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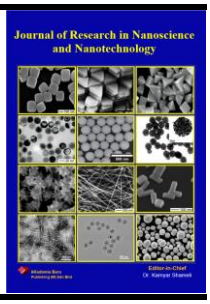

Nanocellulose as a Vehicle for Drug Delivery and Efficiency of Anticancer Activity: A Short-Review

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ABSTRACT

With the high demand of using nanotechnology, nanocellulose has become popular for different biomedical and anticancer applications. Cellulose, a nature gifted material and the most abundant organic polymer on earth, is systematically reviewed. Details of the mechanical and chemical structure of nanocellulose are explained, starting with preparation methods along with physiochemical properties and pH gradient to incorporate innovative polymeric drug delivery vehicles in anticancer applications. A myriad of research fields has introduced nanocellulose as an intriguing candidate for anticancer drug excipient and carrier in modern cancer therapy. Albeit, innovative nanocellulose-based drug carrier systems will be complicated for their commercial use in pharmacies. Of this, it is required to understand the preparation, properties, and potential drug conjugation of nanocellulose to improve its interactions with human tissues.

Keywords:
Nanocellulose, Mechanical properties, Chemical properties, Drug delivery systems, Cancer treatment, Biomedical applications.

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1. Introduction

Nanocellulose can be classified according to their sources and extraction method [1]. Cellulose is distributed throughout nature in plants, animals, algae, fungi, and minerals (Figure 1). However, the major source of cellulose is plant fiber. Cellulose contributes approximately 40% to the carbon fraction in plants, serving as structuring element within the complex architecture of their cell walls. As seen in Table 1, different wood-based sources contain cellulose in a range from 40-75 weight % (wt%). Table 2 shows the annual world production of cellulose from different sources. The highest amount of cellulose is produced from wood fiber. In addition, several fungi and green algae produce cellulose (e.g., Valonia ventricosa, Chaetamorpha melagonicum, Glaucocystis) and some (marine) animals such as ascidians contain cellulose in their outer membrane. Moreover, bacteria of the genera Gluconacetobacter, Agrobacterium, Pseudomonas, Rhizobium, and Sarcina can synthesize bacterial

cellulose from glucose and various other carbon sources. In terms of nanocellulose, the most common method of nanocellulose extraction is acid hydrolysis, resulting in high crystallinity and small dimension of nanocellulose, as termed nanocrystals (CNC) (also known as cellulose nanowhiskers, CNW) with rod-shaped cellulose microcrystals and nanocrystalline cellulose (NCC) [1-3]. Mechanical treatment is another nanocellulose preparation method causing lower crystallinity and bigger dimension of the nanocellulose, which termed as nanofibrous cellulose (NFC) or nanofibrillated cellulose (NFC), and cellulose nanofibers (CNF) [4]. The nanocellulose extracted from bacteria termed as bacterial nanocellulose (BCN) with generally biggest nanocellulose dimension in this classification [2].

Cellulose and nanocellulose based materials have been applied widely in therapeutic excipients, which carboxymethyl cellulose, methyl cellulose, ethyl cellulose, and many different cellulose are also analyzed for oral, topical, implantation and injectable forms. Properties, including crystallinity, surface chemical reactivity, less toxicity, proper mechanical strength, rheological and barrier characteristics and proper specific surface area. Therefore, these fabulous characteristics can lead to obtain structured products of ''nanoenabled'' as well as ''nano-enhanced'' with diverse applications such as drug delivery vehicles for anticancer treatment, advanced composite materials, and rheological modifier [5]. The aims of this current review study is to explain and compare different types of the nanocellulose in terms of their sources, preparation, and physical, chemical, and mechanical properties. Finally, the anticancer, biocompatibility and chemotherapy drug conjugation of nanocellulose were systematically explained.

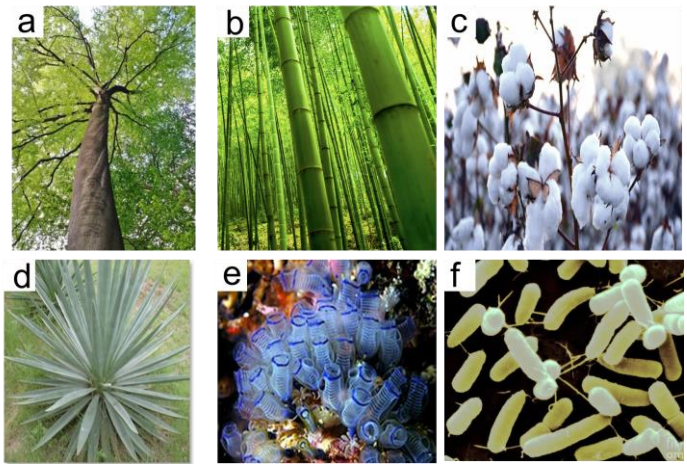

Figure 1. Selection of important cellulose sources: (a) hard wood (beech tree), (b) bamboo, (c) cotton, (d) sisal, (e) *tunicine*, and (f) *Gluconacetobacter xylinum*.

Table 1. The cellulose contents in different wood-based sources.

Wood-Based source	Cellulose content (wt%)
Wood	40–50
Bagasse	35–45
Bamboo	40–55
Straw	40–50
Flax	70–80
Hemp	75–80
Jute	60–65
Kapok	70–75
Ramie	70–75

Table 2. Annual global production of cellulose from different sources.

Source	Annual World Production (Kt)
Trees	1,750,000
Bamboo	10,000
Cotton Linters	18,450
Jute	2,300
Flax	830
Sisal	378
Hemp	214
Ramie	100

2. Fabrications of Nanocellulose

CNC and CNF are derived from plant-based materials include wood, cotton, hemp, flax, wheat straw, sugar beet and etc. Cellulose ($C_6H_{10}O_5$) contains numerous glucoses as linked by β-1,4-glycosidic in linear chain formats [6]. Decreasing the dimension and obtaining crystalline region are obtained by applying chemical treatments, including acid hydrolysis to liberate crystalline cellulose and degrade since the amorphous (disordered) region, while the crystalline (ordered) region is protected [7] (Figure 2). The length and width of CNC are in a range from 100-500 and 5-30 nm, respectively. In case of CNF preparation, mechanical methods such as grinding and high-pressure homogenization are used either before or after the enzyme or chemical processes. Thus, owing to apply various mechanical forces efficiently, separable microfibrils may be unattached from cellulosic fibers. Table 3 indicates typical geometrical features for the isolation of nanocellulose from different sources and procedures.

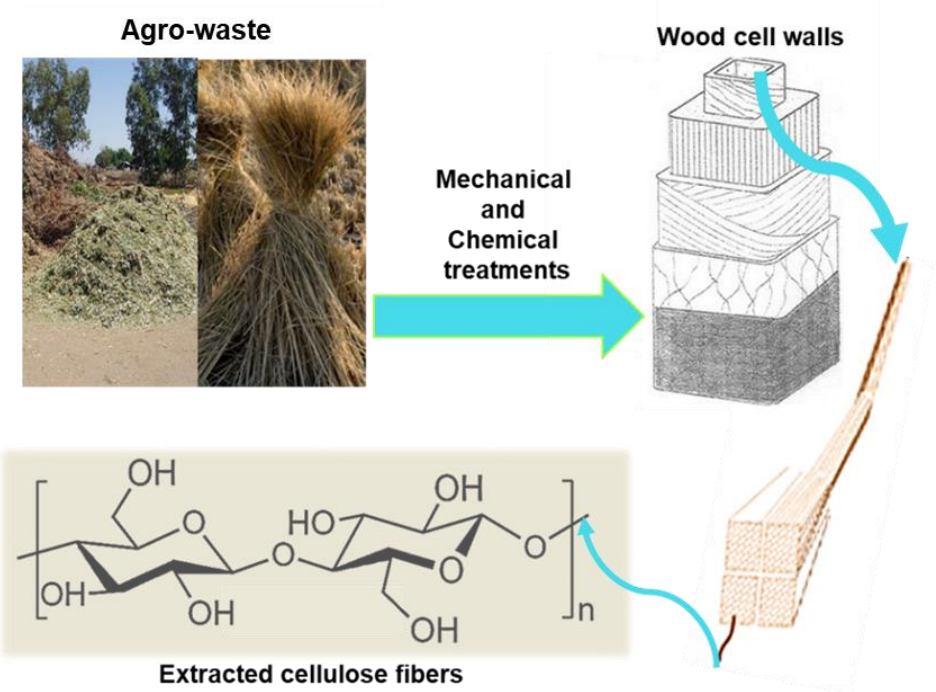

Figure 2. Schematic of cellulose extraction from agro-waste (rice straw) through mechanical and chemical treatments.

Dissimilar to CNC with rigid surface, CNF morphology mainly indicates soft surface in a long chain where formless cellulose regions cause in aggregation of nano-fibrils. The precise

measurement of CNF is challenging because of the agglomeration in the long cellulose; the CNF length is however estimated more than 1μm. Thus, researchers reported that CF dimension with the width of fibril (from 10 to 100 nm), depending on cellulose origin, types of pretreatment and defibrillation method [8]. Different to both CNF and CNC processes, BC anabolism is based on fabrication from small unit (Angstrom) to microscopic unit (nm). Generally BC produced from bacteria (include Acetobacter and Sarcina ventriculi) in a net form without employing any drastic procedure to separate unwanted components, including pectin, hemicellulose and lignin. Subsequently, the glucose chain incorporation results microfibril formation with ribbon dimension. [11]. Therefore, number of nanofibrils in a web-formed structure lead to formation of BC with the width of 20-100 nm.

It should be noted that one of the critical concerns in modern societies is to develop manufacturing rate of nanocellulose for diverse applications. The highest BC production rate was merely reached 0.38 g/(L h) (using aerosol bioreactor), albeit, it is still much lower than other kinds of cellulose production (CNC and CNF); due to huge required funding on BC production with poor yield [9]. Thus, BC production has been reported by only two companies, Jenpoly-mers and Nutrasweet Kelco in Germany and USA, respectively [5, 10]. According to s statement from 'Future Markets Inc.'', using CNC and CNF is different in North America and Europe, CNF is popular for European institutions such as Norway (Borregaard Chemcell) and France (Centre Technique du Papier), however, CNC is popular mostly for North American institutions like in Canada (Bio Vision Company) and US (Forest Service Foerst Laboratory) [2]. Dissimilar to customary materials, nanostructured materials originally contain various. Nanocellulose might be evaluated in terms of surface chemical reactions, biological, and physical characterizations. Relating to the subject, the proper biological characterizations are obtained by improving mechanical strength and the surface bonding groups.

Table 3. Typical geometrical features for the isolation of nanocellulose from different sources and procedures.

Sources of Cellulose	Hydrolysis Procedure	Nanocellulose Dimension	Ref.
Coconut husk fiber	64%brt H_2SO_4 solution at 45 °C for 30 min under continuous stirring.	TEM micrograph Average length 172.34 ± 8.4 nm. Average diameter 13.7 ± 6.2. Aspect ratio 14.23 ± 8 nm.	[11]
Pineapple leaf	Acid coupled steam treatment	TEM size 5-60 nm	[12]
Micro crystalline cellulose	Enzymatic degradation (Clostridium and Coccobacillus–cellulase producing organisms)	AFM micrograph smaller particles 43 ± 13 nm bigger particles 119 ± 9 nm	[13]
Raw cotton	Acid hydrolysis	TEM size 179.3 nm	[14]
Rice husk fibers	10.0 mol L^{-1} of sulphuric acid (pre-heated) at 50 °C for 40 min under continuous stirring. 60 wt	TEM micrograph Diameter and aspect ratio in the range of 15–20 nm and 10–15 respectively AFM micrograpgh Average diameter 12.4 ± 4.6 nm	[15]

	% H_2SO_4 solution at 45 °C for 45 min		
Sisal fibers	47 wt % sulfuric acid with fiber to solution ratio of 1:20 by refluxing for 3 h at 60 °C under strong agitation	TEM micrograph Length of 200–350 nm. Diameter of 40–50 nm	[16]
Sugarcane Baggage	Chemical methods of alkali and bleaching + acid hydrolysis	TEM size of 70-90 nm	[17]
Oil palm	Chemical methods of alkali and bleaching + acid hydrolysis	TEM size of 4-15 nm	[18]

3. Mechanical Properties and Potential Nano-reinforcement

Mechanical characterization of nanocellulose is assessed from crystalline and amorphous regions. Basically, flexural strength as a case of plasticity is associated with the amorphous region, whereas, the impact strength as a case of elasticity is related to the crystalline region [19]. The incorporation manner between the amorphous breakage and crystalline formation may influence in the modulus of nanocellulose. In both of the crystalline and the amorphous regions, thus, CNC with higher crystallinity can indicate greater elasticity and also plasticity compared with those from CNF and BC fibrils [10]. In the 1930s, the first evaluation on elastic modulus of crystalline cellulose was done with employing analysis of Raman spectroscopy, wave propagation, X-ray diffraction (XRD), and atomic force microscopy (AFM). The Young's modulus of CNC is in a range from 100 GPa to 200 GPa; this could be possibly better than steel and similar to Kevlar (200–220 GPa and 60–125 GPa, respectively) [1]. As reported, similar to Kevlar [20], elastic modulus value of 139.50±3.50 was found for CNC [21]. From a separate investigation by Dri et al [5], Young's modulus value of crystalline cellulose was estimated to be 206 GPa (comparable to steel), in which quantum theory and molecular structure were used to measure the Young's modulus. As was adopted from a recent report [7]. Recently, Megan Smyth et al. [22] investigated the mechanical properties of nanocomposite films prepared by solvent casting with different ratios of alginate and cellulose nanocrystals (unmodified and TEMPO oxidized) in different conditions of dry, humid and liquid. The mechanical properties were improved by enhancing the nanocelluose ratio to the composite with the facile alginate fabrication method. In addition, the TEMPO oxidation provided proper surface interaction between nanocellulose and alginate to improve the stability of alginate at phosphate solution. It is well known that employing various methods to prepare CNF and BC result in obtaining a wide range value of longitudinal modulus, whereas, the well-known average value of cellulose microfibril is about 100 GPa [2]. CNF obtained from pulp showed longitudinal modulus of 81±12 GPa and it was reported that the cellulose microfibrils dimension have a significant impact on mechanical characteristics [23]. Owing to fabulous mechanical properties, various materials can host nanocellulose as a load-bearing unit. Homogeneous dispersion and less agglomeration increase adhesion to introduce nanocellulose as a proper nano-reinforcement with proper stress transferring between a matrix (host units) and nanocellulose (reinforcement unit).

4. Chemical Surface Study

Based on structural formula, unites of b-1,4-anhydro-D-glucopyranose are composed in weight homopoly saccharide of high molecular. The units are not placed precisely on the surface of the structure, which is albeit better compared to extra glucose revolved at 180 degree around hydroxyl groups in an equatorial position [24]. These hydroxyl groups cause in creation hydrogen bonds to act an important function for the emergence of fibrillar and semicrystalline packing [24]. The neighboring glucose units with ring of oxygen structure (O5) and carbon (C3) with OH group lead to intramolecular hydrogen bonds. The intermolecular hydrogen bonds occur between the hydrogen of the OH–6 primary hydroxyl and oxygen in position O3 in a cycle of a neighboring unit, as well as the hydrogen of OH–2 and oxygen in position O6. Three hydroxyl agents are sustained in glucose component of each cellulose. This fabulous property of cellulose leads to reactivity for nanocelluose surface, which is covered by plenty of active hydroxyl agents. Furthermore, various hydroxyl position groups result in heterogeneous reactivity of each anhydro-glucose unit [24]. The carbon atom carries the hydroxyl group in the 6 position is only attached to one alkyl group, while the carbons with the hydroxyl groups in the 2 and 3 positions are joined directly to two alkyl groups, which will induce steric influences derived from the supramolecular structure with less reacting agent [2]. It has been stated that hydroxyl group on the cellulose structure, at the three position showed half rate of reactivity compared to that of the two position, whereas the hydrogen group with six position may have the quickest reaction (up to ten times) among different hydrogen groups [25]. Albeit, hydroxyl groups in various positions can be resulted from applying of different solvents in some nanocellulose including CNC. Besides the reactive process in the nanocellulose surface modification, another vital concern is surface charges as is basically related to sulfate esters hydrolysis with negative charges on CNC. Esterification reaction of a sulfuric acid molecule (applying separate sulfuric acid molecule to become a condensation agent) and surface hydroxyls interaction insert sulfate esters on CNC surface throughout processing of sulfuric acid hydrolysis. CNC is hydrolyzed by the great negative charging of sulfuric acid, consequently, set up a proper aqueous colloidal solution. Presence of sulfuric acid hydrolysis, cause volume of charged sulfate groups on CNC. In addition, stability of CNC in solvents as well as proper negative charges of sulfuric acid can influence on biomedical demand of CNC, including electrostatic adsorption of nanoparticles and enzymes proteins[26]. This treatment removes an amorphous region, while the crystal region is protected to obtain CNC with high crystallinity and purity. Therefore, the crystallization of CNC occurs at the external layer by the establishment of a glucan chain through van der Waals and H-bonding forces [27].

5. Nanocellulose in Drug Delivery Systems and Cancer Treatments

Nanoparticles may trigger good water permeability, antioxidant activity, biocompatibility, biodegradability, and lower or no toxicity, as advantages compared to commercial contrast agents used in biomedical applications [28-31]. Compared with such pure conventional chemo drugs, nanosized conjugates may provide for better drug therapy through prolonged circulation and targeted treatment. Chemotherapy can destroy the function of the thymidylate synthetase protein enzyme in CRC treatment [32]. It may also inhibit RNA and DNA damage causing cancer cell inhabitation [33]. It has been shown to

extend cancer cell survival for more than 6 months under the best conditions of metastatic cancer [34]. However, significant side-effects from chemotherapy have been triggered diarrhea and stomatitis, as well as gastrointestinal mucosal injury [35]. The toxicity of chemo-drug is potentially through its long chemotherapy period and nonspecific protective mechanisms over normal healthy cells [36]. These disadvantages can be decreased through minimizing drug dosage used in a targeted drug delivery vehicle [37]. Therefore, researchers have designed new-targeted drug delivery systems with low price, high efficiency, and safety to decrease the side-effects from conventional cancer treatments. Such nano drug delivery vehicles may act as suitable platforms to develop efficient drug delivery processes. For examples as can be seen from Figure 3, the treated nanocellulose fibers can display as a drug carrier system due to its great number of OH groups. In this manner, different polysaccharides (including chitin [38], nanocellulose[39] and their by-products) have been investigated as novel polymer–anticancer drug conjugates, owing to the enzymatic degradation of the most polysaccharides through colonic microbial agents [40]. Nanocellulose has recently become popular for researchers in drug delivery vehicles, due to their optimal physicochemical and biological features, and the ability for delivering drugs to different organs [41]. Such nanocellulose can encapsulate different drugs (including Bevacizumab, Camptosar, Capecitabine, Cetuximab, and 5-fluorouracil) approved for the chemotherapeutic treatment of different cancers (such as colorectal cancer, breast cancer, and esophageal cancer) [42] to improve cancer treatment.

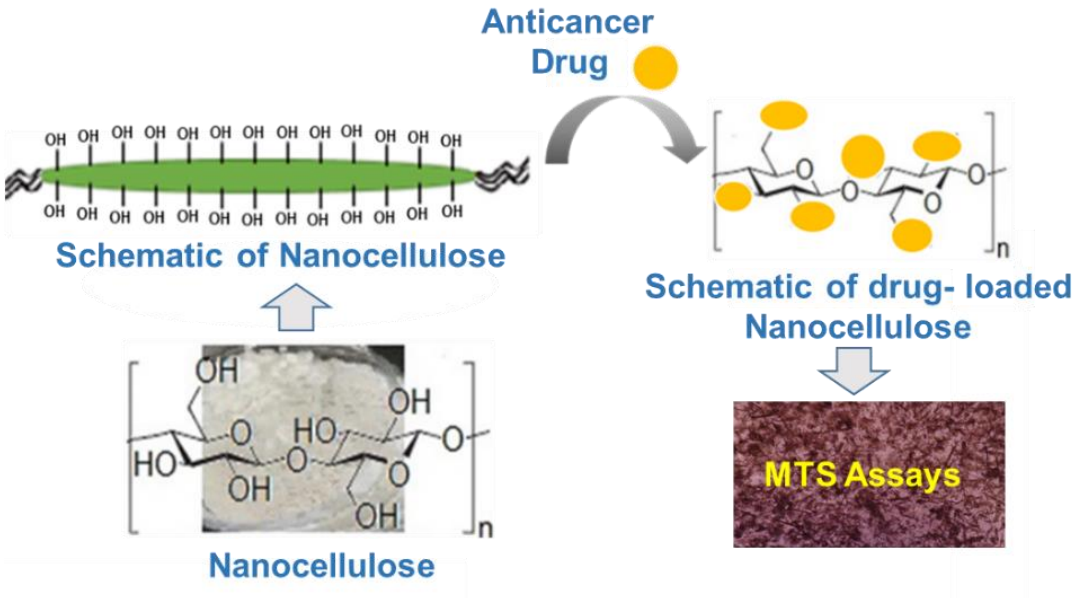

Figure 3. Extracted nanocellulose (cellulose fibers) from plant-based materials after series of chemical treatments with presence of numerous OH groups for high bonding and conjugation to anticancer drugs for MTS assays and cancer treatment.

Based on their preparation technique used, polymeric NPs may be classified into two categories: i) nanospheres that contain a solid support system or as a platform to be loaded with a dispersed drug or ii) nanocapsules that contain embedded drug cavities as the polymeric substance covers the cavity [43]. Drug delivery systems can influence the microenvironment of tumors, which is leaky with a higher sensitivity to macromolecules compared with normal cells [44]. Further, the lymphatic system of tumors is mostly inefficient and even blocked, causing preservation needs in the tumor

interstitial fluid [44]. Polymeric NPs can, thus, accumulate 100 times greater in the cancer cells compared to normal cells [44]. Figure 4 depicts a schematic of extracted nanocellulose from plant-based materials with high porosity and surface area for drug encapsulation efficiency and controlled drug release in cancer treatments.

The amount of NP extravasation relies on the dimension of transendothelial and channels via inter-endothelial cell gaps with the range of 400 – 600 nm [45]. It has been reported that NPs below 200 nm could be appropriately extravasated from the tumor microvasculature [46]. Table 4 shows some studies on nanocellulose-based drug delivery vehicles for biomedical applications. For instance, a platform of chitosan, nanocellulose and sodium alginate could successfully control the release behavior of Levamisole hydrochloride and 5-fluorouracil drugs to provide a high antiproliferation behavior against HT29 colon cancer cells with low side-effects [47]. In a different study, acid hydrolyzed crystal nanocellulose was obtained successfully from rubber wood for hesperidin (hydrophobic drug) delivery, however, cytotoxicity assays were not considered [48]. In a recent survey, a lignosulfonate/mercerized cotton composite was fabricated and caused an acceptable elimination of human colorectal cancer cells HCT116, human breast cancer cells MCF-7, and human liver cancer cells HepG2. However, cytotoxicity assays on the fabricated material against normal healthy cells were not considered [49]. A novel cellulose-based 5-fluorouracil was synthesized and analyzed for the elimination of human breast cancer (MCF-7) cells, although it was not analyzed for normal cells [50].

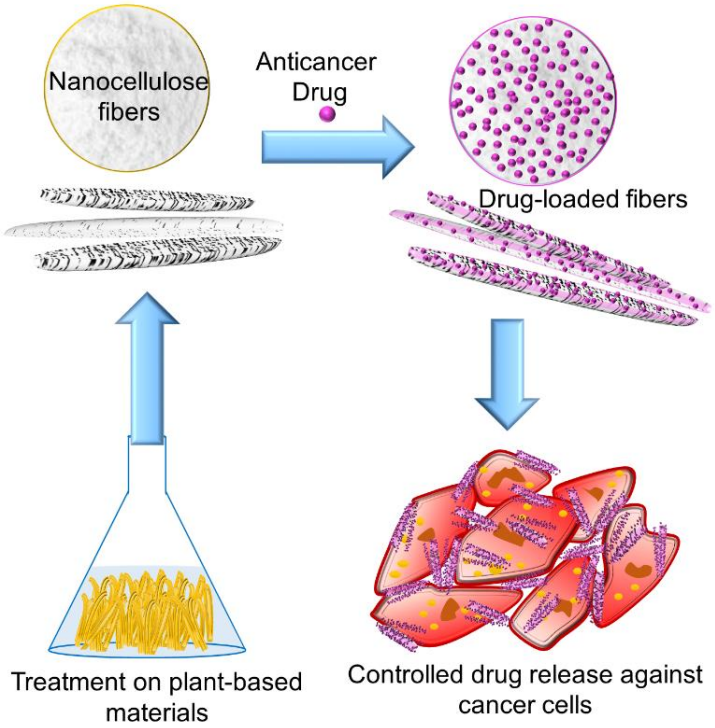

Figure 4. Schematic of extracted nanocellulose from plant-based sources controlled drug release in cancer treatments.

The CNC (isolated from rice husks) was covered by magnetic alginate hydrogel beads using co-precipitation approach to evaluate mechanical strength enhancement and use in drug delivery systems (as Ibuprofen was a model drug) [51]. Three different materials were prepared: i) alginate hydrogel beads, ii) CNC and iii) magnetic CNC (mCNC). The mathematical models including Peppas-Sahlin [52] and Korsmeyer-Peppas [53] were used to understand and analyze the mechanism of the drug release according to data from controlled

release drugs. Rapidly drug release (45-60%) was indicated from mCNC beads in the first thirsty minutes, albeit, after that the release was sustained [54]. This was due to high concentration of trapped drugs on the surface area of the beads and inhomogeneous drug distribution which led to drug mobility onto the surface during the dry steps of the beads preparation.

Table 4. Nanocellulose-based drug delivery systems for cancer treatment and biomedical applications.

Drug delivery system	Material component	Model drug	Drug uses	Drug delivery system results	Ref.
Anisotropic nanocellulose gelmembranes (transdermal drug delivery patches)	CNF	Piroxicam	Non-steroidal anti-infammatory drug (NSAID)	High surface area, small average pore, and tunable surface charge properties Good skin adsorption Sustained drug release	[55]
CNF/Chitosan transdermal film	CNF	Ketorolec tromethamine	Non-steroidal analgesic	Sustained rug release Increased the mechanical strength of transdermal film Swelling behavior based drug release mechanism	[56]
Chitosan, nanocellulose and sodium alginate	CNC	Levamisole hydrochloride and 5-fluorouracil	Colorectal cancer treatment	High antiproliferation behavior against HT29 colon cancer cells with low side-effects	[47]
Acid hydrolyzed crystal nanocellulose	CNC	Hesperidin	-	-	[48]
Lignosulfonate (LS)/mercerized cotton composite	Cotton cellulose fibers	-	Colorectal, breast and liver cancer treatment	Good effects against human colorectal cancer cells HCT116, human breast cancer cells MCF-7, and human liver cancer cells HepG2	[49]

Cellulose	Cellulose	5-fluorouracil	Breast cancer treatment	Good elimination of human breast cancer (MCF-7) cells, although it was not analyzed for normal cells	[50]
Magnetic CNC alginate hydrogel	CNC (isolated from rice husks)	Ibuprofen	-	-	[51]
Cellulose fibers	Rice straw Cellulose Fibers	5-fluorouracil	Colorectal and nasopharyngeal cancer cells	A great killing ratio around 60% and 85% against colorectal HCT116 on nasopharyngeal HONE-1 cancer cells	[7]
BC nanofber microneedle	BNF/Silicone elastomer	Lidocaine	Anesthesia	Increased drug permeation rate Negligible swellability properties Good tissue insertion	[57]
BC membranes	BC /Poly(Nmethacryloyl glycine	_	_	Good thermal, mechanical, and viscoelastic properties Non-cytotoxic and pH sensitive High water uptake capacity	[58]

6. Conclusions

This review explained the fabrication, properties, and anticancer activity of different nanocelluloses include CNC, CNF and BC. Nanocellulose has been gained significant attention for biomedical and anticancer applications due to its multiple functionalities, great physicochemical, and biological properties, biocompatibility and biodegradability. Further evaluation and examination on nanocelluloses can govern their particular applicability for different biomedical applications. In cancer treatments, the mechanisms of cancerous cells and nanocellulose interaction has remained challenges for researcher and require systematic *in vitro* and *in vivo* study. Through understanding the physicochemical properties of nanocellulose, therefore, the prospective of using the nanocellulose network as an anticancer drug vehicle is greatly effective in cancer treatment to decrease the side-effects of conventional chemotherapy treatment in a green and environmentally safe manner.

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