Bioactive Materials 9 (2022) 566–589

Contents lists available at ScienceDirect

Bioactive Materials

journal homepage: www.sciencedirect.com/journal/bioactive-materials

Nanocellulose, a versatile platform: From the delivery of active molecules to tissue engineering applications

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ARTICLE INFO

Keywords:
Nanocellulose
Chemical functionalization
Drug delivery
Protein delivery
Plasmid delivery
Tissue engineering

ABSTRACT

Nanocellulose, a biopolymer, has received wide attention from researchers owing to its superior physicochemical properties, such as high mechanical strength, low density, biodegradability, and biocompatibility. Nanocellulose can be extracted from wide range of sources, including plants, bacteria, and algae. Depending on the extraction process and dimensions (diameter and length), they are categorized into three main types: cellulose nanocrystals (CNCs), cellulose nanofibrils (CNFs), and bacterial nanocellulose (BNC). CNCs are a highly crystalline and needle-like structure, whereas CNFs have both amorphous and crystalline regions in their network. BNC is the purest form of nanocellulose. The nanocellulose properties can be tuned by chemical functionalization, which increases its applicability in biomedical applications. This review highlights the fabrication of different surface-modified nanocellulose to deliver active molecules, such as drugs, proteins, and plasmids. Nanocellulose-mediated delivery of active molecules is profoundly affected by its topographical structure and the interaction between the loaded molecules and nanocellulose. The applications of nanocellulose and its composites in tissue engineering have been discussed. Finally, the review is concluded with further opportunities and challenges in nanocellulose-mediated delivery of active molecules.

1. Introduction

In an effort to progress towards a more sustainable planet, the demand for bio-renewable natural resources continues to increase globally. Non-renewable fossil resources are not sustainable and have adverse environmental effects. Therefore, alternative and eco-friendly resources must be chosen for this requirement [1]. Bio-based feedstocks, such as forest and agricultural residues, wood, and food waste, are considered attractive and renewable sources for producing value-added products. Plants are composed of lignocellulosic biomass, which includes cellulose (40–50 wt %), hemicellulose (20–40 wt %), and lignin (20–30%), and are considered to be the most abundant bio-sources on the earth [2]. Cellulose is the highly produced biomass on earth. The chemical structure of cellulose is composed of a linear chain of homo-polysaccharide glucose units linked by a β-1, 4- glycosidic bond [3]. Each monomer unit consists of hydroxyl groups, forming intra-or inter-molecular hydrogen bonds with adjacent glucose units in the same chain and nearby chains [4]. Nanocellulose is a nanoscale form of cellulose obtained from the disintegration of large cellulose units by breaking their intra-and inter-molecular hydrogen bonding in-betweens chains [5]. The synthesis of nanocellulose from different sources has been previously reported [6].

Nanocellulose can be obtained from different sources such as plants, microorganisms, and aquatic animals (tunicates), rich in cellulose [7]. Among plants, banana leaf, corn cob, cotton, ramie, rice husk, wood, sugarcane bagasse, sisal leaves, wheat straw, wood, and coconut husks are promising sources for the extraction of nanocellulose [8]. However, nanocellulose has recently been extracted from coffee grounds [9], ginger [10], durian rind waste [11], lemon seeds [12], okara [13], pea hull [14], *Phragmites australis* [15], *Hevea brasiliensis* (Rubberwood) [16], and tea stalk [17]. Nanocellulose obtained from bacteria is known as bacterial nanocellulose (BNC) or bacterial cellulose (BC). *Acetobacter*

Peer review under responsibility of KeAi Communications Co., Ltd.
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https://doi.org/10.1016/j.bioactmat.2021.07.006
Received 23 April 2021; Received in revised form 26 June 2021; Accepted 6 July 2021
Available online 27 July 2021

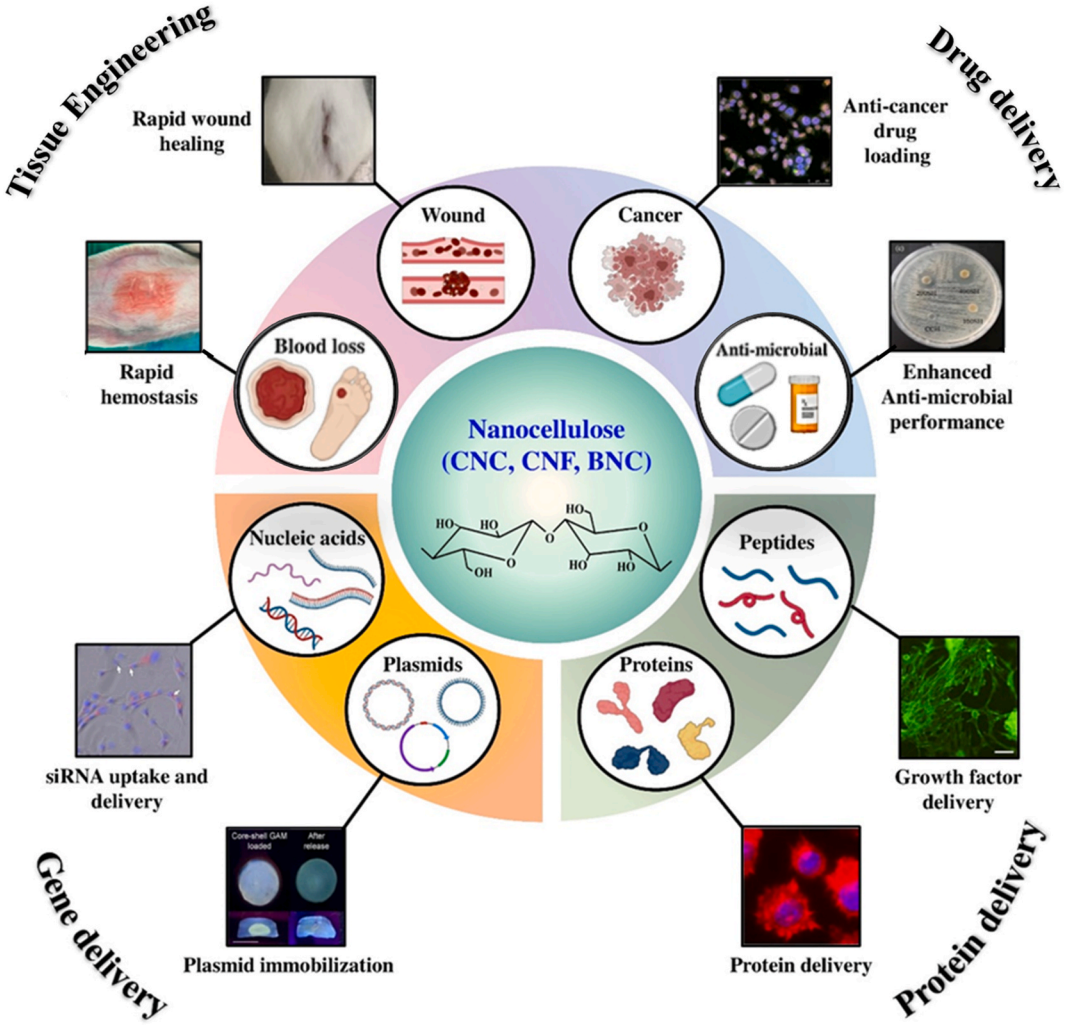


Fig. 1. Nanocellulose as multifunctional delivery vehicle. Nanocellulose could be utilized for sustained delivery of therapeutic molecules, such as anti-microbial drugs [40], as a wound healing agents [41], anti-cancer drugs [42], and various hemostatic agents [43]. Nanocellulose has also been shown to deliver nucleic acids [44,45], proteins [46], and certain growth promoting factors for tissue engineering [47]. CNC; cellulose nanocrystals, CNF; cellulose nanofibrils, BNC; bacterial nanocellulose.

xylinum (*Gluconacetobacter xylinus*) is one of the most efficient bacteria used for nanocellulose production. Other micro-organisms include *Acetobacter, Achromobacter, Agrobacterium, Acanthamoeba, Alcaligenes, Rhizobium, Pseudomonas, Sarcina,* and algal species *Cladophora, Rhizoclonium, Microdiction,* and *Chaetomorpha,* also have the potential to produce nanocellulose [18,19]. A stable and transparent nanocellulose gel was obtained from *Cladophora* species through high-speed sonication [20]. Nanocellulose extracted from *Styela claves* has been tested for stitching fibers, absorbable hemostats, scaffolds for tissue engineering, and hemodialysis [21]. Bacteria-derived nanocellulose is highly pure as compared to nanocellulose derived from plants and can be easily distinguished. Despite different resources, the molecular structures of plants and bacteria-derived nanocellulose are similar [4,22].

Based on the sources and morphological structures, nanocellulose is classified into three main categories: cellulose nanocrystals (CNCs/NCC), cellulose nanofibers (CNFs/NFC), and bacterial nanocellulose (BNC/BC). CNCs are mainly obtained from cellulose-rich sources *via* acid treatment. CNCs are highly crystalline and needle-like structured with typical dimensions of 4–20 nm in width and 100–500 nm in length. Cellulose nanofibers (CNFs) are synthesized by chemical treatment, followed by mechanical disintegration. CNFs are a mixture of crystalline and amorphous cellulose with a typical length of 1 μm. BNC is synthesized from different microorganisms, and it is the purest form of nanocellulose with a diameter range of 20–100 nm and several micrometers in length [23].

Nanocellulose is a biodegradable biopolymer with attractive physical and chemical properties, such as high surface area, low density, high mechanical, thermal, and optical properties, as well as biocompatibility [24–27]. Therefore, nanocellulose is considered a suitable platform to deliver the drugs, proteins, and plasmids [28–30]. It is reported that nanocellulose-based systems demonstrated sustained release of the loaded drug, with great biomedical applications [31]. In addition, nanocellulose can be used in food packaging [10], tissue engineering [32], cosmetic additives, medical implants [33], paper industry [34], 3D printing [35], wastewater treatment [36], biocatalysts [37], bioenergy [38](Zhu et al., 2016), wood adhesives, lenses, fingerprint detection [30](Trache et al., 2020), and textile industries [39](Forsman et al., 2017).

Nanocellulose has received significant attention for biomedical applications because of its high surface area, aspect ratio, mechanical strength, easy to surface modification, non-immunogenic and superior biocompatibility. The present review emphasized the different synthesis approaches of nanocellulose and their potential applications in drug, protein, and plasmid delivery. Furthermore, the applications of nanocellulose for tissue engineering are also highlighted by considering some stunning results. The review is concluded with future scope and

Table 1
Nanocellulose synthesis approaches with their characteristics features, benefits and obstacles.

Details→	Methods	Features	Benefits	obstacles
Chemical approach	Acid base treatment, bleaching, hydrolysis TEMPO oxidation, Ionic liquid treatment, metal salt treatment etc.	Formation of charged CNCs, surface functionalized CNCs, crystalline cellulose with diameter of 5–15 nm and 100–200 nm length, short duration	Tuning of crystallinity and morphology, and properties, high yield of CNCs	Side product formation, separation of reagents, loss of physico-chemical properties, impurity isolation, necessity of additional treatment.
Mechanical approach	Refining, ultra-sonication, Microfluidization, cryocrushing, high pressure homogenization, irradiation, ball milling, blending, extrusion, steam explosion etc.	CNFs with average diameter of 3–50 nm and length of 50–1000 nm.	Tuning of structure and morphology of CNFs, maintain the biocompatibility and biodegradability in CNFs.	Longer duration, clogging the system, corrosion of machine, challenges in scale up of processes.
Biological approach	Synthesized by Microorganisms (enzymes, bacteria, algae) treatment.	Efficient way to generate good quality nanocellulose with good yield. Free of lignin and hemicellulose, 20–200 nm diameter and length of several micrometer	Ecofriendly, less hazardous waste, high purity nanocellulose, etc.	Longer duration, issue related to the life time and storage of expensive microorganism

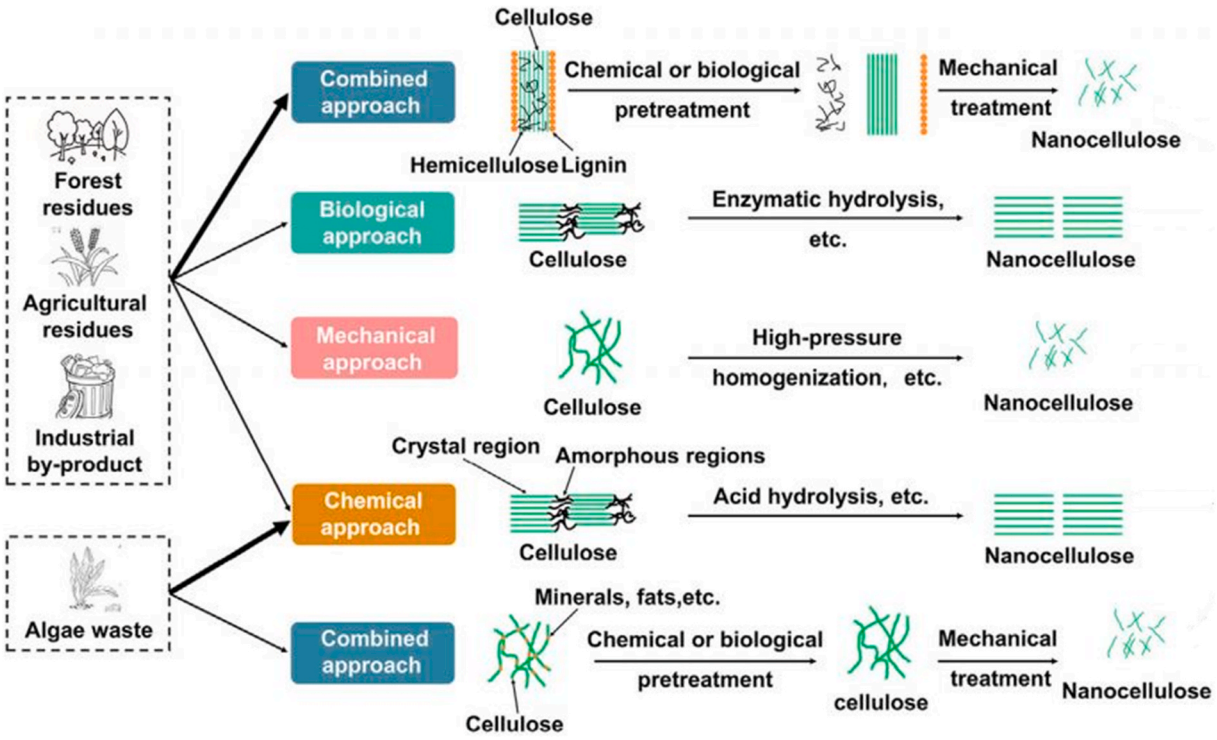


Fig. 2. Schematic representation for the synthesis of nanocellulose with different approaches from different biomass [72].

challenges to overcome in the synergistic progress of cellulose nanomaterials. An overview of nanocellulose applications is presented in Fig. 1.

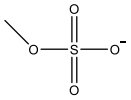
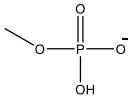
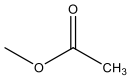
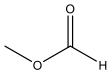
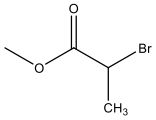
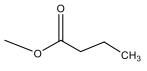
2. Synthesis of nanocellulose

The chemo-mechanical and bacterial synthesis are the two major processes used in the preparation of nanocellulose. The physicochemical properties of nanocellulose are profoundly affected by the extraction sources and methods. Therefore, the selection of a suitable source and method are an essential criteria for nanocellulose production. Here, we discussed the chemical, mechanical and bacterial methods for synthesizing nanocellulose with their merits and demerits by taking some fascinating works, summarized in Table 1. The schematic representation for the synthesis of nanocellulose from different sources is shown in Fig. 2.

2.1. Chemical approach

In this method, the biomass is treated with an alkaline solution to remove hemicellulose from its structure, followed by bleaching and acid hydrolysis or mechanical disintegration. Alkaline treatment cause some disadvantages, such as side reactions, reduction in crystallinity, loss of physicochemical properties, impurity isolation, need for additional treatments, *etc*. [5]. The lignin content is removed by treating the alkaline-treated biomass with a bleaching agent [48,49]. These methods are initial pretreatment processes to remove the impurities like starch, lignin, pectin, hemicellulose, *etc.*, from the biomass. The lignin-free biomass is treated with an acid to obtain crystalline CNCs. The mineral acids such as H_2SO_4, HCl, H_3PO_4, and HBr are commonly used to synthesize CNCs. The acid hydrolysis facilitates the removal of amorphous regions from cellulosic material, leading to generate highly crystalline CNCs with a typical dimension of 5–15 nm, width and 100–200 nm, length [50,51]. The crystallinity and morphology of CNCs can be controlled by changing the acid and their concentrations, as well

Table 2
Various chemical modification of nanocellulose, including mineral acids, organic acids, and ionic liquids, produces functionalized nanocellulose.

Nanocellulose surface functionality	Reagents	Properties	References
	Sulfuric acid	Nanometer, Negative surface charge, Crystalline,	[95,96]
	Phosphoric acid	Nanometer, Thermally stable, Highly crystalline	[97]
	Hydrochloric acid of TEMPO-oxidized CNFs	Nanometer, Increased water contact angle	[98]
	Oxalic acid	Nanometer, Micrometer, Amorphous	[99]
	Acetic acid	Nanometer, Reduces salinity in seawater	[100]
	Maleic acid	Nanometer with aggregates, High tensile strength and elongation at break	[99,101]
	Formic acid	Nanometer, Micrometer, Amorphous, water dispersible	[102]
	Sodium periodate	Nanometer, Low crystallinity, high cationic charges	[103]
	Ammonium persulfate	Nanometer, High charge density, high crystallinity, transparency	[104]
	2-bromopropionic acid	Nanometer with aggregates, High thermal stability	[105]
	Hydrogen peroxide	Nanometer with some aggregates, Electrostatic repulsion between fibers	[106]
	Butyric acid	Nanometer with aggregates, Crystalline	[100]

as pretreatment conditions [31]. CNCs obtained from H_2SO_4 treatment have negatively charged sulfate (–SO_3H) groups in their structure, which assist in the dispersion in different solvents. The removal of negatively charged sulfate groups has been reported at a higher temperature. The HCl hydrolysis generates the more reactive hydroxyl groups on CNCs surface [52]. The acid hydrolysis time and temperature also influence the physicochemical properties of the obtained CNCs [31,53]. The metal-salt-based HCl hydrolysis [54], $FeCl_3$-catalyzed formic acid hydrolysis [55], phosphotungstic acid hydrolysis [56], and hydrothermal treatment under acid conditions [57] are also applied in the synthesis of CNCs.

TEMPO (2, 2, 6, 6-Tetramethylpiperidine-1-oxyl radical)-mediated oxidation generates more surface hydroxyl groups. TEMPO-mediated oxidation produces a high yield of nanocellulose without affecting crystallinity and physicochemical properties [5]. The TEMPO-mediated oxidation occurs at the amorphous regions of cellulose, leaving the crystalline regions. This method generates negatively charged carboxylate (–COO^-) groups and can be carried out under acidic and basic media [58–60]. The TEMPO-mediated oxidation is preferred for synthesizing CNFs with high crystallinity (56 %) [58,61].

Ionic liquid treatment is another useful chemical method, where the ionic media react with cellulose to generate nanocellulose [62]. The ionic liquid consists of ions and salts. The well-known ionic liquids which are utilized in cellulose isolations are 1-butyl-3-methylimidazolium hydrogen sulfate ($bmimH_2SO_4$), 1-allyl-3-methylimidazolium chloride (AmimCl) 1-butyl- 3-methylimidazolium chloride (BmimCl), 1-butyl-3-methylimidazolium acetate (BmimOAc), 2-hydroxyethyl ammonium hydrogen sulfate ([2-HEA]-[H_2SO_4]), and tetrabutylammonium acetate (TBAA) [62–64]. Ionic liquid removes the amorphous cellulose, hemicellulose, and lignin from cellulose and generates high-quality CNCs. The treatment also favors the growth and realignment of nanocellulose [65–67].

The metal salts, including transition metal salts treatment, have additional advantages over the mineral acid treatment, including less corrosion of the reactors, easy separation after a reaction, and fewer safety concerns. Here, the metal salts are used as a catalyst to remove the amorphous regions of cellulose. Chen and co-workers used the $Cr(NO_3)_2$ solution to isolate nanocellulose from municipal waste of different types. This process generates a charged cellulosic structures with variable crystallinity [68,69]. The properties of synthesized nanocellulose can be tuned by varying the reaction conditions. The valence state of the metal can affect the rate of reaction as well as target cellulose molecules. Cr $(NO_3)_2$ isolated nanocellulose is not considered a suitable platform to deliver the active molecules due to the toxicity of chromium metal [70,71].

2.2. Mechanical approach

Mechanical treatment includes several techniques such as refining, ultrasonication, microfluidization, cryocrushing, high-pressure homogenization, radiation, ball milling, blending, extrusion, steam explosion, etc. [73]. In this approach, a critical pressure is generated at the centers of fibrous materials through the mechanical force that facilitates the crack propagation process and breaks the interactions between cellulose fibers, leading to the formation of nanocellulose [31]. CNFs with an average diameter of 3–50 nm and 50–1000 nm length can be produced through this technique. The ultra-sonication and high-pressure homogenization techniques are preferred during biochemical treatments because they do not have a vast influence on the physicochemical properties of the resultant cellulose material. However, a slight change in the surface structure has been previously reported [65]. These techniques could maintain the biocompatibility and biodegradability of cellulose without chemical reagents. The structural and morphological properties of the obtained CNFs can be tuned by altering the mechanical force. Despite its advantages, the clogging of the system, the corrosion of the machine, and upscaling can be challenging for such processes.

High-pressure homogenization is one of the efficient and commonly used for the generation of CNFs from the cellulose slurry [31]. Wang and co-workers examined the effects of the pressure on the CNFs dimensions [74]. The narrow distribution of nanocellulose dimension occurred in the micro-fluidization technique than other techniques due to the easy dissociation of intermolecular hydrogen bonds of cellulose [75]. The refined technique facilitates the generation of a higher surface area in CNFs by decreasing the size. Ultra-sonication has also been utilized to generate nanocellulose and is considered a more beneficial approach for biomedical applications due to the non-involvement of any toxic chemicals during the preparation and maintenance of biodegradable and biocompatible cellulose [76]. Cryo-crushing, radiation, and ball milling methods are also used to generate nanocellulose [31].

2.3. Biological approach

Biological treatment involves the pretreatment of crude cellulose or cellulose feedstocks with microorganisms (bacterial, algae, *etc.*). The obtained BNC can further be modified to crystalline or fibrillar form by external treatments. This process has several advantages over the chemical treatment, including eco-friendly, less hazardous waste, and

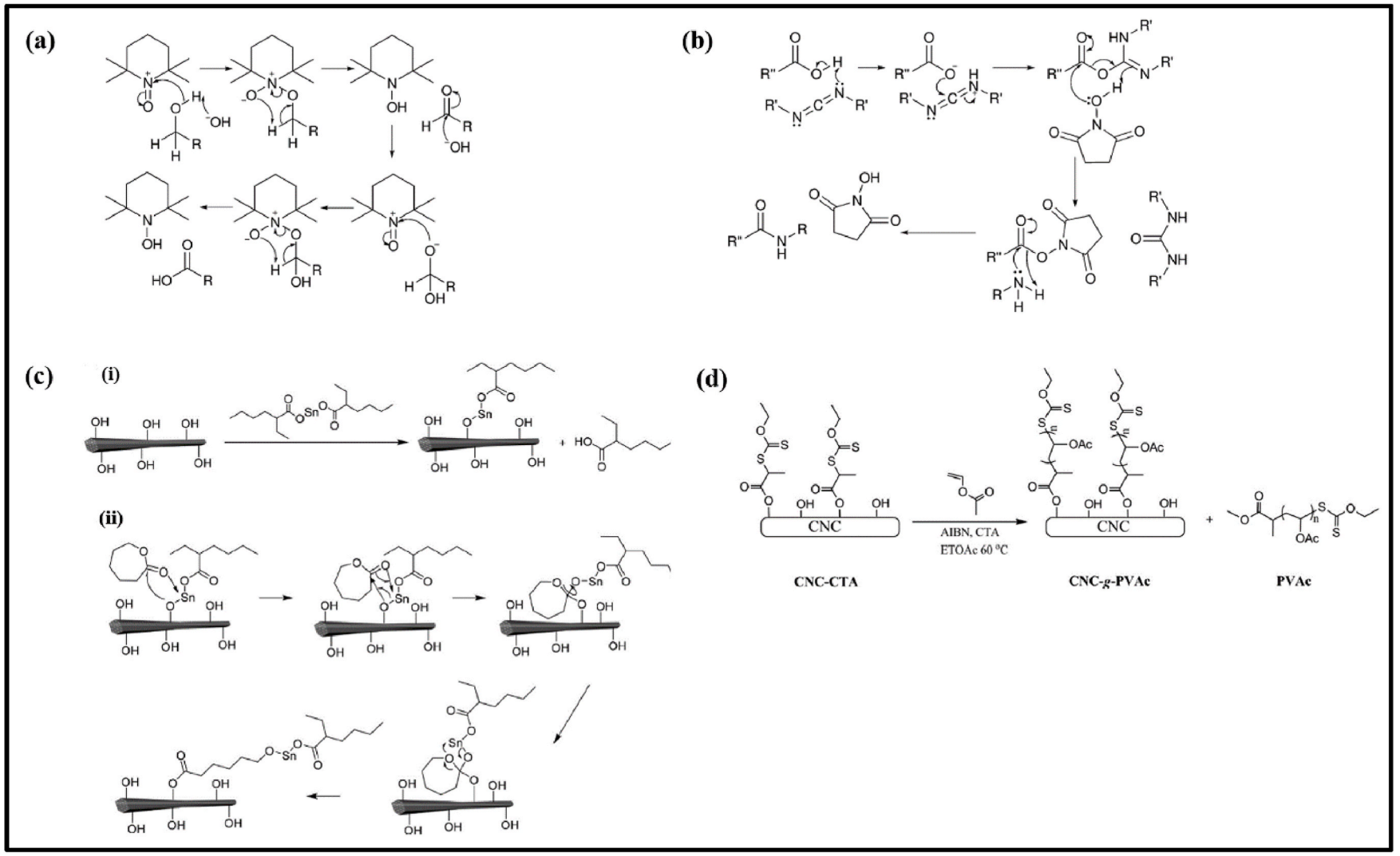


Fig. 3. **(a)** Mechanism for oxidation of primary alcohols with TEMPO with a cyclic transition state [120], **(b)** Mechanism of amidation using carbodiimides to form an N-hydroxysuccinimidyl ester intermediate [90], **(c)** Mechanism of the SI-ROP of ε-CL from CNCs Using $Sn(Oct)_2$ as a catalyst **(i)** Conversion of $Sn(Oct)_2$ into tin alkoxide, **(ii)** Grafting of ε-CL from the surface of CNCs *via* coordination of tin alkoxide with the monomer [130] and **(d)** Illustration of SI-RAFT/MADIX polymerization of vinyl acetate from CNC-CTA [132].

high purity of nanocellulose is obtained through this technique [31]. The optimization of treatment conditions and strain selection are the significant factors in optimizing this method [77–79]. The yield and productivity of BNC are intensively dependent on the bacterial strain and pH of the medium. The static and agitated culture processes are two primary microorganisms-based treatments applied for the production of nanocellulose. The temperature of the static culture medium is maintained to room temperature or slightly up (±5), through which bacterial cellulose accumulates as a white pellicle on the surface, whereas agitated culture produces the dispersed BNC [80].

Biological treatment is considered a better method to obtain nanocellulose than the chemical and mechanical process [81]. Henriksson and co-workers experienced a lower yield for the formation of nanofiber cellulose with higher purity, but it can take a longer duration to complete the reaction [82]. For instance, Anderson et al. has reported only 10% of nanocellulose yield after 62 h of enzymatic pretreatment [83]. The yield and quality of BNC can be improved by biochemical and biomechanical treatments [81,84]. The combined treatments are always beneficial for producing high-quality nanocellulose with high productivity [85,86].

3. Surface functionalization

Nanocellulose can be extracted from different sources, and applied in tissue engineering, shape-memory [87], sensing [88], wound dressing, and drug delivery [89]. Surface functionalization improves the utility ranges of nanocellulose [29]. The chemical functionalization includes self-modulated chemistry of nanocellulose and functional modification of hydroxyl groups present in its structure. The hydroxyl groups in nanocellulose are highly reactive and available for the desired modifications. The surface functionalization chemistry of nanocellulose is widely explored and nicely summarized in several articles [90–92]. The hydrophilicity of nanocellulose can be altered with hydrophobic characteristics and *vice-versa* [93], which could enhance its compatibility, dispersibility, and related performance. Three reactive hydroxyl groups are present near to 1–4 glycosidic bonds of the glucose unit. The reactivity of these groups can be altered by changing the reaction environments [90]. The surface modifications in nanocellulose have significantly raised its potential for a variety of industrial applications. Etherification, esterification, amination, amidation, oxidation, hydrolysis, silylation, polymer grafting, carbamation, sulfonation, phosphorylation, cross-linking, surfactant modification, and fluorescent labeling are commonly used to modify the nanocellulose properties [5,31,94]. The different surface modifications of nanocellulose using various reagents are summarized in Table 2.

The mineral acids, such as sulfuric acid [107], hydrochloric acid [108], hydrobromic acid [109], and phosphoric acid [110] are used for the hydrolysis of cellulose to produce nanocellulose. Sulfuric acid hydrolysis generates the sulfate functional groups on the surface of cellulose facilitating the dispersion of nanocellulose in aqueous media [111]. The hydrolysis time and acid concentrations play important roles in nanocellulose properties. Sulfuric acid hydrolysis produces higher surface charges than the phosphoric acid treatment [110,112]. The reduction in sample crystallinity also occurs through acid hydrolysis due to the breaking of hydrogen-bonded linkages in the structure [113,114]. Acetylation is performed to alter the hydrophilic property of nanocellulose to the hydrophobic surface [115]. Transesterification is a "grafting-from" type of modification that includes ring-opening polymerization [116]. These modifications produce long chains originating from the surface of cellulose. The degree of substitution of these reactions is not yet fully reported [117,118]. Esterification also includes the reaction with citric acid, phosphoryl chloride, and acetic acid. This modified nanocellulose has wide application into transdermal drug delivery systems [119].

The oxidized nanocellulose is used as a hemostatic agent due to its better biodegradability and biocompatibility. The mechanism of oxidation of primary alcohol with TEMPO is shown in Fig. 3(a) [120]. The oxidation process introduces carboxylic acid or aldehyde groups to cellulose surfaces [121]. The properties of oxidized cellulose are profoundly affected by the nature of the oxidant, temperature, reaction duration, and pH [122]. The oxidized nanocellulose can be obtained by reacting it with nitrogen dioxide gas vapor [123], TEMPO-mediated oxidation [124], nitroxyl radicals, and sodium periodate [125]. The improved water-absorbing capacity, antibacterial effect, and well dispersibility make oxidized nanocellulose ideal for wound dressing application than other cellulosic materials [126]. The nanocellulose hydrophobicity can be improved *via* silylation, grafting, and solvent exchange in ionic liquids. Silylation is a technique that includes the reaction of hydroxyl groups of nanocellulose to alkoxysilanes and polysiloxane [127]. The silylated nanocellulose exhibited enhanced hydrophobicity, thermal and mechanical strength and can be applied as biomaterials, adhesives, coatings, and optical devices. Carboxymethylation is performed to generate a negatively charged surface [128]. The charged nanocellulose can be applied to deliver the plasmids and proteins. The nucleophilic molecule attacks on the hydroxyl group of nanocellulose surface to obtain a 6-carboxymethylated derivative. The carboxymethylation process reduces the crystallinity and thermal stability of the products. Eyley et al. mentioned that the nucleophilic substitution reactions are not widely used; it still shows many functionalization options on nanocellulose surfaces [90]. Nucleophilic substitution primarily occurs at the C6 carbon atom. The first reported nucleophilic substitution on nanocellulose was the chlorination with thionyl chloride [129]. The amidation mechanism using carbodiimides to form an N-hydroxysuccinimidyl ester intermediate is shown in Fig. 3 (b) [90]. Amidation causes the insertion of amide groups *via* nucleophilic substitution [90]. Nanocellulose properties can be tuned by grafting it with different polymer chains [130]. Polycaprolactone (PCL) can be grafted on cellulose surface using toluene-2,4-diisocyanate (TDI) [131]. The reaction is performed in toluene in the presence of a triethylamine catalyst. Grafting of PCL with nanocellulose *via* ring-opening polymerization is given in Fig. 3(c).

The diisocyanate-grafted nanocellulose exhibited improved mechanical and thermal properties compared to the pure nanocellulose [91]. The positively charged surface facilitates the binding of plasmids, RNA, and DNA. Ammonia, polyethyleneimine, and poly (N-[3-(dmethylamino)-propyl]methacrylamide) [45,95] are extensively used to generate the positively charged surface. S. Dong and coworkers grafted the ammonia-modified CNCs with folic acid and examined their uptake efficiency in cancer cells. Folic acid conjugated CNCs showed better cellular uptake potential in human brain tumor cells [95]. Grafting of nanocellulose with polymer *via* free radical is given in Fig. 3(d) [132].

Magnetic nanocellulose is considered an emerging class for biomedical applications due to its high active surface area, low sedimentation rate, and decisive role in encapsulation [133]. Magnetic particles incorporated with nanocellulose can open up new materials of ferromagnetic applications [134]. It allows target selectivity, detection, and treatment *via* magnetic resonance imaging and inductive heating [135]. Fe_3O_4, $CoFe_3O_4$, $MnFe_3O_4$, Co, Fe, Ni, $FeNi_3$, $BaFe_{12}O_{19}$, and magnetic cobalt–Prussian blue NPs are often used for magnetic modifications. The aggregation is the major disadvantage of this modification due to their inter-particle dipolar forces.

4. Delivery of active molecules/therapeutic agents

Nanocellulose exhibits excellent biocompatible properties, inertness nature, compatible surface, and mechanical properties, making them an attractive material for the delivery of therapeutic agents. Furthermore, the abundant hydroxyl groups in nanocellulose can provide a broad range of surface functionalization generating the reactive charged nanocellulose composites. The superior properties and various modifications of nanocellulose lead to versatile applications in the biomedical

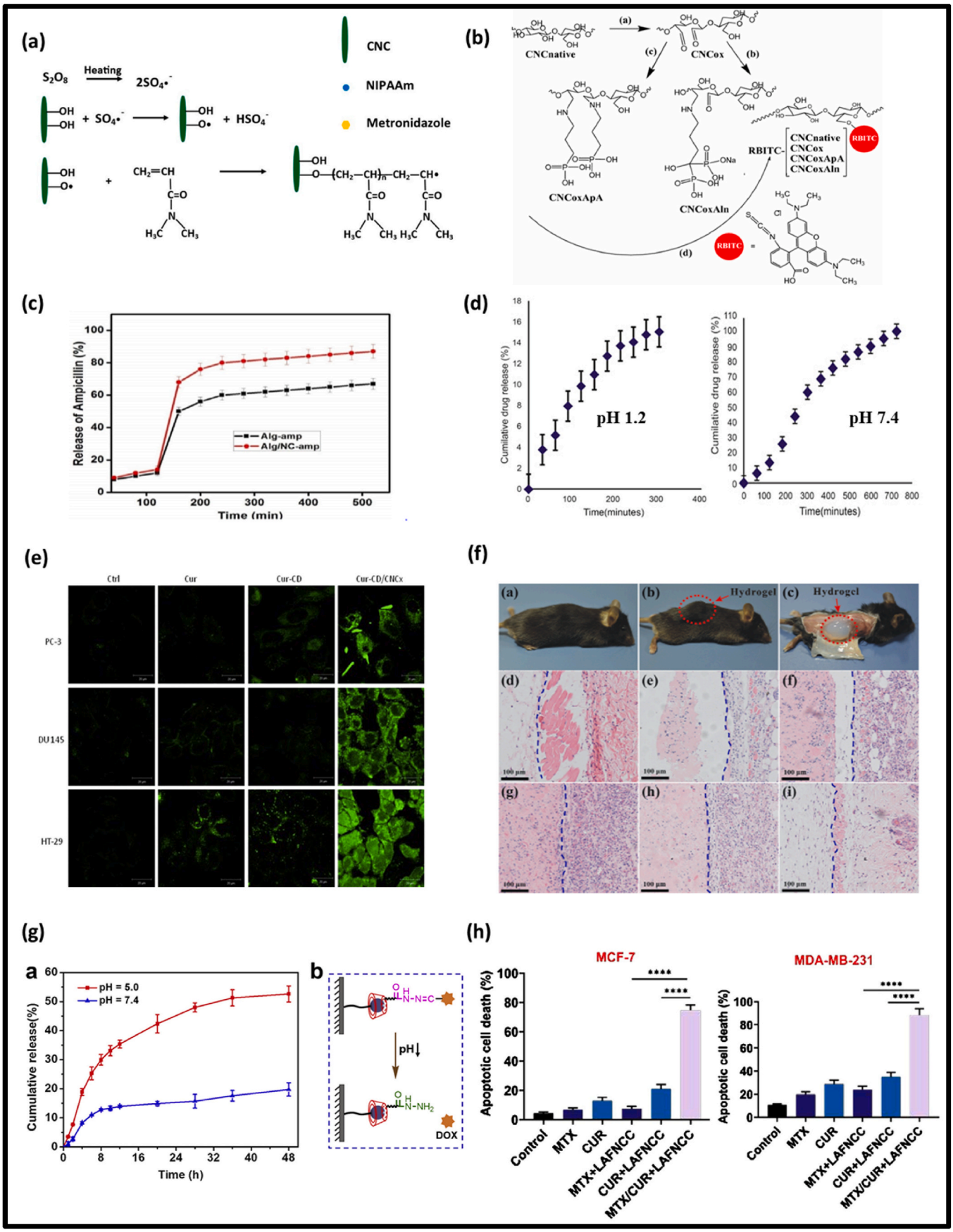


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Fig. 4. **(a)** Synthesis process of PNIPAAm grafted on modified CNC [137]; **(b)** Mechanism of modification of CNC to load with Aln and ApA and conjugation with fluorescent dye RBITC [138]; **(c)** Release profile of ampicillin from alginate-CNC composite [139]; **(d)** Rifampicin drug release profile in gastric (pH 1.2) juices (left) and intestinal (pH 7.4) juices (right) [141]; **(e)** Confocal microscopy images of PC-3, Du 145, and HT-29 cells with treatment of curcumin, curcumin-CD, and Curcumin-CD/CNCs. Green fluorescence shows the presence of curcumin [144]; **(f)** View of before (i) and after (ii) injection of hydrogel, Dissection of mice after 10 min injection of hydrogel (iii), histological images of implantation of gel into mice at 0 (iv), 2 (v), 4 (vi), 8 (vii), 12 (viii) and 16 (ix) days. Hydrogel is present on the left side of blue lines [145]; **(g)** Release of DOX from DOX-SNPs in pH 7.4 and 5.0 medium (left) and schematic illustration of pH-responsive acid-catalyzed hydrolysis of hydrazone bonds presenting the fast release of DOX from DOX-SNPs [146]; **(h)**Apoptotic cell death in MCF-7 and MDA-MB-231 cell line after treatment with single and dual drug-loaded nanoparticles [147].

Table 3
List of nanocellulose composites used in drug delivery systems.

Polymer matrix	Drug	Highlights	Fabrication technique	Reference
NCMC-ALG-Ch hydrogel beads	Dexamethasone	pH-sensitive drug release potential drug delivery system	–	[167]
Ch-CMC	5-Fluorouracil, Tetracycline Hydrochloride	Accelerated release in weak acidic condition Enhanced inhibition to HepG2 cell line	Emulsion crosslinking, Ultra-sonication	[168]
CNC-Chitosan	Repaglinide	~98 % drug encapsulation, Suitable for antidiabetic-controlled release of drug	Ionic gelation, Ultra-sonication	[169]
Magnetic NC-ALG	Ibuprofen	Improved mechanical strength and swelling property, decreased ibuprofen release	Co-precipitation	[135]
BNC	Ceftriaxone	Support in wound dressing to release different antibiotic to treat skin infections	–	[170]
BNC-dinitrogen tetraoxide	Cisplatin	pH-responsive and sustained drug release	Oxidation	[171]
Hordein-Zein-CNC	Riboflavin	Increased mechanical properties, Decreased burst effect and controlled drug release	Electrospinning	[172]
CTAB-CNC microemulsion	Curcumin	Potential microemulsion for controlled release in topical systems	Homogenization (Vortex mixer)	[173]
BNC	α-mangostin	High anticancer activity against MCF-7 breast cancer cells and B16F10 melanoma cells	Impregnation	[174]
Oxidized–CNC–(HDA)	Paclitaxel	Inhibition of A549 and HepG2 cells was increased.	Dispersion, Freeze-drying	[175]
(β-CD)-CNC	Chalcones	Enhanced *in vitro* antiproliferative activity against colorectal and prostatic cancer cells.	Ultra-sonication	[176]
(AND)–CNC–MGO	Curcumin	Dual stimuli-responsive nanoparticle, synergistic therapy against colon cancer cells.	Layer-by-layer assembly	[177]
CS-PEO-CQDs/CMC-PVA	Temozolomide	Cytotoxicity of TZM towards U251 cancer cell line	Coaxial electrospinning technique	[165]
DGN-ALG-Q-NC Pickering emulsion	Quinalizarin, diosgenin	Excellent stability, high encapsulation, and sustained drug release.	Layer-by-layer colloidal stabilization	[178]

NCMC; nano carboxymethyl celluloses, ALG; alginate, Ch; chitosan, CMC; carboxymethyl cellulose, NC; nanocellulose, CTAB; cetyltrimethylammonium bromide, HDA; hexadecyl amine, β-CD; β-cyclodextrin; AND; aminated nanodextran; MGO; modified graphene oxide, PEO; polyethylene oxide, CS; core/shell chitosan, CQDs; carbon quantum dots, PVA; polyvinyl alcohol, DGN; diosgenin.

field. Here, we discussed the potential of nanocellulose or nanocellulose-based polymer composites for the delivery of active molecules, such as drugs, proteins, and plasmids, by considering some significant works.

4.1. Drug delivery

Nanocellulose-mediated drug delivery system is an advanced technology with regular new inventions. In the past few years, researchers have focused on modifying nanocellulose to form nanocomposites and hybrids for the sustainable and target-specific delivery of bioactive molecules [31]. Nanocellulose is utilized as aerogels, cryogels, hydrogels, microparticles, nanoparticles, and membranes in the drug delivery system. Controlled and targeted delivery is considered the most effective approach in the drug delivery system. A potential drug delivery mediator should have a high degree of polymerization, high surface-area-to-volume ratio, high loading and binding capacity, low weight, and, most important, biocompatibility. Additionally, nanocellulose facilitates drug delivery efficiency through cellular binding and uptakes.

Several routes, such as oral, ocular, topical, and transdermal, are recommended to deliver drugs [6]. The drug delivery results show the pharmacokinetics and pharmacodynamics performance of the drugs, including the circulation time, availability of the drug at the desired site, and the impact of the delivered drug on the metabolism pathway. The potential of nanocellulose-based composites has already been proved for application in drug delivery systems due to their biocompatibility, inertness, and outstanding surface and mechanical properties. However, there is still a concern for its clinical application. The lack of antimicrobial and bioactive properties restricts the pure nanocellulose in drug delivery systems for wound healing and hemostasis. Therefore, it is necessary to modify the nanocellulose with antimicrobial and bioactive properties for these applications. The modified nanocellulose can be used for the delivery of various drugs in biomedical applications [136].

Zubik et al. synthesized the CNC-grafted PNIPAAm thermo-responsive hydrogels to deliver the metronidazole drug for wound dressing application [137]. Fig. 4(a) shows the synthesis process of PNIPAAm-CNC hybrid hydrogels [137]. An enhancement in the elasticity and viscosity occurred in CNC-grafted PNIPAAm hydrogels with the increasing amount of CNC as compared to the pure polymer hydrogel (PNIPAAm). An improvement in the mechanical strength was also observed in CNC-grafted PNIPAAm hydrogels vis-à-vis pure polymer hydrogel. However, hydrogel showed a decrease in thermal stability with increasing CNC content. The drug loading capacity and release are profoundly affected by the initial drug loading amounts. The 47.3 mg drug loaded/1 g swollen hydrogel showed 80 % release in 40 min, followed by a sustained release (86 %) to 24 h. At the same time, 9.2 mg drug-loaded composite showed 72 % release in 40 min, continued by the sustained release (82 %). The 100 % drug was not achieved even after 120 h. In another study, cellulose nanocrystals were covalently conjugated with sodium alendronate (Aln) and 3-Aminoropylphosphoric acid

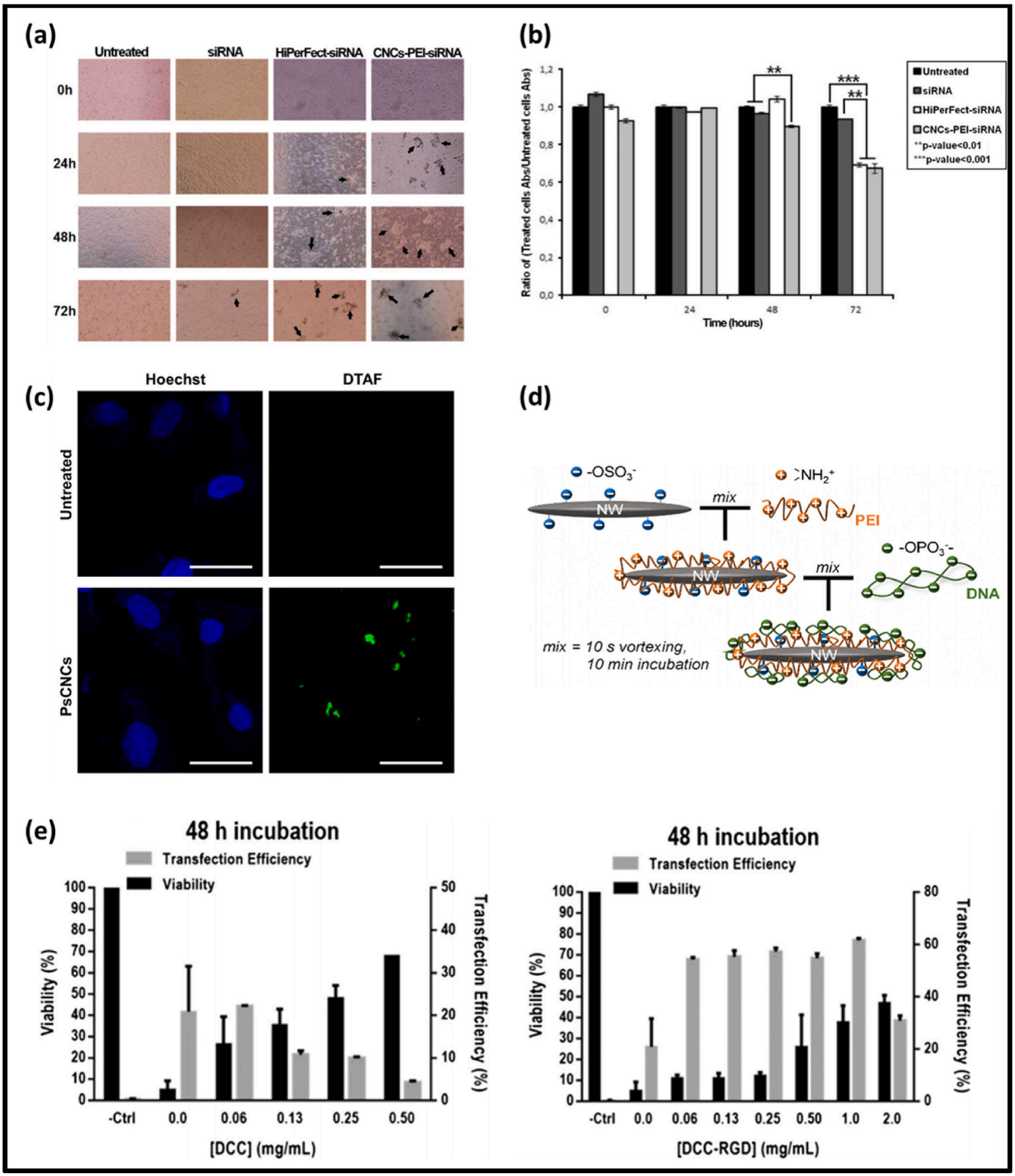

Fig. 5. **(a)** Images of untreated and treated cells with siRNA and siRNA complexes within 72 h under proliferation conditions. The arrows show the aggregates of cellular debris; **(b)** Cell viability was represented by the ratios of the absorbances recorded after MTT assay. Significant differences at 48 and 72 h were indicated by stars; **: p-value < 1 %, ***: p-value < 0,1 %, n = 3 [45]; **(c)** CLSM images of DTAF stained PsCNCs (green fluorescence) treated SKOV3 cells and untreated cells. Nucleus stained with Hoechst-33342 (blue fluorescence) [179]; **(d)** Schematic presentation of loading of DNA on nanocellulose [183]; **(e)** Viability and transfection efficiency of NIH3T3 cells treated with various concentration of DCC (left) and DCC-RGD (right) for 48 h [184].

Table 4
List of nanocellulose based polymer matrix used for delivery of nucleic acids.

Polymer matrix	Plasmid/Gene	Functional properties	Fabrication technique	Reference
CNC-*g*-PPEG/PDMA-Au	pDNA	Promising model multifunctional therapy system.	ATRP, RAFT	[180]
BNC-amine	siRNA	Low cytotoxicity, high cell viability, potential nanocarriers for nucleic acid delivery	Ultra-sonication	[86]
BNC-GAM hydrogel	pSV-β-Gal and pGL3	Promising carrier for local gene delivery	Injection technique	[44]
(OHMPC)-(HA-ADH)-(ori)-alginate microspheres	siRNA-29a	Increased diabetic wound healing, angiogenesis factors production, Inhibited pro-inflammatory factors	Lyophilization, Freeze drying, Dispersion	[181]
Alginate-methylcellulose hydrogel	pDNA	Treatment of injuries and disorders, Regeneration of complex tissues, Controlled release.	3D printing	[182]
CNC-PEI-siRNA	siRNA	Delivery confirmed by EtBr fluorescent labeling, Inactivation of the targeted cell cycle,	Reductive animation reaction, Electrostatic effect	[45]
CNC-CHPTAC	Polymeric siRNA	High enzymatic stability, Gene knockdown ability, Apoptosis, Enhanced dispersity	Hydrothermal sulfation, Electrostatic interaction	[179]

PPEG; PPEGEEMA; poly(poly(ethylene glycol) ethyl ether methacrylate), PDMA– PDMAEMA; poly(2-(dimethylamino)ethyl methacrylate), ATRP; atom transfer radical, OHMPC; oxidized hydroxymethyl propyl cellulose, HA-ADH; adipic dihydrazide-modified hyaluronic acid, ori; oridonin, CHPTAC; 3-chloro-2-hydroxypropyl-trimethyl ammonium chloride.

(ApA) by oxidation/Shiff-base reaction for therapeutic applications [138]. CNC was functionalized with *(bis)* phosphonate molecules, followed by the chemical tagging with the rhodamine B isothiocyanate (RBITC), fluorescent dye to examine the internalization and interaction of functionalized CNC with human osteoblasts. The mechanism for the conjugation of Aln and ApA molecules with CNC and tagging of a fluorescent dye is presented in Fig. 4(b). The pure CNC exhibited better cell growth than Aln and ApA conjugated CNC. However, cellular uptake was detected with Aln and ApA conjugated CNC in human osteoblast cells. They found that the ApA/Aln-modified CNCs can be used in bone diseases and theranostic applications.

Alginate is a natural biopolymer extracted from seaweed and considered a potential drug carrier. Nanocellulose is usually added to enhance the mechanical stability and durability of alginate. Nanocellulose-based alginate films were fabricated by the solution casting method to study ampicillin drug release profiles. Alginate/nanocellulose films exhibited improved swelling and mechanical properties [139]. Increased tensile strength and decreased elongation at break were observed due to the reinforcing effect of nanocellulose. The ampicillin drug release profiles are given in Fig. 4 (c). A higher release of ampicillin drug was seen in alginate/nanocellulose film than in the alginate film. Guo et al. synthesized cellulose/alginate beads by a simple droplet extrusion/precipitation method to study metformin hydrochloride (MH) drug release. They used cellulose fibers (cotton linter (CL)), micro-crystalline cellulose (MCC), and micro-fibrillated cellulose (MFC) and examined the stability, drug release property, and mechanical property of the prepared composites. The MFC/Alg showed improved hardness due to the increased intermolecular interaction of MCF with alginate, and it was to be 11.87 kg. The addition of cellulose increased the drug encapsulation, and 44 % of release was observed within 100 min at pH 1.2 in all the composites. The developed beads demonstrated the sustained release pattern at pH 6.8 and 7.4 [140]. Thomas and co-workers fabricated pH-sensitive alginate/CNCs hybrids for rifampicin oral drug delivery [141]. Rifampicin is a strong antibiotic drug and used in the treatment of tuberculosis. The alginate/CNCs hybrids were synthesized by the ionic gelation technique using divalent calcium ions from natural honey as a stabilizing agent. The size of hybrid nanoparticles was reduced to 100 nm by the probe sonication technique. It has been observed that CNC/ALG in 1:6 and RIF/ALG in 1:4 ratios exhibited high drug entrapment efficiency (69.73 %). The release of rifampicin was pH-sensitive, and the release profiles of rifampicin drug at different pH is shown in Fig. 4 (d). Nearly 10–15 % drug was released at pH 1.2 in 2 h, whereas 100 % drug was released in pH 7.4 within 12 h due to the different swelling efficiency of alginate/CNCs hybrids under different conditions. An improvement in the mechanical strength was also observed in the alginate/CNCs hybrids compared to the pure alginate polymer [141]. Supramaniam and co-workers developed alginate/iron oxide modified CNCs composites to deliver the ibuprofen drug [135]. Enhanced mechanical and swelling potentials occurred in alginate/iron oxide modified CNCs composites than the pure alginate scaffolds, showing the positive effects of nanocellulose. The 3 % magnetic CNCs (m-CNCs) added alginate beads showed high drug loading (3.2 %) and encapsulation efficiency (38.3 %). This was attributed to the large and well-developed pore size on alginate beads compared to other samples, which facilitated the drug loading and encapsulation efficiency. The fast release of the loaded drug occurred within 30 min, followed by the gradual release up to 330 min. The m-CNCs loaded scaffolds exhibited a sustained release of ibuprofen drug than those of pure alginate scaffolds. The addition of metal nanoparticles increased the mechanical strength of alginate hydrogel, which helped to prevent the cracking of hydrogel beads and target selectivity. The sustained release exhibited better therapeutic potential.

Firoati et al. synthesized the branched polyethyleneimine (bPEI)/TEMPO-oxidized CNFs (TO-CNFs) organic porous Aerogels for biomedical applications. Citric acid was used as a cross-linking agent. The release behavior of amoxicillin (AM) and ibuprofen (IB) drugs was evaluated. Citric acid cross-linked Aerogels exhibited superior mechanical strength with the controlled release of the loaded drugs. An enhancement in the adsorption of IB was observed with increasing the citrate moieties on TO-CNFs. Still, the AM loading was unaffected with TO-CNFs content, showing that the drug loading capacity differs with varying drugs [142]. Further, they monitored the release behavior of IB from polyethyleneimine (bPEI)/TEMPO-oxidized and ultra-sonicated CNFs (TOUS-CNFs) hydrogels cross-linked with calcium chloride. Improved mechanical strength was observed in cross-linked hydrogels, and this property was also profoundly affected by the concentrations of cross-linking agents. The cross-linked hydrogels demonstrated the sustained release pattern of the loaded drug [143].

Cellulose-based Aerogels are promising materials in biomedical applications due to their degradability, high porosity, and surface area, non-cytotoxicity, biocompatibility, and availability. Liu and coworkers fabricated the cellulose-based aerogels and examined their drug delivery potential. The fabricated aerogels exhibited low drug loading and fast release properties, which can be controlled by altering the stimulating factors, such as temperature and pH [148]. In another study, Dash et al. synthesized the gamma aminobutyric acid grafted cellulose nanowhisker for drug delivery. The functionalized nanocellulose showed the controlled and fast delivery of syringyl alcohol [149].

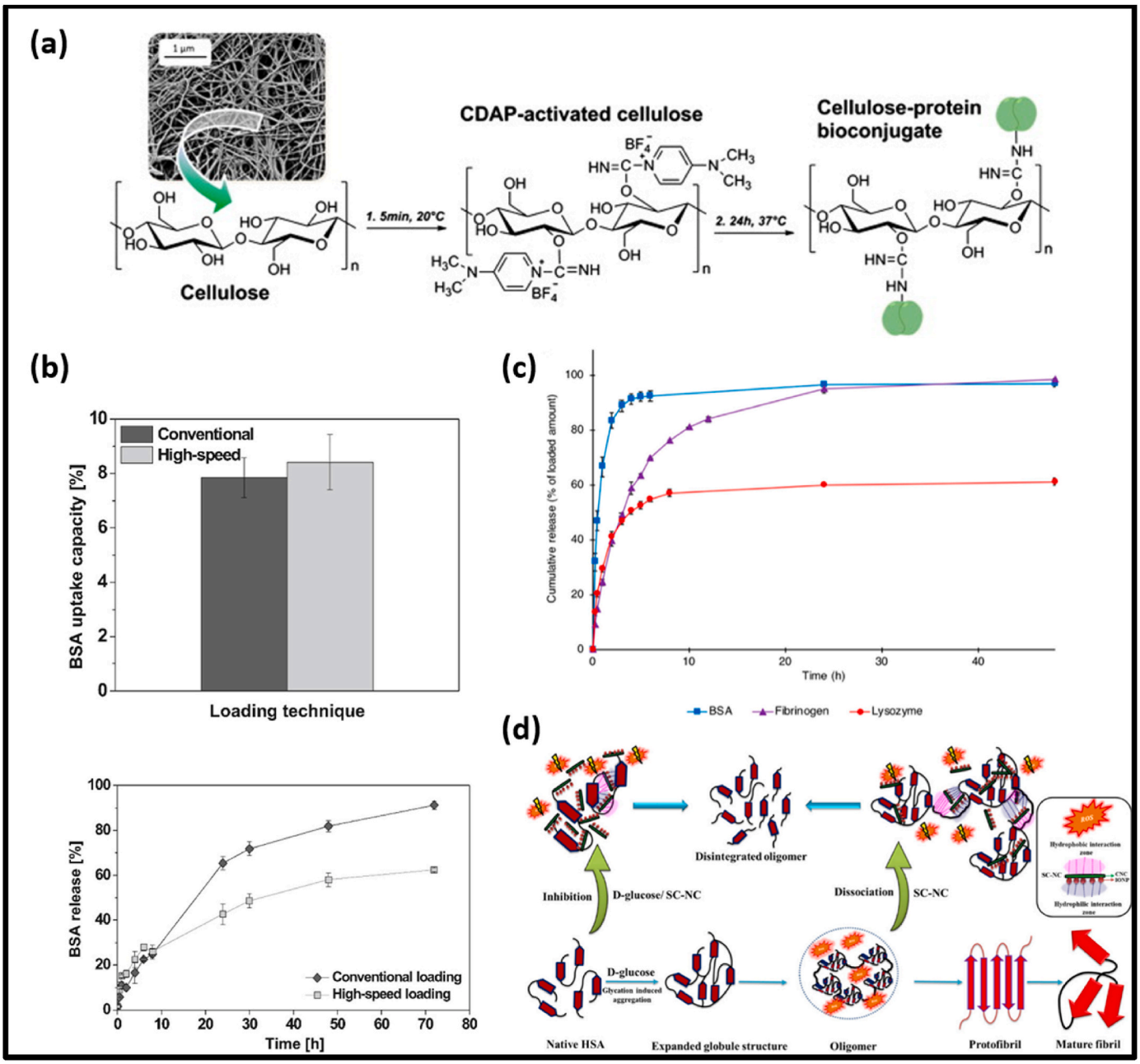

Fig. 6. **(a)** Reaction of CDAP treatment on BNC for protein conjugation [80,189]; **(b)** Comparison of BSA uptake (left) and release (right) profiles through conventional loading and high-speed loading technique [186]; **(c)** *in vitro* protein release profile from nanocellulose hydrogels within first 48 h [190]; **(d)** Schematic presentation of inhibition of glycation-induced aggregation of HSA by Iron Oxide-Functionalized nanocellulose [191].

Chitosan is a polysaccharide widely used in biomedical applications due to its distinct properties, such as low toxicity, biocompatibility, and biodegradability. The hydrolyzed jute CNFs/chitosan matrix composites were synthesized to develop a drug carrier for the potential use in transdermal delivery of ketorolac tromethamine (KT) [150]. The sustained release of the loaded drug was observed in CNFs/chitosan composites compared to the pure chitosan polymer.

Hivechi et al. synthesized polycaprolactone (PCL)/CNCs composites for the delivery of tetracycline drug [151]. The sustained release of tetracycline drug was observed in (PCL)/CNCs composites than the pure PCL due to the presence of CNCs in the polymer matrix, which restricts the release of tetracycline drugs. Saidi and co-workers fabricated the pH-responsive *N*-metharyloyl glycine (MGly)/BNC composites under green reaction conditions to deliver diclofenac drug through transdermal and oral routes [152]. The developed composites exhibited improved mechanical, thermal, and viscoelastic properties. An enhancement in the water uptake potential was also observed in the developed composites. The controlled delivery of diclofenac drug was observed in N-metharyloyl glycine (MGly)/BNC composites compared to N-metharyloyl glycine due to the BNC.

Cancer is a renowned dangerous disease caused by uncontrollable cell division and its spread into surrounding tissues. There are more than 100 types of cancer, and it is the second leading cause of death globally. Various drugs such as curcumin, doxorubicin, methotrexate, 5-fluorouracil, and cisplatin are used in cancer treatment. Surgery, radiation therapy, chemotherapy, and immunotherapy are commonly used approaches in cancer treatment [153]. Curcumin is a phenolic compound extracted from turmeric and has medicinal properties, such as anti-microbial, anti-cancer, and anti-inflammatory. It is also used against Alzheimer's and diabetic disease [154]. Several reports are

Table 5
List of nanocellulose composites for delivery of proteins.

Polymer matrix	Protein	Functional properties	Fabrication technique	Reference
CNF, CNC	Hydrophobin	Synergistic effect in formation and stability of the oil-in-water emulsion.	Injection, compression	[193]
BNC-methoxylated pectin	HSA	Controlled release of molecules.		[194]
NC	Chlorotoxin	Brønsted acid ionic liquids used as both solvent and catalyst	Dispersion	[188]
CNF–Ca^{2+}/Mg^{2+}	RGD peptides	Promising hydrogels for 3D cell culture systems		[195]
Ca^{2+}-CNF hydrogel	BSA, lysozyme, fibrinogen	Large size and positive charge proteins show sustained release; Positive charge protein increased strength of hydrogel, Sustained protein activity	Simple soaking method	[190]
BNC-*g*-Poly(acrylic acid) hydrogels	BSA	Excellent compatibility and safe for oral protein delivery	Irradiation	[196]
CNC-ED-iron oxide	HSA	Disfavors inhibition of protein aggregation	Dispersion, Sonication	[191]

RGD; arginylglycylaspartic acid, HSA; Human Serum Albumin, BSA; Bovine Serum Albumin.

available where the loading of curcumin drug has been reported for therapeutic applications [155]. Zainuddin et al. reported that the binding efficiency of curcumin was dependent on CTAB concentrations. Nearly 150-folds increased risk of amputation has been reported in microbial-infected diabetic patients with foot ulcers [156]. Gunathilake et al. prepared the chitosan/CNCs hydrogels for the stomach-specific delivery of curcumin drugs [157]. Ndong Ntoutoume et al. developed *β*-cyclodextrin (β-CD)/CNCs composites for the delivery of curcumin in PC-3 (human prostate cancer cell line), DU 145 (human prostate cancer cell line), and HT-29 (human colorectal adenocarcinoma cell line) cells, and results are shown in Fig. 4(e). Green fluorescence indicates the presence of curcumin drugs. Enhanced cellular uptake and curcumin delivery was observed with *β*-CD/CNCs composite compared to the pure *β*-CD. The curcumin-loaded composites exhibited improved anticancer potential against PC-3 and HT-29 than pure drugs [144].

You and co-workers developed cationic CNCs reinforced quaternerized cellulose (QC/cCNCs) hydrogels to deliver the doxorubicin (DOX) for cancer treatment. The developed hydrogels were cross-linked with *β*-glycerophosphate (β-GP). The developed hydrogels were injected into the mice and examined their responses. The hydrogels were biocompatible, and the histological images are shown in Fig. 4(f). The developed hydrogels also demonstrated the sustained release of the loaded drug with improved therapeutic efficacy [158]. To deliver DOX at different pH levels, Yang et al. synthesized cellulose-based supramolecular nanoparticles (SNPs) through a host-guest mediated self-assembled approach. *β*-cyclodextrin-grafted glycerol ethoxylate and adamantane-grafted carboxyethyl hydroxyethyl cellulose were developed, and the preparation scheme is given in Fig. 4(g) (right). The diameter of the prepared SNPs was around 25 nm. Approximately 94 % loading of DOX occurred in developed SNPs. *In-vitro* release of the loaded DOX from the developed SNPs at different pH is shown in Fig. 4 (g) (left). The higher release of the loaded drug was observed at a low pH (5.0) compared to high pH (7.0), suggesting its pH-responsive release potential. This property is desirable for cancer treatment [146]. Tortorella and coworkers synthesized the carbamate-linked nanocellulose and evaluated their doxorubicin release behavior. The modified nanocellulose was stable in the aqueous medium and hydrolyzed in the cells [159]. Cacicedo and co-workers performed a comparative study to monitor the cationic DOX release behavior and neutral DOX from BNC/nanostructured lipid carriers (NLCs) hybrid systems (BC-NLC) against MDA-MB-231 cell lines. The drug loading efficiency of BC-NLC hybrids was 48 and 97 % for cationic and neutral DOX, respectively. The cationic DOX-loaded hybrids exhibited the faster release of the drug, whereas the sustained release was observed in neutral DOX-loaded hybrids. A significant decrease in tumor cell growth was observed with drug-loaded hybrids [160]. CNCs-based nanomedicine was developed by the *layer-by-layer* (LbL) assembly technique with a combination of folate (FA), *cis*-aconityl-doxorubicin (CAD) polyethyleneimine (PEI), and CNC [161]. The lysosomal pH-controlled drug release was observed in the nuclei with increased cellular uptake and drug loading potential. Approximately 95 % of doxorubicin (DOX) was released at pH 5.5 within 24 h. Golshan et al. evaluated the release behavior of DOX from poly (propylene imine) grafted CNCs conjugated with folic acid (FA) at different pH. The controlled drug release was observed in FA conjugated composites compared to nonconjugated composites due to the steric hindrance of functional groups, which prevented loaded DOX release [162].

Methotrexate is a well-known anti-cancerous drug that inhibits protein synthesis for cell division by blocking the dihydrofolate reductase (DHFR) enzyme [163]. Fakhri et al. synthesized the quantum dots decorated CNFs composites of Fe_3O_4–Ag_2O to deliver the etoposide and methotrexate drugs. The drug-loaded composites showed better therapeutic efficacy against skin cancer than the pure drugs [164]. Solomevich and co-workers evaluated the release behavior of anti-cancerous cisplatin (CDDP) drug from BNC against Human cervical epithelial carcinoma (HeLa) cell lines. BNC was oxidized with nitrogen dioxide in chloroform and cyclohexane solvents to achieve more carboxylate functional groups. The controlled and pH-responsive release of loaded cisplatin was observed from BNC against HeLa cell lines (Solomevich et al., 2020).

The implantable drug delivery systems are a promising strategy for local drug delivery in treating malignant brain tumors. Shamsipour et al. prepared core/shell chitosan-polyethylene oxide-carbon quantum dots/carboxymethyl cellulose-polyvinyl alcohol (CS-PEO-CQDs/CMC-PVA) nanofibers through a coaxial electrospinning technique for the local delivery of temozolomide (TMZ). The carbon dots act as a fluorescence marker. The TMZ loaded nanofibers showed improved anti-cancerous potential than the pure TMZ drug against U251 cancer cell lines [165].

Multiple drug delivery is a promising strategy in cancer treatment to achieve a synergistic effect and overcome the adverse effects of any single drug used within a combination. Moghaddam et al. developed pH-responsive composites of nanocellulose and L-lysine for the combined delivery of curcumin and methotrexate drugs against MCF-7 and MDA-MB-231 cancer cell lines. Nanocellulose was conjugated with L-lysine amino acid *via* 3-amino propyl-3-methoxy silane (APTMS) molecule and stabilized by the etheric linkages. The combined systems exhibited better anti-cancerous efficiency compared to the single drug-loaded system. The anti-cancerous potential of the dual and single drug-loaded system against MCF-7 and MDA-MB-231 cell lines is presented in Fig. 4(h). The dual drug-loaded systems exhibited a greater apoptosis effect against both cell lines. The results indicated that the combined strategy is a suitable approach for delivering multi-drugs in cancer therapy [147].

Erdagi et al. developed the multilayer emulsion as a nano-carrier for the controlled delivery of quinalizarin and diosgenin drugs. The *layer-by-layer* colloidal stabilization technique was applied to develop the diosgenin-conjugated alginate (DGN-ALG)/quaternerized nanocellulose (Q-NC) composites loaded with drugs. The Q-NC core was coated with anionic DGN-ALG, which enhanced the hydrophobic and sustainability of Q-NC. The developed emulsion exhibited superior stability, improved

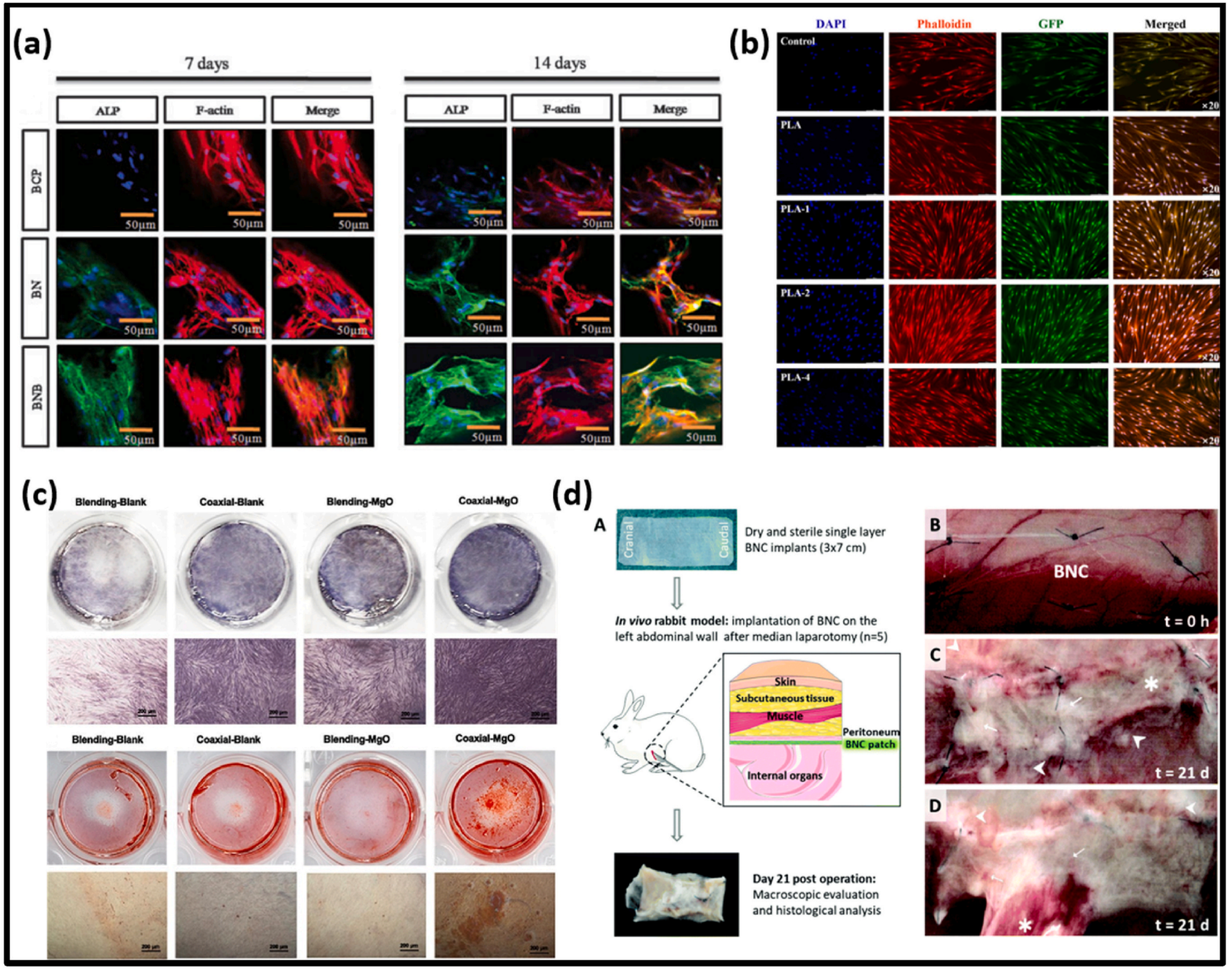

Fig. 7. **(a)** Confocal micrographs showing ALP protein localization (green) at 7 days and 14 days in RBMSCs on the treatment of scaffolds to explore the effect of BMP2 and VEGF [197]; **(b)** Fluorescence microscopy images of growth of BMSCs on CH–CNC scaffolds after 3 days [198]; **(c)** ALP staining (after 7 days) and Alizarin red staining (after 14 days) of hPDLSCs after cultured with electrospun membranes [200]; **(d)** Macroscopic evaluation and membrane adhesion to experimental model (rabbit) at 0 h and 21 days. → shows vascularization, ▸ fibrin accumulations and * depicts to adhesion [201].

Table 6
List of nanocellulose polymer matric for application in tissue engineering.

Polymer matrix	Active molecule	Highlights	Fabrication technique	Reference
CNC-PLA	CNC	Higher cell viability, Improved mineralization	Electrospinning	[203]
CNC-Gel-BG	BG	Enhanced mechanical strength, Bone regeneration	Sol-gel, freeze-drying	[204]
BNC-BSE	BSE	Skin disease treatment, Anti-inflammatory behavior	Emulsification	[205]
CNF-chitosan	Chitosan	High cell viability, bone regeneration	–	[206]
CNF-pectin/alginate	Pectin/alginate	Cytoskeleton development of stem cells	Dispersion, stirring	[207]
BNC	Coenzyme Q10	Delivery of lipophilic drug in porcine skin	Top-down high-pressure homogenization	[208]

PLA; Poly(lactic acid), Gel; gelatin; BG; Bioactive glass, BSE; *Boswellia serrata* extract, AA; Acrylic acid, HDF; Human dermal fibroblasts, HA; Hydroxyapatite.

biocompatibility, high encapsulation, and sustained-release property. The improved therapeutic potential was observed in the developed emulsion against MCF-7 and A549 cancer cell lines [166]. Nanocellulose-mediated drug release behavior is also summarized in Table 3.

4.2. Plasmid/gene delivery

Nanocellulose exhibits excellent biocompatible properties, inertness nature, compatible surface and mechanical properties which are favorable in delivery system. In addition to these outstanding properties, the abundant hydroxyl groups on higher surface area of nanocellulose can provide broad range of modification and surface functionalization, that could resulted into a reactive surface charged nanocellulose composite. Owning to these favorable properties can demonstrate the nanocellulose materials as a promising candidate in plasmid was well as protein delivery system.

The plasmid is an extrachromosomal DNA separated from the main chromosomal DNA and located within the cell. It is a low-molecular-weight biomolecule and can replicate independently. DNA is a negatively charged biomolecule and can strongly bind with the cationic matrix. Plasmid DNA and nanocellulose are negatively-charged molecules and can be assembled on a positively charged polyethyleneimine (PEI) surface *via* the *layer-by-layer* (LBL) approach. These LBL structures can be applied in the delivery systems. Ndong Ntoutoume and co-workers synthesized the PEI/CNCs hybrids for siRNA delivery [45]. CNCs were covalently grafted with the polymer chains of PEI, and the loading of siRNAs was accomplished through electrostatic effects. CNC-PEI showed zero toxicity, helped to protect siRNA from degradation and target delivery. The fluorescence intensity of ethidium bromide confirmed the siRNA delivery in the cell cytoplasm by the developed hybrids. They studied the inactivation of targeted cell cycle-related mRNA and cell death through the intrinsic apoptosis pathway. Fig. 5 (a) and (b) represents the cytotoxicity of siRNA and siRNA complexes. PEI/CNCs-siRNA treated media exhibited cell debris formation, suggesting the cell death Fig. 5(a). This finding was confirmed by MTT-1 assay, where a decrease in cell viability was observed (Fig. 5(b)). The results indicated that the PEI/CNCs-siRNA hybrids were more effectively inhibited the growth of C2C12 myoblastic cells compared to siRNA [45]. Similarly, Kim and co-workers synthesized the cationic CNCs by a hydrothermal process and modified them with 3-chloro-2-hydroxypropyltrimethyl ammonium chloride (CHPTAC) for the delivery of siRNA [179]. The polymeric siRNA was prepared by the two-step processes, including transcription and Mg^{2+} chelation. The modified CNCs were complexed with siRNA by the electrostatic interaction. Cationic CNC was optimized by adjusting the desulfation time to obtain highly positive surface potential and enhanced dispersity. They have chosen the SKOV3 cell lines for the delivery of siRNA. The cellular uptake of PsCNCs treated and untreated SKOV3 cells is represented in Fig. 5(c). The cell nuclei were stained with the Hoechst 33342 (blue fluorescence) to validate siRNA uptake. The appearance of green fluorescence (DTAF dye) in the CLSM image indicated the intracellular delivery of PsCNCs. The nanomaterial exhibited high enzymatic stability, enhanced dispersity, gene knockdown ability, and apoptosis, confirming cancer treatment potential [179]. Table 4 shows the nanocellulose-mediated delivery of different nucleic acids.

Comparatively, Potzinger et al. evaluated the potential of anionic modified BNC for safe and efficient gene delivery [183]. The plasmid DNA was bound with PEI through electrostatic interaction. Fig. 5(d) represents the loading of pDNA with PEI/BNC. They observed that the PEI/BNC hybrids stabilized DNA and facilitated the transfection in CHO–K1 cells with high biocompatibility. Therefore, PEI-modified BNC is suitable for delivering bioactive compounds [183]. In another study, they also evaluated the delivery potential of BNC hydrogels for the pSV-β-Gal and pGL3 plasmids [44]. The release behavior of plasmids was dependent on the type of BNC, plasmid, and loading technique. Small-sized plasmids can release faster than larger ones. Core-shell system-based delivery was sustainable for up to 50 days. The developed BNC-based hydrogels exhibited successful delivery of these loaded plasmids in the desired locations with high efficiency. It also protected plasmids from enzymatic degradation by nucleases. Hujaya et al. prepared the self-assembled arginylglycylaspartic acid (RGD)/dicarboxylic acid-functionalized nanocellulose (DCC) hybrids for gene delivery [184]. RGD/DCC hybrids also electrostatically interacted with positively charged PEI/pDNA polyplex solution and applied for gene delivery. RGD tripeptide improved cell adhesion and targeting, whereas transfection efficiency of fibroblast NIH3T3 cell line revealed that cell viability was increased with increasing nanocellulose concentrations. The viability and transfection efficiency of NIH3T3 cells treated with PEI/pDNA at different concentrations of DCC and RGD/DCC for 48 h is shown in Fig. 5(e). The developed hybrids have no adverse effects on NIH3T3 cells. Targeted uptake of polyplexes was possible with wild-type MDCK and αVintegrin knockout MDCK cells [184].

4.3. Protein delivery

Proteins are widely applied as growth factors, antibodies, and other forms in the biomedical field. BNC has a higher affinity for proteins compared to wood pulp nanocellulose. Müller et al. were first to evaluate the binding and delivery efficiency of BNCs for bovine serum albumin (BSA) protein [185]. BSA-loaded CNCs exhibited superior hydrophilicity, biocompatibility, and controlled drug loading and release capacity. Adsorption is a commonly used technique for loading drugs onto nanocellulose. For example, the synthesis process of 1-cyano-4-dimethylamino pyridinium (CDAP)-activated nanocellulose for protein delivery is shown in Fig. 6(a). Müller et al. developed a benchmark technique (vortexing) useful for high-speed protein loading [186]. This method showed effective loading of the drug without compromising the protein distribution and stability. They found that the loading of BSA was successful with slow release. The uptake of proteins by BNC was predominantly due to capillary forces and the large surface area caused by the presence of pore structures. A comparison of the conventional and high-speed techniques for BSA protein uptake and release profiles is shown in Fig. 6(b). They concluded that this technique could be used to load and deliver proteins with proper optimization [186]. Paukkonen et al. used anionic CNF hydrogels to deliver proteins (BSA) and small molecules [187]. The freeze-dried composites exhibited a highly porous structure, which could be redispersed without affecting the drug-releasing properties. Brønsted acid ionic liquids have proven to be excellent solvents and are considered suitable catalysts for

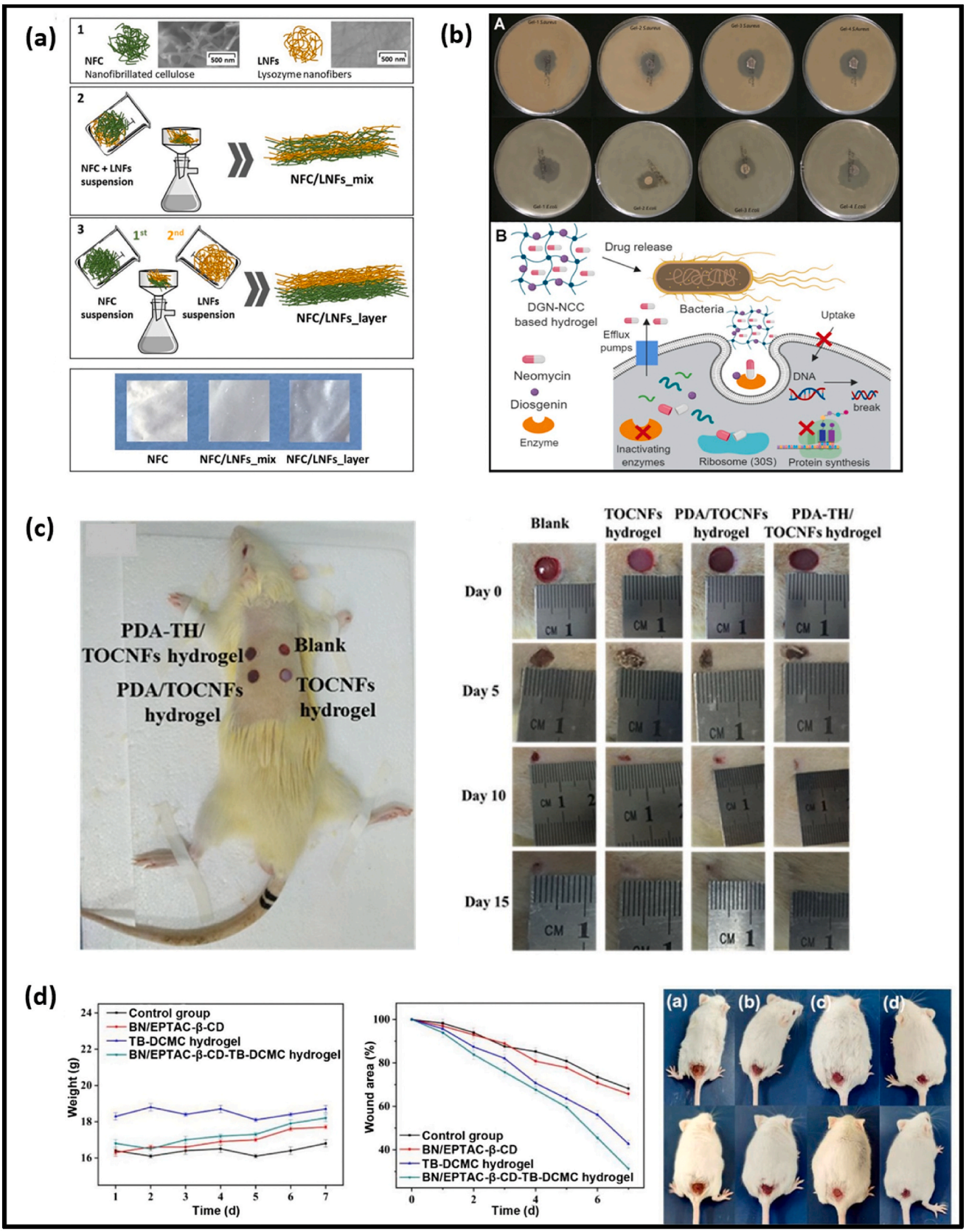

Fig. 8. **(a)** Schematic representation of the preparation of NFC-LNFs mixture and digital photographs of their patches [211]; **(b)** Picture of inhibition zones of neomycin and mechanism of neomycin loaded hydrogels [178]; **(c)** Wound healing of different groups of treatment (left), picture of the gross appearance of a wound treated with PDA/TOCNFs hydrogel and PDATH/TOCNFs hydrogel (14.4 wt% drug loading) at days of 0, 5, 10 and 15 [213]. **(d)** Changes in body weight of experimental mice within 7 days (left), changes in wound area of mice within 7 days (middle), Healing images of a wound of mice in a week (right) [a – control group, b – treatment with BN/EPTAC- β-CD hydrogel, c – treatment with TB-DCMC hydrogel, and d – treatment with BN/EPTAC- β-CD -TB-DCMC hydrogel] [214].

Table 7
List of various nanocellulose-based polymer matrix loaded with wound healing molecules and hemostasis.

Polymer matrix	Active molecule	Highlights	Fabrication technique	Reference
ALG-methylcellulose hydrogels	Honey, Aloe- vera, Eucalyptus essential oil	Good compatibility on human dermal fibroblasts, Stimulating cell growth	Dispersion	[215]
NC-PVP	Honey	Soft and flexible film, Ideal wound dressing for a long period	Simple stirring, Ultra-sonication	[212]
MFC-ODDMAC	ODDMAC	Antibacterial property at low concentration against gram-negative and gram-positive bacteria	Adsorption-curing process	[216]
Ca^{2+} crosslinked CNF hydrogels	Polymyxin B	Excellent biocompatibility towards dermal fibroblasts and blood-derived macrophages	Dispersion Ultra-sonication	[217]
BN/EPTAC-β-CD-DCMC	Borneol, Tobramycin	Self-healing and self-degrading property,	Ultra-sonication, Schiff-base reaction	[214]
CA-zein	Sesamol	Accelerated wound healing of diabetic mice	Electrospinning	[218]
Cotton gauze cellulose-carboxymethyl chitosan-gelatin-ALG	Gelatin, alginate	Superior capability for wound healing than cotton gauze	Layer-by-layer	[219]
Oxidized BC-Ch-collagen	collagen	Efficient and fast material, great potential as an adsorbable hemostat	Dispersion	[220]
Fibrous cellulose-Ch (acid-soluble and water-soluble)	chitosan	Potential application in blood loss control	Wet laying technique	[221]
a–CNC–PL cryogel	Platelet lysate	Fast and high blood absorption, Increased stem cell proliferation	Cryo-gelation	[222]
CNC-PL hydrogel	Platelet lysate	Outstanding biological properties, potential for application in a bioactive cell carrier matrix.	Coagulation cascade induction, Schiff's base reaction	[223]
ONFC-Ch sponge	chitosan	Superior biodegradability and biocompatibility	Lyophilization	[224]
CMC-KC- PEO-PEG	PEO, PEG	Hemorrhage control in 90 s in femoral artery rat bleeding model	Gamma irradiation	[225]
TOCN-PEG-ZnO	ZnO	Efficient and novel candidate as hemostatic agent. Antibacterial property.	Freeze drying	[226]

ALG; alginate, ODDMAC; octadecyldimethyl(3-trimethoxysilylpropyl) ammonium chloride, CA; cellulose acetate, PVP; polyvinylpyrrolidone, BN; borneol, EPTAC; mono-6-(2-hydroxy-3-(trimethylammonium) propyl), β-CD; β-cyclodextrin, DCMC; dialdehyde carboxymethyl cellulose, PL; platelet lysate, ONFC; oxidized nanofibrillar cellulose, Ch; chitosan, KC; kappa carrageenan, PEO; polyethylene oxide, PEG; polyethylene glycol, TOCN; TEMPO-oxidized nanocellulose.

esterification [188]. Fischer esterification is a suitable approach for the insertion of proteins into nanocellulose. The Chlorotoxin (Cltx) protein was conjugated to the surface of nanocellulose through an esterification reaction in a Brønsted acid medium. Chlorotoxin is a protein isolated from the venom of *Leiurus quinquestriatus* and has excellent potential for use in glioblastoma cancer cells. The modified CNC showed excellent results of biocompatibility and internalization of Chlorotoxin in the U87MG glioblastoma cells [188].

Basu et al. developed calcium chloride cross-linked CNF hydrogels for the delivery of biomolecules [190]. The simple soaking method was applied to load the BSA protein into a hydrogel. The positively charged large proteins promoted a sustained release process from CNF. The positively charged proteins also improved the mechanical strength of the hydrogels. The *in vitro* release profiles of proteins from the developed hydrogels are shown in Fig. 6(c). The electrostatic interaction between the protein and hydrogel was the major factor in physical adsorption that facilitated the structural stability and activity of the hydrogel. The Ca^{2+} cross-linked CNF hydrogel is suggested to deliver proteins without compromising its activity [190]. Singla et al. developed a protein-binding model from plant-derived CNCs *via* physical adsorption and chemical conjugation methods. They used BSA and human serum albumin (HSA) as model proteins to study conjugation and release profiles, which showed ≥ 90% bioactivity and desirable structural stability. Highly stable amide bond formed between carboxylate group of CNC and amine group of protein were responsible for chemical conjugation. The protein-conjugated CNC was able to disperse in an aqueous solution which showed that protein bounded CNC increases the hydrophilicity of nanocellulose. It was observed that HSA release profiles from CNC were higher than BSA in a 6.5 pH medium. The developed composites exhibited ~58–85% of cholesterol release from human umbilical vein endothelial cells and can be used in biomedical applications [192]. Protein aggregation leads to an insoluble composite in the body, which can accumulate and cause diseases. In another study, Singla et al. fabricated an organic-inorganic nanocomposite of CNCs conjugated with iron oxide nanoparticles to inhibit HSA protein aggregation [191]. *In vitro* studies have shown that CNC nanocomposites reduce aggregation-induced cytotoxicity in HEK-293 cells by maintaining Ca^{2+} ion channels and scavenging intracellular oxygen molecules (Fig. 6(d)). Thus, the results presented that nanocomposite provides a larger surface area for nanocomposite-protein interactions by opening simultaneous sites for hydrophilic and hydrophobic interactions. Even though the nanocomposite exhibits promising results, more research is required to declare this nanocomposite as a drug delivery mediator [191]. Nanocellulose-based protein delivery is shown in Table 5.

5. Applications in tissue engineering and regenerative medicine

5.1. Bone tissue engineering

Sukul et al. studied the sustainable release of bone morphogenic protein (BMP) and vascular endothelial growth factor (VEGF) from nanocellulose-based hydrogels for bone regeneration [197]. The developed hydrogel scaffolds showed better cell adhesion and proliferation behavior. The BMP2 and VEGF-loaded scaffolds demonstrated the improved new bone formation potential in orthopedic defects of rat bone marrow stem cells (RBMSCs) with and without stem cell treatment. The effects of the growth factors on alkaline phosphatase (ALP) protein expression in RBMSCs after 7 and 14 days of treatment are shown in Fig. 7(a). The greater expression of ALP was observed in BMP2 and VEGF-loaded scaffolds than in control, indicating its improved bone regeneration potential. CNC-incorporated alginate/gelatin scaffolds exhibited better cellular activities in human bone marrow-derived mesenchymal stem cells (hBMSCs) than pure alginate/gelatin scaffolds. The cellular activity was profoundly affected by CNC content in the polymer matrices [198]. An enhancement in the mechanical strength and swelling property was observed in CNC-incorporated alginate/gelatin scaffolds than the pure alginate/gelatin scaffolds. It has been seen that chitosan/CNC (CH/CNC) scaffolds facilitated better cellular activity and consequently improved osteogenic potential compared to the pure chitosan scaffolds. Fig. 7(b) shows the images of BMSCs growth on the surface of CH/CNC scaffolds. Sarkar et al. fabricated the carboxymethyl cellulose/hydroxyapatite (CMC/HA)

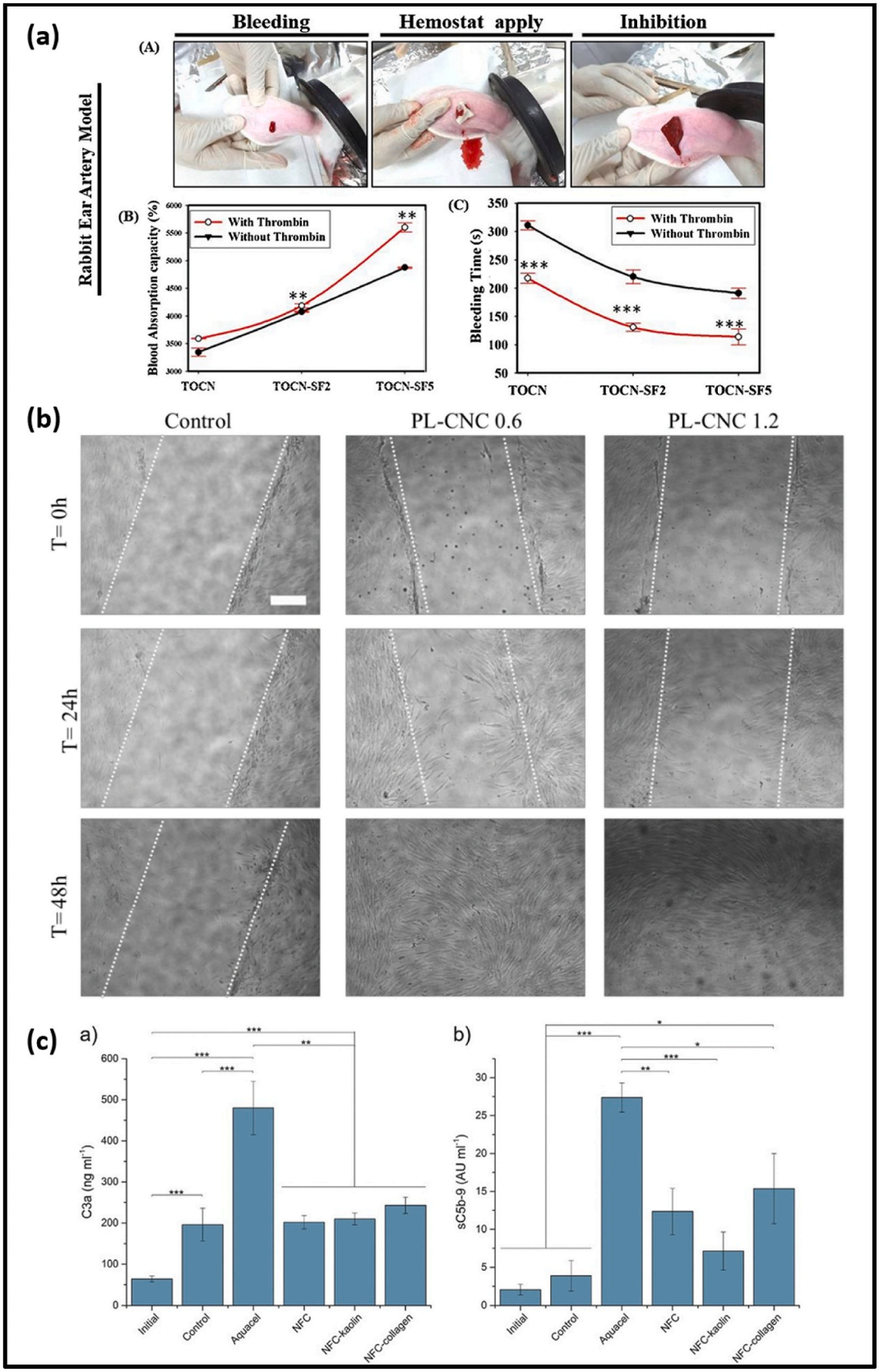

Fig. 9. **(a)** Effect of hemostat application on bleeding ear of rabbit (above), Comparison of blood adsorption capacity of hemostat with and without thrombin (below left) Bleeding time duration after scaffold application (below right) [227]; **(b)** Pictures of wound healing after treatment with PL-CNC 0.6, PL-CNC 1.2 and commercial gelatin (control) after 48 h in culture. Scale bar: 75 μm. [222]; **(c)** C3a and sC5b-9 complement system activation measured after incubating the materials with whole blood at 37 °C for 30 min. Statistically significant differences between sample groups are illustrated in the plots (*p < 0.05, **p < 0.01, and ***p < 0.001) [229].

nanocomposites for drug delivery (DOX) and bone tissue engineering. The CMC/HA nanocomposites were conjugated with carbon dots to trace the delivery of the drug into the cells and tissues [199].

5.2. Dental tissue engineering

Peng et al. developed the magnesium oxide (MgO) nanoparticles that incorporated PCL/gelatin nanocellulose membranes by the coaxial electrospinning method for tissue engineering applications [200]. The developed membrane exhibited improved biocompatibility with human periodontal ligament stem cells (hPDLSCs). The ALP activity of the developed electrospun membranes in the presence of hPDLSCs after 7 days of treatment is presented in Fig. 7(c). Improved ALP activity was detected in MgO nanoparticles-incorporated PCL/gelatin nanocellulose membranes after 7 days of treatment. The developed membrane showed antibacterial potential. Furthermore, upregulation of osteogenic-associated gene markers, such as Col1, and Runx2 was observed in hPDLSCs membrane-treated groups than in the control group.

5.3. Soft tissue engineering

Anton-Sales and coworkers developed the BNC-polypropylene composite to repair hernia surgery [202]. BNC provides mechanical stability and anti-adherent properties for soft tissue reinforcement. The 2–3 layered BNC were mechanically strong to apply for abdominal wall reinforcement. The synthesized wet BNC condenses upon drying and form strong inter-and intra-molecular bonds. The less stretching ability of dried BNC is more suitable for hernioplasty. The material showed resistance to tear beyond 16 N/cm, a threshold value for abdominal wall reinforcement application. Fig. 7(d) shows the macroscopic evaluation and adhesion assessment of BNC patches on the affected area. The tissue engineering application of nanocellulose-based composites is also given in Table 6.

5.4. Skin tissue engineering

Wound healing is associated with tissue engineering, where the damaged cells are replaced with newly produced cells. It is a complex and highly coordinated process performed by a living body. The porous and interconnect materials are considered ideal substrates for wound healings due to their potential to transfer antibiotics or other medicines to the targeted area. It also prevents other external infections and acts as a barrier for microbes, which cause secondary infection. Nanocellulose incorporated polysaccharides, proteins, glycosides, nanoparticles, local anesthetics serve as a potential candidate for wound healing [209,210]. Silva et al. prepared the patch of lysozyme nanofibers (LNFs)/NFC for wound healing applications. LNFs were derived from the white part of eggs. Schematic representation of the preparation of LNFs/NFC is presented in Fig. 8(a). Improved thermal and mechanical properties were observed in the developed patch. The L929 fibroblast cells were properly adhered to LNF/NFC patch, whereas poor adhesion of L929 fibroblasts was detected with a pristine NFC patch. The patch has no adverse effects on L929 fibroblast cell lines [211]. Erdagi et al. developed the gelatin/diosgenin-nanocellulose hydrogels to deliver the neomycin drug in wound healing application. The hydrogels were cross-linked with genipin. The mechanism of drug release is shown in Fig. 8(b). The composite showed remarkable swelling capacity and antibacterial property (Fig. 8(b)). *In vitro* cytocompatibility, the developed hydrogels were performed with human dermal fibroblast cells. The developed hydrogels were biocompatible and exhibited 90 % drug release within 24 h. The synthesized hydrogels showed the synergistic effects of neomycin drug and demonstrated significant potential for wound healing applications [178]. Md Abu et al. prepared the honey incorporated nanocellulose films for wound healing applications. The polyvinylpyrrolidone (PVP) was used as a binder. The honey-incorporated nanocellulose films demonstrated superior wound healing potential, presumably due to their anti-microbial efficacy against gram-positive and gram-negative bacteria [212].

Lie and co-workers developed polydopamine (PDA)/CNFs hydrogels for drug delivery for wound healing. The hydrogels were chemically cross-linked with calcium chloride. The hydrogels showed pH/near-infrared (NIR)-responsive potential [213]. The wound healing efficiency of the developed hydrogels was evaluated in the rat model, and results are given in Fig. 8(c) (left). The hydrogels with the tetracycline-loaded drug showed better wound healing potential after 15 days of treatment than the pure hydrogel (Fig. 8(c) (right)). Fan et al. fabricated the hydrogels of borneol/mono-6-(2-hydroxy-3-(tri-methyl ammonium) propyl)-β-cyclodextrin (BN/EPTAC-β-CD)/di-aldehyde carboxymethyl cellulose (DCMC) for wound healing applications. The hydrogels were cross-linked with tobramycin. The synthesized hydrogel exhibited self-healing and self-degrading properties, which depend on the pH conditions. The breaking of tobramycin imine bonds occurs in an acidic condition, facilitating drug release and promoting wound healing. The wound healing results are presented in Fig. 8(d). The experimental mice exhibited healthy conditions and steady weight during the wound healing process. The BN/EPTAC-β-CD-TB-DCMC hydrogel showed a remarkable decrease in the wounded area than other treatments [214]. The wound healing applications of other polymers are also summarized in Table 7.

5.5. Hemostasis

Hemostats are often applied to stop the bleeding during surgical procedures or accidents and are the initial step towards wound healing. Shefa et al. developed the silk-fibroin (SF)/TEMPO-CNCs scaffolds for hemostatic applications. The thrombin was incorporated in the developed scaffolds to improve its hemostats potential. The effects of the developed hemostat on the bleeding ear of rabbit are shown in Fig. 9(a). The thrombin-loaded scaffolds showed improved blood absorption capacity and biocompatibility. The bleeding time was reduced from 220 s to 114 s in thrombin-loaded scaffolds. This indicates that the developed material can be used as a potential hemostat [227]. Mendes et al. developed the cryogels of aldehyde functionalized CNCs and platelet lysate (PL) and evaluated its hemostatic potential [222]. The PL was covalently cross-linked with the aldehyde functionalized CNCs *via* the cryo-gelation method. The cryogels showed improved mechanical strength with interconnected porous networks. The blood absorption capacity of the developed cryogels was higher and faster than the commercially available porcine hemostat. Increased cellular activity, such as proliferation, metabolic activity, and migration, was observed in human adipose-derived stem cells (hASCs) in the presence of the developed cryogels. The wound healing potential of the commercially available gelatin as control and the developed cryogel after 0 h, 24 h, and 48 h of treatment is shown in Fig. 9(b). The developed cryogels demonstrated better hemostatic potential than the commercially available product in a standardized liver defect model. Therefore, PL/CNCs cryogels can be used as an effective hemostat [222]. Basu et al. evaluated the hemostatic potential of Ca^{2+} cross-linked CNFs hydrogels in wound dressing application. The effects of different hemostats involving CNFs hydrogel, kaolin, and collagen incorporated CNFs hydrogels on the activation of complement systems (C3a and sC5b-9) is presented in Fig. 9(c). The CNFs/collagen's promoted the activation of C3a and sC5b-9 system compared to heparinized PVC control. The kaolin incorporated CNFs hydrogel improved the hemostasis, and collagen incorporated CNFs hydrogels exhibited blood activation property [228]. Different polymer matrices used for the hemostasis application are also given in Table 7.

6. Conclusion and future perspectives

This article provides a state-of-the-art review of synthesis,

modifications, and applications of nanocellulose in the biomedical field. Extensive research has been performed on the production and modification of nanocellulose. Enzymatic hydrolysis and mechanical treatments are preferred to obtain nanocellulose because of its eco-friendly nature. Different types of nanocellulose (CNC, CNF, BNC) exhibit distinct properties. The properties of nanocellulose can be easily altered by surface functionalization. Functionalized nanocellulose has a wide range of applications, including those in drug carriers, medicine, wastewater treatment, food packaging, *etc*. The tunable properties of nanocellulose favor its use as a drug carrier. The sustained and target-specific delivery of the active molecules from nanocellulose can be achieved using different chemical and physical modifications. The drug loading capacity varied with nanocellulose contents and composites. The physicochemical properties and drug loading efficiency of the polymers can be easily enhanced by incorporating appropriate amounts of CNCs in their matrices. The high encapsulation capacity promotes the sustained drug release of the loaded drugs. However, poor adhesion is observed with pristine nanocellulose. Dual drug delivery shows high efficiency as compared to single drug delivery. This area has scope for compatibility and delivery of various combinations of drugs. Plasmids and proteins are usually loaded on nanocellulose complexes by electrostatic interactions. Whereas, Fischer esterification is another suitable approach for insertion of proteins into nanocellulose. Compared to protein and plasmid delivery, drug delivery has been extensively studied. Advancement in delivery of biomolecules can be explored in future. Nanocellulose-based materials have been considerably explored and considered promising for clinical and medical applications due to their superior biocompatibility, biodegradability, and low cytotoxicity. Although nanocellulose-based composites hold great potential in a variety of biomedical and biotechnological applications, the in-depth toxicological evaluation of nanocellulose-based materials is necessary prior to the clinical applications. Nanocellulose lacks antibacterial potential, and modifications are required to gain the antimicrobial property. Nanocellulose-based patches demonstrated better tissue engineering potential. Based on these findings, we concluded that nanocellulose is a promising material that can be used to deliver different molecules, and its antimicrobial properties are essential for biomedical applications. In the future, more studies can be conducted on the development of new hybrids with antimicrobial properties without affecting their original qualities. This review highlights recent developments and the current status of nanocellulose for the delivery of various active molecules and applications in tissue engineering.

Declaration of competing interest

The authors declare there is no conflict of interest.

Acknowledgments

This research was supported by the Basic Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (NRF-2018R1A6A1A03025582), and the National Research Foundation of Korea (NRF-2019R1D1A3A03103828).

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