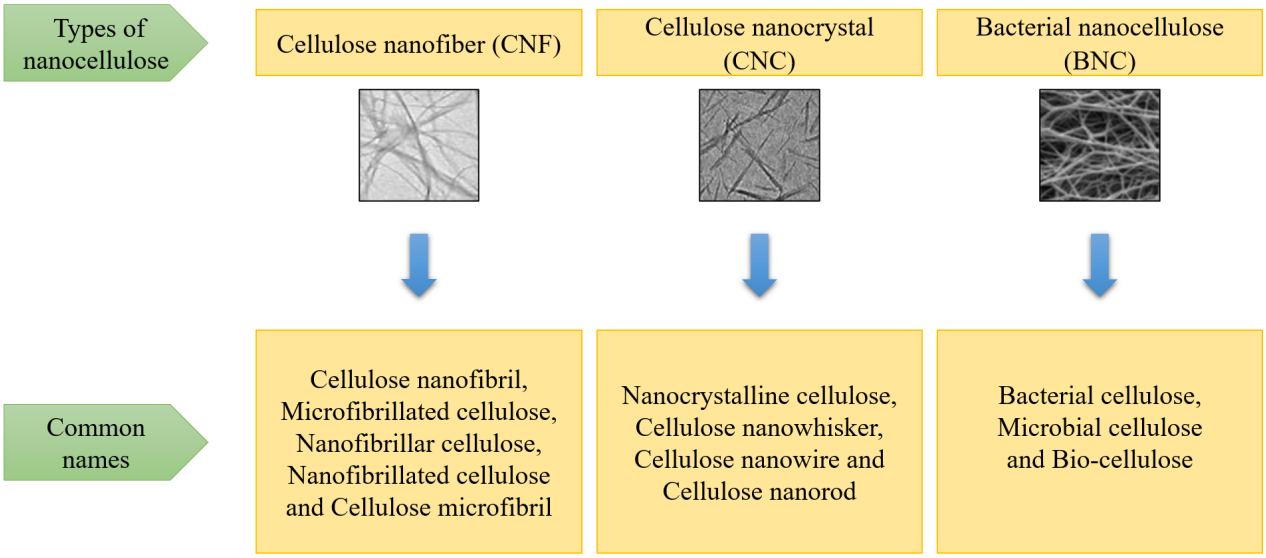

Figure 2: Types of nanocellulose, their morphology and common names

METHODS OF NANOCELLULOSE ISOLATION

Chemical treatments

Chemical treatments remove hemicelluloses and lignin, improves cellulose quality, and improves fibrillation and the transformation of cellulose fibre into micro/nanofibrils.[37] The numerous impurities (*e.g.*, lignin, hemicelluloses, pectin, and wax) serve as a structural barrier that prevents accessing the cellulose material.[38] Pretreatment is often required to eliminate contaminants from the cellulose framework, to provide access to its microstructure.[40] Furthermore, eliminating contaminants reduces the energy consumption of mechanical treatment for cellulose disintegration.[39,43] The pretreatment is beneficial for both the separation of CNFs and the acid hydrolysis extraction of CNCs, and it is mostly reliant on the source of the cellulose.[41] Due to its benefits, the importance of pretreatment in cellulose extraction was heavily explored. To attain the desired efficiency, multiple treatment techniques or methods must be used.[42]

Mechanical treatment

The purpose of mechanical treatment is to achieve defibrillation – to break down cellulose into elementary fibrils. For this, different approaches, with a variety of specific equipment, can be used, including grinding, microfluidization, high-pressure homogenization,[61,62] cryo-crushing, high-intensity ultrasonication,[6] ball milling, steam explosion *etc*.[63]

High-pressure homogenization (HPH)

Microfibrillated cellulose is frequently obtained using a homogenizer. This includes high pressure pumping of the cellulose suspension, which is supplied via a valve assembly with spring load to be used in the homogenizer process. There is substantial drop in the pressure exerted on the fibre with significant shearing force due to the quick opening and closing of the valve.[64] The crushing forces of material particles striking one other, shear forces on particles within interaction chambers, and cavitational forces caused by high-velocity

variations in the material stream are all used to reduce the particle size of cellulose fibrils.[65]

Table 1
Various types of chemical treatments

Treatment	Remarks	Ref.
Alkali	The primary objective is to enable lignin solubilization and depolymerisation, as well as hydrolysis of hemicelluloses, which will expose cellulose and make it more accessible to subsequent processes.	42, 44
Bleaching	Bleaching is necessary to remove any remaining lignin. This procedure is regarded as an essential step since it enhances the surface properties of pure cellulose fibres. Hydrogen peroxide (H_2O_2), chlorine dioxide (ClO_2), ozone (O_3), sodium hypochlorite (NaClO), or peracetic acid (CH_3CO_3H) are used to bleach the alkali-treated fibres.	45, 46
Enzymatic	Enzymes can be used for the degradation of hemicelluloses and lignin, with better retention of cellulose structure and removal of noncellulosic content. A variety of enzymes are utilised: endoglucanases attack the amorphous regions, cellobiohydrolases degrade cellulose. Enzymatic hydrolysis helps minimize excessive cellulose chain breakdown into glucose.	47, 48, 49
TEMPO-mediated oxidation	This is an effective way to change the surface of native cellulose. Under aqueous and moderate conditions, aldehyde and carboxylate functional groups can be incorporated into solid native cellulose. It helps avoid post-aggregation of nanoparticles during the drying step, preventing nanofibril separation due to repulsive forces of ionized carboxylate groups.	50, 51, 52
Ionic liquids (ILs)	Ionic liquids (ILs) have the ability to selectively break down hemicelluloses and lignin or solubilize the complete cellulosic biomass. They break intramolecular hydrogen bonds and minimize cellulose crystallinity. They have a high dissolving capacity, have low toxicity or no toxicity at all, non-flammability, chemical and thermal stability, and low vapour pressure – these are just a few of the valuable qualities they possess.	53,54,55,56
Deep eutectic solvents (DESs)	These are eutectic mixtures, made up two or more eutectic compounds bound together by hydrogen linkages, with chemical and physical properties similar to those of ILs. DESs are capable to selectively eliminating lignin, while maintaining the integrity of the cellulose and hemicellulose fractions.	57, 58
Organosolv	This method depolymerizes lignin and hemicelluloses using acetone, ethylene glycol, acetic/formic acid and ethanol, making it easier for obtaining higher-purity cellulose. These solvents break down lignin, causing the linkages between cellulose and hemicelluloses to break down. This process has the benefit of reusing the solvents.	59, 60, 42

Microfluidization

A microfluidizer, like the HPH, can be used to make nanofibrillar cellulose. The microfluidizer has two main components, namely intensifier pump and interaction chamber, used for pressure raising and defibrillation of the fibres via application of impact and shear forces for collidation of stream and channel walls, respectively. Microfluidization could produce nanofibers with a more uniform size distribution, according to morphological characterizations.[66]

Grinding

The structure of the cell wall is broken due to shearing pressures created by the grinding stone rotation at a high speed. A rotating grindstone and a static grindstone are used to mill the pulp.[67] Grinding applies shear forces on cellulose, which are ultimately responsible for breaking hydrogen bonds and overall cell wall structure, resulting in the individualization of pulp into nanoscale fibres.[68]

Cryocrushing

The process of cryocrushing was reported in 1997.[69] Typically, this method entails crushing frozen pulp with liquid nitrogen.[70] In brief, initially cellulose fibres are soaked in water (steeping) for swelling. Afterwards, they are introduced into liquid nitrogen and then crushed using a mortar and pestle.[71] When significant impact pressures are applied to frozen cellulosic fibres, the cell wall is ruptured due to ice crystal pressure, resulting in nanofibers.[68,72]

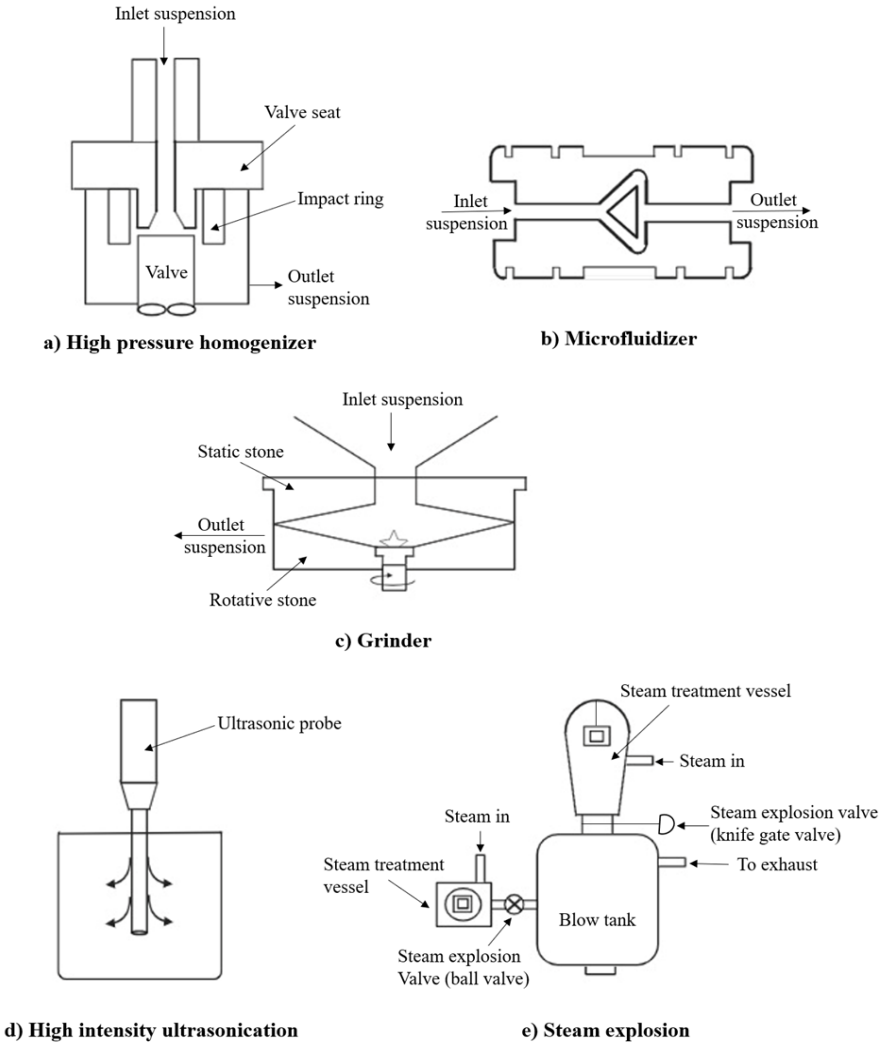

Figure 3: Schematic diagrams of different mechanical treatment equipment

Table 2
Methods used for nanocellulose isolation

Raw material	Type of pre-/treatment	Mechanical treatment	Refs
Mature culms of Moso bamboo	Alkaline and bleaching	Grinding	75
Rice straw	Alkaline and bleaching	High-pressure homogenization	76
Citrus waste	Alkaline, bleaching and enzymatic	Ultrasonication	77
Agave tequilana bagasse	Alkaline, bleaching and Organosolv	Microfluidization	78
Hemp fibres	Alkaline and bleaching	Cryo-crushing	79
Oryza sativa residues	Alkaline, bleaching and TEMPO-mediated oxidation	Ultrasonication	80
Kraft pulp	Deep eutectic solvents (DESs)	Ultrasonication	81
Microcrystalline cellulose	Ionic liquids (ILs)	-	82
Raw banana, jute and pineapple leaf fibres	Alkaline and bleaching	Steam explosion	83
Cellulose powder	Ionic liquids (ILs)	Ball milling	84

High-intensity ultrasonication

High-intensity ultrasonication (HIUS) is a mechanical process that isolates cellulose fibrils by utilising the hydrodynamic forces of ultrasound.[73] Strong mechanical oscillating power produces high intensive waves.[74] This results in the formation, expansion and implosion of microscopic gas bubbles that lead to fragmentation of cellulose fibres as they absorb ultrasonic energy.

Ball milling

The cellulose slurry is stirred inside a cylindrical body in the presence of balls. The cellulose is disintegrated as a result of the high-energy collision between the balls. CNF quality is influenced by ball weight and ball size ratios in comparison to cellulose.[63]

Steam explosion

The cellulose fibre wall is broken using high-pressure steam and a fast release of pressure. Traditionally, this technique has been employed to separate cellulose from lignocellulosic materials. The quality of CNF is inferior to that obtained by other processes.[63]

SURFACE MODIFICATION OF NANOCELLULOSE

Esterification/acetylation

The most well-studied esterification process is the acetylation of nanocellulose. The partial replacement of hydroxyl groups and incorporation of acetyl moieties is the fundamental mechanism of acetylation.[85] Using catalysts like perchloric acid/sulphuric acid and a combination of dry acetic acid and acetic anhydride, the functionalization of nanocellulose's surface by the addition of acetyl groups was carried out.[86,87] The most accessible OH groups on the surface or/and in the amorphous/disordered areas of nanocellulose are used in the initial stage of acetylation. The acetylation process then proceeds onto hydroxy groups that are less accessible, like those found within the cellulose structure.[88,89] Acetylation increases the dispersion of cellulose nanofibres in nonpolar polymeric matrices, by minimizing hydrogen bonding between molecules.[90]

Silylation

Silylation is the addition of hydrophobic alkyl moieties to the surface of nanocelluloses, such as alkoxy silanes or chlorosilanes. Silylation occurs by the interaction of silane coupling agent with the hydroxyl groups on nanocellulose's surface.[91] The OH groups are altered with alkoxyl groups during hydrolysis of nanocellulose using catalyst at an alkaline, acidic, or neutral pH. During silylation, hydrolysis and condensation processes occur.[42] For the modification of nanocellulose in the production of composite materials, a large variety of organofunctional silanes have been studied. Isopropyl dimethyl chlorosilane, triethoxy vinyl silane, noctyl dimethyl chlorosilane, n-butyl dimethyl chlorosilane, n-dodecyl dimethyl chlorosilane, hexamethyl disilazane, and 3-aminopropyltriethoxysilane are some of these.[92]

Sulfonation

The most popular method for introducing sulphate groups into nanocellulose's hydroxyl moieties is sulfonation, which results in a strongly negatively charged surface. Sulfuric acid hydrolysis is still the most common method of nanocellulose modification.[62] The hydrolysis of nanocellulose is catalysed by sulfuric acid, which results in CNCs with sulphate half ester moieties replacing the hydroxyl groups.[93] The sulphate half ester groups present on CNCs carry a negative charge, which enhances its distribution in the liquid medium. This happened by limiting the hydrogen bond formation between cellulose molecules. With this, induced anionic group's electrostatic repulsion is also responsible for this.[94] Temperature, acid concentration, and hydrolysis time are all significant factors in sulfonation.[95,96]

Phosphorylation

Nanocellulose is generally phosphorylated *via* the reaction between an inorganic phosphoric acid and cellulosic pulp. Phosphorylation is commonly performed in the presence of dimethylformamide, urea, or pyridine.[97] The nanocellulose surface is modified by introducing negatively charged phosphite esters or phosphate.[98] The phosphorylation is usually performed under conditions of temperature, time and concentration of 100 °C and 90 minutes and 74 wt% of phosphoric acid, respectively. Surface charge densities in phosphorylated CNCs are nearly 2 orders lower than sulphated CNCs.[99]

Carbamation

Carbamation also called carbanylation or urethanization. Urethane linkage is produced due to the interaction of OH groups with an isocyanate group.[100] Strong reactions occur between the isocyanate moiety (-NCO) and a number of functional moieties like OH, COOH, and NH_2.

Nanocellulose has been modified using aromatic and aliphatic mono-isocyanates, *viz.* n-octadecyl and phenyl isocyanate, as well as di-isocyanates, such as diphenylmethane diisocyanate (MDI), hexamethylene diisocyanate (HMDI), and toluene diisocyanate (TDI). The process is distinguished from other methods of modification by a number of distinctive features, including high reaction rate, short reaction time, no side products and post-reaction urethane bonds with good chemical stability.[101]

TEMPO-mediated oxidation

This technique of surface modification has been discussed in detail above. TEMPO-mediated oxidation is an efficient technique to increase the stability of CNCs in aqueous suspensions, by introducing negative charges to their surfaces.[102] In alkaline conditions (pH between 9-11), catalysts such as NaBr and NaClO are frequently used for TEMPO-mediated oxidation treatment.[103]

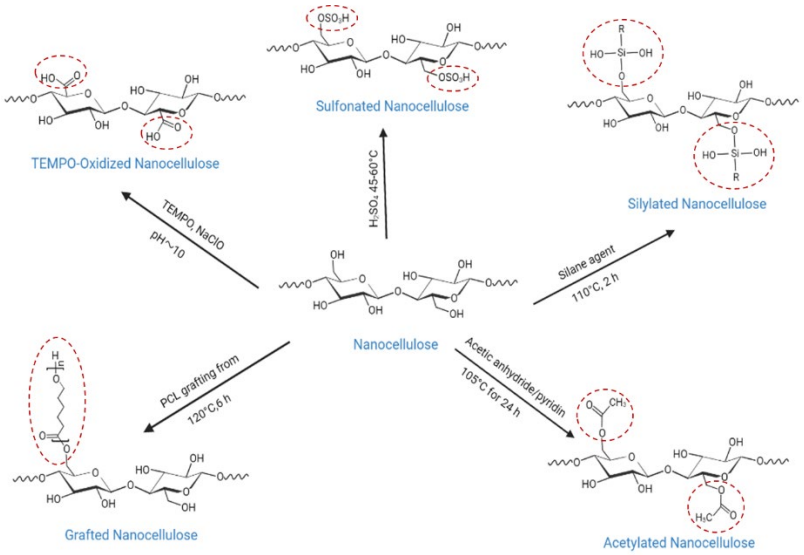

Figure 4: Surface modification routes for nanocellulose

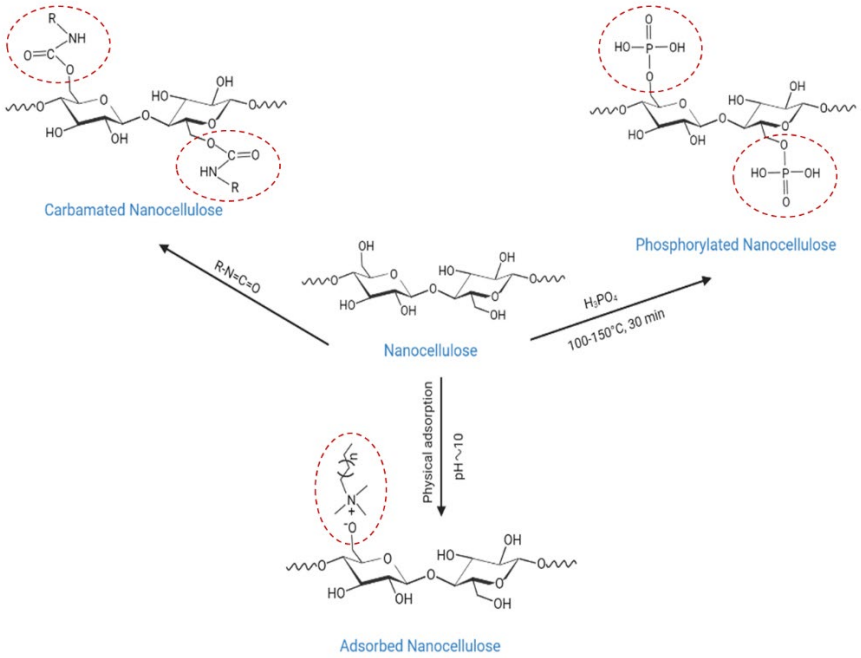

Figure 5: Surface modification routes for nanocellulose

Polymer grafting

"Grafting onto" and "grafting from" are the two types of polymer grafting techniques.[63,86] The "grafting onto" method involves covalently attaching a polymer and linker to the nanocellulose's reactive end group.[45] Direct growth of polymer grafts on the surface of nanocellulose is achieved in the "grafting from" method. In comparison to the "grafting onto" method, the "grafting from" method may produce polymer grafts with a greater density.[104,105] Polymers like polycaprolactone, polylactic acid, polymethyl methacrylate, polyhydroxy alkanoates, polyurethanes, and maleated polypropylene are utilised in both grafting techniques with cellulose.[92] Because the type of grafted polymers might alter the interfacial characteristics, surface grafting is expected to be an efficient as well as adaptable way of achieving a very stable suspension in non-polar media.[104,105]

Non-covalent surface modification

Over chemical modification, adsorption of surfactants on nanocellulose is one of the possible alternatives. Cationic, anionic, zwitterionic, and nonionic surfactants are different types of surfactants that can be used.[62] Surfactants or molecules with opposite charges adhere to the surface of nanocellulose, causing non-covalent surface modifications.[106,107] Electrostatic contacts, hydrophobic interactions, van der Waals forces, and the hydrogen bonds are just a few of the reversible associations that are used in these interactions.[108] Mere physical interaction due to non-covalent bonds is more environmentally friendly as it requires less use of chemicals. Introducing surfactants is a simple and non-covalent approach to improving nanocellulose dispersion in nonpolar matrices. To manage the degree of contact, this approach may be adjusted by modifying the nature and concentration of surfactants.[86] Distribution of nanocellulose in matrix containing non-polar polymer is made possible as its dispersion in water facilitates the spontaneous adsorption of surfactant on its surface. Nanocellulose and surfactant are connected by simple ionic bonds or mere physical adsorption forces, which are weaker and can be readily broken.[109]

APPLICATIONS OF NANOCELLULOSE

Nanocellulose-based products have a wide range of applications in daily life. These include food additives, barrier coatings in paper, reinforcement in composites for the automotive and building industries. Nanocellulose has outstanding electrical and photonic properties to be used in photonic films, recyclable electronics, 3D printing and organic LEDs. The wide range of uses for nanocellulose is due to its outstanding properties, which include nontoxicity, dimensional stability, lightweight, thermal conductivity, thermal stability, reusability, environmental friendliness, biodegradability, and recyclability.[98,110,111]

Due to its low production costs, outstanding mechanical properties, large surface area, easy chemical modifications, biocompatibility and absence of toxicity, nanocellulose is frequently used in biomedical applications.[110,112] Some of the uses in the biomedical area include drug carriers, implants, scaffolds for tissue regeneration and repair, wound dressing materials, and in biosensing and bioimaging.

Drug delivery systems

Drug delivery systems using nanocellulose structures have been develop to modify the drug release rates and the quantity of drugs to reach the targeted site. [113] The interactions of the drug with nanocellulose play an important role in ensuring drug stability and the release of the medication.[114] Nanocellulose has been reported as a drug carrier for different administration routes, including oral, transdermal, ocular, topical, and intratumoral (Fig. 6).[115] The carriers ensure release times ranging from a few minutes to days, according to the literature.[116,117]

Oral delivery

The benefits of the oral route include convenience, comfort of use, safety, non-invasiveness and low cost. This makes oral delivery a preferred method of delivery, especially for chronic conditions that need repeated drug administration. The efficient administration of drug dosage forms is, however, constrained by a number of issues, including hydrolysis, limited intestinal epithelial permeability in the gastrointestinal (GI) tract and enzymatic degradation.[118-120] Innovative approaches overcome these oral delivery-related restrictions and enhance the bioavailability of drugs that are taken orally. In novel drug delivery systems, nanocellulose can be used as a carrier or an excipient due to its distinct features. It has excellent compaction capabilities and may be

combined with other pharmaceutical excipients in a hybrid system.[113]

Topical delivery

The major goal of applying for medicine topically is to administer the treatment directly to skin regions that are injured, irritated, infected, itching, or inflamed. Topical drug delivery provides a number of benefits, including the ability to administer a particular medicine to a specific location, prevention of drug level changes, increased patient compliance, and ability to self-medicate.[121] To get beyond the drawbacks of current topical dose forms, such as limited bioavailability and poor retention, innovative topical drug delivery methods have been developed. Unlike conventional topical drug dose formulations, nanocellulose-based topical drug delivery systems were created as wound dressings or bandages for infected cutaneous wounds. Cellulose nanowhiskers, bacterial cellulose or CNCs are employed in topical medication delivery systems. Membranes, biocomposite films or bilayer-based topical drug delivery systems have been developed to deliver the drugs directly to the wounded area.[122-128] By incorporating nanocellulose into such systems, it is possible to prolong drug release, boost therapeutic effectiveness, and enhance the mechanical qualities of the finished product.[115]

Transdermal delivery

Due to its special characteristics, nanocellulose has the potential to be used in transdermal medication delivery systems.[4] The transdermal drug delivery system (TDDS) allows for systemic drug distribution via the skin to reach therapeutic concentrations. In this way, the medicine avoids the liver and gastrointestinal system, providing therapeutic effects at lower dosages.[15] The primary TDDS, however, is not able to administer larger drugs, which restricts its usage. The skin can only be penetrated by small molecules.[134]

Ocular delivery

Due to the unique anatomy of the eye, effective medication distribution is difficult (*e.g.*, the *substantia propria*, endothelium and epithelium of the human cornea). The eye has a number of defences to prevent the entrance of foreign objects or drug molecules, including nasolacrimal drainage, protein binding, tear turnover, enzymatic destruction and complex penetration barriers (*e.g.*, corneal barrier, blood-retinal barrier and blood-aqueous barrier).[129] Therefore, the drug's bioavailability during topical ocular administration is extremely low (less than 5%), especially for eye drops that will be removed from the eye after application.[130] On the other hand, the requirement for a higher dosage or administration frequency of the drug may result in the development of side effects. An ophthalmic drug delivery system (ODDS) with the capacity to increase ocular residence time is important to address these issues. In topical ophthalmic dosage forms, polymers including cellulose, xanthan gum, pectin, and alginate are frequently utilised.[131] According to research, macromolecule gel formulations based on cellulose have high viscosity and therefore can extend corneal residence duration.[132] Ophthalmic drug delivery systems in the form of an *in situ* produced hydrogel, which is sensitive to pH, ionic strength, and temperature, represent a promising approach. They are used topically as eye drops, and turn into a hydrogel *in situ* upon coming into contact with the eye.[133]

Recent advanced applications

Beyond traditional carrier systems, nanocellulose's biological usefulness has greatly increased in recent years. To enable next-generation biomedical platforms, current research focuses on precise surface modification, multifunctionality, stimuli responsiveness, and biointeractive interfaces, whereas previous studies prioritized extraction, isolation, and fundamental functionalization. The adjustable surface hydroxyl groups that nanocellulose, including BNC, CNC, and CNF, offers enable polymer grafting, esterification, click chemistry, silanization, and regioselective oxidation (such as TEMPO-mediated). Controlled drug conjugation, biomolecule immobilization, and customized cell–material interactions are made possible by these alterations. Recent research demonstrates how these designed systems may be translated into cutting-edge medicinal and regenerative platforms.[136-139]

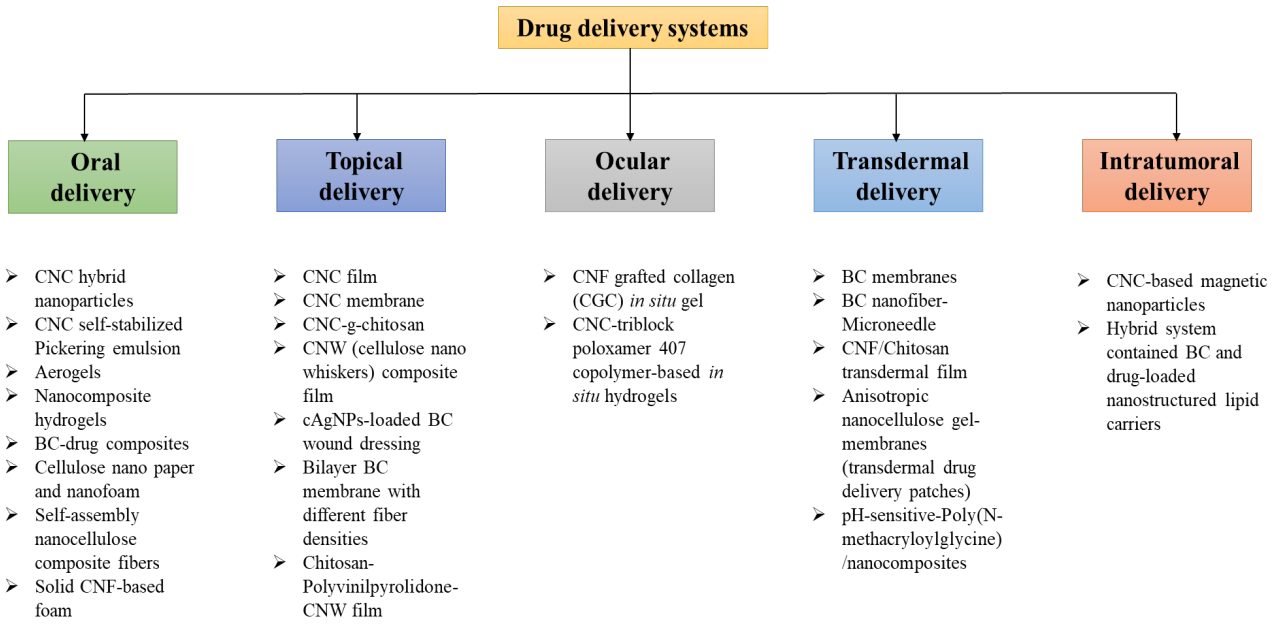

Figure 6: Nanocellulose in drug delivery applications

Advanced drug delivery platforms

The focus of recent developments has been on stimuli-responsive nanocellulose systems that can be released when exposed to light, pH, temperature, redox, or enzymes. Electrostatic drug binding and pH-sensitive desorption are improved by surface carboxylation by TEMPO oxidation, which is especially helpful in tumor microenvironments. The integration of nanocellulose with redox-cleavable linkers or thermosensitive polymers (like PNIPAM) in dual-responsive hydrogels has shown regulated anticancer drug release with less systemic toxicity.[140] Targeting ligands (peptides, antibodies, and folic acid) can be surface-grafted to facilitate receptor-mediated uptake in cancer treatment. Enhanced cellular uptake and increased cytotoxic selectivity have been demonstrated by CNC-based hybrid nanocarriers decorated with folate moieties in models of colon and breast cancer.[96] Controlled degradation patterns and great drug-loading efficiency are combined in these systems. Shear-thinning CNF/BNC hydrogels that may be injected are becoming popular for localized delivery of growth factors, biologics, and chemotherapy drugs. Their prolonged release kinetics and less invasive administration are made possible by their *in-situ* gelation and rheological tunability. Applications in post-surgical localized drug depots and intratumoral treatment are highlighted in recent papers.[141]

Tissue engineering and regenerative medicine

The incorporation of nanocellulose into 3D bioprintable bioinks is among the most important recent advancements. Cell survival, mechanical integrity, and print fidelity are all enhanced by surface-modified CNF. To create cartilage, skin, and vascular constructions with enhanced structural stability, composite bioinks including nanocellulose and either alginate or gelatin methacrylate (GelMA) have been employed.[142] TEMPO-oxidized CNF promotes the growth and development of mesenchymal stem cells (MSCs) and increases crosslinking efficiency. According to recent research, nanocellulose-based scaffolds exhibit osteogenic and chondrogenic differentiation, suggesting potential for bone and cartilage restoration.[143]

Nanocellulose is being used with conductive polymers (such as polypyrrole, PEDOT:PSS) or graphene derivatives to treat electrically active tissues (heart and nerve). These hybrid scaffolds help with brain regeneration and cardiac tissue repair because they have enhanced electrical conductivity while maintaining mechanical flexibility and biocompatibility.[144,145] Surface functionalization with peptides, growth factors, or extracellular matrix (ECM) components alter macrophage polarization and facilitates regenerative repair, according to recent studies. These bioactive nanocellulose scaffolds are

essential for chronic wound and implant integration because they improve angiogenesis and decrease inflammatory responses.[146,147]

Wound healing and antimicrobial platforms

A growing number of contemporary wound dressings use nanocellulose as a biointeractive, mechanically stable, and moisture-retentive matrix. Current developments include antibacterial composites functionalized with zinc oxide or chitosan, nanocellulose membranes loaded with silver nanoparticles (AgNPs), growth factor-embedded nanocellulose dressings, and oxygen-releasing and hemostatic nanocellulose systems. In diabetic wound models, surface-modified BNC dressings show quicker re-epithelialization, regulated exudate absorption, and lower infection rates.[141,148,149] Therapeutic results are further improved by integration with bioactive molecules like VEGF and antimicrobial peptides.

Biosensing and bioimaging applications

Nanocellulose with surface engineering is becoming more popular in wearable and flexible biosensors. Enzymes, antibodies, and fluorescent probes may all be immobilized due to the high surface area and tunable hydroxyl groups. CNC-based electrochemical glucose sensors, nanoparticles with plasmonic properties supported by nanocellulose for colorimetric detection, fluorescently tagged nanocellulose for cellular tracking and bioimaging, and flexible paper-based microfluidic diagnostic devices are examples of recent advancements. Electrical conductivity and sensitivity are enhanced by functionalization with carbon nanotubes or gold nanoparticles.[150,151] These systems complement customized medical approaches and point-of-care diagnostics.

Implantable and load-bearing biomedical devices

Due to its great tensile strength and structural resemblance to collagen, bacterial nanocellulose has promise for use in artificial *dura mater* replacements, vascular grafts, hernia meshes, and tympanic membrane repair. For vascular implants, surface modification enhances endothelialization and hemocompatibility. Increased endothelial cell adhesion to carboxylated BNC surfaces has been reported in recent preclinical investigations.[152,153] For bone implant applications, hybrid nanocellulose composites supplemented with bioactive ceramics (hydroxyapatite) exhibit enhanced mechanical robustness and osteoconductivity.[12,154]

Emerging frontiers

Nanocellulose is a potential substrate for CRISPR/Cas and nucleic acid delivery, including mRNA systems, according to recent transdisciplinary developments. Surface-functionalized cellulose nanofibrils and nanocrystals boost intracellular transport efficiency, prevent enzymatic degradation, and promote gene complexation.[96,155,156] Precision medicine-related electrostatic and covalent conjugation methods are supported by their changeable surface chemistry. Additionally, nanocellulose scaffolds are being investigated for regulated regeneration signaling and exosome loading,[147] and their incorporation into flexible biosensors indicates promise for precision diagnostics.[151]

The rational approach of nanocellulose composites is currently guided by structure-property optimization and AI-assisted material modeling. Drug binding, cell adhesion, immunomodulation, and mechanical reinforcement are all significantly impacted by parameters such crystallinity, surface charge, and degree of oxidation.[12,139] Translational feasibility is being advanced at the same time by scalable and sustainable production methods.[152,157] In order to facilitate clinical translation, more attention is paid to *in vivo* biodegradation, sterilization stability, and regulatory compliance. While standardized physicochemical characterization and biological evaluation are still necessary for reproducibility and regulatory acceptance, injectable and biodegradable nanocellulose hydrogels show promising biocompatibility and structural stability.[141]

CONCLUSION

This work offers a review of extraction, isolation, and functionalization routes of nanocellulose. Pretreatments have an important role in removing non-cellulosic components (like lignin and hemicelluloses) and other impurities, to enable further isolation of high-quality nanocellulose. Mechanical treatment is often used for the isolation of CNF, in combination with other methods. Its major disadvantage is its high energy consumption, therefore, it is complemented by chemical treatment.

The adjustable surface hydroxyl groups that nanocellulose, including BNC, CNC, and CNF, offers enable its surface modification through polymer grafting, esterification, click chemistry,

silanization, and regioselective oxidation (such as TEMPO-mediated). Surface modification techniques facilitate the dispersion of nanocellulose both in hydrophilic and hydrophobic polymer matrices. Surface modification and functionalization can also increase the adsorption capacity of nanocellulose. Due to such modifications, nanocellulose's biological usefulness has greatly increased in recent years much beyond traditional drug carrier systems. Thus, controlled drug conjugation, biomolecule immobilization, and customized cell–material interactions are made possible by these alterations. Recent research demonstrates how these designed systems may be translated into cutting-edge medicinal and regenerative platforms. This review is deemed as a starting point for budding investigators with an interest in nanocellulose research.

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REFERENCES

[1] M. M. de Souza Lima and R. Borsali, *Macromol. Rapid Commun.*, **25**, 771 (2004), https://doi.org/10.1002/marc.200300268
[2] Y. Wang, X. Wang, Y. Xie and K. Zhang, *Cellulose*, **25**, 3703 (2018), https://doi.org/10.1007/s10570-018-1830-3
[3] H. Du, W. Liu, M. Zhang, C. Si, X. Zhang *et al*., *Carbohyd. Polym*., **209**, 130 (2019), https://doi.org/10.1016/j.carbpol.2019.01.020
[4] N. Raghav, M. R. Sharma and J. F. Kennedy, *Carbohyd. Polym. Technol. Appl*., **2**, 100031 (2021), https://doi.org/10.1016/j.carpta.2020.100031
[5] D. Pathania, D. Gupta, N. C. Kothiyal, G. E. Eldesoky and M. Naushad, *Int. J. Biol. Macromol*., **84**, 340 (2016), https://doi.org/10.1016/j.ijbiomac.2015.12.041
[6] H. A. Khalil, Y. Davoudpour, M. N. Islam, A. Mustapha, K. Sudesh *et al*., *Carbohyd. Polym*., **99**, 649 (2014), https://doi.org/10.1016/j.carbpol.2013.08.069
[7] N. Lin and A. Dufresne, *Eur. Polym. J*., **59**, 302 (2014), https://doi.org/10.1016/j.eurpolymj.2014.07.025
[8] A. B. Seabra, J. S. Bernardes, W. J. Fávaro, A. J. Paula and N. Durán, *Carbohyd. Polym*., **181**, 514 (2018), https://doi.org/10.1016/j.carbpol.2017.12.014
[9] N. Mahfoudhi and S. Boufi, *Cellulose*, **24**, 1171 (2017), https://doi.org/10.1007/s10570-017-1194-0
[10] Y. Habibi, L. A. Lucia and O. J. Rojas, *Chem. Rev*., **110**, 3479 (2010), https://doi.org/10.1021/cr900339w
[11] A. D. French, *Cellulose*, **24**, 4605 (2017), https://doi.org/10.1007/s10570-017-1450-3
[12] S. Tortorella, V. V. Buratti, M. Maturi, L. Sambri, M. C. Franchini *et al*., *Int. J. Nanomed*., **15**, 9909 (2020), https://doi.org/10.2147/IJN.S266103
[13] V. Gupta, P. Carrott, R. Singh, M. Chaudhary and S. Kushwaha, *Bioresour. Technol*., **216**, 1066 (2016), https://doi.org/10.1016/j.biortech.2016.05.106
[14] M. R. Mozafari, "Nanocarrier Technologies: Frontiers of Nanotherapy", Springer, 2006, https://doi.org/10.1007/978-1-4020-5041-1
[15] M. Jawaid and F. Mohammad, "Nanocellulose and Nanohydrogel Matrices: Biotechnological and Biomedical Applications", John Wiley & Sons, 2017, https://doi.org/10.1002/9783527803835
[16] A. Dufresne, "Nanocellulose: From Nature to High Performance Tailored Materials", Walter de Gruyter GmbH & Co KG, 2017, https://doi.org/10.1515/9783110254600
[17] M. J. Mitchell, M. M. Billingsley, R. M. Haley, M. E. Wechsler, N. A. Peppas *et al*., *Nat. Rev. Drug Discov*., **20**, 101 (2021), https://doi.org/10.1038/s41573-020-0090-8
[18] A. Farooq, M. K. Patoary, M. Zhang, H. Mussana, M. Li *et al*., *Int. J. Biol. Macromol*., **154**, 1050 (2020), https://doi.org/10.1016/j.ijbiomac.2020.03.163
[19] A. F. Turbak, F. W. Snyder and K. R. Sandberg, *J. Appl. Polym. Sci. Appl. Polym. Symp*., **37**, 815 (1983)
[20] F. W. Herrick, R. L. Casebier, J. K. Hamilton and K. R. Sandberg, *J. Appl. Polym. Sci. Appl. Polym. Symp*., **37**, 797 (1983)
[21] L. Brinchi, F. Cotana, E. Fortunati and J. M. Kenny, *Carbohyd. Polym*., **94**, 154 (2013), https://doi.org/10.1016/j.carbpol.2013.01.033
[22] D. Klemm, F. Kramer, S. Moritz, T. Lindström, M. Ankerfors *et al*., *Chem. Int. Ed*., **50**, 5438 (2011), https://doi.org/10.1002/anie.201001273
[23] K. Kriechbaum, P. Munier, V. Apostolopoulou-Kalkavoura and N. Lavoine, *ACS Sustain. Chem. Eng*., **6**, 11959 (2018), https://doi.org/10.1021/acssuschemeng.8b02278
[24] A. Bhatnagar and M. Sain, *J. Reinf. Plast. Compos*., **24**, 1259 (2005), https://doi.org/10.1177/0731684405049864
[25] E. D. Cranston and D. G. Gray, *Biomacromolecules*, **7**, 2522 (2006), https://doi.org/10.1021/bm0602886
[26] M. Pereda, A. Dufresne, M. I. Aranguren and N. E. Marcovich, *Carbohyd. Polym*., **101**, 1018 (2014), https://doi.org/10.1016/j.carbpol.2013.10.046
[27] R. H. Atalla, J. W. Brady, J. F. Matthews, S. Y. Ding and M. E. Himmel, "Biomass Recalcitrance: Deconstructing the Plant Cell Wall for Bioenergy", 2009, p. 188
[28] M. J. John and S. Thomas, *Carbohyd. Polym*., **71**, 343 (2008), https://doi.org/10.1016/j.carbpol.2007.05.040
[29] D. O. Klemm, T. Lindström, T. Abitbol and D. Kralisch, "Nanocellulose Based Composites for

Electronics", Elsevier, 2021, https://doi.org/10.1016/B978-0-12-822350-5.00001-1
[30] C. Sharma and N. K. Bhardwaj, *Mater. Sci. Eng. C*, **104**, 109963 (2019), https://doi.org/10.1016/j.msec.2019.109963
[31] A. Cañas-Gutiérrez, M. Osorio, C. Molina-Ramírez, D. Arboleda-Toro and C. Castro-Herazo, *Cellulose*, **27**, 9737 (2020), https://doi.org/10.1007/s10570-020-03456-4
[32] Z.-Y. Wu, H.-W. Liang, L.-F. Chen, B.-C. Hu and S.-H. Yu, *Acc. Chem. Res.*, **49**, 96 (2016), https://doi.org/10.1021/acs.accounts.5b00380
[33] Y. Huang, C. Zhu, J. Yang, Y. Nie, C. Chen *et al.*, *Cellulose*, **21**, 1 (2014), https://doi.org/10.1007/s10570-013-0088-z
[34] M. Nogi and H. Yano, *Adv. Mater.*, **20**, 1849 (2008), https://doi.org/10.1002/adma.200702559
[35] C. Tokoh, K. Takabe, M. Fujita and H. Saiki, *Cellulose*, **5**, 249 (1998), https://doi.org/10.1023/A:1009211927183
[36] A. F. Jozala, L. C. de Lencastre-Novaes, A. M. Lopes, V. de Carvalho Santos-Ebinuma, P. G. Mazzola *et al.*, *Appl. Microbiol. Biotechnol.*, **100**, 2063 (2016), https://doi.org/10.1007/s00253-015-7243-4
[37] M. Visanko, H. Liimatainen, J. A. Sirviö, J. P. Heiskanen, J. Niinimäki *et al.*, *Biomacromolecules*, **15**, 2769 (2014), https://doi.org/10.1021/bm500628g
[38] S. Salimi, R. Sotudeh-Gharebagh, R. Zarghami, S. Y. Chan and K. H. Yuen, *ACS Sustain. Chem. Eng.*, **7**, 15800 (2019), https://doi.org/10.1021/acssuschemeng.9b02744
[39] H. Kargarzadeh, M. Ioelovich, I. Ahmad, S. Thomas and A. Dufresne, in "Handbook of Nanocellulose and Cellulose Nanocomposites", edited by H. Kargarzadeh, I. Ahmad, S. Thomas and A. Dufresne, Wiley-VCH, 2017, https://doi.org/10.1002/9783527689972.ch1
[40] Y.-L. Loow, T. Y. Wu, K. A. Tan, Y. S. Lim, L. F. Siow *et al.*, *J. Agric. Food Chem.*, **63**, 8349 (2015), https://doi.org/10.1021/acs.jafc.5b01813
[41] E. Dinand, H. Chanzy and M. R. Vignon, *Cellulose*, **3**, 183 (1996), https://doi.org/10.1007/BF02228800
[42] K. Dhali, M. Ghasemlou, F. Daver, P. Cass and B. Adhikari, *Sci. Total Environ.*, **775**, 145871 (2021), https://doi.org/10.1016/j.scitotenv.2021.145871
[43] G. Chinga-Carrasco, *Nanoscale Res. Lett.*, **6**, 417 (2011), https://doi.org/10.1186/1556-276X-6-417
[44] D. P. Maurya, A. Singla and S. Negi, *3 Biotech*, **5**, 597 (2015), https://doi.org/10.1007/s13205-015-0279-4
[45] H.-M. Ng, L. T. Sin, T.-T. Tee, S.-T. Bee, D. Hui *et al.*, *Compos. Part B Eng.*, **75**, 176 (2015), https://doi.org/10.1016/j.compositesb.2015.01.008
[46] S. Nandi and P. Guha, *J. Packag. Technol. Res.*, **2**, 149 (2018), https://doi.org/10.1007/s41783-018-0036-3
[47] S. Janardhnan and M. M. Sain, *BioResources*, **1**, 176 (2006), https://doi.org/10.15376/biores.1.2.176-188
[48] A. K. Kumar and S. Sharma, *Bioresour. Bioprocess.*, **4**, 7 (2017), https://doi.org/10.1186/s40643-017-0137-9
[49] Z. Karim, S. Afrin, Q. Husain and R. Danish, *Crit. Rev. Biotechnol.*, **37**, 355 (2017), https://doi.org/10.3109/07388551.2016.1163322
[50] S. Iwamoto, A. Isogai and T. Iwata, *Biomacromolecules*, **12**, 831 (2011), https://doi.org/10.1021/bm101510r
[51] K. Xhanari, K. Syverud, G. Chinga-Carrasco, K. Paso and P. Stenius, *Cellulose*, **18**, 257 (2011), https://doi.org/10.1007/s10570-010-9482-y
[52] T. Saito, S. Kimura, Y. Nishiyama and A. Isogai, *Biomacromolecules*, **8**, 2485 (2007), https://doi.org/10.1021/bm0703970
[53] A. A. Elgharbawy, M. Z. Alam, M. Moniruzzaman and M. Goto, *Biochem. Eng. J.*, **109**, 252 (2016), https://doi.org/10.1016/j.bej.2016.01.021
[54] O. Kuzmina, E. Sashina, S. Troshenkowa and D. Wawro, *Fibres Text. East. Eur.*, **18**, 32 (2010)
[55] A. Pinkert, K. N. Marsh, S. Pang and M. P. Staiger, *Chem. Rev.*, **109**, 6712 (2009), https://doi.org/10.1021/cr9001947
[56] Y. Xiong, Z. Zhang, X. Wang, B. Liu and J. Lin, *Chem. Eng. J.*, **235**, 349 (2014), https://doi.org/10.1016/j.cej.2013.09.031
[57] A. P. Abbott, D. Boothby, G. Capper, D. L. Davies and R. K. Rasheed, *J. Am. Chem. Soc.*, **126**, 9142 (2004), https://doi.org/10.1021/ja048266j
[58] A. Satlewal, R. Agrawal, S. Bhagia, J. Sangoro and A. J. Ragauskas, *Biotechnol. Adv.*, **36**, 2032 (2018), https://doi.org/10.1016/j.biotechadv.2018.08.009
[59] W.-C. Tu and J. P. Hallett, *Curr. Opin. Green Sustain. Chem.*, **20**, 11 (2019), https://doi.org/10.1016/j.cogsc.2019.07.004
[60] H. Chen, J. Liu, X. Chang, D. Chen, Y. Xue *et al.*, *Fuel Process. Technol.*, **160**, 196 (2017), https://doi.org/10.1016/j.fuproc.2016.12.007
[61] V. Pakharenko, M. Pervaiz, H. Pande and M. Sain, in Interface/Interphase in Polymer Nanocomposites, edited by A. N. Netravali, John Wiley & Sons, Hoboken, 2016, p. 283, https://doi.org/10.1002/9781119185093.ch8
[62] V. B. Lunardi, F. E. Soetaredjo, J. N. Putro, S. P. Santoso, M. Yuliana *et al.*, *Polymers*, **13**, 2052 (2021), https://doi.org/10.3390/polym13132052
[63] F. Rol, M. N. Belgacem, A. Gandini and J. Bras, *Prog. Polym. Sci.*, **88**, 241 (2019), https://doi.org/10.1016/j.progpolymsci.2018.09.002
[64] G. Siqueira, J. Bras and A. Dufresne, *Polymers*, **2**, 728 (2010), https://doi.org/10.3390/polym2040728
[65] S.-Y. Lee, S.-J. Chun, I.-A. Kang and J.-Y. Park, *J. Ind. Eng. Chem.*, **15**, 50 (2009), https://doi.org/10.1016/j.jiec.2008.07.008
[66] A. Ferrer, I. Filpponen, A. Rodríguez, J. Laine and O. J. Rojas, *Bioresour. Technol.*, **125**, 249 (2012), https://doi.org/10.1016/j.biortech.2012.08.108

[67] S. Iwamoto, A. Nakagaito and H. Yano, *Appl. Phys. A*, **89**, 461 (2007), https://doi.org/10.1007/s00339-007-4175-6
[68] I. Siró and D. Plackett, *Cellulose*, **17**, 459 (2010), https://doi.org/10.1007/s10570-010-9405-y
[69] A. Dufresne, J. Y. Cavaillé and M. R. Vignon, *J. Appl. Polym. Sci.*, **64**, 1185 (1997), https://doi.org/10.1002/(SICI)1097-4628(19970509)64:6<1185::AID-APP19>3.0.CO;2-V
[70] A. Chakraborty, M. Sain and M. Kortschot, *Cellulose*, **12**, 221 (2005), https://doi.org/10.1515/HF.2005.016
[71] A. N. Frone, D. M. Panaitescu, D. Donescu, C. I. Spataru, C. Radovici *et al*., *BioResources*, **6**, 487 (2011)
[72] H. Kargarzadeh, M. Mariano, D. Gopakumar, I. Ahmad, S. Thomas *et al*., *Cellulose*, **25**, 2151 (2018), https://doi.org/10.1007/s10570-018-1723-5
[73] Q. Cheng, S. Wang and T. G. Rials, *Compos. Part A Appl. Sci. Manuf.*, **40**, 218 (2009), https://doi.org/10.1016/j.compositesa.2008.11.009
[74] P. Chen, H. Yu, Y. Liu, W. Chen, X. Wang *et al*., *Cellulose*, **20**, 149 (2013), https://doi.org/10.1007/s10570-012-9829-7
[75] K. Abe and H. Yano, *Cellulose*, **17**, 271 (2010), https://doi.org/10.1007/s10570-009-9382-1
[76] S. Srithongkham, L. Vivitchanont and C. Krongtaew, *J. Mater. Sci. Eng. B*, **2**, 213 (2012)
[77] M. Mariño, L. Lopes da Silva, N. Durán and L. Tasic, *Molecules*, **20**, 5908 (2015), https://doi.org/10.3390/molecules20045908
[78] H. Palacios Hinestroza, J. A. Hernández Diaz, M. Esquivel Alfaro, G. Toriz, O. J. Rojas *et al*., *Adv. Mater. Sci. Eng.*, **2019**, 1 (2019), https://doi.org/10.1155/2019/1342547
[79] B. Wang, M. Sain and K. Oksman, *Appl. Compos. Mater.*, **14**, 89 (2007), https://doi.org/10.1007/s10443-006-9032-9
[80] E. S. Madivoli, P. G. Kareru, A. N. Gachanja, S. M. Mugo, D. M. Sujee *et al*., *J. Nat. Fibers*, **19**, 1 (2022), https://doi.org/10.1080/15440478.2020.1764454
[81] Y. Ma, Q. Xia, Y. Liu, W. Chen, S. Liu *et al*., *ACS Omega*, **4**, 8539 (2019), https://doi.org/10.1021/acsomega.9b00519
[82] M. Babicka, M. Woźniak, K. Dwiecki and S. Borysiak, *Molecules*, **25**, 1544 (2020), https://doi.org/10.3390/molecules25071544
[83] E. Abraham, B. Deepa, L. Pothan, M. Jacob, S. Thomas *et al*., *Carbohyd. Polym.*, **86**, 1468 (2011), https://doi.org/10.1016/j.carbpol.2011.06.034
[84] P. Phanthong, S. Karnjanakom, P. Reubroycharoen, X. Hao, A. Abudula *et al*., *Cellulose*, **24**, 2083 (2017), https://doi.org/10.1007/s10570-017-1238-5
[85] X. Zhou, X. Lin, K. L. White, S. Lin, H. Wu *et al*., *Cellulose*, **23**, 811 (2016), https://doi.org/10.1007/s10570-015-0856-z
[86] M. Ghasemlou, F. Daver, E. P. Ivanova, Y. Habibi and B. Adhikari, *Prog. Polym. Sci.*, **119**, 101418 (2021), https://doi.org/10.1016/j.progpolymsci.2021.101418
[87] A. Ashori, M. Babaee, M. Jonoobi and Y. Hamzeh, *Carbohyd. Polym.*, **102**, 369 (2014), https://doi.org/10.1016/j.carbpol.2013.11.067
[88] R. Barbosa, A. Souza, F. Ferreira and D. Rosa, *Carbohyd. Polym.*, **218**, 208 (2019), https://doi.org/10.1016/j.carbpol.2019.04.072
[89] J.-F. Sassi and H. Chanzy, *Cellulose*, **2**, 111 (1995), https://doi.org/10.1007/BF00816384
[90] P. Nechita and D. Panaitescu, *Cellulose Chem. Technol.*, **47**, 711 (2013), https://www.cellulosechemtechnol.ro/
[91] V. K. Thakur and M. K. Thakur, *Carbohyd. Polym.*, **109**, 102 (2014), https://doi.org/10.1016/j.carbpol.2014.03.039
[92] J. B. Daud and K. Y. Lee, in "Handbook of Nanocellulose and Cellulose Nanocomposites", edited by H. Kargarzadeh, I. Ahmad, S. Thomas and A. Dufresne, Wiley-VCH, 2017, p. 101, https://doi.org/10.1002/9783527689972.ch3
[93] J. A. Sirviö, M. Visanko and H. Liimatainen, *Green Chem.*, **17**, 3401 (2015), https://doi.org/10.1039/C5GC00398A
[94] O. Nechyporchuk, M. N. Belgacem and J. Bras, *Ind. Crop. Prod.*, **93**, 2 (2016), https://doi.org/10.1016/j.indcrop.2016.02.016
[95] N. Lin and A. Dufresne, *Nanoscale*, **6**, 5384 (2014), https://doi.org/10.1039/C3NR06761K
[96] P. Singhsa, R. Narain and H. Manuspiya, *ACS Appl. Nano Mater.*, **1**, 209 (2017), https://doi.org/10.1021/acsanm.7b00105
[97] D. Aoki and Y. Nishio, *Cellulose*, **17**, 963 (2010), https://doi.org/10.1007/s10570-010-9440-8
[98] B. Thomas, M. C. Raj, J. Joy, A. Moores, G. L. Drisko *et al*., *Chem. Rev.*, **118**, 11575 (2018), https://doi.org/10.1021/acs.chemrev.7b00627
[99] O. M. Vanderfleet, M. S. Reid, J. Bras, L. Heux, J. Godoy-Vargas *et al*., *Cellulose*, **26**, 507 (2019), https://doi.org/10.1007/s10570-018-2175-7
[100] H. Abushammala and J. Mao, *Molecules*, **24**, 2782 (2019), https://doi.org/10.3390/molecules24152782
[101] Y. Habibi, *Chem. Soc. Rev.*, **43**, 1519 (2014), https://doi.org/10.1039/C3CS60204D
[102] G. Pierre, C. Punta, C. Delattre, L. Melone, P. Dubessay *et al*., *Carbohyd. Polym.*, **165**, 71 (2017), https://doi.org/10.1016/j.carbpol.2017.02.028
[103] A. Isogai, T. Hänninen, S. Fujisawa and T. Saito, *Prog. Polym. Sci.*, **86**, 122 (2018), https://doi.org/10.1016/j.progpolymsci.2018.07.007
[104] G. Zhu and N. Lin, in "Nanocellulose: From Fundamentals to Advanced Materials", edited by J. Huang, A. Dufresne and N. Lin, John Wiley & Sons, 2019, https://doi.org/10.1002/9783527807437.ch5
[105] J. Huang, A. Dufresne and N. Lin, "Nanocellulose: From Fundamentals to Advanced Materials", John Wiley & Sons, 2019
[106] M. Mariano, F. Pilate, F. B. de Oliveira, F. Khelifa, P. Dubois *et al*., *ACS Omega*, **2**, 2678 (2017), https://doi.org/10.1021/acsomega.7b00387

[107] B. L. Tardy, S. Yokota, M. Ago, W. Xiang, T. Kondo *et al*., *Curr. Opin. Colloid Interface Sci*., **29**, 57 (2017), https://doi.org/10.1016/j.cocis.2017.02.004
[108] L. Liang, S. Bhagia, M. Li, C. Huang and A. J. Ragauskas, *ChemSusChem*, **13**, 78 (2020), https://doi.org/10.1002/cssc.201901676
[109] M. A. Hubbe, O. J. Rojas, L. A. Lucia and M. Sain, *BioResources*, **3**, 929 (2008)
[110] T. Abitbol, A. Rivkin, Y. Cao, Y. Nevo, E. Abraham *et al*., *Curr. Opin. Biotechnol*., **39**, 76 (2016), https://doi.org/10.1016/j.copbio.2016.01.002
[111] P. Phanthong, P. Reubroycharoen, X. Hao, G. Xu, A. Abudula *et al*., *Carbon Resour. Convers*., **1**, 32 (2018), https://doi.org/10.1016/j.crcon.2018.05.004
[112] J. M. Rajwade, K. M. Paknikar and J. V. Kumbhar, *Appl. Microbiol. Biotechnol*., **99**, 2491 (2015), https://doi.org/10.1007/s00253-015-6426-3
[113] J. K. Jackson, K. Letchford, B. Z. Wasserman, L. Ye, W. Y. Hamad *et al*., *Int. J. Nanomed*., **6**, 321 (2011), https://doi.org/10.2147/ijn.s16749
[114] R. K. Mishra, A. Sabu and S. K. Tiwari, *J. Saudi Chem. Soc*., **22**, 949 (2018), https://doi.org/10.1016/j.jscs.2018.02.005
[115] N. Hasan, L. Rahman, S.-H. Kim, J. Cao, A. Arjuna *et al*., *J. Pharm. Investig*., **50**, 553 (2020), https://doi.org/10.1007/s40005-020-00499-4
[116] R. Kolakovic, L. Peltonen, T. Laaksonen, K. Putkisto, A. Laukkanen *et al*., *AAPS PharmSciTech*, **12**, 1366 (2011), https://doi.org/10.1208/s12249-011-9705-z
[117] R. Kolakovic, L. Peltonen, A. Laukkanen, J. Hirvonen and T. Laaksonen, *Eur. J. Pharm. Biopharm*., **82**, 308 (2012), https://doi.org/10.1016/j.ejpb.2012.06.011
[118] L. Liu, W. Yao, Y. Rao, X. Lu and J. Gao, *Drug Deliv*., **24**, 569 (2017), https://doi.org/10.1080/10717544.2017.1279238
[119] Q. Liu, Y. Lu, M. Aguedo, N. Jacquet, C. Ouyang *et al*., *ACS Sustain. Chem. Eng*., **5**, 6183 (2017), https://doi.org/10.1021/acssuschemeng.7b01108
[120] Y. Liu, B. Guo, Q. Xia, J. Meng, W. Chen *et al*., *ACS Sustain. Chem. Eng*., **5**, 7623 (2017), https://doi.org/10.1021/acssuschemeng.7b00954
[121] V. Nalamothu, *Drug Dev. Deliv*., **1** (2015)
[122] S. P. Akhlaghi, D. Tiong, R. M. Berry and K. C. Tam, *Eur. J. Pharm. Biopharm*., **88**, 207 (2014), https://doi.org/10.1016/j.ejpb.2014.04.012
[123] A. M. Barbosa, E. Robles, J. S. Ribeiro, R. G. Lund, N. L. Carreño *et al*., *Materials*, **9**, 1002 (2016), https://doi.org/10.3390/ma9121002
[124] S. C. Lazarini, R. de Aquino, A. C. Amaral, F. C. Corbi, P. P. Corbi *et al*., *Cellulose*, **23**, 737 (2016), https://doi.org/10.1007/s10570-015-0843-4
[125] Y. Alkhatib, M. Dewaldt, S. Moritz, R. Nitzsche, D. Kralisch *et al*., *Eur. J. Pharm. Biopharm*., **112**, 164 (2017), https://doi.org/10.1016/j.ejpb.2016.11.025
[126] W. Y. Tong, A. Y. K. bin Abdullah, M. I. A. bin Wahid, M. Hossain, L. C. Ring *et al*., *Cellulose*, **25**, 631 (2018), https://doi.org/10.1007/s10570-017-1562-9
[127] A. Gupta, S. M. Briffa, S. Swingler, H. Gibson, V. Kannappan *et al*., *Biomacromolecules*, **21**, 1802 (2020), https://doi.org/10.1021/acs.biomac.9b01724
[128] M. de Lima Fontes, A. B. Meneguin, A. Tercjak, J. Gutierrez, B. S. F. Cury *et al*., *Carbohyd. Polym*., **179**, 126 (2018), https://doi.org/10.1016/j.carbpol.2017.09.061
[129] R. Bisht, A. Mandal, J. K. Jaiswal and I. D. Rupenthal, *WIREs Nanomed. Nanobiotechnol*., **10**, e1473 (2018), https://doi.org/10.1002/wnan.1473
[130] M. Zhu, J. Wang and N. Li, *Artif. Cells Nanomed. Biotechnol*., **46**, 1282 (2018), https://doi.org/10.1080/21691401.2017.1368024
[131] M. Patchan, J. Graham, Z. Xia, J. Maranchi, R. McCally *et al*., *Mater. Sci. Eng. C*, **33**, 3069 (2013), https://doi.org/10.1016/j.msec.2013.03.037
[132] E. C. Mohan, J. M. Kandukuri and V. Allenki, *J. Pharm. Res*., **2**, 1089 (2009)
[133] A. K. Agrawal, M. Das and S. Jain, *Expert Opin. Drug Deliv*., **9**, 383 (2012), https://doi.org/10.1517/17425247.2012.665367
[134] S. Dhiman, T. G. Singh and A. K. Rehni, *Int. J. Pharm. Pharm. Sci*., **3**, 26 (2011)
[135] M. L. Cacicedo, G. A. Islan, I. E. León, V. A. Alvarez, I. Chourpa *et al*., *Colloids Surf. B Biointerfaces*, **170**, 596 (2018), https://doi.org/10.1016/j.colsurfb.2018.06.056
[136] D. Klemm, E. D. Cranston, D. Fischer, M. Gama, S. A. Kedzior *et al*., *Mater. Today*, **21**, 720 (2018), https://doi.org/10.1016/j.mattod.2018.02.001
[137] A. Dufresne, *Mater. Today*, **16**, 220 (2013), https://doi.org/10.1016/j.mattod.2013.06.004
[138] D. Trache, M. H. Hussin, M. M. Haafiz and V. K. Thakur, *Nanoscale*, **9**, 1763 (2017), https://doi.org/10.1039/C6NR09494E
[139] H. T. Phuong, N. K. Thoa, P. T. A. Tuyet, Q. N. Van and Y. D. Hai, *Crystals*, **12**, 106 (2022), https://doi.org/10.3390/cryst12010106
[140] X.-R. Ong, A. X. Chen, N. Li, Y. Y. Yang and H.-K. Luo, *Small Sci*., **3**, 2200076 (2023), https://doi.org/10.1002/smsc.202200076
[141] M. Li, Y. Mu, Q. Xu, L. Jin and Y. Fu, *Ind. Crop. Prod*., **208**, 117876 (2024), https://doi.org/10.1016/j.indcrop.2023.117876
[142] K. M. Håkansson, I. C. Henriksson, C. de la Peña Vázquez, V. Kuzmenko, K. Markstedt *et al*., *Adv. Mater. Technol*., **1**, 1600096 (2016), https://doi.org/10.1002/admt.201600096
[143] S. S. Athukoralalage, R. Balu, N. K. Dutta and N. R. Choudhury, *Polymers*, **11**, 898 (2019), https://doi.org/10.3390/polym11050898
[144] G. Kandhola, S. Park, J.-W. Lim, C. Chivers, Y. H. Song *et al*., *Tissue Eng. Regen. Med*., **20**, 411 (2023), https://doi.org/10.1007/s13770-023-00530-3
[145] R. Sunasee, U. D. Hemraz and K. Ckless, *Expert Opin. Drug Deliv*., **13**, 1243 (2016), https://doi.org/10.1080/17425247.2016.1182491
[146] S. Gorgieva and J. Trček, *Nanomaterials*, **9**, 1352 (2019), https://doi.org/10.3390/nano9101352

[147] Y. Liu, H. Liu, S. Guo, J. Qi, R. Zhang *et al*., *Tissue Eng*. *Regen*. *Med*., **20**, 1017 (2023), https://doi.org/10.1007/s13770-023-00575-4
[148] R. Portela, C. R. Leal, P. L. Almeida and R. G. Sobral, *Microbiol*. *Biotechnol*., **12**, 586 (2019), https://doi.org/10.1111/1751-7915.13392
[149] J. Li, R. Cha, K. Mou, X. Zhao, K. Long *et al*., *Adv*. *Healthc*. *Mater*., **7**, 1800334 (2018), https://doi.org/10.1002/adhm.201800334
[150] K. B. Teodoro, R. C. Sanfelice, F. L. Migliorini, A. Pavinatto, M. H. Facure *et al*., *ACS Sens*., **6**, 2473 (2021), https://doi.org/10.1021/acssensors.1c00473
[151] H. Golmohammadi, E. Morales-Narváez, T. Naghdi and A. Merkoçi, *Chem*. *Mater*., **29**, 5426 (2017), https://doi.org/10.1021/acs.chemmater.7b01170
[152] D. Klemm, B. Heublein, H. P. Fink and A. Bohn, *Angew*. *Chem*. *Int*. *Ed*., **44**, 3358 (2005), https://doi.org/10.1002/anie.200460587
[153] W. Czaja, A. Krystynowicz, S. Bielecki and R. M. Brown Jr, *Biomaterials*, **27**, 145 (2006), https://doi.org/10.1016/j.biomaterials.2005.07.035
[154] D. Trache, A. F. Tarchoun, M. Derradji, T. S. Hamidon, N. Masruchin *et al*., *Front*. *Chem*., **8**, 392 (2020), https://doi.org/10.3389/fchem.2020.00392
[155] E. Bencurova, M. Kunz and T. Dandekar, "Systems Biology", Springer, 2018, pp. 373-401, https://doi.org/10.1007/978-3-319-92967-5_19
[156] Z. Bao, Y. Xue, X. Chen, Y. Wang, J. Wang *et al*., *Ind*. *Crop*. *Prod*., **234**, 121461 (2025), https://doi.org/10.1016/j.indcrop.2025.121461
[157] M. N. Norizan, S. S. Shazleen, A. H. Alias, F. A. Sabaruddin, M. R. M. Asyraf *et al*., *Nanomaterials*, **12**, 3483 (2022), https://doi.org/10.3390/nano12193483