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REVIEW

Natural Polymers Based Biocompatible Nanomedicines for Targeting Colon Cancer: Prospects and Challenges

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Abstract: Natural polymers have gained significant attention as materials for the development of biocompatible nanomedicines, offering promising potential for the targeted treatment of colon cancer. These biopolymers are derived out of renewable resources and possess many beneficial characteristics such as biodegradability, low immunogenicity and easy functionalisation to allow precise targeting, making them highly applicable to nanomedicine applications. They can be used to prepare nanoparticles that can effectively deliver therapeutic agents to tumor sites, improving therapeutic effects and reducing systemic toxicity. In addition, the versatile chemical structures of natural polymers allow conjugation with targeting ligands, which allows increased specificity in colon cancer therapy. However, despite these benefits, there are still a number of challenges in the development and clinical translation of natural polymer-based nanomedicines. The complexity of nanoparticles design, including careful control of particle size, physicochemical properties of the surface, and drug-loading capacity, makes the synthesis process and scale-up difficult. Moreover, the realization of consistent and reproducible production at an industrial level is a significant obstacle. Also, although the phenomenon of enhanced permeability and retention (EPR) increases passive tumour targeting, its heterogeneity in colorectal cancer patients compromises predictability of therapeutic responses, which necessitates individualised treatment plans. The possible cytotoxicity of nanoparticles, especially those with complex structures, highlights the need to have more realistic preclinical models to carefully test safety and therapeutic efficacy. The review provides an in-depth evaluation of the present situation of natural polymer-based nanomedicines in the treatment of colon cancer, their unique properties, therapeutic potential, and the challenges that need to be overcome to achieve clinical success. Novel technologies, including microfluidic systems and individualised treatment plans, are given particular focus as they are likely to reduce these challenges and open the path to safer, more effective, and scalable nanomedicine solutions to colon cancer.

Keywords: natural polymers, nanomedicine, biocompatability, targeted delivery, colon cancer

Introduction

Colorectal cancer (CRC) is one of the strongest malignancies in the world, which has ensured that it has been ranked as the third most frequently diagnosed cancer and as the second-most frequent cancer-related mortality in the world.[1,2] The latest epidemiological evidence is specifically frightening, and reports show an annual burden of more than 1.9 million new cases and almost 1 million deaths, and the estimates project that the number of new cases will go to 3.2 million, and the number of deaths will reach 1.6 million by 2040.[3] Although the overall incidence and mortality rates among the elderly population in developed countries are steadily decreasing, and in most cases, it can be explained by effective screening techniques, there is a worrying pattern that the prevalence of CRC among the population that are younger than 50 years of age has been steadily

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increasing.[4] This early-onset CRC is often found at an advanced age, which also adds to the reason as to why CRC is the leading cancer killer of men under 50 in the United States.[1] The growing epidemic in the domain of public health, as well as the complexity of the disease, which is conditioned by both modifiable (diet, physical activity, obesity) and non-modifiable (genetic) risk factors, requires a paradigm shift in the approach to its treatment,[5] as illustrated in Figure 1.

The contemporary standard of care of CRC is a multimodal strategy that incorporates surgery, chemotherapy (CT), and, in the case of rectal cancer, radiotherapy (RT) and includes target agents or immunotherapy as adding supplements.[7] Even though these traditional treatments have increased the general survival rates, they essentially have extreme gross weaknesses that cannot achieve full recovery of a considerable proportion of patients.[8] The most severe and general disadvantage is the lack of specificity in the systemic distribution of conventional cytotoxic agents such as 5-Fluorouracil (5-FU), Oxaliplatin and Irinotecan.[9] These agents act without selectiveness attacking fast dividing cells such as normal proliferating cells in the bone marrow, hair follicles, and the gastrointestinal tract causing dose-limiting systemic toxicities;[10] comparative overview of general solid tumour characteristics is mentioned in Table 1. The most common adverse effects are myelosuppression (neutropenia), disabling gastrointestinal toxicity, and peripheral neuropathy that substantially diminishes health-related quality of life (HRQoL) in patients, and often requires a reduction in dose or discontinuing the treatment, thus weakening treatment efficacy.[11]

In addition to systemic toxicity, Multi-Drug Resistance (MDR) is one of the leading causes of failed treatment and cancer recurrence, which cause cancer-related deaths up to 90%.[31] MDR in CRC is a multifactorial phenomenon and a complex phenomenon with both cell-intrinsic and tumor microenvironment (TME)-tied mechanisms.[32] One of the significant cell-intrinsic processes is the up-regulation of ATP-binding cassettes (ABC) transporter proteins, including P-glycoprotein (P-gp/MDR1) and Breast Cancer Resistance Protein (BCRP).[33] Such efflux pumps are actively engaged in ejection of a broad spectrum of chemotherapeutic agents out of the cancer cell, before they can reach their intracellular targets, radically reducing the concentration of effective drugs.[33] Moreover, CRC cells may resist due to a change in drug

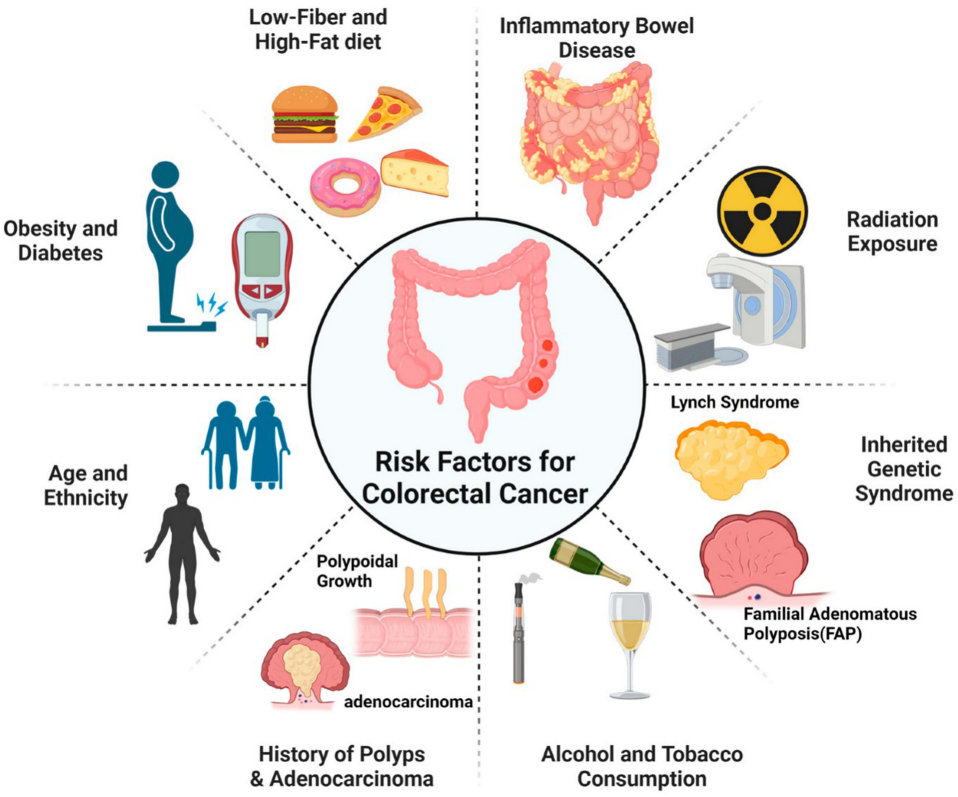

Figure 1 Factors associated to cause colon cancer. Adapted from [6] under a creative common license.

Table 1 Comparative Overview of General Solid Tumour Characteristics versus Features Specific to CRC, Highlighting Key Biological and Clinical Distinctions Across Major Domains

Category	Features Common to Many Solid Tumours	Features Distinctive or Highly Characteristic of Colorectal Cancer (CRC)	Key References
Tumour Microenvironment (TME)	• Hypoxia in tumour cores • Acidic pH • Dense extracellular matrix • Chronic inflammation	• Unique gut-associated microenvironment influenced by microbiota • High exposure to dietary carcinogens • Mucus barrier and colon-specific immune milieu	[12–15]
Pathogenesis & Molecular Drivers	• Oncogene activation (eg., KRAS) • Tumour suppressor loss (eg., TP53) • Genomic instability	• Adenoma–carcinoma sequence • Frequent APC mutations initiating tumorigenesis • Distinct molecular subtypes (CMS1–CMS4) • Microsatellite instability (MSI-H) common in CRC	[16–18]
Anatomical & Physiological Context	• Solid tumour mass formation • Angiogenesis • Local invasion	• Clear right- vs left-sided biological differences (embryology, microbiome, mutation spectrum) • Proximity to gut lumen affects drug exposure and delivery • High interstitial pressure due to peristalsis and luminal forces	[19–22]
Drug Delivery Barriers	• Dense stroma limiting penetration • Hypoxia reducing drug efficacy • Efflux pumps (eg., P-gp)	• Mucus layer as a physical barrier • High bacterial enzyme activity degrading some carriers • Colon-specific pH gradients (proximal vs distal colon)	[21, 23, 24]
Clinical Behaviour	• Metastasis to liver, lung, lymph nodes	• Liver metastasis is disproportionately common due to portal circulation • Distinct metastatic patterns for right vs left colon cancers	[25, 26]
Therapeutic Considerations	• Chemotherapy resistance • Need for targeted delivery	• 5-FU-based regimens remain foundational • MSI-H CRC responds strongly to immune checkpoint inhibitors • Colon-specific triggers (pH, enzymes, microbiota, hypoxia) are uniquely exploitable for polymer nanomedicine	[27–30]

metabolism (eg., increased inactivation of drugs by enzymes such as glutathione S-transferases), increase in DNA repair capability, and dys-regulation of apoptotic processes.[31,32]

Traditional surgical and radiation techniques also have unique constraints that do not allow the full elimination of the illness. Surgery is the primary method to get rid of CRC, but the minimal residual disease (MRD) in most cases complicates the use of surgery, and the risk of local or distant tumor recurrence, especially in intestinal obstructions.[34] Also, radiotherapy which is used in most cases of rectal tumors is characterized by the occurrence of radio resistance in cancerous cells and the emergence of serious long-term repercussions on healthy tissues within the area that remains observable in the lives of the patients years after the administration of radiotherapy.[35,36] Together, the high incidence, growing prevalence among the younger age groups, and the inheritable, unresolved shortcomings of traditional therapies, ie., systemic toxicity, lack of specificity, and deep-rooted multi-drug resistance, spawn a strong need to develop new, targeted therapeutic platforms. This is the critical gap that is being increasingly being bridged by the state-of-art nanomedicine, more so systems by which biocompatible natural polymers are used to deliver drugs precisely and specifically to the tumor site within the colorectum.

The Emergence of Nanomedicine in Cancer Therapy

The pitfalls of traditional cancer treatment, especially the problem of non-specific systemic toxicity and the widespread effect of multi-drug resistance (MDR), have inherently predetermined a rational change in strategy towards precision medicine.[9,31] This is the urgent need that has led to nanomedicine taking the center stage in the study of oncology.

Nanomedicine is a new, interdisciplinary specialty that utilizes the physical, chemical, and biological characteristics of nanoscale (1–100nm) materials to diagnose, monitor, prevent, and treat the disease.[37,38] Nanomedicine, especially in cancer therapy, entails utilization of nanocarriers, which may be liposomes, polymeric nanoparticles, solid lipid nanoparticles, and inorganic nanoparticles, to deliver therapeutic agents.[39] These nanosystems are designed to address the shortcomings of small-molecule drugs by modulating their pharmacokinetics and biodistribution, radically redesigning the interactions of anticancer drugs with the body and the tumor microenvironment (TME).[8]

The inherent benefit of nanomedicines is that they can be used to achieve high tumor selectivity based on two main concepts: passive and active targeting.[40] Passive targeting takes advantage of a physiological process occurring in solid tumors, called the Enhanced Permeability and Retention (EPR) effect.[41] Moreover, poor lymphatic drainage is common in the tumor tissue. Because of size, nanoparticles can easily extravasate (leak) out of the blood through these permeable abnormal vessels and thereafter, accumulate in the interstitial space of the tumor as a result of inefficient lymphatic clearance.[42] The above mechanism inherently focuses the drug-loaded nanocarriers into the tumor site with minimal exposure to healthy organs directly to the site of systemic toxicity.[43] This accumulation is further enhanced by the fact that the nanocarriers ensure that the encapsulated drug is not prematurely degraded and also increases the half-life of the accumulation in the bloodstream, giving the EPR effect a chance to take place.[44]

Besides passive accumulation, nanomedicines also allow complex active targeting by strategic surface functionalization. It entails conjugation of certain targeting ligands, including antibodies, peptides, aptamers, or small molecules onto the surface of the nanocarrier.[45] These ligands are constructed to specifically target overexpressed receptors on the surface of colorectal cancer cells or the cells in the TME, including the folate receptor, epidermal growth factor receptor (EGFR) or integrins.[46] Active targeting offers a second-level specificity to enable receptor-mediated endocytosis and allow the therapeutic payload to be internalized by the malignant cells themselves, which is especially important to overcome the heterogeneous nature of the EPR effect between tumors and stages.[47] Moreover, the nano-formulation as such is a source of vital physicochemical benefits: it can elevate aqueous solubility of low-solubility chemotherapy agents (eg., paclitaxel or Curcumin) to a clinically viable level and can increase the stability of the drug - payload against enzyme degradation in the biological fluids.[48] Stimuli-responsive nanocarriers that can release their cargo when exposed to specific TME conditions are also desirable - the reason why nanomedicine should be focused on Colorectal Cancer (CRC) treatment is overwhelmingly strong, and the solution to all the main therapeutic constraints of the disease is provided on a case-by-case basis.

Nanocarriers are uniquely designed to achieve high local concentrations of cytotoxic agents at the primary tumor and metastatic foci of disease, thereby increasing treatment efficacy and radically lowering the systemic side effects of the traditional chemotherapy regimen eg., FOLFOX or FOLFIRI.[49,50] The distribution of the drug in the nanocarrier physically isolates the drug against action by ABC efflux pumps (eg., P-gp) until the entire nanoparticle is internalized through endocytosis, and the drug effectively avoids the efflux mechanism.[31] More than the straightforward delivery of chemotherapy, complex nanomedicine enables the simultaneous co-delivery of synergistic payloads, eg., using a chemotherapy agent together with gene-silencing payload (eg., siRNA), to silence MDR-related genes and thereby re-sensitize cancer cells that have developed resistance to therapy.[51,52] This also finds additional support in the possibilities of theranostic uses, in which the same nanocarrier can contain both a therapeutic agent as well as a diagnostic imaging agent (eg., a magnetic resonance imaging contrast agent), allowing real-time tracking of drug delivery and treatment response.[53]

Natural Polymers in Nanomedicine

The move to safer, more efficient nanocarriers has driven the interest in biologically derived materials, which are more generally referred to as natural polymers or biopolymers.[54] Living organisms synthesize these macromolecules, which are mainly classified as Polysaccharides (eg., chitosan, alginate, hyaluronic acid, starch) and proteins (eg., gelatin, collagen).[55] The clear superiority of biopolymers over synthetic materials is mainly attributed to the high biocompatibility and low toxicity.[56] Their natural chemical analogy with the native biological entities guarantees positive contact with the cellular and host surroundings, reducing immunogenicity, systemic adverse effects, which go a long way to facilitate regulatory acceptance and clinical safety.[57] This inherent safety profile is combined with a high level of biodegradability; natural enzymes and hydrolysis can readily convert them into harmless, easily excretable compounds, eliminating accumulation in the long term, which is the bane of non-degradable nanoparticles.[58] Moreover, natural polymers have highly chemically active hydroxyl,

amine, and carboxyl groups in their molecular structures, which offers an easy platform to functionalize.[59] This chemical versatility is most important in conjugation of targeting ligands, which allows development of active-targeted and stimuli-responsive nanocarriers.

This review has a specific focus on natural-based polymer nanomedicines in the targeting of colon cancer (CRC). This specificity is strategically decided since the unique anatomical and physiological characteristics of the lower gastrointestinal tract, especially the high levels of microbial enzyme activity and the unique pH gradients in the colon, can be exploited spectacularly by some biopolymers. The polysaccharides such as pectin, guar gum and certain dextran derivatives are largely degraded by the abundant colonic microflora, providing an inbuilt system of localized, enzyme-mediated release of drugs only upon reaching the target site.[60] Therefore, the purpose of the review is to analyse the engineering of these natural polymers in detail such as core-shell structures, mucoadhesive nanogels and hybrid conjugates to improve oral bioavailability, protect the drug payload through the upper GI tract, and release a concentrated therapeutic dose directly to the CRC lesion and its microenvironment.

Natural versus Synthetic Polymers: Comparative Advantages and Limitations

Natural polymers like chitosan, alginate, hyaluronic acid and pectin are well valued in colon cancer nanomedicine because of their natural biodegradability, biocompatibility, and biological functionality such as receptor affinity and microbiota-responsive degradation.[61–64] Hyaluronic acid, for instance, is used to allow CD44 feasible targeting without the need for intensive chemical modification.[65] Additionally, polysaccharide matrices can be selectively degraded by colonic bacterial enzymes, and this promotes colonic-specific drug release strategies.[66] However, compared to synthetic polymers (eg., PLGA or PEG), natural polymers can exhibit structural heterogeneity, batch-to-batch variability, inferior mechanical robustness and less predictable degradation kinetics, all of which can impact reproducibility and long-term stability.[67,68] Some positive aspects are that synthetic systems allow for precise control of molecular weight and tunable release properties, as well as scalable consistency for malabrication, but also often times additional functionalisation is needed to deliver similar bioactivity as could be found in natural polymers.[69–71] Accordingly, in the present instance, the manuscript underscored how hybrid systems that consist of both natural and synthetic polymers could serve as an optimal balance of biological compatibility and tunable structure for translational nanomedicine for colon cancer.

Biological and Physiological Barriers for Colon Cancer Targeting

Delivery of therapeutic agents to the colon is extremely attractive in the management of colorectal cancer (CRC) to improve both therapeutic and reduce systemic toxicity, but it encounters many biological and physiological challenges, which require sophisticated drug delivery methods.[72]

The Gastrointestinal Tract (GIT) Environment

The passage through the upper GIT is the initial significant obstacle of orally taken drugs.[73] Low pH in the stomach (pH 1.0–3.0) is immediately destructive to acid-sensitive drugs, particularly large biomolecules such as peptides and proteins, which become denatured and inactive.[74] It is further destabilized by the enzymatic breakdown along the stomach and small intestine which is primarily catalyzed by proteins such as pepsin and pancreatic enzymes. Small intestine has a large surface area that is meant to absorb nutrients and, therefore, non-specifically uptakes drugs or breaks them down before the compound can reach the colon.[75] The intestinal mucus barrier is a critical physical barrier that is a size-exclusion barrier, a dense and viscoelastic layer, the major component of which is composed of mucins that is a critical physical barrier, trapping and clearing large therapeutic agents and conventional drug carriers in large quantities and, therefore, severely restricting drug bioavailability.[73,76] Moreover, the tight junctions between intestinal epithelial cells (IECs), which inhibit paracellular transport, and the lipophilic properties of the cell membranes, which inhibit passive diffusion of hydrophilic drugs, inhibit drug absorption.[72] The short transit time in the small intestine (usually 3–4 hrs) also leaves a small-time frame in which drug release can occur and in most cases results in premature drug absorption or clearance.[77]

The Colonic Microenvironment

The colonic microenvironment provides special physiological conditions which can be used to target drugs with high localization, however, which also present new challenges.[75] The most important feature is the presence of the gradient of the pH: the small intestine is about neutral (6.5–7.4) whereas the colon has a slightly lower or variable pH (6.0–7.0) because of the presence of fermentation products of bacteria.[75,78] This is the main triggering shift in the controlled drug delivery system (CDDS), which makes use of the pH-responsive polymers, which will dissolve only when reaching the colon.[79] The greatest concentration of the microflora in the whole GIT is in the colon with up to 10^{12} CFU/mL of the microflora.[77] These bacteria have reductive and proteolytic enzymes, namely azoreductases and glycosidases (such as -galactosidase and -glucuronidase), which are practically absent in the upper GIT.[75] To eliminate the active drug payload of prodrugs or polymeric coats, these enzymes are used to break the specific chemical bonds in the drugs and trigger the release of the drug payload only when the drug reaches the targeted colonic location.[80] In addition to this enzymatic capacity, the microenvironment of colon cancer is highly endowed with distinct receptors/biomarkers, including those of folate uptake or unique tumor-associated antigens (TAAs), which can be exploited with functionalized nanocarriers.[43] Other novel targets are the hyaluronan-rich extracellular matrix (ECM) which physically hinders the absorption of drugs into solid tumors and necessitates the co-delivery of agents such as hyaluronidase to degrade the hyaluronan.[81]

Tumor Microenvironment (TME) Barriers

Biological and physical barriers in the Tumor Microenvironment (TME) seriously limit the efficacy of nanomedicines in colon cancer, even when they have successfully traversed the gastrointestinal tract,[82] the difference between the physiological and tumour microenvironment is presented in Figure 2. The most common physical barrier is the thick Extracellular Matrix (ECM), in the case of colorectal cancer (CRC), it is frequently highly enriched with such components as hyaluronan (HA) and collagen and creates a hard desmoplastic stroma.[81,83] This ECM is thick, forming physical mesh which can limit the convection and diffusion of nanocarriers into the tumor core creating uneven distribution of the drugs and lowering the therapeutic concentration.[43,72]

Moreover, the high rate of proliferation of the tumor, as well as the disorganized vascular structures, causes inadequate lymphatic drainage, which causes the Interstitial Fluid Pressure (IFP) to increase in the solid mass of the tumor.[72,83] Such a high IPF causes the pressure gradient to the outside, which resists the convective delivery of nanomedicines across the

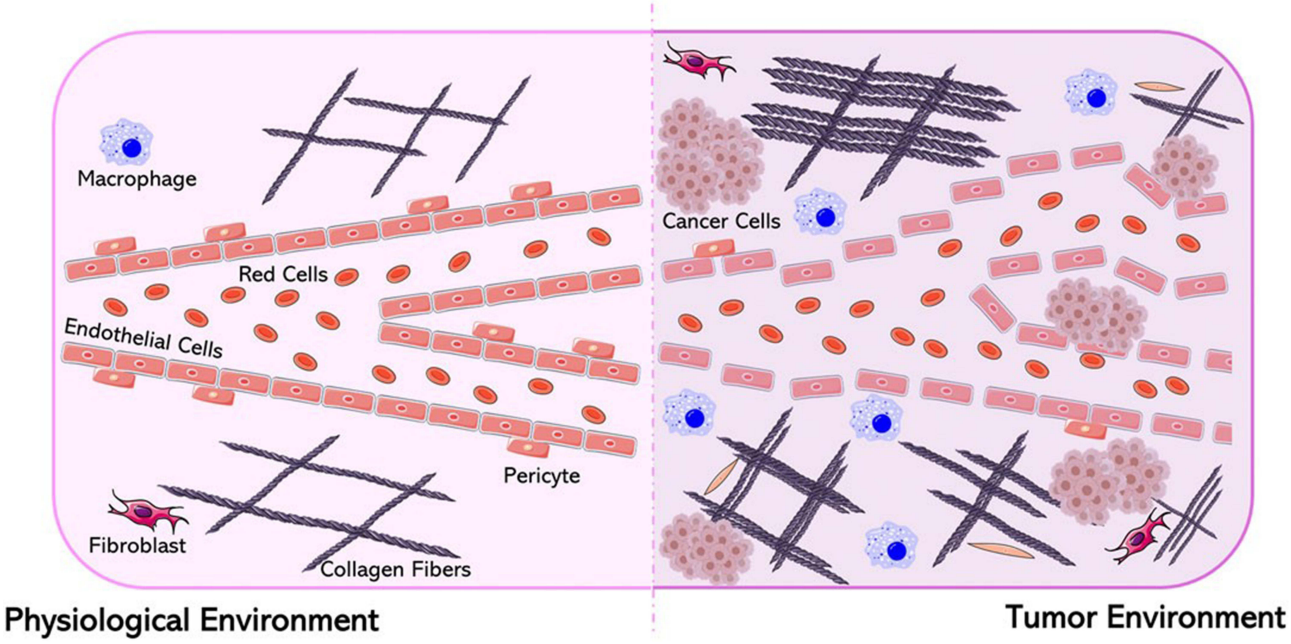

Figure 2 Difference between physiological and tumour micro-environment adapted from [84] under a Creative common license.

bloodstream into the tumor tissue, which in effect pushes drugs away being repulsive to the cancer cells.[43,85] Making things worse, there is poor and disorganized vascularization; the malformed blood vessels of the TME tend to be tortuous, structurally and functionally impaired and have lower blood flow rates. This hypoperfusion causes severe hypoxia (low oxygen levels) in large tumor areas that, in addition to conferring resistance to traditional chemotherapy and radiotherapy, restricts the number of nanocarriers to reach the tumor via the circulation as well as allows spreading of nanocarriers into the tumor area is limited by hypoxia.[86] All these TME barriers contribute to the development of multidrug resistance (MDR), ie., restricted therapeutic penetration and facilitated efflux of internalised drugs, highlighting the importance of TME-responsive delivery systems that can break down the ECM or react to low pH and hypoxia to treat CRC effectively.

Despite being widely accepted for several decades as a cornerstone in passive tumour targeting, the EPR effect has been increasingly questioned with regard to its clinical relevance. Quantitative analyses show that on average, less than one percent of the administered nanoparticles dose is delivered to tumour tissue using preclinical models.[87] Moreover, there is a noteworthy heterogeneity of the magnitude of the EPR effect, and significant attenuation in human tumours compared to murine xenograft models, which is largely due to differences in vascular architecture, stromal density, and the interstitial fluid pressure.[88,89] Recent analyses highlight that nanoparticle tumour accumulation remains highly heterogeneous in human cancers, underscoring the need for delivery strategies beyond sole reliance on the EPR effect.[90]

Importantly, whilst ligand mediated active targeting can enhance cellular internalisation after nanoparticle extravasation into tumour tissue, there is no clear benefit on overall tumour accumulation at the systemic level.[91,92] These observations suggest that active targeting does not preferentially increase intracellular delivery as compared to bypassing the constraints associated with vascular delivery. As such, the use of EPR alone may prove insufficient for effective clinical translation, especially in colorectal cancer given the heterogeneous tumour perfusion and stromal heterogeneity that relates to the pathway of nanoparticle distribution.

Natural Polymers Used in Biocompatible Nanomedicines

Nanomedicines that have been made from natural polymers are emerging as a significant approach in the management of colon cancer. Natural polymers offer a few advantages in drug delivery systems such as biocompatibility, biodegradability and their capacity to further differentiate malignant cells makes them a good choice in the treatment of colon cancer, as illustrated via Figure 3 and some examples are mentioned in Table 2. Polysaccharides are among other natural polymers making them especially appealing with their distinct structural and functional characteristics.

Polysaccharides

Chitosan

Chitosan is a polysaccharide of chitin, and it is one of the most commonly used natural polymers in drug delivery systems, especially the treatment of colon cancer. It has a positive charge, is pH sensitive, and mucoadhesive, which makes it extremely effective in targeting the colon. The positive charge helps the drug to interact with the negatively charged cell membranes and facilitate uptake by colon cancer cells.[101,102] The mucoadhesive characteristic of chitosan helps the drug to remain in the target site longer, and the pH-sensitive characteristic enables the drug to release drugs according to the pH levels in the gastrointestinal tract especially in the colon where the pH is more alkaline.[103] This is a controlled release system that improves the delivery of the drug to colon cancer cells, thereby improving therapeutic effects and reducing side effects on the body. It has been shown that nanoparticles prepared using chitosan are effective in improving oral absorption and colonic delivery of anticancer agents, thus chitosan-based nanoparticles have huge potential in the treatment of colon cancer.[104]

Alginate (AG)

Another significant substance in nanomedicine that is utilized in the treatment of colon cancer is alginate, which is a natural polysaccharide obtained by extracting it out of brown seaweed.[105,106] Its ability to entrap divalent cations like calcium form gels makes it a very great material in preserving drug-packed nanoparticles against acid environment in the stomach. This characteristic enables the agents that are made of algae to release the drug specifically in the colon where gel is more favorable to form and release the drug.[107] Alginate is biocompatible, thus making it even more attractive as

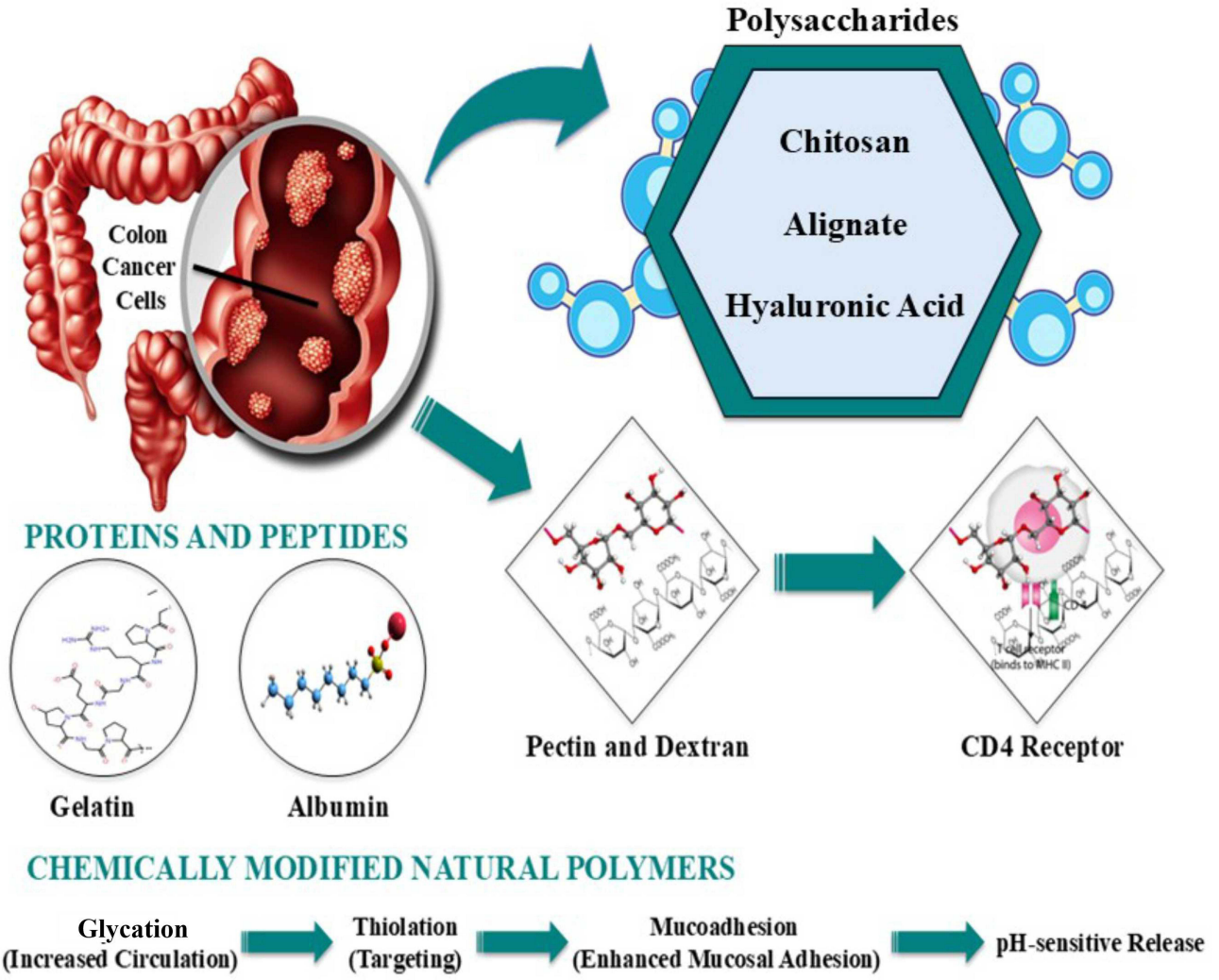

Figure 3 The schematic illustration of the natural polymers in biocompatible nanomedicines to deliver drugs into cancerous colon using targeted methods. The figure underlines the theme of employing different polysaccharides, proteins, peptides and chemically modified natural polymers to improve therapeutic targeting, circulation, mucosal adhesion and controlled release using effective treatment of colon cancer.

a drug carrier of oral colon-targeted delivery systems.[108] The use of alginate based nanocarriers to deliver anticancer drugs orally has been reported by several studies with promising outcomes in increasing the efficacy of the colon cancer treatments by providing a controlled, sustained release of the drugs in the colon.[109,110]

Pectin and Dextran

Natural polysaccharides such as pectin or dextran have been of interest in colon-targeted drug delivery systems because of their properties of being enzymatically degraded by the colonic microbiota.[111,112] The site-specific release of drugs is best achieved with this form of degradation because they are enzyme-responsive in the colon, where they may disintegrate and release the therapeutic agents to the exact location of the tumor.[113,114] An example is pectin which has been found to release drugs based on the enzymatic activity of pectinase which is an enzyme present in large amounts in the colon.[113,115] On the same note, colon-specific release of dextran-based nanoparticles can be developed to increase the targeting and therapeutic efficacy of colon cancer treatment.[116] Pectin and dextran are both promising agents in pacing the release of drugs, making them more precise and reducing the side effects associated with treating colon cancer.

Table 2 Comprehensive Overview of Natural Polymer-Based Nanomedicines for Colon Cancer Targeting

Polymer Type	Source	Nanocarrier Formulation	Targeting Strategy	Biocompatibility	References
Chitosan	Chitin (shellfish)	Nanoparticles, micelles, hydrogels	pH-sensitive, EPR effect	High (non-toxic, biodegradable)	[93]
Inulin	Chicory, Jerusalem artichoke	Nanoparticles, micelles, hydrogels	Receptor-mediated (eg., folate)	High (non-toxic, biodegradable)	[94]
Fucoidan	Brown seaweed	Nanoparticles, hydrogels	Apoptosis induction, immune modulation	Moderate (bioactive, immunomodulatory)	[95]
Guar Gum	Cyamopsis tetragonoloba	Microspheres, nanoparticles	pH-sensitive, mucoadhesive	High (non-toxic, biodegradable)	[96]
Gelatin	Animal collagen	Nanoparticles, hydrogels	Thermosensitive, biocompatible	High (biodegradable, biocompatible)	[97]
Pectin	Citrus Fruit	Nanoparticles, hydrogels	pH-sensitive, mucoadhesive	High (non-toxic, biodegradable)	[98]
Xanthan Gum	Xanthomonas campestris	Nanoparticles, hydrogels	pH-sensitive, mucoadhesive	High (non-toxic, biodegradable)	[99]
Cyclodextrin	Starch	Nanoparticles, nanosponges	Inclusion complexation	High (non-toxic, biodegradable)	[100]

Hyaluronic Acid

Hyaluronic acid (HA) is a naturally occurring glycosaminoglycan that is largely important in tumor biology particularly in the targeting of colon cancer. The cell surface glycoprotein binding HA, called CD44, is overexpressed in most cancerous cells, such as those in colon cancer.[117,118] HA and CD44 interaction led to a range of cell responses, including cell migration, adhesion, and survival which are vital in cancer progression, and metastasis.[119] This binding enables HA to serve as a good ligand to attack cancer cells because it can specifically bind to tumor cells that express CD44 and deliver drugs.

Recent research has drawn attention into the application of HA-functionalized nanoparticles as better ways of delivering and targeting anticancer drugs. HA-coated NPs are better targeted to colon cancer cells and therefore increase drug concentration at the tumour location with minimal systemic toxicity.[120] HA-based nanocarriers are especially beneficial due to using the CD44 receptor overexpression of cancer cells to cause receptor-mediated endocytosis and the drug-delivery efficacy.[121] Moreover, the capacity of HA to alter the tumor microenvironment and influence the extracellular matrix (ECM) has an extra therapeutic advantage because interplay between tumor cell and the surrounding matrix is essential in movement and metastasis of cancerous cells.[122]

Besides improving the delivery of drugs, HA-based NP can resolve challenges like multidrug resistance (MDR) in colon cancer. MDR is a major challenge to cancer treatment as it is the overexpression of efflux pumps that shrink drugs out of cancer cells. HA-coated NPs can avoid these pumps by attacking CD44, thus allowing the drug to be kept within the tumor cells and have its therapeutic effect.[123] Consequently, HA-targeted nanomedicines form one of the potential ways of making the process of colon cancer treatment more efficient and resolving the issue of overcoming the difficulties of traditional chemotherapy.

Proteins and Peptides

Gelatin and Albumin

Two natural polymers that have been promising in the creation of biocompatible nanocarriers for treatment of colon cancer are albumin and gelatin. Gelatin is a collagen derivative which is especially useful because of its thermoresponsive behavior, large

drug loading capacity, and biodegradation. Gelatin nanoparticles (GNPs) can encapsulate both hydrophilic and hydrophobic drugs so that they can have diverse therapeutic applications.[124,125] The ability of loading large doses of anticancer drugs like paclitaxel and doxorubicin into GNPs increases the bioavailability and stability of the drug consequently increasing its effectiveness in fighting colon cancer cells.[126,127]

Equally so, another natural polymer which has attracted interest in nanomedicine is albumin, which is highly abundant plasma protein. Albumin nanoparticles (ANPs) have a number of advantages such as having the properties of being biocompatible, low immunogenicity and the capacity to entrap hydrophobic and hydrophilic drugs.[128,129] Naturally, the tumor cells absorb albumin, as the permeability and retention (EPR) effect can be used to passively accumulate nanoparticles in the tumor microenvironment.[130] The property is specifically useful in the targeting of solid tumors such as colon cancer whereby conventional chemotherapies are not always successful in attaining sufficient level of drugs at the location of the tumor. Also, the inherent capacity of albumin to bind certain receptors, including the albumin-binding receptor, can further target the drug delivery of therapeutic agents to cancer cells to further therapeutic results.[131] Nanocarriers based on gelatin and albumin can provide an attractive platform on which targeted drug delivery systems can be developed to enhance the pharmacokinetics of the chemotherapeutic agent and to minimize the side effects of systemic drug delivery methods. They are natural and biocompatible that makes them the perfect choice in designing nanomedicines to enhance the cure of colon cancer.

Chemically Modified Natural Polymers

Natural polymers HA, gelatin and albumin have many benefits in drug delivery, but when it comes to nanomedical applications, they are frequently modified chemically to enhance their efficacy in treating colon cancer. PEGylation, which refers to the addition of polyethylene glycol (PEG) molecules to the polymer backbone, is one of the most widespread alterations. PEGylation enhances the stability, solubility and circulation of nanoparticles hence lowering their rapid clearance of the immune system and increasing their bioavailability.[132,133] Such modification assists the nanoparticles to stay longer in the blood, and this is especially needed to enhance the concentration of drugs in the tumor tissues by the EPR effect.[134]

Thiolation is another modification that includes the inclusion of thiol groups to the polymer structure. Thiolated polymers are also better in mucoadhesive properties and therefore long-term retention of drug-loaded nanoparticles at the site of action, especially in the gastrointestinal tract which is important in treating colon cancer.[135] Also, the nanocarrier stability of thiolation may be improved in the harsh microenvironment of tumor, which is often low pH, high enzyme conditions.[136] It is also established that thiolated polymers enhance the efficiency of cellular uptake, which occurs by interacting with cell surface receptors, and may further increase drug delivery specificity to colon cancer cells.[137]

Moreover, natural polymers can be crosslinked or grafted with other materials like peptides or other functional groups that may be of great significance to the targeting ability and the drug release profile of the nanocarriers. As an example, it is possible to graft HA onto the nanoparticles to increase the specificity of the carriers on the CD44-positive cancer cells, whereas the pH-sensitive groups can be grafted to release the drugs in the acidic tumors on demand.[138] These modifications assist in addressing certain limitations of natural polymers, including their rather fast clearance and inadequate targeting capabilities.

Design Strategies for Targeted Colon Cancer Nanomedicines

Passive Targeting Mechanisms

In passive targeting, the abnormal attributes of tumor vessel, namely the vessels being dilated and leaky because of the high and disorganized angiogenesis, are used,[139] the features are mentioned in flow chart via Figure 4. This creates gaps among the endothelial cells in the blood vessels whose diameter varies between 100 nm and 1 μm through which the nanoparticles can extravasate passively into the tumor interstitium.[140] The presence of these large gaps in the vasculature is not common in normal vasculature, and it gives the nanoparticles a selective route of accumulating in tumor tissues. Moreover, tumors in most cases have poor lymphatic drainage, thus, making it hard to remove nanoparticles in the tumor

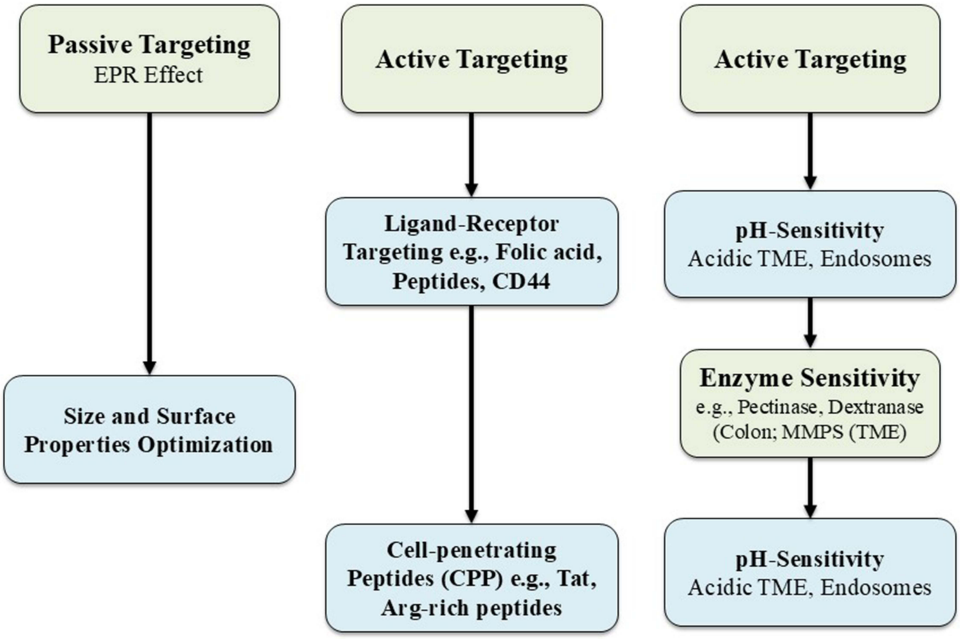

Figure 4 Schematic illustration of various targeting approaches (passive and active) to nanomedicine in drug delivery to the treatment of colon cancer.

site effectively. This causes the nanoparticles to remain in the tumor thereby increasing the exposure of the drug to the cancer cells.[141]

Nanoparticles' size and characteristics determine how to passive target. Nanoparticles between 10 and 200 nm are the best since they are large enough to build up in the tumor via the leaky vasculature yet small enough not to be cleared out by the renal system too quickly.[142] The nanoparticles can be modified on their surface which can inhibit their rapid recognition and clearance by the immune system and improve their circulation time and ability to concentrate at the tumor site.[143] PEGylation is now an established method of nanoparticle-based passive targeting, which has greatly enhanced the pharmacokinetics of nanoparticles.[144]

Passive targeting techniques are used in colon cancer exploiting the EPR effect, which also increases the uptake of chemotherapeutic agents by tumors. Taking advantage of the EPR effect, nanoparticles have the potential to preferentially target colon cancer tissues, further enhancing the delivery of drugs to the tumor with reduced systemic toxicity.[145] This has been applied to several types of nanoparticles such as liposomes, polymeric nanoparticles and mesoporous silica nanoparticles that have garnered preclinical and clinical trial successes in the treatment of colon cancer.[43,146,147]

Active Targeting

Ligand-modified nanoparticles have selective accumulation at tumour sites by ligand -receptor interactions, thus enabling targeted delivery of therapeutic agents; the nature of these interactions is modelled in Figure 4. These nanostructures are normally termed as actively targeting nanoparticles.[148] Cancer cells often overexpress certain receptors and release biomolecules that stimulate the growth of tumorous and surrounding tissues, often through paracrine or autocrine signalling pathways.[149] There are two major methods of conjugating ligands to nanoparticles, one is a chemical functionalisation of nanoparticles in the synthesis step and the other is a ligand conjugation to polymers before nanoparticles are produced.[150,151] Passive accumulation in tumour tissue can also be realised using ligand-modified nanoparticles and then these particles can be internalised by cancer cells through active targeting, which increases the specificity and therapeutic efficacy of the intervention.

In the last three years, nanodrug delivery systems against colorectal cancer have been developed with the primary emphasis on receptor-ligand binding approaches with the use of receptors that are highly expressed in colorectal cancer, including the folate receptor,[152] epidermal growth factor receptor (EGFR),[153] CD44, epithelial cell adhesion molecule

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(EpCAM),[154] nucleolin,[155] hyaluronic acid receptor,[61] and many more. Among these, nanoparticles targeting EpCAM, folate receptor, EGFR, and CD44 have been the subject of extensive research. For instance, to enhance CRC targeting following systemic administration, DNA aptamers specific to EpCAM (eg., SYL3C), which exhibit a strong affinity for EpCAM proteins on cancer cells, have been conjugated to nanoparticles. To minimize drug toxicity and improve therapeutic outcomes, Ge et al[154] synthesized biological conjugates loaded with celastrol, which were effectively captured by CRC cells overexpressing EpCAM. These conjugates consisted of EpCAM aptamers, polyethylene glycol (PEG), and dendrimers, resulting in extensive apoptosis in SW620 cells upon exposure. Moreover, in both xenograft mouse and zebrafish models, the biological conjugates demonstrated low toxicity. The dendrimer component of the study, composed of biocompatible materials, also exhibited a multivalent effect, thereby enhancing the safety profile of the chemotherapeutic drugs.[154]

In another study, miR-139-5p was delivered to colorectal carcinoma (CRC) cells using cationic liposomes. The liposomal preparation was a mixture of HSPC, DOTAP, Chol, and DSPEPEG2000COOH lipids. The nanoparticle surface was functionalised with an EpCAM aptamer to provide colorectal-specific targeting. The resultant construct exhibited a high level of inhibitory action against HCT cells and in vivo pharmacodynamic evaluation of murine models showed a strong inhibitory effect of tumor growth in CRC mice inoculated with HCT8 cells subcutaneously.[156]

Along with targets that are distinctly specific to CRC, several antigens that are commonly overexpressed in other neoplasma are also expressed in colorectal carcinoma and can therefore be utilized to deliver nanotherapeutic agents with specificity. Folate receptor is a membrane-bound glycoprotein that is typically absent or lowly expressed in normal tissues but highly up-regulated in a range of malignant cells, such as CRC.[148] It, therefore, forms a logical object of therapeutic exploitation. Self-assembled nanoparticles based on biocompatible and biodegradable biopolymers, such as chitosan and chondroitin sulfate, have been used to entrap the hydrophobic proteasome inhibitor bortezomib. These particles were modified on the surface to obtain active folate receptor targeting. Soe et al[152] conjugated folate to DSPEPEG which was then conjugated to the nanoparticles. This adjustment did not only increase the stability of the particles and the efficiency of drug loading but also promoted prolonged systemic circulation. The nanomedicines showed strong antitumour effects in animal models with little toxicity to non-tumour tissues.[152]

Design Strategies for Targeted Colon Cancer Nanomedicines

While nanoparticle size has been widely acknowledged as being a critical determinant of passive tumour accumulation, exclusive consideration of average particle diameter can present a confusing picture of the challenges of translating nanoparticle technology from bench to bedside because of size polydispersity. Polymeric nanoparticle preparations, especially those from natural polymers like chitosan, alginate, or gelatin, often have a measurable size distribution instead of monodisperse population. Consequently, the polydispersity index (PDI) has a direct influence on circulation half-life, biodistribution and clearance kinetics.[157–159]

Smaller hence nanoparticle fractions (<50nm) are susceptible to rapid renal clearance and thus reduce effective exposure to tumour, while larger fractions (>200nm) are more vulnerable to the mononuclear phagocyte system (MPS) – particularly in the liver and spleen.[87,160] In contrast, heterogeneous size distributions may lead to divergent biological behaviour within a single formulation of the therapeutic element and hence inconsistent tumour accumulation profiles and variable therapeutic outcomes. Importantly, tumour extravasation is very size sensitive, and nanoparticles ranging in diameter of ca. 50–150 nm tend to show an optimal balance between prolonged circulation and effective tumour penetration, with broader size distributions lowering the predictability of EPR-mediated localisation.[87,161–163] Moreover, advanced nanoparticle engineering increasingly focuses on precise control of physicochemical properties and structural uniformity to improve translational performance.[164]

Aside from biological performance, size polydispersity poses challenges in both manufacturing and regulatory perspectives. Batch-to-batch variation in polymer crosslinking, kinetics, and the solvent diffusion rates can cause a shift in size distribution profiles, affecting the reproducibility and scalability of the natural polymers nanoparticles systems.[165] In addition, small changes in PDI can affect the dynamics of protein corona formation, which influences clearance behaviour and tumour-targeting efficiency.[166] Accordingly, optimisation of the natural-polymer nanoparticle synthesis should be prioritised not only for the desired mean size but also for tight control on the size distribution (PDI <0.2 where possible and scalable fabrication

protocols, robust physicochemical characterisation). Addressing heterogeneity in size at the formulation stage is vital to achieving predictable pharmacokinetics, reproducible tumour accumulation and successful clinical translation of nanotherapies. Moreover, pH-responsive drug delivery systems take advantage of small but biologically relevant pH-gradients, which occur along the gastrointestinal tract and in the tumour microenvironment. In colorectal cancer, luminal pH goes from very acidic in the stomach (pH (1–3)) to almost neutral in the colon (pH (6–7)), whereas tumour extracellular pH is generally slightly acidic (pH (6.5–6.8)) compared to normal tissue.[167,168]

Natural polymer-based systems are based on several molecular mechanisms for pH-responsive release. Polymers that contain ionisable functional groups, eg., carrier containing carboxyl or amine group, undergo protonation/deprotonation due to the local pH value, leading to electrostatic repulsion, the relaxation of polymer chains and the swelling of the polymer matrix allows the drug to diffuse faster.[169,170] For example, chitosan can become protonated under acidic conditions affecting its solubility and permeability behaviour, while alginate exhibits pH dependent swelling and dissolution behaviour under near neutral colonic conditions.[171,172] Acid-labile linkages, such as hydrazone bonds, acetal or Schiff base bonds can be introduced between the polymer backbone and the therapeutic payload. These covalent bonds are stable at physiological pH but are cleaved in slightly acidic tumour conditions to allow for controlled and selective intracellular drug-release.[173,174]

Mechanistic Pathways of Natural Polymer Nanocarriers Overcoming Biological Barriers

Natural polymer based nanocarriers for colon specific drug delivery natural polymer based nanocarriers exploit their inherent physicochemical characteristics to pass through hostile gastrointestinal milieu and the dense TME for colon specific drug delivery. Different therapeutic agents are susceptible to degradation within the acidic gastric compartment, nevertheless, polymeric carriers such as chitosan and alginate provide protective matrices which enhance the stability of the drug.[175] The pH responsive behaviour of chitosan allows its integrity to be preserved in the presence of acidity in the stomach, to swell up or dissolve only under the high pH typically found in the intestine and colon, preventing premature drug release and/or degradation by the proteins of gastric proteases.[176,177] Similarly, Alginate, a pH responsive polysaccharide, forms ionically crosslinked gels that resist acidic degradation and undergo controlled swelling with a rise in pH to induce controlled drug release at the desired site.[178–180]

Enzymatic catabolism is another challenge to be overcome since the degradation of sensitive therapeutic compounds by proteolytic and pancreatic enzymes in the upper gastrointestinal tract may occur. Polysaccharides such as pectin and dextran are designed to resist hydrolysis in the gastric and jejunal portions but are selectively hydrolyzed by gut-releasing enzymes by the gut microbiota in the colon. Consequently, the enzymatic degradation of these polymers in the colonic environment causes the release of the drug payload only at the target site and therefore increases the site specificity and reduces the systemic adverse effects.[181,182]

The thick layer of mucus on the intestinal epithelium forms a strong barrier to drug permeation and absorption. Natural polymers often have inherent mucoadhesive properties which allow nanocarriers to bind to mucus, prolonging the time of residence at the site of action and enhancing local drug absorption. Notably, chitosan, due to its cationic nature, electrostatically interacts with the anionic components of mucus, namely mucins, to promote an adhesion, and promotes the sustained release of drugs.[104,183] In addition, techniques of surface engineering, like grafting of hydrophilic polymers, can attenuate unspecific mucoadhesion and deeper diffusion through the mucus network.[184,185]

Once it reaches the colon, more challenges are encountered in the tumoral microenvironment. The extracellular matrix of colorectal neoplasms is often enriched with hyaluronan and collagen and provide a compact stroma which limits nanoparticle infiltration into the neoplasm. Nanocarriers assembled from HA take advantage of overexpression of CD44 receptors on colon carcinoma cells which promote receptor mediated endocytosis with enhancing tumour specificity. HA functionalisation has the added benefit of facilitating deeper tumoral penetration through interaction with the constituents of the ECM and transient matrix modulation for improved delivery efficacy.[186,187] Moreover, hybrid systems that combine chitosan with HA have shown synergistic effect in colon targeting by combining pH responsiveness and receptor-mediated uptake and thus improve treatment.[188]

Coordinated Multi-Component Integration in Natural Polymer Matrices

Recent developments in the field of natural polymer-based nanomedicine have helped to co-encapsulate the chemotherapeutic agents, imaging modalities and gene - regulatory payloads in a single multifunctional platform. Nevertheless, the successful transfer of such systems to clinical use requires more than simple co-encapsulation; more than that, it requires that the polymeric matrix has structural integrity and biological activity and orchestrates a temporally controlled release of therapeutics.

Natural polymers such as chitosan, HA, alginate and gelatin form hierarchical structural networks, which can segregate multiple functional agents. Possessing directly cross linked ionic and cross conjugated spherically discrete microdomains by utilizing hydrogen bonding strategies of an ionic cross-linking polymer and covalent conjugation strategies of a covalent cross-linking polymer, these matrices prevent premature interactions between sensitive payloads like nucleic acids and small molecule chemotherapeutics.[189–191] Furthermore, stimuli-responsive polymeric nanosystems integrating therapeutic and diagnostic elements have emerged as promising precision platforms.[192]

Stimuli-responsible linkers built in the natural polymer frameworks enable the sequential or environment-trigger release of the therapeutic constituents. For example, pH-sensitive or enzyme cleavable linkages are used to allow the delivery of chemotherapeutics in the acidic environment of tumours while protecting siRNA or miRNA constructs from exposure until they are taken up into cells.[193,194] In addition, hyaluronic acid-based matrices exhibit receptor-mediated endocytosis by targeting CD44 to deliver the coordinated intracellular trafficking of both imaging and therapeutic modules without compromising the functional integrity of gene-regulatory elements.[176,195] The preservation of biological activity is of particular importance in the case of nucleic acids and imaging probes. Natural polymers offer soft fabrication conditions which reduce the risk of denaturation compared to synthetic polymer systems. Apart from this, electrostatic complexation within nanostructures built on Chitosan is shown to stabilize RNA payloads against enzymatic degradation until they are released into the cytosol.[196,197] Consequently, multifunctional carrier natural polymer matrices possess not only a carrier function but also the capability of acting as dynamic structural frameworks that include spatial isolation, stimuli triggered activation, and synchronized payload release.

Optimizing Mucoadhesion–Penetration Balance in Natural Polymer Nanocarriers

The strong mucoadhesive properties of natural polymers may lead to an extension in the residence time at the mucosal surfaces and thus enhance the local drug retention, however too high adhesion may hinder deeper diffusion through the tumour-associated mucous and stromal barriers. Mucoadhesion is the outcome of specific polymer-mucin interactions, such as hydrogen bonding and electrostatic forces, which can improve carrier residence but may adversely affect nanoparticle mobility within thick mucus layers, which in turn limit the access to underlying tumour tissues.[198,199] Chitosan is one of the most widely used natural polymers, with intrinsic mucoadhesive behaviour due to its positive charge, which allows for the interaction with mucins with a negative charge, but can also increase the sequestration if not optimised.[104,200]

For example, in order to improve this inherent trade-off, rational design strategies are focused on modulating polymer composition, hydration kinetics and surface chemistry. Reducing excessive surface charge density or mixing with neutral polymers can reduce mucin binding that would otherwise be too strong while retaining a level of adhesion that results in controlled release. Surface engineering techniques include the partial protection with hydrophilic layers or with motifs that can be infiltrated by mucus, which can interact with the mucus transiently and then with tumour tissue, ie., they diffuse deeper.[199] Moreover, adjusting the hydration behaviour by a controlled cross-linking and controlled network density can be used to avoid overly dense gel layers hindering the transport, not to mention that regulated swelling promotes the gradual relaxation of polymers and favours the penetration of viscous mucus structures.[198] Emerging dual functional strategies combine both mucoadhesive and mucopenetrating components into one formulation to balance the state of retention as well as mobility. By adding mucolytic constituents or surface ligands that limit the interaction between irreversible mucin and these systems, enhanced mucosal contact without compromising deeper tumour accessibility is achieved.[199]

Intelligent Tumour Microenvironment-Responsive Natural Polymer Nanocarriers

The colorectal tumour microenvironment is characterised by a compact and rigid ECM, high interstitial fluid pressure (IFP), abnormal vasculature and areas of profound hypoxia, all of which are associated with metastasis and invasion.[23] These features are not independent, but are mechanistically interlinked, and this collectively limits the penetration of nanocars carrying drugs and the nanocarrier uniform drug distribution. Rational engineering of natural polymer-based nanomedicines is increasingly directed towards such pathological cues used as triggering activation rather than only being a barrier.

Stiff ECMs with natural polymer collagen and hyaluronan limit convective transport and diffusion. Natural polymer nanocarriers can be engineered with enzyme-responsible breakdown connections, for example, matrix metalloproteinase (MMP)-degradable peptides or hyaluronidase-sensitive components to make it possible for selective matrix reconfiguration when they reach tumour tissue. Such strategies allow controlled structural loosening and better intratumoral penetration while maintaining systemic stability.[201,202]

Increased interstitial pressure also acts to restrict the inward diffusion flow and promote peripheral accumulation of nanoparticles. Stress-responsive polymer networks with mechano-adaptive deformation have manifested potential in modulating release profiles in compressive forces as too characteristic of solid tumours. Hydrogels and cross-linked polysaccharide systems in which structural relaxation is controlled through mechanical stressing can be used to facilitate better deeper penetration and longer-lasting release.[203–205]

A further exploitable trigger is hypoxia, which is characteristic of a far-advanced colorectal tumour. Hypoxia responsive moieties such as azobenzene linkers, nitroimidazole derivatives and reductively cleavable bonds can be incorporated into natural polymer matrices. When starved of oxygen, these linkers become bioreduced, destabilising the formation of the nanostructure and releasing the drug in a localised manner, specifically in hypoxic tumour cores.[206–208] Importantly, by incorporating several tumour-responsive elements into the same natural polymer matrix, it is possible to achieve hierarchical modes of activation, with ECM-sensitive degradation aiding penetration with subsequent hypoxia-triggered release inside the tumour core. Such multitargeted systems increase the therapeutic specificity with minimum premature systemic release. Therefore, natural polymer nanocarriers can be conceptualised not simply as passive delivery systems but as intelligent biomaterials that can dynamically respond to the heterogeneity of the tumour microenvironment, in terms of mechanical, enzymatic and metabolic heterogeneity.

Microbiota-Triggered Release: Managing Inter-Patient Variability

Polysaccharide-based colon delivery systems that are based on commensal bacterial degradation (eg., pectin, dextran, inulin or azobond linkers) are attractive as they can be relatively stable in the proximal gastrointestinal tract and to be cleaved in the colon. This strategy, though, relies inherently on the capacity of the microbes involved, which will vary substantially across individuals because of diet, age, disease state, antibiotic exposure and other host related factors.[112,209] Inter- patient variations in the abundance and activity of bacterial enzymes involved in colonic activation including glycosidases, azoreductases and beta glucuronidase-related activities may thus be translated into clinically meaningful changes in polymer degradation and drug release timing. These shifts can be either delayed or inadequate liberation resulting in the risk of under exposure or premature cleavage resulting in the risk of premature release with altered profiles of local concentrations.[210,211]

Importantly, although taxonomic compositions can differ, in many gut communities there is functional redundancy, in that similar metabolic capabilities may be preserved although any taxa producing them may differ. However, functional production is not uniform across patients and dysbiosis may affect or redirect important enzymatic activities relevant in microbiota triggered delivery.[212,213]

To increase translational robustness, microbiota-based polysaccharide systems can be designed with attributes that minimize the need for a single patient-specific microbial step. Practical strategies involve integrating microbiota sensitivity with an added independent trigger, such as pH responsive outer coatings or time controlled matrices, to guarantee colon localisation even when decomposition of the polymer is not as fast as expected; to prioritise polymer chemstries that rely on cleavage by broadly distributed enzymatic functions; and to control cross linkage

density, substitution pattern and layer thickness to increase the "activation window" and avoid sharp dependence on a particular microbiome state.[112,214] From the translation perspective, ex vivo fecal fermentation or enzyme-activity assays can be incorporated into the development process to help quantify variability in release kinetics and serve as a guide to formulate parameter ranges that can be used to ensure a maintenance of efficacy across patient populations.

Molecular and Microbiome Signatures for Patient-Tailored Nanomedicine Design

Beyond the conventional ligand-receptor targeting, tumour-specific molecular and microbiome signatures are a tantalizing way forward for personalization of polymer-based formulations. The integration of patient-derived multi-omics (ie., genomics, transcriptomics, proteomics and metabolomics) data sets enables the determination of idiosyncratic expression patterns, such as receptor over-protection, tumour subtypes, metabolic dependencies and immune modulators. The resultant molecular atlas can be used to inform the optimisation of both targeting ligands and stimuli-responsive chemistries that have the greatest potential of being suited to an individual patient's tumour, thereby augmenting specificity and clinical efficacy.[215]

Contemporary frameworks encourage the use of machine - learning approaches in tumour -omics profiles, which have made it possible to transfer heterogeneous biological aspects into quantitative design rules for nanocarrier optimisation. These rules include using a smart choice of ligand, composition of polymer and release triggers calibrated to the biochemistry of individual tumours. Empirical evidence has shown that such data-driven design enhances the performance of nanomedicine in patient-derived organoid models that can be seen as a paradigm shift from empirical approaches to precision nanotherapeutic design.

Simultaneously, the tumour-associated microbiome has emerged as a key player in colorectal cancer progression and responsive therapy. Specific microbial communities are associated with different tumour subtypes, tumour stages and immune phenotypes with influence on drug metabolism, immune activity and local inflammation (Long et al manage Theoretical Bayes CC, 2024). Intratumoural microbiota can affect epithelial signalling pathways, influence the state of the immune microenvironment and induce therapeutic resistance mechanisms, therefore requiring the design of nanocarriers that can either make use of or counter-act specific microbial interactions for improved clinical outcomes.

Personalised nanomedicine strategies additionally recognize receptor heterogeneity haunting traditional paradigms of targets. Tumours with unique expression profiles for integrins, growth factor receptors, immune checkpoints or stemness markers can be paired with polymers functionalised with ligands with the capacity to preferentially bind these markers and enhance cellular uptake and delivery of a therapeutic payload. Recent investigations show that the combination of molecular profiling and targeted design of nanocarriers will improve tumour selectivity and potentially overcome the problem of resistance due to receptor variability.

Isoform-Specific CD44 Targeting in HA-Based Nanomedicines

CD44 is not a homogeneous receptor, but rather a family of alternatively spliced receptors including the standard form (CD44s) and several variant forms (CD44v) including CD44v3 and CD44v6. The above-mentioned variants show structural disparities within their extracellular domains and are implicated in various biological processes which influence colorectal cancer development, metastasis, and regulation of stemness.[216,217] Importantly, several CD44 variant isoforms, and in particular CD44v6, have been found to strongly correlate with aggressive tumour phenotypes and enhanced metastatic potential in colorectal cancer.[218,219]

Hyaluronic acid-based nanomedicines take advantage mainly of the conserved hyaluronan-binding domain found among the CD44 isoforms that permit receptor-mediated uptake in tumour cells that express larger numbers of CD44 receptors. However, this approach fails to distinguish between the standard and variant isoforms, although there is a growing body of evidence suggesting that CD44 variants exhibit distinct clustering behaviour, co-receptor interactions and downstream signalling properties that may affect nanoparticle internalisation as well as intracellular trafficking.[218,220]

Given the heterogeneous expression of CD44 variants across tumour subtypes and within tumour microenvironments, incorporating isoform-aware targeting strategies may significantly enhance precision. Potential approaches include

combining HA with isoform-specific antibodies or peptide ligands targeting CD44v6-enriched tumour populations, thereby improving selectivity toward invasive or stem-like cancer cell subsets while reducing off-target interactions.[221,222] Such refinement moves HA-based systems beyond general receptor targeting toward tumour isoform-specific precision medicine, improving translational relevance in heterogeneous colorectal cancers.

Natural Polymer Nanomedicine Formulations for Colon Cancer

Polymeric Nanoparticles

To achieve the best therapeutic effects in colorectal cancer (CRC), nanoparticle engineering must be advanced significantly. This advancement requires accurate control of the size, morphology and surface ligands of nanoparticles, which are central to improving drug delivery systems. Close assessment of synthesis guidelines is essential to produce the desired nanostructures, along with the rational choice of polymers to produce nanocarriers, covalent coupling methods, and targeting ligands.[223,224] Moreover, polymeric systems provide significant flexibility in customization and optimization of nanoparticles to enable effective drug delivery, which is a requirement to translate these technologies into clinical practice; examples are given in Table 3. However, due to the large number of parameters that can be adjusted, strategic and thought-over design of nanoparticle systems is essential to achieve the required therapeutic effects.[225]

Polymeric nanoparticles are usually solid in shape, in the form of a sphere, which is formed by self-assembly. Nanospheres and nanocapsules are two major subclasses that are formed through different mechanistic routes. The active agents are uniformly distributed in the polymeric structure of nanospheres, but in nanocapsules the drug is encased in a core that is surrounded by a single polymeric membrane.[233] Polymeric nanoparticles of different kinds have been investigated in the treatment of CRC. As an example, Shashank Tummala et al designed a 5-fluorouracil (5-FU) enteric-coated polymeric nanoparticle that targets the colon and maintains the concentration of the drug in the tumour tissues, significantly shrinking the size of the tumour compared to the unencapsulated 5-FU controls.[234]

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Table 3 Polymeric Nanoparticle for Colon Cancer Therapy

Polymeric Nanoparticles	Drugs Encapsulated	Model (in vitro and/or in vivo)	Effects Observed	References
Polymeric micelles	Quercetin	In vitro in CT26 cells, in vivo in mice and rats	Sustained drug release, 37% reduction in IC50, increased apoptosis, tumor volume reduction	[226]
Polymeric micelles	Curcumin	In vitro in CT26 cells	Enhanced cellular uptake, tumor growth inhibition, increased apoptosis	[227]
Polymeric micelles	DOX and α-TOS	HCT 116 cells, in vivo in mice	Increased drug accumulation in tumor, similar tumor inhibition, reduced systemic toxicity	[228]
Polymersomes	DOX	HCT 116 cells, in vivo in mice	Increased cellular uptake, tumor accumulation, enhanced tumor inhibition	[229]
Polymeric nanoparticles with targeting ligands	SN38	C26 mouse colon carcinoma, in vivo	Enzyme-responsive release, increased cytotoxicity at low concentration, tumor regression	[230]
Lipid-based and polymeric nanomedicines	Various drugs	Preclinical models	Improved efficacy, stability, and selectivity	[231]
Polymer-based NPs	Various drugs	Preclinical models	Targeted delivery with enhanced tumor specificity	[232]

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assembled micelle with an average diameter of 22 +3nm. Compared to unencapsulated fisetin, the micellar formulation had sustained and prolonged release in vitro, increased cytotoxicity and cellular uptake. In vivo studies demonstrated that there were a major tumour-growth inhibition and prolonged survival in the CT26 tumour model.[236]

Shin-Yu Lee et al utilized cationic PDMA-block-poly(ε-caprolactone) (PDMA-b-PCL) micelles to load SN-38, ultra-small superparamagnetic iron oxide (USPIO) nanoparticles, and small interfering RNA (siRNA) to create a multifunctional micellar drug delivery system. Their results demonstrated that SN-38/USPIO-loaded siRNA–PEG mixed micelles could passively target tumor sites, suppress VEGF action, and simultaneously deliver chemotherapy. This multi-dose therapy significantly reduced tumor growth.[237]

Polymersomes, another class of self-assembled polymer vesicles, are also employed for encapsulating and protecting sensitive molecules such as drugs, enzymes, and nucleic acids. Although similar in structure to liposomes, polymersomes exhibit enhanced stability and higher loading efficiency.[238,239] Matthew A. Petersen et al developed PR_b-functionalized, bioresorbable polymersomes for the targeted delivery of cisplatin to human colon cancer cells. PR_b is a peptide targeting the a5b1 integrin, which is overexpressed on human colon cancer cells. Their findings demonstrated that this delivery system minimized side effects, extended circulation time, and improved the survival of mice. These advanced nanostructures exhibit tremendous potential for improving the therapeutic efficacy of CRC treatments, thus opening new avenues for cancer therapy.[240]

Other Drugs for Colon Therapy

5-Fluorouracil (5-FU) is widely utilized in the treatment of breast, colorectal, gastric, and pancreatic cancers. Although 5-FU activates multiple pathways, its primary mechanism of action involves inhibition of thymidylate synthase (TS), a critical enzyme in DNA synthesis, thereby limiting excessive DNA proliferation. Nonetheless, the combination of 5-FU with folinic acid has demonstrated improved therapeutic outcomes in colon cancer, as folinic acid enhances the effect of 5-FU by further inhibiting thymidylate synthase. Capecitabine, an oral prodrug of 5-FU, is metabolized in vivo to release the active drug. This compound increases the bioavailability of 5-FU and inhibits the synthesis of thymidine monophosphate, which is essential for de novo DNA synthesis. Numerous studies have demonstrated that capecitabine induces a higher tumor response rate compared to intravenous 5-FU. Furthermore, capecitabine has a more favorable side-effect profile and improved tolerability, offering significant clinical benefits over 5-FU.[241] Oxaliplatin is a third-generation platinum analogue that differs with cisplatin and carboplatin by having a 1, 2-diaminocyclohexane ligand instead of two monodentate amine ligands. Irinotecan, a semi-synthetic analogue of camptothecin, is a topoisomerase I inhibitor, which hinders the replication of DNA and reduces the stress of superhelix. Its active metabolite, 7-ethyl-10-hydroxy-camptothecin (SN −38), is approximately a thousand times more cytotoxic than irinotecan. Even though the bioconversion of orally or intravenously administered irinotecan in humans is only 2–8% into SN-38, the drug is still an important chemotherapeutic, especially when used in optimized vehicle preparations.[242] Cyclooxygenase-2 selective, non-steroidal anti-inflammatory agent (celecoxib) has shown a strong antineoplastic effect in preclinical models. The drug regulates key genes and signalling pathways involved in tumour-related inflammation, thus suppressing the development of colonic polyp. However, its use in clinical practice is limited by severe adverse events, including hypersensitivity reactions, cardiovascular events, including myocardial infarction and cerebrovascular accident, and high plasma clearance, which all reduces its clinical efficacy.[243]

Prospects and Future Directions

The prospects for natural polymer-based biocompatible nanomedicines in targeting colon cancer are highly promising, driven by advancements in nanotechnology and a growing understanding of tumor biology. Natural polymers eg., chitosan, alginate, dextran and hyaluronic acid have inherent biocompatibility, biodegradability and low toxicity which make them the best carriers of colon cancer therapeutics. The ability to functionalise these polymers with targeting ligands enables specific accumulation of drug-laden nanoparticles in tumour locations thereby increasing therapeutic effect whilst reducing systemic side effects. Future directions in this area are concerned with the development of multifunctional nanomedicines, which combine diagnostic and therapeutic properties, and hence allow real-time monitoring of therapeutic response. Stimuli-responsive natural polymer nanocarriers can be used to control and release drugs site-specifically through innovations in stimulus-responsive nanoparticles based on changes in pH, enzymatic activity, or

redox conditions within the tumour microenvironment. The use of colon cancer specific biomarkers and active targeting receptors is expected to further improve the precision of delivery. Combining natural polymer nanomedicines with novel immunotherapeutic approaches has significant potential in overcoming tumour immune evasion and improving clinical outcomes. Also, the personalised nanomedicine plans, which will depend on individual tumour genotypes and micro-environmental features, will help streamline therapeutic regimens. However, there are still several issues, such as the mass reproducible production of these nanomaterials, their stability, and regulatory approval. To enhance the speed of translating these technologies into clinical practice, comprehensive preclinical studies based on advanced patient-derived models are needed. Interdisciplinary teams involving materials scientists, oncologists, and the pharmaceutical industry are essential to the promotion of innovation and a faster process of creating safe and effective polymer-based nanomedicines. In conclusion, natural polymer chemistry, nanotechnology, and tumour biology convergence offer strong prospects of transforming colon cancer treatment using safer, more targeted and highly effective nanomedicine platforms. Further interdisciplinary studies and stringent clinical validation are essential in order to realise the clinical potential of these biocompatible nanotherapeutics to the fullest.

Challenges and Clinical Translation

The translation of nanoparticles into clinical practice is highly successful because of the efficacy of nanoparticles that has been observed in preclinical models of CRC. Nevertheless, nano-drug delivery systems have several problems that persist in their development. The most difficult task is associated with the mass production of nanoparticle formulations and stringent testing of their preclinical safety and effectiveness. Currently, nanoplatforms, which are to be used in the treatment of a specific cancer type (CRC), are becoming increasingly complex in terms of design and composition, and production is becoming more challenging, as well as it is impossible to achieve the consistency of synthesis at large scale. In addition, physical and chemical characteristics of these nanoplatforms must be strictly regulated throughout the production procedure, which places an additional burden on the manufacturing facilities and causes the large-scale manufacturing to be even more complicated and costly. In this respect, microfluidic technology has attracted much interest. Indicatively, Valencia et al have shown successful self-assembly of lipid-polymer and lipid-quantum dot (QD) nanoparticles by microfluidics and the particles formed were stable, uniform.[244] It is important to note, however, that the complicated structure of nanoparticles poses a possible risk of toxicity to patients, which makes the need to have models that better reflect the pathogenesis of human CRC in toxicity assessment in preclinical trials a necessity.[245] Besides, clinical trials have shown that, although nanoplatforms usually decrease drug toxicity, they do not always increase therapeutic efficacy.[245] It has been observed by scholars that even though most nanoparticles can localise at tumour sites due to the enhanced permeability and retention (EPR) effect- and even actively targeted particles are also dependent upon the same effect, the EPR effect is predictable in animal models but not in CRC patients. Such inconsistency of the EPR effect in patients can significantly affect the efficacy of nanoparticle-based therapies.[246] Consequently, personalized treatment approaches are required, wherein nanoparticles are employed in patients exhibiting a strong EPR effect for optimal efficacy, or alternative formulations that can accumulate in tumors independently of the EPR effect, such as temperature-responsive hydrogels for localized CRC treatment, may be considered. Shelf-life limitations arise from the potential for drug leakage or premature release from the nanoparticle matrix before reaching the tumor site. Natural polymers might also undergo physicochemical changes during long-term storage, including changes in crystallinity or molecular weight distribution, leading to diminished performance. Furthermore, maintaining sterility and preventing microbial contamination pose additional challenges for shelf-stable formulations of natural polymer-based nanomedicines.[247]

Although the enhanced EPR effect is an appropriate mechanism for accumulation, a growing body of evidence shows that many human tumours have limited endothelial interstitial volumes and heterogeneous vascular permeability, which compromises the passive accumulation of certain broad classes of patients and lesions.[41,248] Within settings of low EPR microenvironments, natural polymer-based nanomedicines may be designed with the prevailing objective of maintaining therapeutic efficacy by focusing on mechanisms that do not require significant vascular "leakiness". First, active targeting strategies can be used to potentially augment cellular engagement and uptake following the contact with the tumour. In view of the colorectal cancer, the HA based systems are of particular relevance as they are able to bind to CD44 and

RHAMM mediated pathways, which have been characterised in CRC and integrated with protective or colon specific designs of delivery systems.[118,249]

Second, tumour access may be improved by taking advantage of the transendothelial transport processes, such as transcytosis, combined with access facilitating strategies. These approaches are increasingly recognised as complementary to, or as replacement of, conventional EPR-mediated extravasation in a variety of solid tumours.[41,250]

Third, intratumoural dispersion, which is often limited by compactness and extracellular matrix architecture of the stroma, may be enhanced using multistage and stimuli-responsive polymer constructs for example size or charge switching designs and tumour microenvironment induced drug release mechanisms.[251] Additionally, the incorporation of penetration promotional moieties, such as tumour penetrating peptides such as the iRGD when applicable, can improve more profound drug dissemination beyond perivascular zones.[252,253] Taken together, these design considerations provide a pragmatic framework for improving the resilience of nanocarriers based on natural polymer materials against heterogeneous tumour vascular phenotypes.

Molecular Ageing and Release-Phase Instability of Natural-Polymer Carriers

Beyond macroscopic "shelf-life" considerations, the question of functional longevity of nanocarriers formed using natural polymers is often hampered by sluggish, coupled molecular phenomena which occur during storage and go on to modulate the release of the drug. In hydrated or partially hydrated conditions, relaxation of polymer chains re-organises the network over time - a process called physical ageing-, which can thus alter mesh size, permeability and mechanical integrity and so the kinetics of drug release over time. Concurrently, swelling by moisture-induced can plasticise polysaccharide matrices, increasing the rate of diffusion-driven drug escape, and can also provoke structural rearrangements that may not be apparent by routine sizing and evaluation techniques, and yet yield significant difference in performance in vivo.[254,255]

During extended storage or sustained release, the progressive hydrolytic and enzymatic breakage of glycosidic bonds or labile points of crosslinking (as well as, in some formulation, oxidative chain damage) may result in decreased molecular weight and decreased degree of cohesive strength and increase the premature drug leakage. These phenomena of degradation - relaxation are formulation - dependent (influenced eg., by polymer source, crosslink density, ionic milieu) and are strongly affected by the residual water content. Consequently, stabilisation strategies regularly use freeze - drying or lyophilisation with suitable protectants and strict moisture - control protocols once the biological activity structure have to be preserved upon reconstitution.[256,257]

Microfluidic Control of Flow Regime and Shear in Scalable Nanoparticle Fabrication

Microfluidic manufacturing has become an attractive platform for synthesis of natural polymer nanoparticles for better batch-to-batch reproducibility and better structural precision. In contrast with conventional bulk mixing strategies, microfluidic devices largely fall in the field of laminar flow regime (Reynolds number < 100), where the fluids stream parallel to one another and the mixing is achieved by controlled diffusion across sharply defined interfaces. Within this regime nucleation and growth of the nanoparticle are determined by rapid and reproducible solvent-anti-solvent interactions, allowing precise control of size and polydispersity of the finally obtained particles.[258–260]

More careful control of shear gradients within microchannels further affects the assembly of polymer chains and cross-linking kinetics. In natural polymer systems like chitosan or alginate nanoparticles, the ionic cross link formation can be controlled through shear-controlled mixing which limits uncontrolled aggregation and heterogeneity in size.[261,262] It should also be noted that high shear rates can promote homogeneous supersaturation and binding uniform nucleation while poorly controlled gradients could result in wider size distributions and irregular structures.[263,264]

On one hand, rapid mixing times, often on the millisecond time, are particularly important in the definition of particle morphology and internal architecture. Short mixing times minimise uncontrolled growth phases and favour kinetically trapped and structurally uniform nanoparticles. This has direct implications for reproducibility, as by reducing this variability in clearance kinetics and tumor accumulation profiles improving distributions in size are less variable[265,266] From an industrial point of view microfluidic platforms also provide scalability via parallelisation ("numbering-up") as opposed to traditional scale - up approaches. By insuring identical hydrodynamic problems in replicated channels, structural porosity can be maintained at higher production rates, which overcomes a key limitation of classical bulk nanoprecipitation techniques.[267,268] Consequently, a deep

understanding of how the laminar flow condition, shear gradients, and mixing kinetics interact for preserving the structural fidelity and segregation of the therapeutic load through from laboratory synthesis to industrial manufacture is required for translating natural polymers nanoparticle systems.

Translational Limitations of Preclinical Tumour Models

The translation of preclinical efficacy of treatment is limited by biological differences between animal tumour models and human colorectal tumours, which by their nature is a limitation. Common murine models such as syngeneic and xenograft systems often do not match human cancers in terms of vascular architecture and stromal composition. Preclinical tumours are often characterized by an increased vessel density and more homogeneous perfusion (this can increase nanoparticle extravasation and retention in comparison with human tumours with more chaotic and heterogeneous vasculature - a factor which is directly relevant to nanocarrier accumulation by the EPR effect).[269]

In addition, the density of stroma and the composition of extracellular matrices (ECM) differ dramatically from one model to the next. For example, models of murine pancreatic and breast carcinoma display harder ECM with higher levels of collagen and hyaluronic acid which changes the diffusion of nanoparticles versus colon carcinoma models; this variation indicates that data obtained from one murine model may not be generalizable across tumour types or across to human disease.[270] Moreover, patient-derived xenografts (PDX) have been widely used to maintain the human tumour histology, but the human stroma and immune cells are gradually replaced by host murine cells, and the microenvironment within the PDX develops differently from the original tumour with different cellular interactions, different enzymatic profile and the matrix dynamics.[271]

These discrepancies highlight that structural and functional attribute of tumours, including endothelial fenestration, interstitial pressure profiles, and the host enzymatic repertoires, can have differential effects on nanomedicine delivery, clearance and activation. Therefore, although data generated from preclinical models are still invaluable, the extent to which they are predictive in comparison with human CRC needs careful consideration. Complementary use of advanced models (eg., organoids, humanised animals and patient derived (humanised) systems) may enhance translational relevance through better recapitulating key aspects of human tumour biology.

Conclusion

Natural polymer-based nanomedicines represent a promising frontier in the targeted treatment of colon cancer, offering numerous advantages such as biocompatibility, biodegradability, and the ability to be functionalized for precise targeting. These nanomedicines have the potential to improve therapeutic efficacy while reducing systemic toxicity, making them a favorable alternative to traditional treatment modalities. Despite these promising prospects, significant challenges remain in the widespread clinical application of natural polymer-based nanoparticles. Issues related to the complexity of synthesis, scale-up production, and precise control over nanoparticle characteristics continue to hinder their commercialization. Additionally, the variability of the EPR effect in colon cancer patients underscores the need for personalized therapeutic approaches to optimize nanoparticle-based treatments. Addressing these challenges will require continued advancements in nanotechnology, manufacturing techniques, and the development of more predictive preclinical models. Innovative strategies, such as microfluidics for nanoparticle synthesis and the use of targeted formulations independent of the EPR effect, hold the potential to overcome some of the current limitations. Furthermore, personalized treatment regimens, tailored to the individual patient's tumor characteristics and response profiles, will be essential in maximizing the clinical efficacy of natural polymer-based nanomedicines. While several hurdles remain, the continued development of natural polymer-based nanomedicines for colon cancer offers significant promise. With ongoing research and technological advancements, these nanomedicines could play a pivotal role in the future of targeted cancer therapy, offering more effective, safer, and personalized treatment options for colon cancer patients.

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