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REVIEW

Cellulose Based Nano-Scaffolds for Targeted Cancer Therapies: Current Status and Future Perspective

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Abstract: In the last few years, cellulose has garnered much interest for its application in drug delivery, especially in cancer therapy. It has special properties like biocompatibility, biodegradability, high porosity, and water permeability render it a good candidate for developing efficient carriers for anticancer agents. Cellulose based nanomaterials like cellulose nanofibers, bacterial cellulose, cellulose nanocrystals and microcrystalline cellulose as delivery vehicles for targeted drug delivery to cancer cells are reviewed. This review elaborates on the synthesis, functionalization, and application strategies of these nanocarriers, and shows how they facilitate to improve drug stability, bioavailability and targeted delivery to tumor sites. Their possibilities as a tool to overcome the limitations of conventional cancer therapeutics are also discussed. We also explore future directions for improving the efficacy of cellulose based carriers in cancer therapy.

Keywords: cellulose – nanocarriers, cellulose scaffold, cellulose based cancer therapy, biomedical applications

Introduction

In recent years, the field of cancer drug delivery has seen tremendous progress, especially in novel carrier development which has led to significant improvements in therapeutic efficacy and decreased off-target effects.[1] However, these advancements are limited by the inherent shortcomings of traditional drug delivery systems, including poor bioavailability, low drug targeting specificity, and the lack of ability to overcome the biological barriers of tumors, including the tumor microenvironment and the tumor drug resistance mechanisms.[2] Now attention has increasingly been given to the development of materials that can deliver drugs more efficaciously and maintain release profiles, penetrate tumors, and combat resistance.[3] Conventional cancer drug delivery systems suffer from poor drug selectivity and negligible tissue toxicity. However, current strategies, such as liposomes, micelles, or polymer-based nanoparticles face common challenges regarding stability, leakage of the drug, and deficiency in accumulation at the tumor site caused by the "EPR effect" (enhanced permeability and retention), which precludes successful therapy.[4] These challenges highlight the need for new materials to counter the barriers to therapeutic outcomes.

Cellulose based materials have great structural properties that may be used to overcome some of these limitations. Cellulose exhibits unique features like bio-renewability, high strength, and biodegradability which make it a suitable and efficient carrier in drug delivery systems.[5] Their high surface area and tunable surface chemistry can be used with targeting ligands to specifically interact with cancer cells. Additionally, they can be developed into multi-functional platforms for synergistic therapy by conjugating other therapeutic agents, including chemotherapeutic drugs, RNA, or gene editing tools, into cellulose nanomaterials.[6]

Large surface area and number of hydroxyl groups are responsible for the potential of cellulose based materials for the delivery of genes and drugs at the target site.[7] These materials are capable of easy surface modification.[8] Cellulose

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Nanofibrils, bacterial cellulose, cellulose nanocrystals, cellulose acetate, carboxymethyl cellulose, and microcrystalline cellulose are various types of cellulose used as carrier.[9] Cellulose based materials have been used as versatile carrier candidates to replace blood vessels, wound healing devices and other tissue engineering applications[10,11] and also utilized as tissue scaffolds[12] make them promising carriers for cancer therapy.[13]

In chemotherapeutics, surface modification results in high efficiency of drug delivery.[14] Cellulose based materials offer more choices and platform for cancer therapy as their surface modification has resulted in the designs of formulations that not only enhance but also can control the drug release.[15] These nanocomposite systems have been developed to target tumors, by virtue of the compatibility of drug candidates with cellulose.[16] In this review article, we are focusing on recent advancements in cancer therapy by use of cellulose based nano carriers. Additionally, this article offers some representative examples of cellulose based materials as scaffolds for cancer therapy by introducing their specific properties as well as updates on the synthesis and application of cellulose based materials. We conclude with a discussion of existing problems and future perspectives on using cellulose based materials as cancer therapy carriers.

Cellulose Based Scaffolds

Cellulose is mainly extracted from natural sources, such as algae, plants, tunicates, and wood, and sometimes their sources are synthesized by microbes.[17] Using different homogeneous and heterogeneous preparation methods, cellulose has been isolated and reported, which includes cellulose nanofibrils, bacterial cellulose, cellulose nanocrystals, and carboxymethyl cellulose.[18] Therefore, to improve and broaden their applications in cancer therapy, the development of a suitable synthetic method and the study of its influence on cellulose sources are of great importance.

Carboxymethyl Cellulose

Esterification and etherification are two major processes involved in the surface modification of cellulose.[19] Etherification followed by carboxymethylation led to the development of carboxymethyl cellulose, which has various applications in the paper, medicine, petroleum, textile, and food industries.[20] Carboxymethyl cellulose plays an important role in the delivery of anticancer drug cargoes. Curcumin is a hydrophobic anticancer drug that was loaded into zinc oxide–carboxymethyl cellulose nanocomposites and showed excellent drug entrapment efficiency, providing a vehicle platform for the delivery of anticancer drugs.[21] During the treatment of non-small cell lung cancer, doxorubicin-loaded carboxymethyl cellulose-based oxirane was evaluated in antiangiogenic therapy to investigate a multi-model combination with a 0.7 degree of substitution for cellulose. The fabricated system showed high encapsulation efficiency and efficient drug loading. The in vivo results mimicked the antitumor efficacy along with long-term systemic circulation, neglected blood toxicity, tolerability, safety, and optimized biodistribution. A synergistic effect between antiangiogenic agents and chemotherapy was displayed by a multimodal combination, resulting in efficient tumor suppression.[22] This shows that the resultant synergistic combination could be an advanced approach in clinical applications, owing to its potential regimen during cancer therapy. Carboxymethyl cellulose was functionalized using a methacrylation strategy and fabricated into a redox-sensitive spherical cellulose-based nanogel. The resultant composite was linked to the negatively charged disulfide bonds on its surface. The composite system displayed stability in a high-salt environment, but was unstable under reducing conditions. Then doxorubicin was loaded and the composite showed 82% encapsulation efficiency and 35% drug loading efficiency. The in vivo results showed excellent antitumor effects.[23] Furthermore, doxorubicin was loaded onto a self-assembled LDL/sodium carboxymethyl cellulose nanogel with a spherical morphology, and drug release was found to be dependent on the pH inside the cancer cells. Tremendous high encapsulation efficiency (98%) was observed for the fabricated system. The results of in vitro studies have shown effective killing of cancer cells.[24]

Sodium carboxymethyl cellulose was used as a potent platform to target cancer cells using the self-assembly technique to prepare zein sodium nanoparticles. The cellulose-based composite was stable in the pH range 3–11. The fabricated system was investigated in drug resistant MCF–7 cancer cells and drug-sensitive HepG2 cancer cells, where it was shown to be an effective transporter and carrier system with efficient anticancer potential.[25] Similarly, cellulose-based paclitaxel-loaded nanoparticles were targeted to the tumor and extravasation of the nanoformulation resulted in passive targeting. In addition, enhanced permeability was observed in the tumor vasculature.[26] Podophyllotoxin-loaded

acetylated carboxymethylcellulose-based nanoparticles were prepared. The size of the nanoparticles was adjusted by adjusting the PEG and Podophyllotoxin molar ratio, and particles with 20 nm size displayed 5-fold more killing potency and boosted drug delivery upto 20-fold. Overall, the fabricated carboxymethyl cellulose-based formulation displayed enhanced efficacy against MDR in mouse tumors against multidrug resistance.[27]

Bacterial Cellulose

Bacterial cellulose is a microfibril extracted from a bacterial source that has a large aspect ratio.[28] It exhibits a structure similar to that of conventional cellulose but displays better performance.[29] Bacterial cellulose possesses effective features, like biocompatibility, purity, greater tensile strength, and efficient permeability, making them suitable candidates as carriers for drug delivery.[30] In addition, other unique features of bacterial cellulose that make it attractive are its high crystallinity, high capacity for holding water, and its potential to release water slowly.[31] These features have led to its use as a carrier scaffold in drug delivery, tissue engineering, artificial skin, and blood vessels.[32] The first artificial blood vessel using bacterial cellulose was prepared in 1991 in Japan, followed by Brazilian research in 2001, which developed artificial blood vessels with a diameter range of 1–3 mm.[33,34] Almost 400 reports have been published on bacterial cellulose applications in skin grafts and burns; however, the low yield and high cost of immature technologies limit their use in the commercial market.[35] In an in vitro cancer model, nanofibrous biomaterials based on bacterial cellulose were investigated and it was found that on bacterial cellulose there was limited cancer cell growth and adhesion on BC. The cells cultured on bacterial cellulose showed spherical morphologies with no protrusions and indicated adhesion to the surface because of the hydrophilic nature of bacterial cellulose.[36] In addition, Chen et al investigated bacterial cellulose nanocomposites based on thermo-responsive poly (N-isopropylacrylamide), which showed high biocompatibility in hepatocellular carcinoma. Also, after 24 and 48 hour cultures, the cell viability study were greater than 80%, showing no cytotoxicity of the nanocomposite.[37] Overall, these findings suggest they are suitable for use as a biomedical material.

Cellulose Acetate

Cellulose acetate (CA) is a porous cellulose derivative that exhibits high water permeability and selectivity.[38] An anticancer drug-loaded starch cellulose acetate formulation that showed sustained release behaviors for approximately 20 days showed controlled release behaviors of cellulose acetate.[39] Cellulose acetate nanofiber-based rectorite-intercalated composites were developed using a layer-by-layer deposition method and were evaluated for lung cancer therapy. The results of this study showed that cellulose-acetate-based formulations displayed affinity for normal cells and were compatible with each other. In addition, the fabricated composite system selectively killed epithelial cells in human lung carcinoma.[40] The same fabrication technique was used to prepare negatively charged electrospun cellulose acetate nanofibers modified with multifunctional dendrimers to evaluate their application in cancer cell capture. The resultant cellulose acetate nanofiber formylation displayed efficient capturing ability of cancer cells, that is, KB cells of the employed cancer cell line.[41] Similarly, folic acid-modified cellulose acetate mats showed a greater capturing capacity than non-targeted cellulose acetate mats.[42]

Microcrystalline Cellulose

Microcrystalline cellulose (MCC) has a wide range of applications in the pharmaceutical and food industries. It has a diameter of 5–50 μm, and the acid hydrolysis of wood fiber leads to its production in the laboratory.[43] For the treatment of skin cancer, microcrystalline cellulose extracted from bamboo was used to prepare biodegradable paclitaxel-loaded nanocomposite fibers. Microcrystalline cellulose acts as a fibrous mesh to cover the skin-affected area. Using the MTT assay, the anticancer potential and biocompatibility of the microcrystalline cellulose were evaluated in MCF–7 and Vero cells. The results showed 96% cell viability for nanocomposite fibers, followed by 7% cell viability for drug loaded nanocomposites after three days. Overall, the fabricated system exhibited a good anticancer activity.[44] Similarly, biologically compatible microcrystalline cellulose-based nanocrystals with different shapes and sizes were prepared using an acid hydrolysis technique and were targeted to colon adenocarcinoma and human fibroblast cells. The resultant nanocrystals showed cytotoxicity irrespective of size in two types of cell lines, HCT116 colon adenocarcinoma and

NIH3T3 murine embryo fibroblasts, and concentration-dependent toxicity was observed for the as-obtained microcrystalline cellulose-based nanocrystals.[45]

Hydroxypropyl-Based Cellulose Polymer

Hydroxypropyl-based cellulose is a surface-active polymer whose solubility is related to the temperature.[46] For tumor-targeting therapy, an amphiphilic hydroxypropyl cellulose polymer-based composite has been prepared to target anticancer drugs at the tumor site. The prepared composite was evaluated in MDA – MB – 231 and HeLa cancer cell lines, which showed strong adsorption, leading to strong anticancer activity.[47] In another study, cisplatin and 7–ethyl–10–hydroxycamptothecin hydroxypropyl cellulose core-based biocompatible and biodegradable electrosprayed microparticles were synthesized and evaluated in esophageal cancer cells. The release of the entrapped agents was controlled by the magnitude of the applied strain. Within the coating area, the propagating cracks resulted in water infiltration, which led to a graded response.[48]

Cellulose-Based Nanocarriers Targeting Cancer

Cellulose-Based Nanogel

In the field of cancer therapy, various cellulose based nanocarriers have resulted in significant outcomes. In this regard, monodispersed cellulose-based nanogels were fabricated with dual responses, that is, acidic and temperature responsiveness. This study aimed to deliver cargo via tumor-targeting nanocarriers for cancer therapy. The results showed negligible interactions with proteins and efficient colloidal stability. In response to acidic pH, synergistic drug release was observed for the fabricated bio-nanogels, which was attributed to the pH sensitivity provided by carboxymethyl cellulose.[49] The herbal polyphenol honokiol was co-delivered with pemetrexed using a carboxymethyl cellulose-based self-assembling nanogel platform. An amide bond was first used to link pemetrexed with lactoferrin, and the resultant conjugate was electrostatically assembled into carboxymethyl cellulose, which led to the production of the nanogel. The in vivo results showed an efficient antitumor effect (breast cancer) in a mouse model and inhibition of tumor growth through the fabricated pemetrexed–honokiol loaded lactoferrin–carboxymethyl cellulose nanogel.[50] This indicates that, in targeted combinatorial breast cancer, self-assembled cellulose-based nanogels could be used as a biocompatible strategy.

Similarly, to explore radiochemotherapy, carboxymethyl cellulose, bovine serum albumin-based camptothecin and radionuclide 131I loaded nanogel were fabricated using an electrostatic interaction protocol. The results showed negligible damage to the normal tissues because of the nanogel–pH dependent drug release profile. In addition, the cellulose based nanogel showed significant tumor tissue accumulation, improved cellular uptake, and prolonged retention time in systemic circulation. Based on in vivo and in vitro results, chemo-radioisotope therapy can lead to excellent therapeutic effects in cancer.[51] Furthermore, carboxymethyl cellulose-based nanogels reduce systemic toxicity, improve drug release, and mimick safety.[52] Therefore, a doxorubicin-loaded pH-sensitive nanogel based on carboxymethyl cellulose and lipoproteins was developed. The hydrophobic interactions between carboxymethyl cellulose and doxorubicin resulted in enhanced drug loading into the nanogel. Under acidic conditions, the electrostatic repulsion and low hydrophobic interaction with the nanogel resulted in excellent payload delivery triggered by low pH. The in vitro results indicated high antitumor activity for drug loaded cellulose based nanogels as compared to free drug.[53] This shows that drug release at low pH could be a clue toward the stability of antitumor drugs, and the therapeutic effect could be improved.

Nanogels synthesized from 2-(2-(2-methoxyethoxy)ethoxy)ethyl methacrylate (MEO3MA), methacrylic acid (MAA), and carboxymethyl cellulose (CMC) exhibited temperature and pH responsive behavior with large changes in particle size and turbidity. The nanogels have been shown to have high drug loading capacity (31.47%) as well as efficient release of doxorubicin (92.20% in 24 h at 45°C, pH 3.0). The nanogels demonstrated excellent biocompatibility and ability to inactivate cancer cell activity, and we demonstrate their potential as smart drug delivery systems for anticancer therapies.[54]

In a recent study, a curcumin-doxorubicin-loaded carboxymethyl cellulose-linked gelatin and folic acid-based bio nanogel was prepared. The results from the in vitro antitumor activity showed excellent antitumor effect of the fabricated

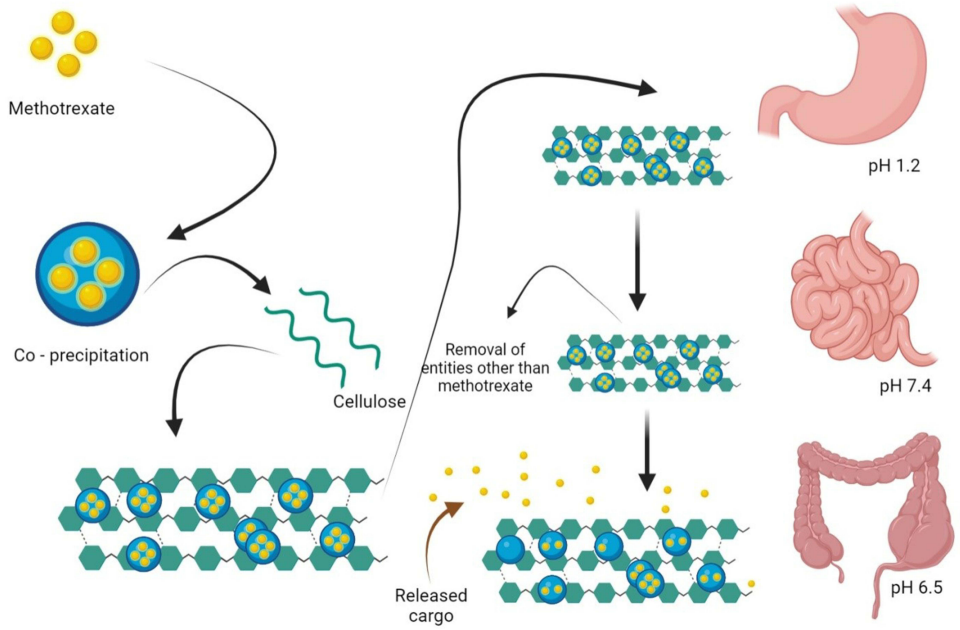

Figure 1 Cellulose based pH responsive Nanocomposites designed with methotrexate and aspirin for the targeted delivery to colon cancer. No drug release was observed under acidic conditions, which simulate the stomach environment. Aspirin was released at pH 7.4 (small intestine), methotrexate gradually released at pH 6.5 (colon) to achieve targeted drug delivery to the intended site.

system compared to free curcumin and doxorubicin, providing an efficient nanosystem for chemotherapy.[55] Other studies also have reported on the excellent stability of cellulose and its derivative based nanocarriers in cancer therapy.[56,57] To manage colorectal cancer-associated pain and improve the efficacy of chemotherapy, methotrexate- and aspirin-loaded calcium carbonate- and carboxymethyl cellulose-based hydrogels have been fabricated. This helped in the targeted delivery of loaded drugs into the colorectal site, bypassing their absorption in the stomach and small intestine. The important aspect of this study was the dual pH-responsive drug delivery because of the pH variation in the colorectum and small intestine.[58] This concept is illustrated in Figure 1. Such aspects could contribute to significant outcomes in the pharmaceutical and medical sciences. A paclitaxel-loaded cellulose-based hydrogel that was biocompatible and pH-responsive was fabricated. The resultant formulation showed 8 folds more reactive oxygen species production than the control, along with greater cell affinity, strong cytotoxicity, and efficient tumor-killing effects.[59]

Cellulose Based Microspheres

Cellulose-based microspheres have shown effective outcomes in cancer treatment using various drug delivery systems. Daunorubicin-loaded cellulose succinate-based microspheres were prepared using uniform silica-3-methacryloxy-propyltrimethoxysilane microspheres as the templates. Electrostatic interactions were used for the absorption of cellulose powder and cellulose succinate on the surface of microspheres. The resultant complex carrier system was evaluated for its effect under acidic and slightly basic conditions in vivo, and its behavior was observed against pathogenic and healthy tissues. A significant therapeutic effect was observed compared to free daunorubicin.[60] Similarly, another research group prepared daunorubicin-loaded double-layer hollow microspheres composed of folic acid-modified hydroxypropyl cellulose, which offer a versatile drug nanocarrier for targeting cancer. The fabricated nanocarrier system was evaluated in HeLa and MCF–7 cell lines. Drug release was observed in the acidic environment of the tumor along with higher cellular uptake. In addition, sustained release behaviors were shown by the fabricated system with a MIC value of 0.91 μM against HeLa cells and 0.56 μM against MCF–7 cells.[61] The same group fabricated daunorubicin-loaded poly(methyl acrylic acid-co-N-isopropylacrylamide-coethyleneglycol dimethacrylate)-based cellulose succinate microspheres using a sol–gel method. In contrast to the neutral pH, the prepared microspheres displayed an effect in the acidic environment of the affected area of the tumor with targeted release of the cargo. The microspheres also showed cytotoxic effects in the

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evaluated cells, that is, at different time intervals and in a concentration-dependent manner, and the drug-loaded cellulose-based microspheres showed significant cytotoxic effects compared to the free drug in HeLa cells of cervical cancer and MCF–7 cells of breast cancer. The in vitro results of cellulose-based microspheres indicate that they are non-toxic and biocompatible nanocarriers.[62]

For dual drug delivery, anticancer and antibiotic drugs were loaded into composite hydrogel films through chitosan microspheres and incorporated into carboxymethyl cellulose hydrogels. 5–Fluorouracil and tetracycline were used as model anticancer and antibiotic drugs, respectively. Under weakly acidic conditions, accelerated drug release was observed in the fabricated system during in vitro studies. In HepG2 cells, an enhanced inhibitory effect was observed for the prepared nanosystem during the cell apoptosis and cytotoxicity studies.[63] This shows that the resultant cellulose based nanosystem can be used as an efficient carrier system for anticancer and antibiotic drug cargoes. Furthermore, 5–fluorouracil loaded epoxy cross-linked cellulose and epoxy-based microspheres were prepared, and their effects on the cellulose–guar gum ratio, drug loading capacity, and in vitro release were evaluated. The particle size increased from 394 to 458 nm as the cellulose-to-guar gum ratio increased from 3:1 to 5:1, respectively. It was also observed that this ratio influenced the drug-loading capacity and drug release behavior.[64]

Cellulose Based Nanocrystal

Cellulose nanocrystals are an important class of carriers with a length of 100–500 nm and diameter of 3–5 nm obtained from cellulose, and their high crystallinity makes them versatile candidates for drug delivery.[65] It also exhibits certain potential features, such as an efficient Young's modulus, the presence of many hydroxyl groups, and a large surface area, which make it suitable for targeted gene and drug delivery.[66] In human and rat brain tumor cells, cellulose nanocrystals conjugated with folic acid have been administered to target folate receptor-positive cancer cells to facilitate the delivery of chemotherapeutic agents. The value of the crystallinity index for the folic acid-conjugated cellulose-based nanocrystals was 0.91, compared to 0.88 for cellulose nanocrystals. The targeted cellulose nanocrystals showed cellular uptake many times higher than the non-targeted system.[67]

The surface modification of nanodelivery systems has attracted the attention of researchers. siRNA-loaded surface-modified cellulose nanocrystals were fabricated and delivered to cancer cells. Similarly, cationic cellulose nanocrystals were prepared through chemical modification and hydrothermal desulfation, and complexed with siRNA via electrostatic interactions. Cytoplasmic drug release and loading were efficiently achieved by optimizing the linking process between the loading cargo and nanocarrier. In vitro results showed that apoptosis induction, enzymatic stability, and excellent gene knockdown lead to significant therapeutic effects in cancer.[68] Apoptosis associated with skin cancer was targeted by a cellulose nanocrystal-based nanoemulsion and was characterized using standard methods. The fabricated nanosystem through the generation of singlet oxygen showed no cell proliferation or toxicity. In cancer cells, the high expression levels of proteins are regulated through the stimulation of specific molecules involved in cancer cell differentiation, proliferation, and migration.[69] In another study, commercialized oil palm empty fruit bunch cellulose nanofibers were hydrolyzed using sulfuric acid and cellulose nanocrystal were isolated to evaluate their use as a safe nanocarrier. The results showed a low degree of cytotoxicity in normal fibroblasts and C6 glioma cells. Confocal laser microscopy showed negligible cellular accumulation, exhibiting nonselective and poor adsorptive endocytosis.[70] This demonstrated the safe use of cellulose nanocarrier for targeted cancer therapy.

Cellulose nanocrystals are considered to exhibit certain important chemical, biological, and physical properties; therefore, based on these properties tosufloxacin tosilate-loaded maleic anhydride cellulose nanocrystals were fabricated and targeted for colon cancer. After 30 h, 73% of drug was released in simulated colon fluid with enzyme and in simulated gastric fluids, no drug was observed with enzyme pepsin. These findings suggest that cellulose nanocrystals efficiently entrap drug candidates and exhibit significant behaviors toward targeted release in the colon.[71] Natural cotton wool was used as a source of cellulose, and the extracted nanocrystals were surface-functionalized via disulfide bonds linked to polymer brushes, as illustrated in Figure 2. The resultant isolated cellulose nanocrystal exhibited low cytotoxicity and excellent transfection efficiency. Using cotton wool as raw material, cellulose nanocrystals were fabricated by hydrolysis using sulfuric acid at 45°C for 30 minutes. The prepared cellulose nanocrystal exhibited a good transfection efficiency. In addition, in vivo and in vitro results from a suicide prodrug/gene system showed

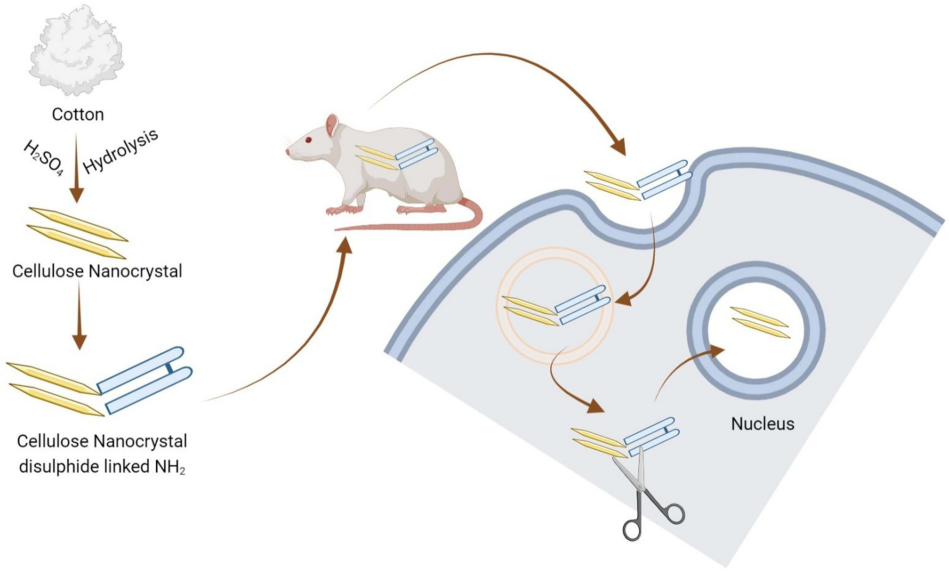

Figure 2 Representation of the extraction and cellular uptake of cellulose nanocrystals. Cellulose nanocrystals synthesized from hydrolysis of cotton with sulfuric acid and modified with disulfide linked NH_2 group. Cellular intake of cellulose nanocrystals in mice lead to cleavage of NH_2 linker in the cytosol and driven into the nucleus, triggering a cellular response.

that cellulose nanocrystal functionalization via redox-responsive polycations has an effective antitumor effect and high cancer treatment efficiency. Furthermore, in low-weight tumors evaluated in mice, efficient delivery of cargo into these tumors along with tumor inhibition was achieved via the fabrication of cellulose nanocrystals.[72] These findings reveal that polycation chains can be efficiently used in smart drug/gene delivery systems through grafting of redox-responsive polycation chains. Similarly, curcumin–cyclodextrin-based cellulose nanocrystals were prepared and evaluated and showed a 4-fold higher cytotoxic effect against cancer cell lines than free curcumin. The results of in vitro experiments suggested that cellulose nanocrystals boost curcumin solubility, which in turn results in excellent antiproliferative effects on prostatic and colorectal cell lines.[73] This shows that easy surface modification of cellulose has led to the development of new delivery systems for anticancer drugs. To promote the delivery of hydrophobic drugs into cancer cells, Qing et al prepared cationic cetyltrimethylammonium bromide-modified torispherical cellulose nanocrystals. It was observed that, within cetyltrimethylammonium bromide solution, cellulose nanocrystals were found to be stable. Luteolin and luteoside were then loaded onto the fabricated cellulose nanocrystals, which showed high drug-loading capability and efficient cargo release at the tumor site.[74]

Controlled release and stimuli-responsive release of the drug play an important and crucial role in reducing side effects and improving therapeutic efficacy.[75] Cellulose nanocrystals were functionalized with the protein glyceraldehyde-3-phosphate dehydrogenase and fluorescent molecules to create a novel biocarrier. The presence of this functionalized cellulose nanocrystal accelerated cancer cell proliferation, suggesting its potential as a therapeutic carrier. When loaded with doxorubicin, the formulation significantly inhibited HepG2 cell growth, with selective mitochondrial dysfunction observed in HepG2 and Cal27 cells, but not in A375 cells. These findings highlight the potential of cellulose nanocrystals grafted with glyceraldehyde-3-phosphate dehydrogenase as a targeted drug delivery system, offering a promising approach for more effective and safer cancer therapies.[76] To evaluate the efficiency of circulating tumor cell capture in Head and neck cancer blood using cellulose nanocrystals and nanofibers. Chemically modifying both cellulose nanocrystals and nanofibers with an EpCAM antibody and iron oxide nanoparticles to improve circulating tumor cell capture and enable magnetically assisted separation. Cellulose nano crystals-based scaffolds were able to more efficiently capture circulating tumor cells, compared to scaffolds. These insights ultimately lead to chemical design of cellulose based materials for real time cancer monitoring.[77]

Curcumin-loaded pickering emulsions stabilized by iron oxide–cellulose nanocrystals were fabricated and delivered to colon cancer cells to evaluate their in vitro efficacy. The results of MTT assay showed that, in the presence of an

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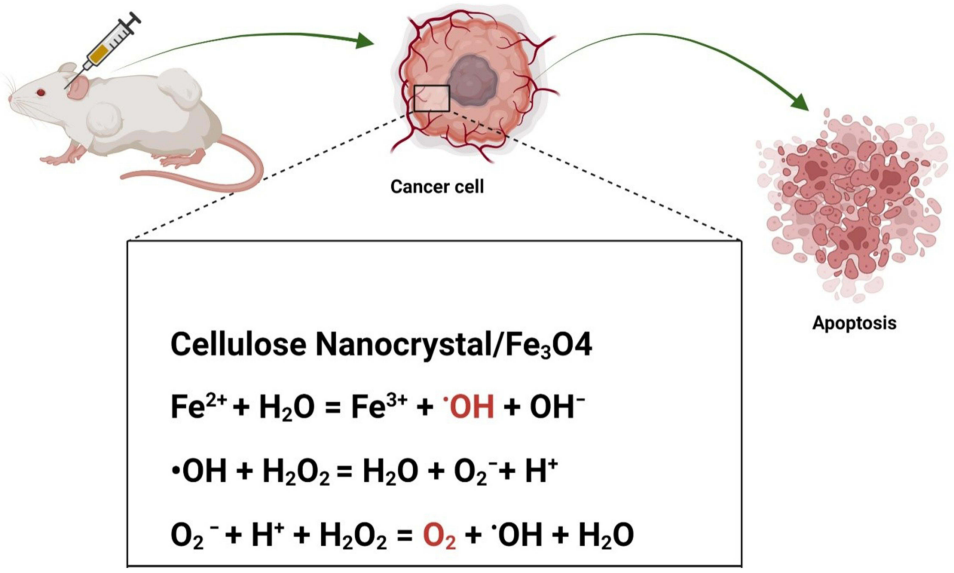

Figure 3 Aldehyde modified cellulose nanocrystals functionalized with iron oxide nanoparticles for cancer therapy. The treatment results in modification of the cellulose by Schiff base reaction and the iron oxide triggers the Fenton reaction to produce free radicals to alleviate tumor hypoxia and improve therapeutic effect by inducing apoptosis in cancer cells.

electromagnetic field, the fabricated cellulose based nanosystem inhibited the growth of colon cancer cells down by almost 18%. In addition, compared to the control sample, the fabricated formulation reduced the 3D multicellular spheroid volume of HCT116 cells by 2-fold.[78] It can be concluded from this study that, for the magnetically triggered release of therapeutics, cellulose nanocrystal-based Pickering emulsions can be used as an efficient colloidal drug delivery system. Hypoxia is a major barrier.[79] To address this dilemma, aldehyde-modified cellulose nanocrystals were designed using a Schiff base reaction and decorated with iron oxide nanoparticles. The results showed that the addition of iron oxide promoted the Fenton reaction, which effectively relieved the hypoxia. Furthermore, the hydroxyls produced during the reaction enhance the efficiency of tumor therapy.[80] This convenient strategy promotes the preparation and design of advanced biomaterials to explore their multiple functions during cancer therapy, as shown in Figure 3.

Cellulose Based Nanofibrills

Nanofibrils are a type of nanocellulose extracted from wood pulp through chemical or enzymatic treatment that exhibit amorphous or crystalline regions.[81] Multifunctional polymeric colloidal cellulose nanofibrils were fabricated via green electrospinning and modified with folic acid using carboxymethyl cellulose.[82] In bone cancer cells, nanofiber-composite-based colloidal electrolytes exhibit excellent responses and conductivities. The experimental results from apoptosis, necrosis, and cytotoxicity analysis showed significant anticancer activity of folic acid-based nanofibrils against osteosarcoma cells.[83] In another study, cellulose-based nanofibrils were fabricated and evaluated for their cellular uptake in folate receptor-positive breast cancer. The prepared nanosystem was surface-functionalized using an imaging agent, fluorescein isothiocyanate, and a targeting ligand, folic acid, and it was observed to be an eco-friendly method. The fluorescent-labeled nanocomposite showed no cytotoxicity in breast cancer cells and was stable under both physiological and non-physiological conditions. In addition, the functionalized cellulose-based nanosystem showed efficient cellular internalization in a concentration-dependent manner, and the fluorescence intensity increased 5-fold with increasing folic acid content. Furthermore, an antiproliferative effect was observed after the exposure of MDA – MB – 231 breast cancer cells to the fabricated cellulose-based nanofibril system.[84] It can be concluded from the study that the resultant nanocomposite system fabricated through an eco-friendly strategy offers greater affinity toward folate receptor-positive breast cancer cells that aid in targeting cancers, and that nanofibrils are a suitable nanocarrier for active targeted cancer therapy.

Electrospun oxycellulose has been developed as a potential nanocarriers for the delivery of anticancer drugs in the treatment of lung cancer. The resultant nanofibrils showed biocompatibility with eukaryotic cells, as well as an inhibitory effect against E. coli. Biocompatibility studies were obtained from evaluation of the adenocarcinoma NCI–H441 cell line. Under water-based conditions, the cells displayed long-term stability and their shape was regular without protrusion.[22,85] Chronic inflammation and wounds associated with cancer were treated with a cellulose nanofibril using a dendritic cell model to investigate the immunological mechanisms of biocompatible CNFs. Cellulose nanofibrils at non-toxic concentrations were observed during the maturation of monocyte-derived dendritic cells, which was attributed to the impairment caused by differentiation. It was also observed that cellulose nanofibril induced tolerogenic dendritic cells and ultimately resulted in the induction of active immune tolerance.[86] The therapeutic potential of a nanoemulsion containing astaxanthin, alpha-tocopherol, and cellulose nanocrystals/nanofibrils was assessed in the treatment of gastric cancer. In vitro, the nanoemulsion was found to be highly cytotoxic to cancer cells and potentiated photodynamic therapy in a xenograft mouse model. In vivo, tumor growth was markedly inhibited by modulation of the PI3K/AKT signaling pathway. These findings indicate that the nanoemulsion may have potential to enhance anticancer effects by immunomodulatory mechanisms, which could suggest the possibility of a novel gastric cancer therapy.[87]

In clinical practice, it is important to reduce adverse effects and improve therapeutic efficacy at the tumor site. In this study, a biocompatible DOX-loaded injectable hydrogel based on cellulose nanofibril was fabricated and evaluated. It was concluded from a research study that, in the clinical treatment of tumors, the fabricated cellulose nanofibril-based hydrogel could be used as an efficient diagnostic agent with significant potential in chemo-photothermal therapy.[88] Similarly, doxorubicin- and berberine-loaded redox- and temperature-responsive hydrogels were prepared for controlled drug delivery; however, owing to their weak temperature strength, cellulose nanofibrils were introduced into the system to cope with such issues. The results of the in vitro studies showed 99% and 40% cumulative drug release for doxorubicin and berberine, respectively. Drug release was found to be dependent on environment and temperature. No cytotoxicity was observed for the fabricated CNF-based system following cytotoxicity experiments.[89]

Disulfiram is an anticancer drug with poor selectivity and solubility issues.[90] To address this issue, electrospinning was used to fabricate disulfiram-loaded cellulose-acetate-based nanofibrils. Standard characterization of the nanofibrils confirmed the incorporation of the drug into the fabricated nanofibrils. The inhibitory potency of disulfiram against aldehyde dehydrogenase and the maintenance of apoptotic activity led to high selectivity of the drug-loaded nanofibril system toward cancer cells in comparison to healthy cells. Flow cytometry results showed that the inhibitory potency of the nanosystem helped eradicate breast and colon cancer stem cells. In addition to its anticancer potential, it also shows antimicrobial potential.[91] Thus, the disulfiram-loaded cellulose nanofibril system can be used as a versatile scaffold against microbes and cancers. The development of biocompatible multifunctional nanomaterials is crucial for effective biomedical applications. Silk fibroin/cellulose acetate/gold-silver nanoparticle composite nanofibers were fabricated and evaluated for anticancer potential. The results showed a strong cytotoxic effect against the human breast cancer cell lines MDA–MB–231 and MCF–7. The findings of this study suggest the use of cellulose-based nanofibrils as safe and effective nanocarrier systems for cancer therapy.[92] In another study, cellulose- and hyaluronic acid-based nanofibers were prepared and used to capture overexpressed cells on the surface of the CD44 receptors. The resultant nanofibers showed high capture capability, significant cytocompatibility, and efficient compatibility with blood.[93] This shows that nanofibers can be used in the future to capture tumor cells that circulate in the body for cancer diagnosis.

Cellulose Based Nanospheres

In the field of nanotheranostics, cellulose nanospheres have been designed and modified via internal and surface functionalization, which has led to their versatile effects in cancer therapy.[94] It has been reported that in cancer cells that express epidermal growth factor protein, the interaction of nanospheres with cancer cells is facilitated by surface functionalization. In contrast, bulk functionalization of cellulose-based nanospheres facilitates diagnosis by providing imaging contrast through gold nanoparticle immersion in a cellulose sphere matrix.[95] Betulinic acid-loaded cellulose–graft–poly (L–lactic acid) nanospheres were fabricated with a size range of 90–180 nm for the delivery of anticancer drug cargoes. The resultant nanospheres in vitro in LLC and A549 cell lines of a mouse tumor xenograft model showed efficient tumor inhibition efficacy.[96] A host–guest self-assembly strategy was adopted for the development of cellulose-

Table 1 Overview of Recent Research on Cellulose-Based Nanoparticles for Cancer Drug Delivery

Type of Cellulose	Nanoparticle Type	Particle Size	Drug(s) Delivered	Outcome	Ref
Cellulose Nanocrystals (CNCs)	CNC-based micelles	50–100 nm	Doxorubicin	Improved tumor targeting, reduced cardiotoxicity, higher therapeutic index.	[76]
Carboxymethyl Cellulose (CMC)	CMC-coated lipid nanoparticles	80 nm	Cisplatin	Increased cancer cell uptake, enhanced cytotoxicity, reduced systemic toxicity.	[99]
Regenerated Cellulose	Cellulose-Silver Nanocomposites	150 nm	5-Fluorouracil (5-FU)	Synergistic anti-tumor effect, significant tumor growth inhibition in xenografts.	[100]
Hydroxypropyl Cellulose (HPC)	HPC-based NPs with folate targeting	60 nm	Methotrexate	Targeted delivery to colorectal cancer cells, reduced toxicity to normal cells.	[101]
Nanocellulose composites (CNC/alginate)	CNC/alginate nanoparticles	100 nm	Doxorubicin, Curcumin	Dual-drug system; significantly inhibited tumor growth, enhanced cellular uptake.	[102]
Cellulose Nanocrystals (CNCs)	CNC-based micelles with PEGylation	120 nm	Paclitaxel, Doxorubicin	Enhanced stability, prolonged drug release, improved in vivo therapeutic efficacy.	[103]
Cellulose Acetate	Acetate-cellulose microspheres	200 nm	Cisplatin	Reduced renal toxicity, enhanced delivery efficiency to tumor sites.	[104]
Oxidized Carboxymethyl Cellulose (OCMC)	Silver Nanogels (Ag Nanogels)	Approximately 22 nm		Antimicrobial properties of the silver nanogels against bacteria.	[105]

based supramolecular nanoparticles, and β-cyclodextrin-modified doxorubicin was loaded onto the fabricated composite nanosystem. The resultant nanosystem showed quasi-spherical morphology, higher drug loading efficiency, and pH-responsive drug release. The fabricated nanosphere system also showed excellent inhibition of HeLa cell proliferation and efficient cell compatibility. Furthermore, the drug-loaded nanospheres followed endocytosis, entered the HeLa cells, and released the payloads at a given pH. Thus, this nanocarrier system could be effectively used as a potential carrier system for the delivery of cargo during personalized nanomedicines and translational cancer therapy.[97] Nanocrystalline cellulose derived from agricultural residues demonstrates favorable morphological, biological, and chemical properties, making it a suitable candidate for drug delivery systems. Folic acid-functionalized nanocrystalline cellulose, with rod-shaped structures measuring 4–32 nm in width and 20–100 nm in length, was shown to have a strong binding affinity for folate receptors. Binding studies on colon cancer cell lines, such as HT-29 and SW620, confirmed the nanoparticles' high efficiency in targeting folate receptor-positive cells. Moreover, both the nanocrystalline cellulose and its folic acid-functionalized form exhibited excellent biocompatibility, highlighting their potential as effective drug carriers for targeted cancer therapy and diagnostic imaging applications.[98] Table 1 below enlists some recent studies using cellulose-based nanoparticles for cancer drug delivery.

Limitations and Challenges

Cellulose-based nanoscaffolds have great promise for targeted cancer therapies, but a number of challenges need to be overcome before they can make the leap into clinical translation. Variability in the physicochemical properties of cellulose derivatives affects their biocompatibility, stability and drug delivery efficiency is one key limitation. Such differences in degree of substitution, molecular weight, or crystallinity may affect release profiles and targeting capabilities of these nanomaterials. Further, in preclinical studies cellulose-based scaffolds have excellent biocompatibility but safety of long term in humans and immunogenicity are unclear and need to be further investigated. Another hurdle to the scalability of production methods for cellulose nanomaterials is the fact that many current fabrication methods lack scalability to meet the clinical needs. There is another major challenge: while precise tumor targeting and efficient intracellular delivery are obviously critical, lack of homogeneity of tumors makes it impossible to ensure

uniform distribution of these scaffolds in vivo. Additionally, although the degradation products of cellulose and its derivatives (typically) do not cause unintended effects in vitro, the actual effects in vivo cannot be taken for granted and deserve careful evaluation in preclinical and clinical settings. Interdisciplinary approaches using material science, pharmacology, and clinical experience will be required to overcome these challenges to achieve optimum design, production and delivery of cellulose based nanoscaffolds for cancer therapy.

Conclusion and Future Perspectives

Cellulose-based nanomaterials and their potential applications in cancer therapy have been reported as scaffolds that efficiently deliver therapeutic cargo to cancer sites. The special features and properties of cellulose-based nanomaterials make them interesting and promising stars in the field of biomedical sciences. However, in the near future, some research trends need attention, that is, during cancer therapy, the selection and exploitation of cellulose sources are important for its application. The behavior of these cellulose-based nanocarriers is affected by certain factors such as the degree of substitution, crystallinity, and degree of polymerization. Therefore, there is a need for detailed investigation of these factors and their effects on cellulose nanocarriers in cancer therapy. Obviously, the application of whole cellulose in cancer therapy is not true; that bacterial cellulose could not be properly adopted for commercial applications because of its immature technology, high cost, and low yield. Such factors should be considered in the near future along with the relationship between cellulose-based materials and the microstructural properties of these nanocarriers. Furthermore, there is a need to elucidate the intrinsic relationship between antitumor drug targeting and cellulose-based materials. There is an in-depth need to clarify the synergistic effects of the cellulose based nanocarriers. In addition, the existing literature is insufficient and needs further exploration; thus, more examples related to in vivo and in vitro drug delivery, cytotoxicity, and antitumor assays should be provided. Finally, the drawbacks, shortcomings, and disadvantages of cellulose-based nanomaterials must be addressed, considered, and understood. Further investigations, explorations, and coping with all of the aforementioned scenarios associated with cellulose nanomaterials could open new avenues and horizons in the field of cancer therapy.

Data Sharing Statement

Not applicable. This is a review article, and all the relevant information is provided in this article.

Ethical Approval and Consent to Participate

Not Applicable. This review did not involve direct research on humans or animals.

Consent for Publication

Not applicable as this manuscript does not contain data from any individual person.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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