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Original Article

Nanocellulose In Cancer Therapy: Drug Delivery, Photothermal And Theranostic Applications

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ABSTRACT

The recent development of nanocellulose as a biomaterial platform to treat cancer is based on the excellent physicochemical characteristics, biocompatibility, and the ability to functionalize it in diverse ways. This review examines the current state of nanocellulose-based systems in oncological applications, focusing on three major areas: drug delivery, photothermal therapy, and theranostic approaches. Cellulose nanocrystals, cellulose nanofibrils, and bacterial nanocellulose are nanocellulose materials with high surface area, tunable surface chemistry, and biodegradability and therefore are excellent targets in targeted cancer therapeutics. We address the latest developments in strategies of nanocellulose modification, loading mechanisms for anticancer agents, and their efficacy in preclinical trials. Moreover, we emphasize the combination of nanocellulose with photothermal agents and image modalities to apply in therapeutic and diagnostic purposes. Current challenges and future perspectives for clinical translation are discussed as well.

Keywords: Nanocellulose, cancer therapy, drug delivery, photothermal therapy, theranostics, biocompatibility.

INTRODUCTION

Cancer is among the principal causes of death throughout the world, and the treatment strategies require continuous innovations. Although effective, conventional chemotherapy is usually characterized by systemic toxicity, lack of tumor selectivity, and bioavailability. Nanomedicine has revolutionized cancer treatment by enabling targeted delivery, controlled release, and multifunctional therapeutic platforms. Nanocellulose has attracted much attention among other nanomaterials because of its renewable source, high biocompatibility, and superb structure characteristics [1].

Nanocellulose refers to cellulose materials with at least one dimension in the nanoscale range. Three main forms have been identified, including cellulose nanocrystals (CNCs), cellulose nanofibrils (CNFs), and bacterial nanocellulose (BNC) [2]. These materials have high specific surface area, high mechanical strength, low immunogenicity, and high surface hydroxyl groups that enable chemical modification. Their attractiveness as green nanomaterials in biomedical applications is further improved by the sustainable production of them using different sources such as plants, bacteria, and agricultural waste.

This review thoroughly discusses the application of nanocellulose in cancer therapy and specifically drug delivery systems, photothermal therapy, and theranostic systems that integrate therapy and diagnostics.

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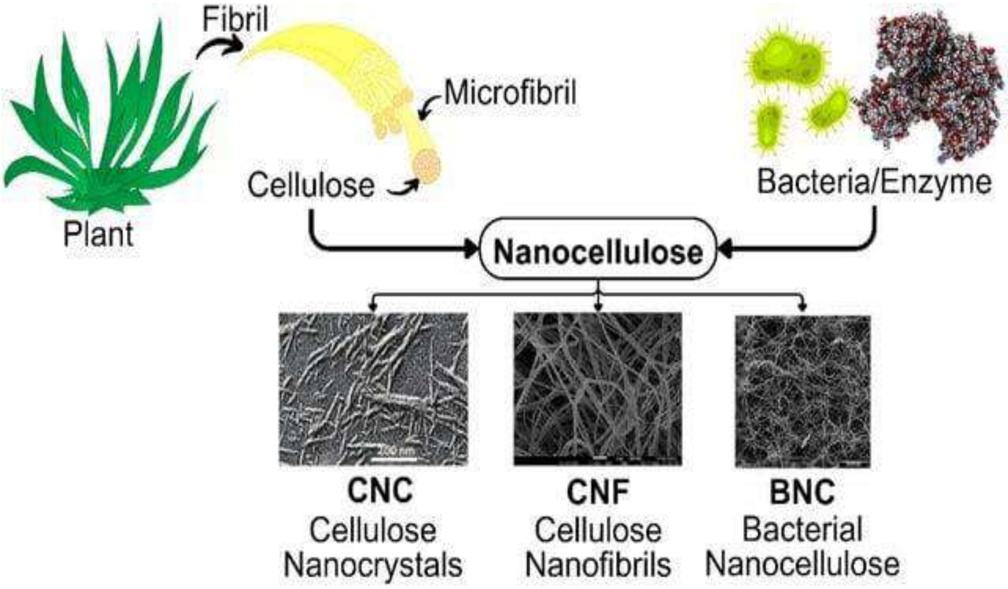

Fig. 1: Different types of nanocellulose: Cellulose nanofibrils (CNF), cellulose nanocrystals (CNC), and bacterial nanocellulose (BNC).

Source:https://www.researchgate.net/publication/393249619_A_review_on_fabrication_of_nanocellulose_and_carbon_nanomaterials_hybrid_film_for_solar_energy_device_applications_via_3D_printing_opportunities_limitations_and_prospects/figures?lo=1

NANOCELLULOSE: STRUCTURE, PROPERTIES, AND TYPES

1. Types of Nanocellulose

Cellulose nanocrystals are rod-shaped particles that are normally 5-70 nm in width and 100-250 nm in length and are produced by acid hydrolysis of cellulose fibers. They are rigid and have high mechanical strength because of their crystalline structure. CNFs are longer, flexible structures that have widths of 5-60 nm and lengths up to several micrometers and are formed by mechanical treatments or enzyme activity. Bacterial nanocellulose is a type of water-retaining, high-purity, and bacterially synthesized three-dimensional network, which is produced by bacteria *Komagataeibacter xylinus* [3].

2. Physicochemical Properties Relevant to Cancer Therapy

Hydroxyl groups on the nanocellulose surfaces are very numerous, which also allows a wide range of functionalization approaches such as esterification, etherification, and grafting of many moieties [4]. This surface chemistry enables conjugation with targeting ligands, therapeutic agents, and imaging probes. The large surface-to-volume ratio allows the drug to be loaded in large quantities, and the nanoscale size allows the cells to absorb and permeate the tumors due to increased permeability and retention [5].

Notably, nanocellulose exhibits good biocompatibility with low cytotoxicity in therapeutic doses, as was observed in numerous studies conducted in vitro and in vivo [6]. The enzyme degradation of nanocellulose makes it biodegradable so that it can be eliminated by the body in due time, eliminating the risk of accumulation over time.

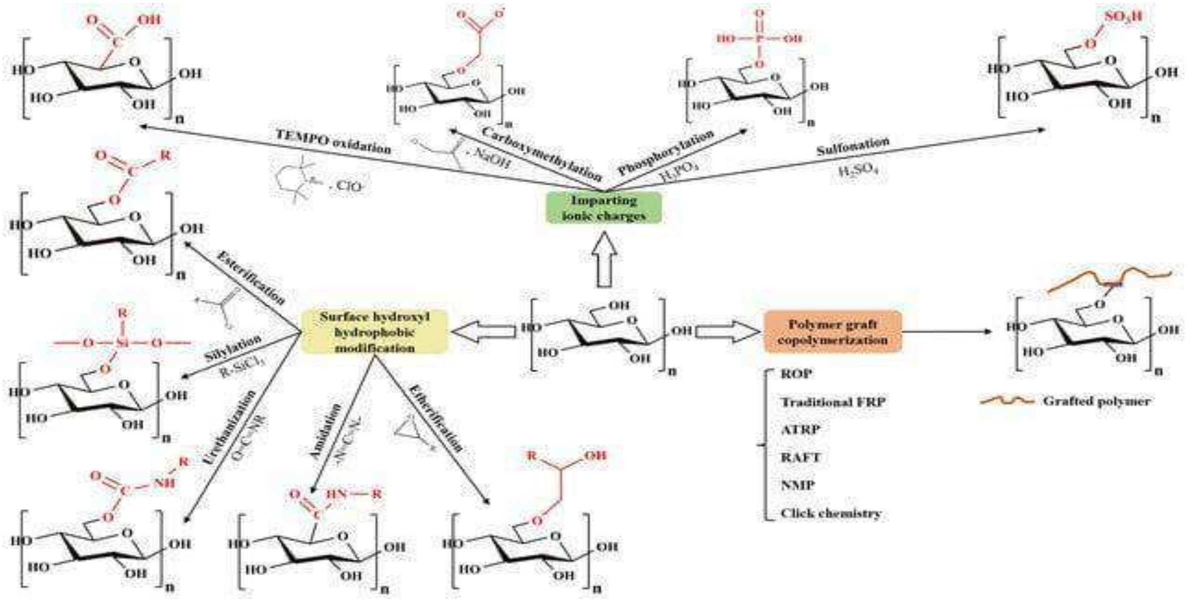

Fig. 2: Schematic representation of nanocellulose surface chemical modification

Source:https://www.researchgate.net/publication/372826502_Functionalization_of_nanocellulose_using_atom_transfer_radical_polymerization_and_applications_a_review/figures?lo=1

NANOCELLULOSE-BASED DRUG DELIVERY SYSTEMS

1. Drug Loading Strategies

Nanocellulose carriers use various anticancer drug loading methods. Physical adsorption is based on electrostatic interactions, hydrogen bonding, and van der Waals forces to immobilize drugs on surfaces of nanocellulose. Covalent bonding offers chemical conjugation to offer stable drug attachment with defined release profiles. The labile drugs can be encapsulated in nanocellulose-based compounds or hydrogels, which provide protection and allow controlled release [7].

Polymers like polyethylene glycol, chitosan, or carboxymethyl cellulose can be surface modified to form amphiphilic systems that can be used to load hydrophilic and hydrophobic drugs [8]. As an example, TEMPO-oxidized nanocellulose offers negative charges, which electrostatically attach cationic drugs, and hydrophobic modification allows the loading of water-insoluble chemotherapeutics such as paclitaxel and doxorubicin.

2. Targeting and Controlled Release

Active targeting is carried out through conjugation of the nanocellulose carriers with certain ligands such as folic acid, antibodies, peptides, or aptamers, which identify overexpressed receptors on cancer cells. It increases cellular uptake via receptor-mediated endocytosis and boosts therapeutic efficacy and reduces off-target effects.

Some of the controlled release strategies are pH-responsive systems, which utilize the acidic environment of the tumor, enzymatic degradation by tumor-associated enzymes, and redox-responsive systems by the high glutathione levels in cancer cells [9]. Multi-stimulus-responsive nanocellulose systems with multiple stimuli have shown to be improved spatiotemporal control of drug release.

3. Performance in Preclinical Studies

Nanocellulose-based drug delivery systems have been proven in many preclinical studies. Doxorubicin-functionalized nanocellulose that was studied demonstrated increased cytotoxicity to different cancerous cell lines, such as breast, lung, and colon cancer cells, compared to free drugs [10]. The nanocellulose formulations were shown to have improved tumor accumulation, lower systemic toxicity, and better therapeutic results in vivo tumor models.

PHOTOTHERMAL THERAPY APPLICATIONS

1. Principles and Advantages

Photothermal therapy uses light energy to generate heat, which kills cancer cells and produces hyperthermia in the area [11]. This is a minimally invasive procedure that provides spatial and temporal control, has fewer systemic side effects, and may be repeated. Nanocellulose is also a good scaffold to incorporate photothermal agents because of its stability, biocompatibility, and simple functionalization.

2. Integration with Photothermal Agents

Nanocellulose has been functionalized with various photothermal agents such as gold nanoparticles, carbon nanomaterials, polydopamine, and near-infrared dyes. Nanocellulose nanoparticles coated with gold nanoparticles have high localized surface plasmon resonance, which converts the near-infrared light to heat effectively. Graphene oxide and carbon nanotubes are carbon-based materials with good photothermal conversion efficiency when mixed with nanocellulose [12].

Nanocellulose polydopamine coating is one of the most promising methods, which is characterized by a strong near-infrared absorption, good biocompatibility, and added drug loading capacity. Polydopamine has a melanin-like structure that offers strong photothermal characteristics and allows the release of drugs in response to pH [13].

3. Combined Chemo-Photothermal Therapy

The synergistic effects on anticancer of the integration of chemotherapy and photothermal therapy on nanocellulose platforms are observed [14]. Hyperthermia improves drug penetration, cellular uptake, and sensitization of cancer cells to chemotherapeutic drugs. A number of investigations have shown that dual-functional nanocellulose systems are more effective in tumor ablation than single-modality therapy, and some preparations can completely eliminate tumors in animal models using lower doses of drugs.

THERANOSTIC APPLICATIONS

1. Multimodal Imaging Integration

Theranostic nanocellulose systems combine therapeutic and diagnostic capabilities into a single system. Other imaging modalities have been integrated, such as fluorescence imaging, magnetic resonance imaging, computed tomography, and photoacoustic imaging. Real-time biodistribution and tumor accumulation can be monitored with fluorescent dyes or quantum dots conjugated to drug-loaded nanocellulose. Magnetic nanoparticles embedded in nanocellulose matrices can be used as MRI contrast agents and for magnetic hyperthermia. Gold nanoparticles offer CT imaging and, at the same time, act as photothermal agents. This multimodal system helps to visualize the tumor and monitor its treatment in a comprehensive manner [15].

2. Treatment Monitoring and Personalization

Theranostic nanocellulose systems enable monitoring of treatment response by quantitative imaging of drug delivery and therapeutic responses. Variations in the fluorescence intensity or imaging signal are related to drug release dynamics and tumor response to allow treatment protocols to be adjusted. This ability underpins the personalized medicine strategy in which treatment optimization in accordance with the responses of the individual patients is possible.

COMPARATIVE ANALYSIS OF NANOCELLULOSE TYPES

Table 1: Comparison of Different Nanocellulose Types for Cancer Therapy

Property	Cellulose Nanocrystals	Cellulose Nanofibrils	Bacterial Nanocellulose
Dimensions	3-50 nm × 100-2,000 nm	5-50 nm × several µm	3D network structure
Crystallinity	High (54-88%)	Moderate (40-60%)	High (84-90%)
Surface area	50-200 m²/g	30-150 m²/g	55-200 m²/g
Mechanical strength	Excellent	Very good	Excellent

Production method	Acid hydrolysis	Mechanical/enzymatic	Bacterial fermentation
Drug loading capacity	High	Moderate to high	Very high
Primary applications	Targeted delivery, imaging	Sustained release, scaffolds	Implants, wound dressing

BIOCOMPATIBILITY AND SAFETY CONSIDERATIONS

1. In Vitro and In Vivo Biocompatibility

Nanocellulose materials have also been shown to be associated with minimal cytotoxicity when used in different cell lines even at concentrations that can be used in therapeutic contexts, as shown by extensive studies on biocompatibility. The safety of hemolysis assays, complement activation, and immune cell response tests are typically favorable. There are however factors such as surface modification, particle size, dose, and duration of exposure that determine biocompatibility [16].

2. Biodegradation and Clearance

Although human cells do not have cellulase enzymes to directly degrade cellulose, nanocellulose can be partially degraded by oxidative degradation and mechanical degradation. Nanocellulose with functional groups added can have an increased sensitivity to enzymatic or hydrolytic degradation. The clearance mechanisms are renal filtration of small particles and hepatobiliary excretion of large aggregates. The long-term accumulation studies are the key to a thorough safety evaluation [17].

3. Immunogenicity and Inflammation

Little evidence of immunogenicity with pure nanocellulose is reported in most studies, but care should be taken to prevent endotoxin contamination by bacteria. The alterations of the surface may affect immune recognition, and some of the chemical groups can cause inflammatory reactions. Immunological safety is important and requires proper purification protocols and quality control measures [18].

CURRENT CHALLENGES AND FUTURE PERSPECTIVES

1. Manufacturing and Standardization

Nanocellulose that is produced in large scale with uniform quality and reproducible properties remains a challenge. Clinical translation requires standardization of preparation procedures, characterization procedures, and quality measures. Commercialization will be achieved through the development of cost-effective and environmentally friendly production processes.

2. Clinical Translation Barriers

Although their preclinical data are encouraging, challenges such as regulatory approval processes, long-term safety verification, and clinical efficacy evidence exist in clinical translation. To determine therapeutic value, comprehensive pharmacokinetic and pharmacodynamic investigations and properly designed clinical trials are required.

3. Future Research Directions

The next generation of nanocellulose-based systems that are multi-responsive and combine several different therapeutic modalities and react to more complex tumor microenvironmental signals should be investigated in the future. As a combination with immunotherapy is a promising future direction, nanocellulose carriers may deliver immune checkpoint inhibitors or cancer vaccines. Individualized nanocellulose preparations based on personal tumor properties can improve the treatment.

The use of complex fabrication methods, including 3D printing, may allow patient-centric nanocellulose implants to treat cancer locally. The combination with artificial intelligence to predictively model drug release and therapeutic response can optimize treatment regimes. Moreover, nanocellulose has potential in new applications, including cancer stem cell targeting, prevention of metastasis, and modulation of the tumor microbiome, which are yet to be explored.

CONCLUSION

Nanocellulose has shown exceptional promise in the use of a multipurpose platform in cancer therapy by drug delivery, photothermal therapy, and theranostics. Its ability to be biocompatible, sustainably sourced, tunable, and multifunctional makes it a competitive substitute to traditional nanomaterials. Significant advancements have been made in the use of nanocellulose-based systems that are able to mitigate some of the major challenges in cancer therapy, such as targeted delivery, controlled release, and the combination of therapeutic agents.

Although there is compelling preclinical data that nanocellulose platforms are effective, clinical testing is necessary to achieve their therapeutic value. Critical aspects such as the current issues in standardization of manufacturing, regulatory approval, and long-term safety evaluation will make clinical implementation possible. With further development of research, nanocellulose-based systems will play a major role in the dynamic future of precision cancer medicine, bringing hope of more effective and safer cancer therapeutic options to cancer patients.

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