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Review Article

Chitosan and Its Derivative-Based Nanoparticles in Gastrointestinal Cancers: Molecular Mechanisms of Action and Promising Anticancer Strategies

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Gastrointestinal cancers account for a significant health concern as the existing treatment modalities, such as surgery, chemotherapy, and radiation therapy, exhibit considerable drawbacks, including a high probability of recurrence, insufficient drug specificity, and severe adverse effects. Hence, novel therapeutic approaches and enhanced tissue-specific targeting are required. Nanomedicine is a field of medicine that uses nanoscale carriers for targeting and administering drugs or diagnostic agents to particular tissues. In the field of nanomedicine, chitosan nanoparticles are well-established delivery technologies used as polymeric carriers. Chitosan is a natural carbohydrate that is biocompatible, biodegradable, polycationic, and mucoadhesive. Chitosan has shown promise in the administration of chemotherapeutic drugs, gene therapy, and immunotherapy for the treatment of gastrointestinal cancers. The limited water solubility of chitosan is one of its major disadvantages as a drug delivery system. Thus, solubility may be increased by chemically treating chitosan. Chitosan derivatives improve the activity, selectivity, biocompatibility, and therapeutic dose reduction of anticancer drugs when used in hydrogel, emulsion, surfactant formulations, and nanoformulation. Chitosan and its derivatives have shown effectiveness in nanoparticle production and exhibit unique surface properties, enabling them to interact selectively with gastrointestinal tumors through both active and passive targeting mechanisms. This review focuses on the molecular signaling pathways of chitosan nanoparticles and their derivatives as potential anticancer agents. The potential of future chitosan applications in gastrointestinal cancers is additionally highlighted.

1. Introduction

The majority of cancer-associated mortality is caused by gastrointestinal (GI) malignancies, which mostly include esophageal, gastric, colorectal, pancreatic, and hepatocellular carcinomas [1–4]. Incidence rates of GI cancers vary across industrialized and developing countries [4]. The mortality rate of GI malignancies has remained constant despite diverse treatment methods, leading to a vast worldwide burden of disease and an unfavorable prognosis. The poor survival rates of GI cancer patients are primarily attributable to the following conditions: delayed diagnosis at late stages, lack of prognostic indicators, progression of recurrence and metastasis, and treatment resistance [1, 5]. A significant proportion of cancer patients depend on chemotherapy drugs to reduce the burden of malignant tumors and prolong their lives [6]. Although chemotherapy improves the efficacy of cancer treatments, some patients may experience adverse effects [7]. Chemotherapeutic medicines have several drawbacks, including high dose needs, poor absorption, a low selectivity index, nonspecific interactions, and the emergence of drug resistance [8, 9]. Therefore, creating a suitable drug delivery system (DDS) that may successfully reduce the therapeutic dosage or frequency of anticancer medications while attenuating their adverse effects is urgently needed [10].

Existing data support the urgent need for more targeted therapies to improve therapeutic effectiveness and lessen side effects [7, 11]. Drug administration to specific tissues, organs, cells, or subcellular structures is accomplished using various DDSs. To improve pharmacological effectiveness, mitigate problems such as poor bioavailability, restricted solubility, inadequate selectivity, and insufficient biological distribution, or lessen adverse effects, it is necessary to control drug release and absorption [12]. To overcome the drawbacks of insoluble medications, lessen the adverse effects of hazardous pharmaceuticals, and extend their half-life, polymer-based DDSs have the potential to improve current disease treatment techniques.

Recent studies have shown that chitosan (CS)-based derivatives are exciting, adaptable, and biocompatible [13–17]. Chitin is a naturally existing biopolymer that is found in fungal cell walls, crustacean shells, and insect exoskeletons. CS is chitin in its partial deacetylated form. This substance is a linear copolymer whose chemical composition consists of b-(1/4)-2-amino-d-glucose and b-(1/4)-2-acetamido-d-glucose subunits. According to reports [18, 19], CS has been shown to have a variety of adaptive biological properties, including biocompatibility, biodegradability, and a comparatively low degree of toxicity. CS is a potential biomaterial as it has been shown to induce a modest immunological response in the mammalian system after injection, implantation, topical treatment, or ingestion [20, 21]. Because of its biological features, which include antioxidant, anticancer, antibacterial, anti-inflammatory, and immunostimulatory activities, the biopolymer has been widely used in various industries, including food industry, agriculture, biomedical, pharmaceutical, and tissue engineering [22]. Therefore, it has been acknowledged as a unique physiologically bioactive substance [23–25].

The focus of this review will be the molecular signaling pathways and therapeutic implications of CS and its derivatives as potential anticancer agents in GI cancers. The detailed abbreviations and definitions used in the paper are listed in Table 1.

2. CS-Based Nanomedicine in the Treatment of GI Cancers: A Challenge to Conventional Therapy

The administration of drugs by oral route has significant potential. However, it is crucial to address many physiological obstacles inside the GI tract, such as stomach pH, GI enzymes, the mucus layer, and efflux pumps. Overcoming these barriers is necessary to ensure the medication reaches the systemic circulation and effectively produces its desired effects at the intended site of action. Various barriers exist that restrict the absorption of several medications, such as anticancer, anti-inflammatory, and antibacterial treatments. Consequently, these problems also hinder the oral bioavailability of these drugs [26–30].

However, the administration of conventional chemotherapy for GI cancer involves its own challenges, including limited specificity and selectivity, resulting in potential harm to healthy cells and tissues. Inadequate infiltration and persistence inside tumor tissues lead to a decrease in therapeutic effectiveness. Development of drug resistance and toxicity, constraining the dose and duration of treatment [31, 32], and insufficient early detection and real-time monitoring result in delays in intervention and therapy evaluation [31].

To overcome these GI hurdles, researchers have invented and developed medication delivery vehicles. CS is thought to be a good candidate for bioinspired drug delivery because it is made up of polymers that come from natural sources and have a lot of different functional groups. This characteristic allows for the chemical modification of CS to enhance its physiochemical properties, such as permeating-enhancing effect, mucoadhesive capabilities, efflux inhibition, and controlled drug release [33]. The use of CS nanoparticles (CSNPs) in treatment exhibits considerable potential for addressing these obstacles, as it capitalizes on the distinctive biological, chemical, and physical attributes of nanomaterials. There are many benefits associated with nanoparticle-based treatments. The use of microenvironments, molecular markers, or external stimuli allows for the precise targeting of tumor cells and tissues, resulting in high levels of specificity and selectivity. The use of nanocarriers with suitable shape, charge, size, and surface modification may lead to improved drug delivery and release, resulting in enhanced penetration and retention inside tumor tissues [31, 32]. The utilization of nanomaterials possessing biodegradability, biocompatibility, or stimulus responsiveness has the potential to enhance the therapeutic index and safety of treatments by mitigating drug resistance and toxicity. Additionally, the application of nanomaterials with magnetic, optical, electrical, or electrochemical properties holds promise for improved diagnosis and monitoring, enabling early detection and real-time imaging of tumors [34, 35].

Table 1: List of abbreviations.

Abbreviation	Full description
GI	Gastrointestinal
NPs	Nanoparticles
DDS	Drug delivery system
CS	Chitosan
CSNPs	Chitosan nanoparticles
DA	Degree of acetylation
DD	Degree of deacetylation
MW	Molecular weight
CMC	Carboxymethyl chitosan
SBCS	Sulfated benzaldehyde chitosan
PPC	Polypyrrole-chitosan
CTC	Chitosan-thymine conjugate
SCS	Sulfated chitosan
IL	Interleukin
IFN	Interferon
NF-Kb	Nuclear factor kappa-light-chain-enhancer of activated B cells
TGF-β	Transcriptional growth factor beta
EAC	Ehrlich ascites carcinoma
TNF-α	Tumor necrosis factor α
VEGF	Vascular endothelial growth factor
COS	Chitosan oligosaccharide
EC	Esophageal cancer
EAC	Esophageal adenocarcinoma
ESCC	Esophageal squamous cell carcinoma
FGF	Fibroblast growth factor
HGF	Hepatocyte growth factor
CAFs	Cancer-associated fibroblasts
EMT	Epithelial-mesenchymal transition
GC	Gastric cancer
CdtB	Cytolethal distending toxin
BRAF	v-Raf murine sarcoma viral oncogene homolog B1
HCC	Hepatocellular carcinoma
TACE	Transarterial chemoembolization
MMP-9	Matrix metalloproteinase-9
CRC	Colorectal cancer
TOPK	T-lymphokine-activated killer cell (T-LAK)-originated protein kinase
PC	Pancreatic cancer
EGFR-1	Epidermal growth factor receptor-1
SiRNAs	Small interfering RNAs
MRNAs	Messenger RNAs
v7-CMG	7-silica-coated gold nanoparticle

Hence, the use of nanoparticle-based therapy presents a promising avenue for enhancing the efficacy and customization of treatment for GI cancers. Nevertheless, some obstacles and constraints persist in the practical implementation of nanoparticle-based treatments. These include issues related to biodistribution, stability, immunogenicity, clearance, and regulatory aspects of nanomaterials [31, 32]. Further investigation and experimentation are required to effectively tackle these challenges and enhance the efficiency and implementation of nanoparticle-mediated treatment for GI cancers.

3. CS and Its Derivatives: Natural and Biological Properties

CS is a linear amino polysaccharide composed of monomeric units of N-acetyl-D-glucosamine and β-D-glucosamine linked by β-bonds [36, 37]. This biopolymer has multiple attractive properties such as reactive functional groups for functionalization and crosslinking [38], solubility in acidic aqueous media, biodegradability, nonoxidation, biocompatibility, muco-adhesivity, and FDA approval for use in dietary products and wound dressings [39, 40]. CS is found in several natural resources, such as invertebrate shelves [41, 42]. Lobsters, shrimp, crayfish, crabs, and oysters are the most familiar sources of CS preparation [43].

Chitin is a rich organic polymer composed of N-acetyl-D-glucosamine monomers that are linked together. Partial deacetylation of chitin, resulting in the absence of β-1,4-D-glucosamine functional groups in the repeating units, leads to the formation of CS [44]. The degree of acetylation (DA) is determined by the mole fraction of N-acetylated repeating units. In contrast, the degree of deacetylation (DD) is defined as the percentage of β-1,4-D-glucosamine repeating units in the polysaccharides [12, 45, 46]. CS may be

categorized into low-molecular-weight, medium-molecular-weight, or high-molecular-weight CS based on its DD. The efficacy of low-molecular-weight CS has been demonstrated in terms of solubility enhancement, size reduction, and stability of nanocrystal formulation. As a result, it is regarded as a promising nanocarrier for the development of oral sustained-release drugs with the aim of enhancing bioavailability [47]. Generally, CS oligosaccharide refers to CS with a molecular weight of up to 10 kDa, which is derived from the degradation of CS. This form of CS displays a range of interesting biological properties dependent on its molecular weight, including antitumor activities [48]. Consequently, there have been numerous investigations aimed at transforming CS into CS oligosaccharides possessing distinct molecular weights, to discover more efficient nanocarriers that exhibit both cost-effective and eco-friendly characteristics. CS is widely acknowledged as a polymer that is both biocompatible and safe. The cationic property of CS is considered one of its most significant features. CS possesses an advantageous characteristic as an ideal drug carrier due to its ability to enhance bonding to the negatively charged mucosal surface through electrostatic interaction. This property facilitates the absorption of drugs into targeted cells [42, 49]. CS is generally regarded as a safe biomaterial due to its low or negligible toxicity, as indicated by most research studies. CS exhibits various biomedical characteristics, including antitumor, antimicrobial, and hemostatic activities, contingent upon the CS's DD and MW [50]. The degree of deacetylation is a crucial parameter in the CS structure as it represents the unbound amino groups. Various methods can be employed to determine DD, and it plays a significant role in the physical, chemical, and medical properties of CS [51]. The positive charge density and the capacity to bind with DNA or siRNA are determined by it. Increased DD can enhance transfection efficacy by evading the endolysosomal compartment. CS can also be classified into four distinct forms based on its DD percentage. These forms include low-DD CS, medium-DD CS, high-DD CS, and ultra-high-DD CS. The DD values for these forms range between 55–70%, 70–85%, 85–95%, and 95–100%, respectively. In general, it can be observed that NPs with high surface charge density are produced with high DD, which can lead to an improvement in cell uptake and antitumor efficacy [52]. The chemical and physical properties of CSNPs are significantly impacted by their molecular weight. Typically, an increase in molecular weight (MW) enhances the stability of CS-based complexes and prolongs the duration of nanoparticle circulation in the bloodstream. However, this also leads to a delay in their dissociation and subsequent impact on cells, ultimately ensuring a high level of tumor selectivity. Conversely, decreased MW has the opposite effect, as reported in previous studies [52].

The biochemical efficacy of CS particles is significantly influenced by the attributes of CS and its derivatives. It is essential to acknowledge that these factors do not operate in isolation but rather exert a collective influence on the CS conjugates. Therefore, it is imperative to maintain a balance between stability, solubility, and nanoparticle deformability to achieve optimal efficacy of *in vivo* tumor targeting. The physical, biochemical, and antitumor efficacy of CS can be influenced by the degree and location of substitutions that are grafted onto it. The location of carboxymethylation on CS has been found to impact the deformability and stability of nanoparticles. This factor is closely associated with the cellular absorption and antitumor efficacy of conjugates of carboxymethyl CS (CMC). The significant impact of hydrophobic groups and deoxycholic acid abundance on nanoparticle size, drug loading content, and entrapment efficiency is evident. The solubility of CS in acidic conditions is determined by the prevalence of protonated NH_2 groups in its structure, which possess a pKa value of approximately 6.5. The solubility range of CS can be altered through the utilization of hydrogen bond disruptors, including but not limited to urea or guanidine hydrochloride. Indeed, a diverse spectrum of solubility can be attained via the chemical or physical disruption of hydrogen bonding. Functional groups such as glycosidic bonds and acetyl amine groups can facilitate many modifications, resulting in the creation of polymers that display novel characteristics and behaviors.

Moreover, from a technical perspective, the viscosity of polymers constitutes a crucial parameter, as solutions with high viscosity pose challenges in handling [53, 54]. The comprehensive selection of suitable CS as nanocarriers necessitates thoroughly considering the interplay between the abovementioned factors, payload characteristics, nanoparticle preparation techniques, and targeted ailments [54]. Numerous CS derivatives have been synthesized to improve the properties of CS or incorporate new functions or properties into it. The CS skeleton possesses multiple amino and hydroxyl groups that can be selectively modified, enhancing its water solubility and conferring novel functionalities such as targeted and environmentally responsive drug delivery. These modifications can improve the therapeutic efficacy of CS while minimizing undesirable side effects. Today, several CS derivatives are commonly utilized as drug carriers, such as ethylene glycol CS, CMC, trimethyl CS, thioCS, CS hydrogels, and CS-modified hydrogels [55–59].

4. CS and Its Derivatives: Anticancer Activity in GI Cancers and Corresponding Molecular Signaling Pathways

The utilization of CS, a biopolymer of natural origin, has been documented to exhibit preventive effects against carcinogenesis through the regulation of antioxidant, anti-angiogenic, inflammatory, and apoptotic pathways [60–62]. CS has been utilized to augment bioavailability, drug release, and drug cytotoxicity, as evidenced by previous studies [63, 64].

CS and its derivatives, namely CMC, sulfated benzaldehyde CS (SBCS), polypyrrole-CS (PPC), CS-thymine conjugate (CTC), and sulfated CS (SCS), have demonstrated potential anticancer properties against various types of cancer cells, including GI cancer cells [60, 65]. The antiproliferative activity of low-molecular-weight water-soluble CSs (21 and 46 kDa) was observed toward cancer cells, whereas water-soluble CS with a high molecular weight

of 130 kDa did not exhibit any antitumor activity. The activation of macrophages was observed through the production of cytokines such as interleukin (IL)-12, interferon (IFN)-γ, and IL-18 from the intestinal intraepithelial lymphocytes due to the administration of CSs with molecular weights of 21 and 46 kDa [66]. According to a study, low-molecular-weight CS can arrest the progression of cancer cells during the G1/S phase and induce apoptosis [67]. In addition, it has been observed that CS plays a regulatory role in genes related to the cell cycle, such as Cdc25A, p21/Cip, and p27/Kip. Moreover, by modulating the signaling pathways mediated by the nuclear factor kappa-light-chain enhancer of activated B (NF-kB) cells, it induces apoptosis and upregulates transcriptional growth factor beta (TGF-β) [67, 68]. CTC exhibited antiproliferative effects on HepG2 liver carcinoma cells but not on NIH3T3 normal murine fibroblast cells. This suggests a targeted approach to cancer cells [69]. PPC exhibited anticancer properties against Ehrlich ascites carcinoma (EAC) cells, as reported in a previous study [70]. In addition, it was observed that PPC and CTC exhibited antimicrobial properties, suggesting their potential utility in mitigating secondary infections among individuals with cancer [70, 71]. CMC was found to enhance the immune response by upregulating the levels of tumor necrosis factor α (TNF-α) and interferon γ (IFN-γ), while simultaneously reducing angiogenesis by reducing the expression level of vascular endothelial growth factor (VEGF) [72]. This property of CMC makes it a potential candidate for the transportation of chemotherapeutic drugs such as 5-fluorouracil and doxorubicin, as well as anticancer agents such as curcumin [8]. Similarly, the anticancer potential of SBCS and SCS was observed through the induction of apoptosis and inhibition of FGF-2-mediated activation of extracellular signal-regulated kinases in cancer cells [73]. Regarding IC_{50} value, SBCS exhibited slightly greater potency than SCS, between the two aforementioned derivatives. Furthermore, the apoptotic activity exhibited by SBCS and SCS was notably higher than that of CS. According to a study, the induction of apoptosis in cancer cells was notably higher (over 46%) when compared to CS [73]. Additionally, the anticancer properties of CS oligosaccharide (COS) have been observed in both positively and negatively charged Hep3B (hepatocellular carcinoma cells) and SW480 (colorectal cancer cells). The IC_{50} value indicated that SCOS with a negative charge exhibited greater potency toward SW480 cells than QCOS with a positive charge. According to a study conducted, it was observed through fluorescence microscopic analysis and DNA fragmentation that the charged COS derivatives led to necrosis instead of apoptosis [74]. The antiproliferative activity of chitopentaose, chitohexose, chitobiose, and chitotriose is analogous to COS. The downregulation of prosurvival protein *Bcl-xL* and cell cycle-associated cyclin D1 mRNA expression by chitohexose resulted in the induction of apoptosis [10, 75] (Figure 1).

4.1. Esophageal Cancer. Esophageal cancer (EC) ranks as the sixth most common cause of cancer-related mortality globally. It is the second most lethal GI cancer, accounting for approximately 5% of all cancer-related mortalities [76]. EC is composed of two primary histological subtypes that exhibit unique clinicopathological features: esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC) [77]. Despite the significant advancements in therapeutic modalities in recent years, the quality of life for patients remains suboptimal, and the 5-year survival rate is typically below 40% [78]. This is primarily because EC is frequently asymptomatic in its early stages. Furthermore, it is common for EC to give rise to micrometastases during the initial phases. The proportion of EC patients who are suitable for immediate surgical intervention upon diagnosis is only 10% [77]. Resectable EC is typically managed through a multimodal approach involving surgical intervention, with or without adjuvant chemotherapy, and chemoradiotherapy [79, 80]. Chemotherapy, chemoradiotherapy, immunotherapy, and targeted therapy are potential treatment options for patients declared inoperable [81–83]. Additionally, several potential therapeutic interventions, including thermotherapy, photothermal therapy, and oxidation therapy, have been proposed to manage EC [77, 84, 85]. However, despite their therapeutic benefits, these strategies can potentially cause recurrence and result in the rapid destruction of healthy cells. Although systemic drugs and therapies can restrict tumor growth to a certain degree, they often lack specificity in distinguishing between normal and malignant cells, leading to nonselective cytotoxicity and adverse effects. In addition, the targeting of cells within a tumor by certain drugs may not always be a viable option due to limited diffusion capabilities and challenges in regulating the drug release mechanism, which can be attributed to the unpredictable nature of the approach. Hence, there is an urgent need for therapeutics that can actively and passively target malignant cells [86, 87].

It has been found that the proliferation of tumor cells in EC has been linked to the expression of fibroblast growth factor (FGF) and hepatocyte growth factor (HGF) in cancer-associated fibroblasts (CAFs) [88]. The signaling molecule wnt2, derived from CAF, was found to have the ability to augment the process of epithelial-mesenchymal transition (EMT). The observed phenomenon relates to the loss of intracellular adhesion and polarity by neoplastic cells derived from epithelial tissue. According to a previous study [89], it is possible to induce the transformation of these cells into mesenchymal cells that possess the ability to migrate and invade. The protein levels of cancer-associated fibroblasts are significantly associated with an unfavorable prognosis in patients diagnosed with EC. It has been observed that specific proteins, namely, periostin, α-smooth muscle actin, and CD-10, exhibit a correlation with unfavorable patient survival outcomes [90]. The significance of fibroblasts in EC is apparent as they are linked to an unfavorable prognosis, invasion, and migration of tumor cells. The process of tumor development includes a wide variety of chemokines released by malignant cells. Chemokines such as CXCR7, CCR5, CXCR4, and SDF-1α have been identified. The manifestation of CXCR4 in EC has been demonstrated to be associated with tumor dissemination and an unfavorable long-term prognosis [91]. The involvement of

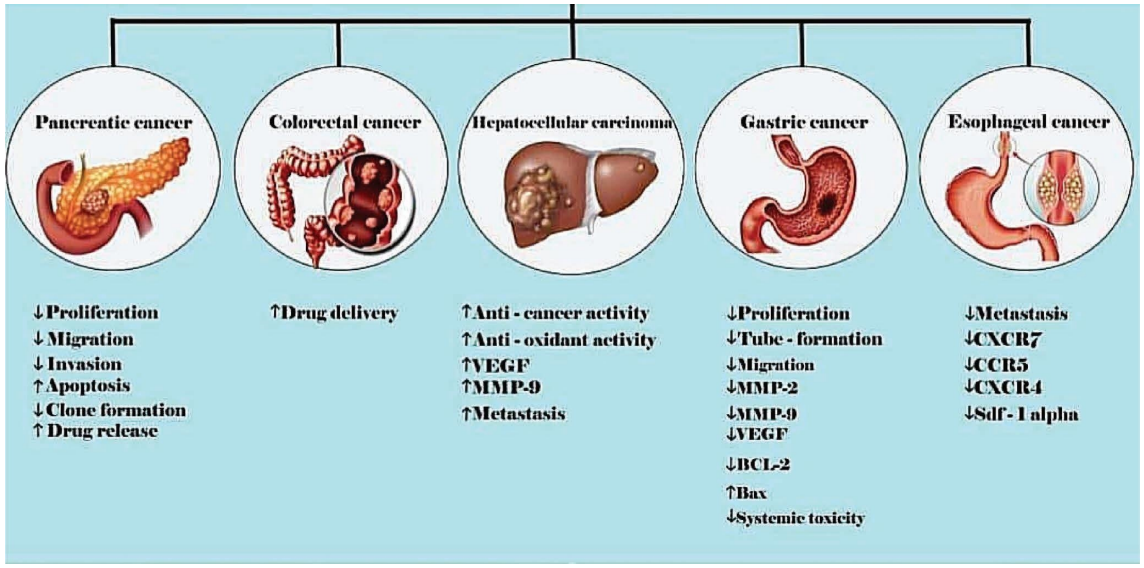


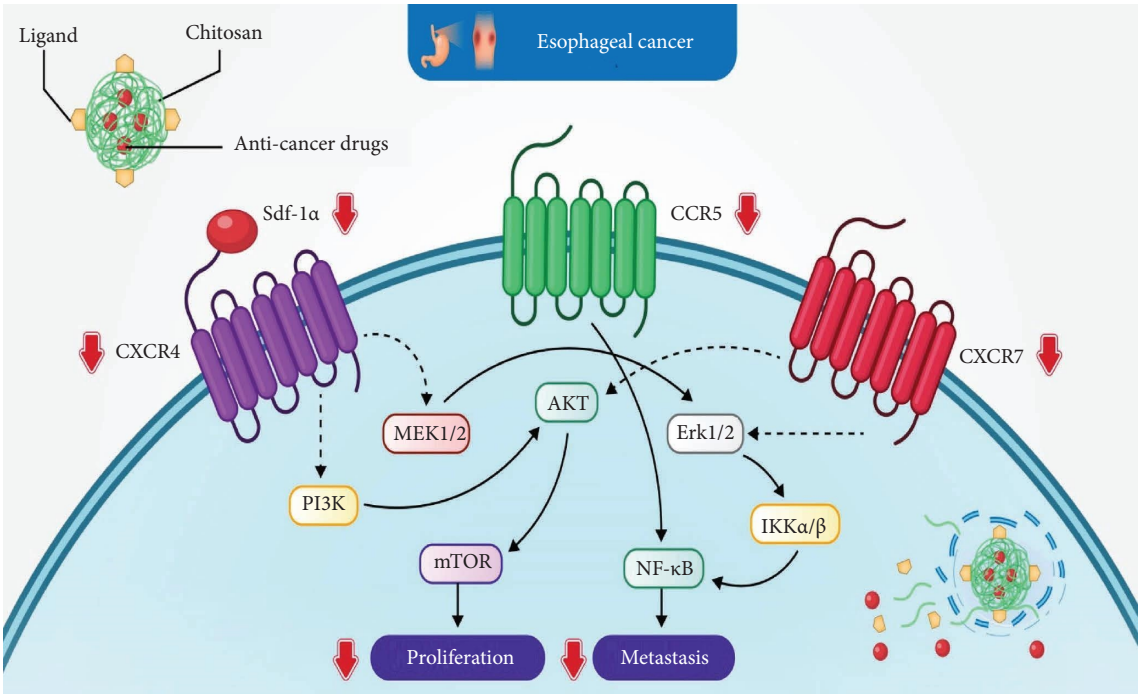
Figure 1: Biological and cellular effects of CS and its derivatives in various GI cancers.

CXCR4 and its ligand, SDF-1α, in the metastasis of EC was observed in an in vivo model [92]. The precise function of CCR5 and CXCR7 in esophageal cancer remains inadequately comprehended; however, in breast cancer, their involvement in proliferation and metastasis has been established [93, 94]. Therefore, it can be inferred that chemokines are crucial as metastatic genes in the context of EC. Targeting metastatic genes is crucial for developing an efficient treatment approach for EC [95].

Studies have been consistently conducted by researchers investigating the utilization of nanomedicine in the treatment of EC, revealing that the platform system of nanomedicine holds promising clinical potential for EC treatment [96–99]. The researchers utilized a CAF cell line obtained from a patient with metastatic EC to investigate the potential of CSNP treatment to alter the metastatic phenotype of cancer cells. This approach has been previously explored for human gastric carcinoma cells. This study involved the use of diverse molecular and cellular markers [100]. The findings of a recent study indicate that CSNPs may possess antimetastatic properties, as evidenced by the observed downregulation of CXCR7, CCR5, CXCR4, and SDF-1α expression in esophageal cancer cells treated with the indicated nanoparticles. Additional evidence supporting the hypothesis of the antimetastatic properties of CSNPs was obtained through the scratch assay. The results indicated that the treated esophageal cancer cells did not exhibit metastatic activity in the scratched region. The observed reduction in the expression of multiple genes upon administration of CS suggests its potential as a pharmacological agent for managing metastatic cancer. Therefore, it is imperative to acknowledge that CS possesses inherent pharmacological properties and should not solely be regarded as a vehicle for drug molecules [95]. Therefore, the utilization of CSNPs for the encapsulation of an anticancer drug has the potential to serve as a dual approach in the fight against cancer, as it can target both tumor-associated fibroblasts and cancer cells [101] (Figure 2, Table 2).

4.2. Gastric Cancer. Annually, 990,000 individuals worldwide are diagnosed with gastric cancer, resulting in roughly 738,000 fatalities. According to research, gastric cancer (GC) ranks as the fourth most prevalent type of cancer and is the second leading contributor to cancer-related mortality [118, 119]. According to research, the occurrence rate of gastric cancer is significantly greater in males than females, with a ratio of 2 to 3 [4, 120]. Gastric carcinoma and gastric antrum cancer are prevalent forms of gastric cancer, with gastroesophageal junction cancer representing an emerging subtype that is rapidly on the rise. The incidence of gastric cancer is gradually increasing in the younger age group [121]. Gastric cancer exhibits certain features, such as elevated rates of metastasis and mortality, coupled with reduced rates of timely detection, radical resection, and 5-year survival [122]. Surgical intervention and subsequent chemotherapy have been employed in treating patients diagnosed with early-stage gastric cancer, resulting in a 5-year survival rate of 90% postoperation. Moreover, in the later stages of the disease, certain cases may not be amenable to surgical intervention, and the likelihood of metastasis is elevated in these individuals, resulting in an unfavorable prognosis [104, 119]. Therefore, developing an appropriate DDS for chemotherapeutic drugs in the treatment of gastric cancer has been a significant area of interest among researchers in recent years.

Notwithstanding the recent progress in gastric cancer therapy, various challenges such as drug resistance, local recurrence, and hematogenous metastasis have led to treatment failure. A primary concern in the application of chemotherapeutic drugs pertains to identifying a suitable drug delivery mechanism that can effectively address existing challenges, such as tolerance to gastric pH, limited



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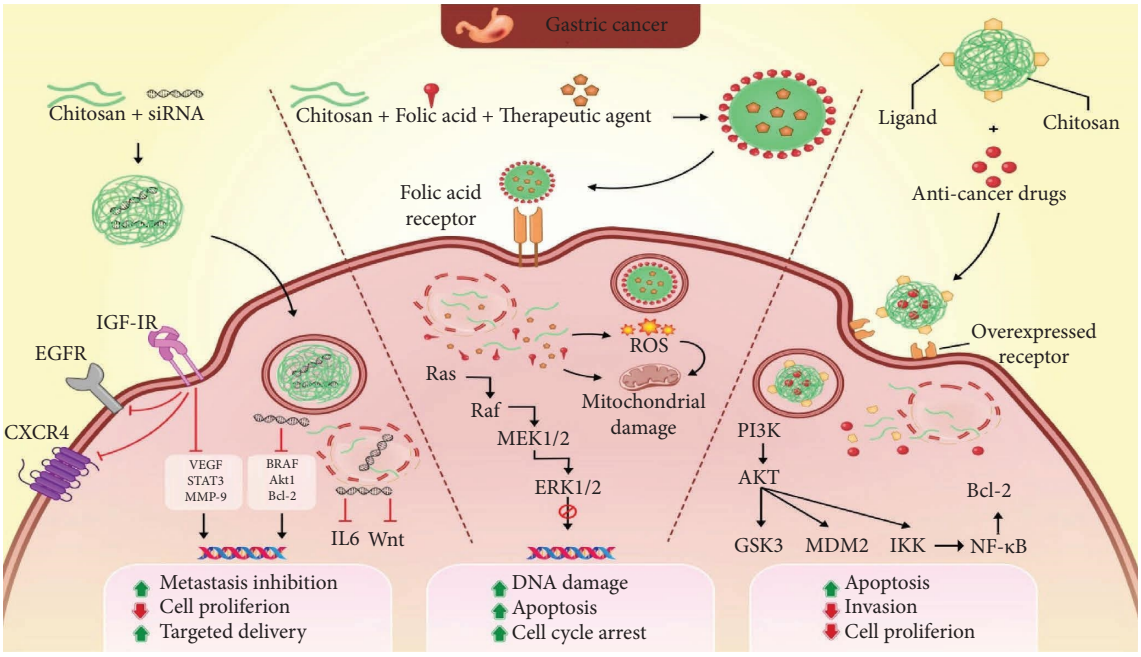

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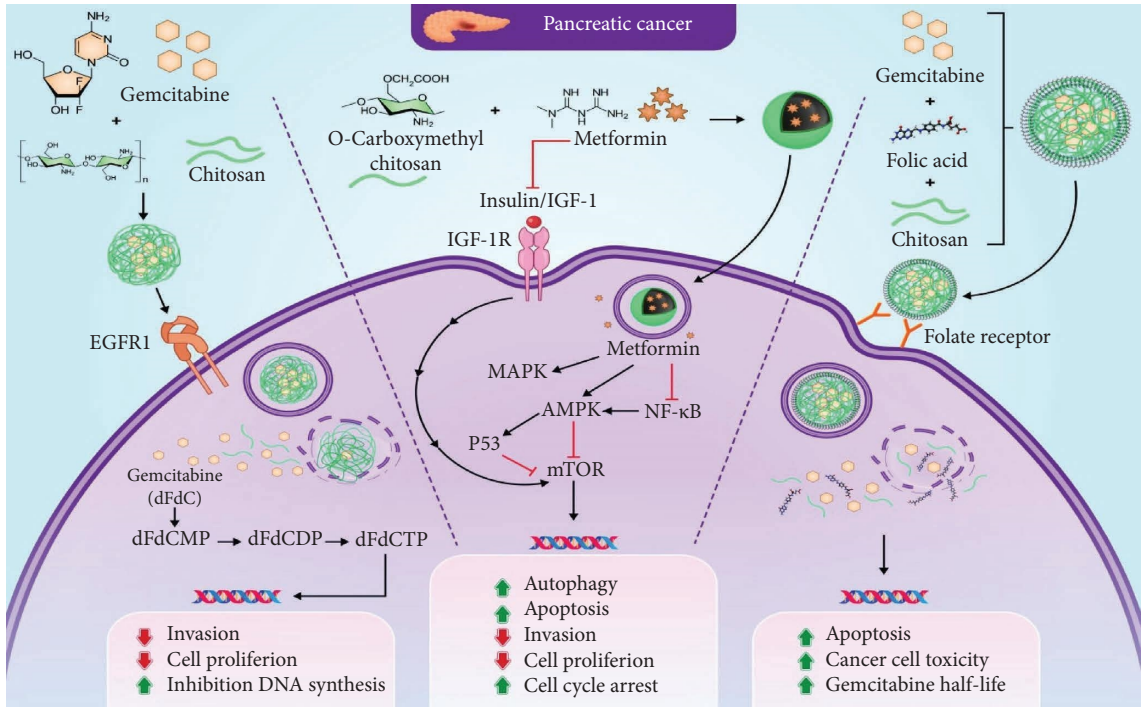

(c)

Figure 2: Anticancer strategies and molecular mechanisms of chitosan and its derivatives in gastrointestinal cancers.

water solubility, and intracellular diffusion [123]. The advancement of DDS has the potential to significantly contribute to the management and outcome of gastric cancer.

CS has emerged as a viable polymer for the development of DDS in various cancer research studies, including those focused on gastric cancer. CS has been identified as a suitable compound for delivering chemotherapy drugs in cancer therapy owing to its exceptional biocompatibility and biodegradability. Additionally, CS's mucoadhesive and cationic properties improve its interaction with mucous membranes, facilitating transmucosal drug delivery [124]. CSNPs can serve as carriers for administering drugs that are both hydrophilic and hydrophobic [125]. The process of conjugating chemotherapeutic drugs involves the participation of multiple free amine groups. Norcantharidin is a potential anticancer drug, and a recent study conjugated it with CMC by an amidation process. This study aimed to evaluate the antitumor efficacy of the conjugate against gastric tumors and compare it with that of the unbound or unconjugated state of the drug. The findings indicated that the drug conjugated with CMC significantly inhibited the proliferation, tube formation, and migration of gastric tumor cells. The CMC-conjugated variant exhibited a higher efficacy in triggering apoptosis of gastric tumor cells than the unbound drug. Furthermore, the administration of CMC resulted in a notable reduction in systemic toxicity and a concomitant enhancement of the anticancer properties of norcantharidin. The study findings indicated that the administration of CMC resulted in an upregulation of Bax and TNF-α gene expression while downregulating the gene expression of MMP-2, MMP-9, VEGF, and Bcl-2. These results suggest that CMC has potential as a conjugative agent for gastric cancer therapy [126]. A recent study was conducted to assess the efficacy of a ligand-based approach utilizing CSNPs for treating gastric cancer. Docetaxel, a chemotherapy medication, was attached to N-deoxycholic acid glycol CSNPs in this study. Additionally, GX1, a ligand appropriate for antiangiogenic drugs in the context of gastric cancer treatment, was employed. The novel approach to drug administration exhibited superior cytotoxicity against gastric tumor cells compared with unbound drugs in gastric cancer cells [127]. The objective of the study was to assess the effectiveness of CS/heparin NPs as an encapsulating method for cytolethal distending toxin (CdtB) in the treatment of gastric cancer. According to a study, this particular approach exhibited the potential to inhibit the growth and multiplication of gastric cancer cells while also inducing cell cycle arrest at the G2/M phase and promoting apoptosis [128]. The study conducted by Li and colleagues aimed to assess the efficacy of N-((2-hydroxy-3-trimethylammonium) propyl) CS chloride (HTCC)/alginate-encapsulated Fe_3O_4 magnetic NPs (HTCCMNPs) in inhibiting multidrug resistance (MDR) in gastric tumor cells. The high-temperature carbonized cellulose magnetic NPs (HTCCMNPs) exhibited notable attributes such as high water solubility and biocompatibility, along with reduced viability of tumors. The observed effects were primarily attributed to apoptosis, autophagy, loss of mitochondrial membrane potential, and decreased generation of reactive oxygen species [129]. A previous study investigated the impact of CSNPs on the delivery of epigallocatechin-3-gallate, a green tea polyphenol extract, for gastric cancer therapy. The herbal compound was

Table 2: Anticancer activities of CS and its derivatives and molecular mechanisms of action in GI cancers.

GI cancer type	CS/its derivative	Biological features	Molecular/cellular mechanisms of action	Outcome	References
Esophageal cancer	CSNPs (e.g., CSP-Cr-NCs, TMC-IRN-SLNs)	Nanocarriers with high bioavailability, solubility, stability, sensitivity, and specificity both hydrophilic and hydrophobic	Modulate the metastatic phenotype of cancer-associated fibroblast cells by using various cellular and molecular markers, increasing ROS production in tumor cells, inducing apoptosis	Inhibition of cell growth and proliferation, antimetastatic effect	[79, 82, 83]
Gastric cancer	CMC	High viscosity, large hydrodynamic volume, low toxicity, and biocompatibility	Inhibit the proliferation, tube formation, and migration of gastric tumor cells by upregulating and downregulating various factors	Antiproliferative and antimetastatic effect	[93, 94]
	CSNPs (e.g., HTCCMNPs, HTCCMNPs)	Nanocarriers with high bioavailability, solubility, stability, sensitivity, and specificity both hydrophilic and hydrophobic	Inducing cell cycle arrest at the G2/M phase, promoting apoptosis and autophagy, decreasing generation of ROS, inhibiting cancer cell proliferation, and suppressing their invasion change in the expression level of various factors	Cell senescence, inhibition of cell growth and proliferation, antimetastatic effect	[95–101]
Hepatocellular carcinoma	CMC	High viscosity, large hydrodynamic volume, low toxicity, and biocompatibility	Antitumor, antiproliferative, decreased generation of ROS, inhibit metastasis through the upregulation of metastasis-related proteins	Antiproliferative and antimetastatic effect	[102, 103]
	CSNPs	Nanocarriers with heightened bioavailability, sensitivity, and specificity while decreasing pharmacological toxicity	Disrupt cellular membranes and induce apoptosis	Inhibition of tumor growth and proliferation	[104, 105]
Colorectal cancer	CSNPs (e.g., CS-TPP/IL-12, LMWC/COS)	Nanocarriers with high bioavailability, solubility, stability, sensitivity, and specificity both hydrophilic and hydrophobic	Inducing apoptosis, attenuating the toxicity of IL-12, inhibiting tumor metastasis by inducing NK cells and T-cell infiltration, inhibiting NO and iNOS	Cell death and antiproliferative and antimetastatic effect	[106, 107]
Pancreatic cancer	CSNPs (e.g., MiaPaCa-2, DEMC)	Nanocarriers with high bioavailability, solubility, stability, sensitivity, and specificity both hydrophilic and hydrophobic	Altering intracellular signaling pathways, antiproliferative, antiapoptotic, anti-invasive, and antimigratory properties	Antiproliferative and antimetastatic effect	[108–117]

CSNPs, CS nanoparticles; CMC, carboxymethyl CS; CSNPs, colloidal superstructures of nanoparticles; CSP-Cr-NCs, CS-sodium alginate-polyethylene glycol-crocin nanocomposites; HTCCMNPs, N-((2-hydroxy-3-trimethylammonium) propyl) CS chloride (HTCC)/alginate-encapsulated Fe_3O_4 magnetic nanoparticles; HTCCMNPs, high-temperature carbonized cellulose magnetic nanoparticles; MiaPaCa-2, metformin encapsulated in O-carboxymethyl CS (OCMCS) NPs on pancreatic cancer cells; DEMC, N,N-diethyl N-methyl CS; DDS, drug delivery system; ROS, reactive oxygen species.

encapsulated using a complex comprising CS conjugated with fucose and CS conjugated with polyethylene glycol. The study demonstrated that NPs can potentially reduce drug release in stomach acids, resulting in a regulated release of epigallocatechin-3-gallate. This controlled release was found to downregulate the expression of vascular endothelial growth factor (VEGF) protein, increase apoptosis, and inhibit the proliferation of gastric cancer [130]. Trimethyl CS, a derivative of CS, was utilized for encapsulating paclitaxel, a well-known microtubule inhibitor, to aid in the treatment of gastric cancer. The utilization of trimethyl CSNPs loaded with paclitaxel has been found to induce cell cycle arrest in the G2/M phase and apoptosis in gastric cancers. The drug formulation exhibited a reduction in tumor growth without notable systemic adverse effects, indicating its potential as a secure and encouraging drug delivery method for treating gastric cancer [131]. CS-encapsulated BRAF siRNA NPs have been employed in treating gastric cancer in recent years. The study reported decreased v-Raf murine sarcoma viral oncogene homolog B1 (BRAF) expression in gastric tumors, a reduction in cell invasion, and suppression of their invasion upon observation of CSNPs [132]. In the same investigation, the impact of PIK3CA/siRNA CSNPs on gastric tumor cells was examined. The findings of the study indicated that the utilization of PIK3CA/siRNA CSNPs led to a significant reduction in the expression of PIK3CA/siRNA and the invasive potential of gastric tumor cells [133]. The available evidence indicates that CS and its derivatives have the potential to act as drug delivery agents in the form of microspheres and NPs that are linked to chemotherapeutic drugs. This approach may enhance the efficacy of anticancer drugs and facilitate gastric cancer therapy [31, 134] (Figure 2, Table 2).

4.3. Hepatocellular Carcinoma. Hepatocellular carcinoma (HCC) is frequently associated with prolonged liver damage and cirrhosis, rendering it a prevalent and highly lethal malignancy that ranks as the fourth leading cause of cancer-associated mortality globally [105, 135]. It represents over 80% of primary liver cancers [102]. HCC is a malignancy that originates from the parenchymal liver cells [103]. It typically manifests as nodular lesions, which may present as a solitary large tumor or multiple smaller ones. HCC exhibits an oval or circular morphology and manifests as a distinct border demarcating its interface with adjacent hepatic parenchyma. In contrast, infiltrative HCC exhibits indistinct demarcations with adjacent hepatic cells and may occasionally invade the hepatic or portal veins [136]. HCC is linked to various risk factors, including chronic alcohol consumption, viral infections such as hepatitis B virus (HBV) and hepatitis C virus (HCV), tobacco usage, and aflatoxins [136, 137]. HCC is associated with additional risk factors, such as obesity and diabetes [138]. It is also caused by the accumulation of copper and iron in the liver [139].

There are two primary modalities for managing HCC, namely nonsurgical and surgical interventions [140]. The main therapeutic approach for HCC involves surgical intervention, followed by conventional chemotherapy [141]. Approximately half of the patients with HCC diagnosed with intermediate to advanced stages of the disease underwent surgical resection [142]. Remarkably, a mere 10–35% of patients who have been diagnosed with an early stage have undergone surgical resection [143, 144]. The available noninvasive modalities for treatment include systemic chemotherapy, radiation therapy, percutaneous ethanol injection, transarterial chemoembolization (TACE), microwave ablation, cryoablation, radiofrequency ablation, and molecular targeted therapies [145]. The primary treatment modality utilized is traditional chemotherapy. Conventional treatments have significant limitations, such as suboptimal drug bioavailability, high-dose demands, a lack of specificity, and adverse effects [146]. The limitations associated with traditional therapy have instigated a demand for alternative treatment modalities.

CS has been believed to be safe for human consumption and has received dietary supplement approval from the FDA [147]. According to the literature, CS is a biopolymer that ranks second in abundance and possesses properties that enhance permeability and exhibit mucoadhesion [148]. CS finds application in the fields of food additives and metal chelation as well [137]. CS exhibits a variety of biological activities, including antifungal, antimicrobial, and immunoenhancing properties. CS's reactive groups are utilized for surface modification [149] to target various types of cancer, such as HCC [146]. The utilization of CSNPs, such as colloidal superstructures of NPs, exhibits significant promise in the domains of nanomedicine and biomedical engineering, owing to their heightened bioavailability, decreased pharmacological toxicity, and augmented sensitivity and specificity [103]. Vongchan et al.'s findings suggest that CSNPs exhibit antitumor properties in both in vitro and in vivo conditions. The potential antitumor effects of CSNPs may be attributed to their ability to disrupt cellular membranes and induce apoptosis [150]. In addition, CMC is a hydrophilic form of CS that exhibits enhanced physicochemical characteristics. Due to its capacity to retain water, it has a broad spectrum of uses in the pharmaceutical, cosmetic, food, and biomedical industries. The compound CMC has demonstrated antitumor and antioxidant properties, as well as the ability to inhibit metastasis in HCC through the upregulation of metastasis-related proteins, including VEGF, matrix metalloproteinase-9 (MMP-9), and E-selectin, both in vitro and in vivo [151]. The pH responsiveness of CMC is attributed to the protonation process of its amino group [152]. In a recent study, scientists developed pH-responsive CSS-LA/DOX to treat HCC [152]. Researchers also formulated a CS/dimethyl maleic anhydride-modified CS (CS/CS-DMMA) loaded with DOX and pH-responsive CSS-LA. This formulation was intended for the treatment of HCC [153]. The combination of multiple drug loadings and dual surface functionalization within a CS-based formulation may hold significant potential as a treatment option for HCC.

The primary focus of research on CS relates to its potential as a pH-responsive vehicle for drug delivery and is attributed to its susceptibility to neutral or slightly acidic pH. The utilization of CSNPs for covert drug delivery can be achieved through the process of conjugation with particular

ligands. This process facilitates lysosomal escape and ultimately results in the targeting of mitochondria. Formulations based on CSNPs ultimately result in the controlled release of the drug payload at the specific intracellular site. The utilization of CSNPs as nanocarriers for the targeted delivery of anticancer drugs to the mitochondria is highly effective. Currently, there are ongoing endeavors to develop CSNPs that possess the capability of serving as DDS with organelle specificity [105, 106] (Table 2).

4.4. Colorectal Cancer. According to research studies, colorectal cancer (CRC) ranks as the third most common type of cancer globally [154]. It is estimated that the global morbidity rate will rise to 1.1 million by 2030 [155]. CRC is commonly observed in individuals who are under 50 years of age. This condition is linked to dietary patterns and eating behaviors that promote a bacterial imbalance in the GI tract, which, in turn, leads to the development of colon cancer [156]. CRC is a form of malignancy that influences the regions of the large intestine and rectum [107]. The development of this condition can be attributed to the adenomatous polyposis coli gene or deactivation of the p53 pathway, as well as the accumulation of mutations in genes such as K-Ras, alterations in the transforming growth factor-beta pathway, and the formation of small polyps [157].

The CRC is categorized into five distinct phases, each requiring specific treatment strategies [158]. The initial stage of colon cancer, characterized by polyps or abnormal colon cells on the mucosal lining, can be effectively treated through surgical resection if detected in its early stages. In the same way, the standard approach for addressing stages I–II is surgical excision, although the 5-year survival rate ranges from 37% to 74% in most instances. The survival rate of patients with advanced stages of CRC significantly decreases to 6% [159]. In such cases, adjuvant pharmaceutical therapies, such as chemotherapy, are typically recommended after surgical resection [160]. The administration of these medications has been associated with unfavorable outcomes, including nausea, vomiting, and hair loss, while the anticipated effectiveness has not been demonstrated [161]. Anticancer drugs have several limitations, including low water solubility, hydrophobicity, susceptibility to multiple drug resistances, and inadequate biodistribution [162]. The abovementioned circumstances have necessitated inventive methodologies to amplify the pharmacodynamic and physicochemical characteristics of conventional chemotherapeutic agents or accomplish target-oriented administration to enhance therapeutic efficacy while mitigating nonspecific side effects [163].

The development of CRC is a complex process that occurs throughout 10 to 40 years, progressing from adenoma to carcinoma. CRC arises due to the inactivation of the adenomatous polyposis coli gene, or p53 pathway, the accumulation of mutations in genes such as K-Ras, alterations in the TGF-β pathway, and the development of small polyps. Small polyps tend to undergo transformation into larger polyps, which can subsequently initiate tumorigenesis. Aberrant crypt foci in colon tissue serve as a preneoplastic indication, and chemoprevention can be utilized to prevent or postpone the process of carcinogenesis [164]. Aberrations in the signaling of T-lymphokine-activated killer cell- (T-LAK-) originated protein kinase (TOPK) have been observed to facilitate cancer progression. This kinase is highly expressed and functionally active in colorectal cancer, promoting the proliferation, survival, and inflammation of cancer cells. Furthermore, it has been proposed that TOPK may serve as a viable therapeutic target for combating colorectal cancer by modulating the transcriptional expression of p21, a downstream target of p53, through its interaction with the DNA-binding domain of the latter. The compound 3-deoxysappanchalcone, derived from *Caesalpinia sappan* L., has been found to possess the ability to induce apoptosis through a p53-dependent pathway. As a result, it can inhibit the proliferation of colon cancer cells by directly targeting the signaling pathway of TOPK [165]. Colorectal cancer is commonly considered a sporadic condition; however, the likelihood of developing the disease is heightened in individuals with a familial history of the ailment. Frequently occurring mutations in CRC comprise TP53, KRAS, BRAF, FAM123B, TGFBR2, APC, ERBB2, PIK3CA, SMAD4, SOX9, ARID1A, and CTNNB1 [166]. The occurrence of tumorigenesis is attributed to mutations in genes that disrupt crucial signaling pathways. The early stages of CRC are characterized by mutations in the WNT signaling pathway, whereas TP53 mutations tend to manifest at a later stage [167]. Contemporary investigations on biomarkers for CRC are directed toward identifying molecules that can be targeted for the development of specialized carriers and novel drugs for targeted cancer therapy.

Numerous investigations have been conducted in the past few years to find an efficacious mechanism for administering oral drugs and genes. However, the current approaches have not advanced beyond animal experimentation and have not demonstrated significant effectiveness in human subjects. The identified benefits of CS, such as nontoxicity, ability to adhere to mucosal surfaces, facile modifiability, affordability, biodegradability, and capacity to form complexes with proteins or DNA, involve the ongoing enhancement of auspicious vehicles for effective drug administration for individuals with CRC. It is anticipated that CS incorporation in DDS targeted at cancer will enhance future biotechnology and biomedical applications [108, 157]. In recent decades, significant attention has been directed toward the field of nanomedicine to devise innovative approaches for implementing intelligent DDS with targeted capabilities. The primary objective of this approach is to selectively target CRC tissues while minimizing any cellular toxicity and associated side effects [109]. CS nanocarriers have demonstrated a remarkable capacity to transport therapeutic agents to precise anatomical locations based on the distinctive features of the polymer. The utilization of CS and its derivatives in oral nanocarrier systems for treating CRC, as discussed earlier, has exhibited their adaptability and compatibility with biological systems. CSNPs regulate the administration of drugs through their surface pliability, pH-responsive characteristics, penetration capabilities, and mucoadhesive attributes. The efficacy of anticancer drugs

can be improved through the modification of CS, which leads to an increase in their accumulation, retention time, cytotoxicity, and cellular uptake by tumor cells [110]. Research conducted on various cell lines, including HT-29, HCT-116, HT-29, MCF-7, Caco-2, CT26, and SW480, has demonstrated a noteworthy reduction in cancer volume and substantial antitumor efficacy [111–114]. To summarize, using oral CS-based nanocarriers that are either conjugated with targeting ligands or therapeutic agents holds significant potential for the development of colon-targeted DDS that exhibits low toxicity levels and requires less monitoring during cancer therapy (Table 2).

4.5. Pancreatic Cancer. Pancreatic cancer (PC) is a highly fatal malignancy with a mortality rate of nearly 100% globally. The 5-year survival rate, even under optimal conditions, was reported to be less than 9% in 2019 [115–117]. The preliminary diagnosis of this particular cancer is the primary factor contributing to its ranking as the seventh most common cause of cancer-related mortality globally [115, 168, 169]. Selecting a suitable therapeutic modality is closely linked to the scope and stage of cancer. However, surgery, chemotherapy, and radiotherapy are frequently considered the most effective interventions for extending survival. However, there remains an urgent need for an effective cure for PC patients who are in the late stages of the disease [170]. The reduction of PC-related mortalities and patient distress is dependent on two factors: the implementation of reliable and precise diagnostic tests instead of current procedures and the substitution of conventional therapies that are associated with high risk and limited efficacy with innovative approaches [171].

From a therapeutic perspective, numerous investigations have focused on augmenting traditional chemotherapeutic agents through CS-based nanoformulations. Gemcitabine is a pharmaceutical agent utilized for the management of neoplastic disorders. However, its efficacy in patients with advanced PC has not been deemed satisfactory. CSNPs were employed as a vehicle for the co-delivery of gemcitabine. The abovementioned agent functions as an antibody targeting epidermal growth factor receptor-1 (EGFR-1), a protein whose excessive expression is known to facilitate the proliferation of cancerous cells [172]. The study findings indicate that CSNPs can potentially enhance the efficacy of gemcitabine against the PC cell line (SW1990) by modulating their proliferation, migration, and invasion mechanisms [173]. Recently, scientists examined a specific modification in PC: upregulation of the folate receptor. Regarding this matter, researchers developed core-shell NPs consisting of folate, CS, and gemcitabine. The NPs were effective in reducing the adverse effects and prolonging the half-life of gemcitabine. Additionally, they demonstrated increased toxicity toward cancerous cells [174]. A group of researchers also attempted to enhance the effectiveness of 5-fluorouracil, a cytotoxic medication commonly employed in chemotherapy. The researchers synthesized a binary pharmaceutical formulation comprising 5-fluorouracil and quercetin, which served as an antioxidant agent. Subsequently, they administered this formulation via CSNPs. The study revealed that the co-administration of 5-fluorouracil with an antioxidant agent increased drug encapsulation and expedited drug release [175]. Another group of scientists [176] conducted research on metformin, a medication frequently prescribed for managing type 2 diabetes. The selection of this particular drug was based on the fact that metformin can impact cancer cells through two distinct mechanisms. Firstly, it can reduce tumor cell proliferation by reducing insulin levels. Secondly, it can alter intracellular signaling pathways [177]. The impact of metformin encapsulated in O-CMC-NPs on pancreatic cancer cells (MiaPaCa-2) was explored by the researchers, who noted an increase in apoptosis and a decrease in colony formation in these cells [176, 178]. The impact of curcumin on pancreatic cancer was investigated by Arya et al. [179]. In their study, curcumin-loaded poly-D, L-lactide-co-glycolide (PLGA) NPs were synthesized and subsequently coated with polyethylene glycol (PEG) and CS for surface modification. The utilization of these NPs presented several benefits when compared to using curcumin in isolation. These advantages include heightened curcumin absorption, anti-invasive and antimigratory properties, and an augmentation of cytotoxicity.

Multiple mutations that activate proto-oncogenes or deactivate genes that promote tumor suppression and apoptosis resistance are to blame for the chemotherapy and radiotherapy resistance that pancreatic ductal adenocarcinoma exhibit [180]. The fact described earlier has directed researchers toward seeking a resolution to normalize gene expression in malignant cells. The implementation of gene therapy has been proposed as a viable approach for managing various forms of cancer. The transportation of genes to the cancerous site necessitates the utilization of suitable vectors. Safari et al. [181] synthesized N, N-diethyl N-methyl CS (DEMC) to investigate its potential as a vector, citing its favorable cell viability. However, further research is required to explore this subject fully. A plausible approach could involve the utilization of small interfering RNAs (siRNAs) to impede the expression of the corresponding messenger RNAs (mRNAs) associated with these genes. Using folic acid-modified PEG-CS oligosaccharide lactate NPs [182], Taniuchi et al. [183] investigated the delivery of particular siRNAs. The present investigation effectively targets mTOR, LAMTOR2, and NUP85, impeding the metastasis and invasion of pancreatic cancer cells. Regarding the effectiveness of this methodology, further advancements can be made by investigating additional mutated genes implicated in prostate cancer, such as HER-3, HER-2, and NF-B [180].

The researchers have reported the development of CSNPs that have dual applications in tumor detection and drug delivery. The researchers developed a theranostic agent consisting of pH-sensitive CS-coated mesoporous silica-coated gold nanoparticles, which were utilized for tumor imaging via multispectral optoacoustic tomography. They determined that this NP is not suitable for drug delivery alone, but when it was combined with other substances, its tumor targeting and drug delivery capabilities were revealed. The researchers concluded that the variant 7-silica-coated

gold nanoparticle (v7-CMG) is suitable for tumor detection, facilitating drug delivery and improving tumor targeting with minimal side effects [184, 185]. Other researchers have also successfully developed CS nanoformulations to aid in diagnosing PC. Wang et al. [186] studied the antiapoptotic protein named survivin and found that its expression undergoes modification in cancerous cells, indicating its corresponding mRNA could serve as a promising candidate for molecular imaging. This study involved the encapsulation of antisense oligonucleotides, which exhibit binding affinity toward the surviving RNA, within magnetic nanoparticles. The NPs were further coated with CS for enhanced biocompatibility and stability. The findings of this investigation indicate that the presence of NPs in cancerous locations, both *in vitro* and *in vivo*, may serve as a means of detection. Several research groups, including Tong et al. [187], Xu et al. [188], Rong et al. [189], Soares et al. [190], and Dobiasch et al. [191], have endeavored to reduce mortality rates associated with PC through early detection (Figure 2, Table 2).

5. Conclusions and Perspectives

In the following years, GI cancer will continue to be a main global health issue. Despite decades of cancer therapy advances, cancer remains the leading cause of death globally. CS, a natural, biodegradable, and biocompatible polymer, is one of the most promising polymers for treating GI cancers due to extensive studies. CS showed promise in chemotherapeutic drug delivery, gene therapy, and immunotherapy for cancer. Nanoformulation, emulsion, surfactant, and hydrogel formulations using CS derivatives improve anticancer drug efficacy, selectivity, biocompatibility, and dose reduction. Thus, CS nanoparticle-based therapy may improve GI cancer treatment effectiveness and personalization. The actual deployment of nanoparticle-based therapy faces several challenges. CS's limited water solubility is the most significant drawback for pharmaceutical administration. Nanomaterial biodistribution, stability, immunogenicity, clearance, and regulation are concerns.

The findings in this review may address several stomach cancer questions. Nanomedicine has created carriers that boost cancer cell cytotoxicity and reduce chemotherapy side effects. Novel GI malignancy diagnostic approaches that may become mainstream were also highlighted. The latest diagnostic and therapy options need further research to prove them.

Data Availability

The authors confirm that the data supporting the findings of this study are available within the article.

Ethical Approval

As the current study is considered as a review article, obtaining both ethics approval and consent statements was not mandatory in this research.

Consent

As the current study is considered as a review article, obtaining consent for publication was not mandatory in this research.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

AA and ZSE contributed to the conceptualization and study design. AA, SPT, and ZSE completed data curation and formal analysis. AN, JA, and HH gathered information and contributed to the preparation of the original draft. FM and ZSE managed and completed the study using specific software. AA and SPT designed and supervised the work. All authors have reviewed/revised and validated the whole text.

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References

[1] M. Arnold, C. C. Abnet, R. E. Neale et al., "Global burden of 5 major types of gastrointestinal cancer," *Gastroenterology*, vol. 159, no. 1, pp. 335–349.e15, 2020.

[2] I. D. Nagtegaal, R. D. Odze, D. Klimstra et al., "The 2019 WHO classification of tumours of the digestive system," *Histopathology*, vol. 76, no. 2, pp. 182–188, 2020.

[3] R. L. Siegel, K. D. Miller, H. E. Fuchs, and A. Jemal, "Cancer statistics, 2021," *CA: A Cancer Journal for Clinicians*, vol. 71, no. 1, pp. 7–33, 2021.

[4] H. Sung, J. Ferlay, R. L. Siegel et al., "Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries," *CA: A Cancer Journal for Clinicians*, vol. 71, no. 3, pp. 209–249, 2021.

[5] M. F. Bijlsma, A. Sadanandam, P. Tan, and L. Vermeulen, "Molecular subtypes in cancers of the gastrointestinal tract," *Nature Reviews Gastroenterology & Hepatology*, vol. 14, no. 6, pp. 333–342, 2017.

[6] L. Falzone, S. Salomone, and M. Libra, "Evolution of cancer pharmacological treatments at the turn of the third millennium," *Frontiers in Pharmacology*, vol. 9, Article ID 1300, 2018.

[7] E. Pérez-Herrero and A. Fernández-Medarde, "Advanced targeted therapies in cancer: drug nanocarriers, the future of chemotherapy," *European Journal of Pharmaceutics and Biopharmaceutics*, vol. 93, pp. 52–79, 2015.

[8] S. Senapati, A. K. Mahanta, S. Kumar, and P. Maiti, "Controlled drug delivery vehicles for cancer treatment and their performance," *Signal Transduction and Targeted Therapy*, vol. 3, no. 1, p. 7, 2018.

[9] M. A. Rayhan, M. S. Hossen, M. S. Niloy, M. H. Bhuiyan, S. Paul, and M. S. Shakil, "Biopolymer and biomaterial conjugated Iron oxide nanomaterials as prostate cancer theranostic agents: a comprehensive review," *Symmetry*, vol. 13, no. 6, p. 974, 2021.

[10] M. S. Shakil, K. M. Mahmud, M. Sayem et al., "Using chitosan or chitosan derivatives in cancer therapy," *Polysaccharides*, vol. 2, no. 4, pp. 795–816, 2021.

[11] S. Assadpour, M. R. Shiran, P. Asadi, J. Akhtari, and A. Sahebkar, "Harnessing intranasal delivery systems of sumatriptan for the treatment of migraine," *BioMed Research International*, vol. 2022, pp. 1–9, 2022.

[12] N. J. Vickers, "Animal communication: when i'm calling you, will you answer too?" *Current Biology*, vol. 27, no. 14, pp. R713–R715, 2017.

[13] J.-T. Lin, Z.-K. Liu, Q.-L. Zhu et al., "Redox-responsive nanocarriers for drug and gene co-delivery based on chitosan derivatives modified mesoporous silica nanoparticles," *Colloids and Surfaces B: Biointerfaces*, vol. 155, pp. 41–50, 2017.

[14] P. F. Monteiro, A. Travanut, C. Conte, and C. Alexander, "Reduction-responsive polymers for drug delivery in cancer therapy—is there anything new to discover?" *Wiley interdisciplinary reviews. Nanomedicine and nanobiotechnology*, vol. 13, no. 2, Article ID e1678, 2021.

[15] S. Naskar, K. Kuotsu, and S. Sharma, "Chitosan-based nanoparticles as drug delivery systems: a review on two decades of research," *Journal of Drug Targeting*, vol. 27, no. 4, pp. 379–393, 2019.

[16] J. Zhao, Y. Yang, X. Han et al., "Redox-sensitive nanoscale coordination polymers for drug delivery and cancer theranostics," *ACS Applied Materials and Interfaces*, vol. 9, no. 28, pp. 23555–23563, 2017.

[17] S. Assadpour, J. Akhtari, and M. R. Shiran, "Pharmacokinetics study of chitosan-coated liposomes containing sumatriptan in the treatment of migraine," *Caspian journal of internal medicine*, vol. 13, no. 1, pp. 90–99, 2022.

[18] R. Pichyangkura and S. Chadchawan, "Biostimulant activity of chitosan in horticulture," *Scientia Horticulturae*, vol. 196, pp. 49–65, 2015.

[19] D.-S. Lee, Y.-S. Cho, and J.-Y. Je, "Antioxidant and antibacterial activities of chitosan-phloroglucinol conjugate," *Fisheries and aquatic sciences*, vol. 16, no. 4, pp. 229–235, 2013.

[20] L. J. R. Foster, S. Ho, J. Hook, M. Basuki, and H. Marcal, "Chitosan as a biomaterial: influence of degree of deacetylation on its physiochemical, material and biological properties," *PLoS One*, vol. 10, no. 8, Article ID e0135153, 2015.

[21] M. N. Ravi Kumar, "A review of chitin and chitosan applications," *Reactive and Functional Polymers*, vol. 46, no. 1, pp. 1–27, 2000.

[22] R. de Sousa Victor, A. Marcelo da Cunha Santos, B. Viana de Sousa, G. de Araújo Neves, L. Navarro de Lima Santana, and R. Rodrigues Menezes, "A review on Chitosan's uses as biomaterial: tissue engineering, drug delivery systems and cancer treatment," *Materials*, vol. 13, no. 21, p. 4995, 2020.

[23] S.-H. Lee, B. Ryu, J.-Y. Je, and S.-K. Kim, "Diethylaminoethyl chitosan induces apoptosis in HeLa cells via activation of caspase-3 and p53 expression," *Carbohydrate Polymers*, vol. 84, no. 1, pp. 571–578, 2011.

[24] S.-H. Lee, M. Senevirathne, C.-B. Ahn, S.-K. Kim, and J.-Y. Je, "Factors affecting anti-inflammatory effect of chitooligosaccharides in lipopolysaccharides-induced RAW264. 7 macrophage cells," *Bioorganic & Medicinal Chemistry Letters*, vol. 19, no. 23, pp. 6655–6658, 2009.

[25] S.-K. Kim, N. Rajapakse, and F. Shahidi, "Production of bioactive chitosan oligosaccharides and their potential use as nutraceuticals," in *Marine Nutraceuticals and Functional Foods*, C. Barrow and F. Shahidi, Eds., pp. 183–196, CRC Press, London and New York, GB and US, 2007.

[26] D. Patel, R. Bertz, S. Ren, D. W. Boulton, and M. Någård, "A systematic review of gastric acid-reducing agent-mediated drug–drug interactions with orally administered medications," *Clinical Pharmacokinetics*, vol. 59, no. 4, pp. 447–462, 2020.

[27] C. Stillhart, K. Vučićević, P. Augustijns et al., "Impact of gastrointestinal physiology on drug absorption in special populations––An UNGAP review," *European Journal of Pharmaceutical Sciences*, vol. 147, Article ID 105280, 2020.

[28] B. C. Roland, M. M. Ciarleglio, J. O. Clarke et al., "Small intestinal transit time is delayed in small intestinal bacterial overgrowth," *Journal of Clinical Gastroenterology*, vol. 49, no. 7, pp. 571–576, 2015.

[29] N. Pathomthongtaweechai and C. Muanprasat, "Potential applications of chitosan-based nanomaterials to surpass the gastrointestinal physiological obstacles and enhance the intestinal drug absorption," *Pharmaceutics*, vol. 13, no. 6, p. 887, 2021.

[30] W. Huang, S. L. Lee, and L. X. Yu, "Mechanistic approaches to predicting oral drug absorption," *The AAPS Journal*, vol. 11, no. 2, pp. 217–224, 2009.

[31] S. Deng, J. Gu, Z. Jiang et al., "Application of nanotechnology in the early diagnosis and comprehensive treatment of gastrointestinal cancer," *Journal of Nanobiotechnology*, vol. 20, no. 1, p. 415, 2022.

[32] B. Brar, K. Ranjan, A. Palria et al., "Nanotechnology in colorectal cancer for precision diagnosis and therapy," *Frontiers in Nanotechnology*, vol. 3, Article ID 699266, 2021.

[33] B. Homayun, X. Lin, and H.-J. Choi, "Challenges and recent progress in oral drug delivery systems for biopharmaceuticals," *Pharmaceutics*, vol. 11, no. 3, p. 129, 2019.

[34] Z. Yang, D. Wang, C. Zhang et al., "The applications of gold nanoparticles in the diagnosis and treatment of gastrointestinal cancer," *Frontiers in Oncology*, vol. 11, Article ID 819329, 2021.

[35] A. Akbari, H. Hashemzadeh, Z. S. Eshkiki et al., "Detection of plasma miR-223 by a novel label-free graphene oxide/gold nanocomposite immunosensor in colorectal cancer patients: an electrochemical biosensor approach," *Biosensors and Bioelectronics X*, vol. 14, Article ID 100331, 2023.

[36] E. S. dos Santos, V. P. Wagner, J. Cabral Ramos et al., "Epigenetic modulation of the tumor microenvironment in head and neck cancer: challenges and opportunities," *Critical Reviews in Oncology*, vol. 164, Article ID 103397, 2021.

[37] L. Wiegrebe, "An autocorrelation model of bat sonar," *Biological Cybernetics*, vol. 98, no. 6, pp. 587–595, 2008.

[38] M. T. Taghizadeh, H. Ashassi-Sorkhabi, R. Afkari, and A. Kazempour, "Cross-linked chitosan in nano and bead scales as drug carriers for betamethasone and tetracycline," *International Journal of Biological Macromolecules*, vol. 131, pp. 581–588, 2019.

[39] S. Naskar, S. Sharma, and K. Kuotsu, "Chitosan-based nanoparticles: an overview of biomedical applications and its preparation," *Journal of Drug Delivery Science and Technology*, vol. 49, pp. 66–81, 2019.

[40] S. Rodrigues, M. Dionísio, C. R. Lopez, and A. Grenha, "Biocompatibility of chitosan carriers with application in drug delivery," *Journal of Functional Biomaterials*, vol. 3, no. 3, pp. 615–641, 2012.

[41] B. Farhadihosseinabadi, A. Zarebkohan, M. Eftekhary, M. Heiat, M. Moosazadeh Moghaddam, and M. Gholipourmalekabadi, "Crosstalk between chitosan and

cell signaling pathways," *Cellular and Molecular Life Sciences*, vol. 76, no. 14, pp. 2697–2718, 2019.

[42] S. Assadpour, M. Reza Shiran, and J. Akhtari, "Chitosan coating of anionic liposomes containing sumatriptan succinate: a candidate for nasal administration," *Nanomedicine Journal*, vol. 8, no. 2, pp. 132–139, 2021.

[43] L. Marsili, M. Dal Bo, F. Berti, and G. Toffoli, "Chitosan-based biocompatible copolymers for thermoresponsive drug delivery systems: on the development of a standardization system," *Pharmaceutics*, vol. 13, no. 11, p. 1876, 2021.

[44] Z. Mármol, G. Páez, M. Rincón et al., "Quitina y Quitosano polímeros amigables. Una revisión de sus aplicaciones/ Chitin and Chitosan friendly polymer. A review of their applications," *Revista Tecnocientífica URU*, vol. 1, pp. 53–58, 2011.

[45] I. Younes and M. Rinaudo, "Chitin and chitosan preparation from marine sources. Structure, properties and applications," *Marine Drugs*, vol. 13, no. 3, pp. 1133–1174, 2015.

[46] U. Shahbaz, "Chitin, characteristic, sources, and biomedical application," *Current Pharmaceutical Biotechnology*, vol. 21, no. 14, pp. 1433–1443, 2020.

[47] S. Naqvi and B. M. Moerschbacher, "The cell factory approach toward biotechnological production of high-value chitosan oligomers and their derivatives: an update," *Critical Reviews in Biotechnology*, vol. 37, no. 1, pp. 11–25, 2017.

[48] M. Bonin, S. Sreekumar, S. Cord-Landwehr, and B. M. Moerschbacher, "Preparation of defined chitosan oligosaccharides using chitin deacetylases," *International Journal of Molecular Sciences*, vol. 21, no. 21, p. 7835, 2020.

[49] M. Kurakula, A. M. El-Helw, T. R. Sobahi, and M. Y. Abdelaal, "Chitosan based atorvastatin nanocrystals: effect of cationic charge on particle size, formulation stability, and in-vivo efficacy," *International Journal of Nanomedicine*, vol. 10, pp. 321–334, 2015.

[50] J. K. Park, M. J. Chung, H. N. Choi, and Y. I. Park, "Effects of the molecular weight and the degree of deacetylation of chitosan oligosaccharides on antitumor activity," *International Journal of Molecular Sciences*, vol. 12, no. 1, pp. 266–277, 2011.

[51] M. Á. V. Rodrigues, C. A. Marangon, V. D. C. A. Martins, and A. M. D. G. Plepis, "Chitosan/gelatin films with jatobá resin: control of properties by vegetal resin inclusion and degree of acetylation modification," *International Journal of Biological Macromolecules*, vol. 182, pp. 1737–1745, 2021.

[52] J. Ding and Y. Guo, "Recent advances in chitosan and its derivatives in cancer treatment," *Frontiers in Pharmacology*, vol. 13, Article ID 888740, 2022.

[53] W. Wang and D. Xu, "Viscosity and flow properties of concentrated solutions of chitosan with different degrees of deacetylation," *International Journal of Biological Macromolecules*, vol. 16, no. 3, pp. 149–152, 1994.

[54] D. Narayanan, R. Jayakumar, and K. P. Chennazhi, "Versatile carboxymethyl chitin and chitosan nanomaterials: a review," *WIREs Nanomedicine and Nanobiotechnology*, vol. 6, no. 6, pp. 574–598, 2014.

[55] H. Hu, Q. Qi, Z. Dong et al., "Albumin coated trimethyl chitosan-based targeting delivery platform for photothermal/chemo-synergistic cancer therapy," *Carbohydrate Polymers*, vol. 241, Article ID 116335, 2020.

[56] R. Grosso and M.-V. de-Paz, "Thiolated-polymer-based nanoparticles as an avant-garde approach for anticancer therapies—reviewing thiomers from chitosan and hyaluronic acid," *Pharmaceutics*, vol. 13, no. 6, p. 854, 2021.

[57] M. Li, Y. Zhao, W. Zhang, S. Zhang, and S. Zhang, "Multiple-therapy strategies via polysaccharides-based nano-systems in fighting cancer," *Carbohydrate Polymers*, vol. 269, Article ID 118323, 2021.

[58] Y. Zheng, W. Wang, J. Zhao et al., "Preparation of injectable temperature-sensitive chitosan-based hydrogel for combined hyperthermia and chemotherapy of colon cancer," *Carbohydrate Polymers*, vol. 222, Article ID 115039, 2019.

[59] Z. Liang, J. Gao, Z.-Z. Yin, J. Li, W. Cai, and Y. Kong, "A sequential delivery system based on MoS2 nanoflower doped chitosan/oxidized dextran hydrogels for colon cancer treatment," *International Journal of Biological Macromolecules*, vol. 233, Article ID 123616, 2023.

[60] H. S. Adhikari and P. N. Yadav, "Anticancer activity of chitosan, chitosan derivatives, and their mechanism of action," *International Journal of Biomaterials*, vol. 2018, pp. 1–29, 2018.

[61] J.-W. Ai, W. Liao, and Z.-L. Ren, "Enhanced anticancer effect of copper-loaded chitosan nanoparticles against osteosarcoma," *RSC Advances*, vol. 7, no. 26, pp. 15971–15977, 2017.

[62] T. Ramasamy, H. B. Ruttala, N. Chitrapriya et al., "Engineering of cell microenvironment-responsive polypeptide nanovehicle co-encapsulating a synergistic combination of small molecules for effective chemotherapy in solid tumors," *Acta Biomaterialia*, vol. 48, pp. 131–143, 2017.

[63] M. M. Badran, A. H. Alomrani, G. I. Harisa, A. E. Ashour, A. Kumar, and A. E. Yassin, "Novel docetaxel chitosan-coated PLGA/PCL nanoparticles with magnified cytotoxicity and bioavailability," *Biomedicine & Pharmacotherapy*, vol. 106, pp. 1461–1468, 2018.

[64] M. M. Badran, M. M. Mady, M. M. Ghannam, and F. Shakeel, "Preparation and characterization of polymeric nanoparticles surface modified with chitosan for target treatment of colorectal cancer," *International Journal of Biological Macromolecules*, vol. 95, pp. 643–649, 2017.

[65] V. K. Sharma, V. K. Sharma, X. Liu et al., "Microbial polysaccharides: an emerging family of natural biomaterials for cancer therapy and diagnostics," *Seminars in Cancer Biology*, vol. 86, pp. 706–731, 2022.

[66] Y. Maeda and Y. Kimura, "Antitumor effects of various low-molecular-weight chitosans are due to increased natural killer activity of intestinal intraepithelial lymphocytes in sarcoma 180–bearing mice," *The Journal of Nutrition*, vol. 134, no. 4, pp. 945–950, 2004.

[67] Y. S Wimardhani, D. F Suniarti, H. J Freisleben, S. I. Wanandi, N. C Siregar, and M.-A. Ikeda, "Chitosan exerts anticancer activity through induction of apoptosis and cell cycle arrest in oral cancer cells," *Journal of Oral Science*, vol. 56, no. 2, pp. 119–126, 2014.

[68] A. Nawaz and T. W. Wong, "Chitosan as anticancer compound and nanoparticulate matrix for cancer therapeutics," *Encyclopedia of Marine Biotechnology*, vol. 3, pp. 1737–1752, 2020.

[69] S. Kumar, H. Kim, M. Gupta, P. Dutta, and J. Koh, "A new chitosan–thymine conjugate: synthesis, characterization and biological activity," *International Journal of Biological Macromolecules*, vol. 50, no. 3, pp. 493–502, 2011.

[70] N. Salahuddin, A. A. Elbarbary, M. L. Salem, and S. Elksass, "Antimicrobial and antitumor activities of 1, 2, 4-triazoles/ polypyrrole chitosan core shell nanoparticles," *Journal of Physical Organic Chemistry*, vol. 30, no. 12, Article ID e3702, 2017.

[71] V. Vedham, R. L. Divi, V. L. Starks, and M. Verma, "Multiple infections and cancer: implications in epidemiology,"

Technology in Cancer Research and Treatment, vol. 13, no. 2, pp. 177–194, 2014.

[72] Z. Jiang, B. Han, H. Li, Y. Yang, and W. Liu, "Carboxymethyl chitosan represses tumor angiogenesis in vitro and in vivo," *Carbohydrate Polymers*, vol. 129, pp. 1–8, 2015.

[73] M. Jiang, H. Ouyang, P. Ruan et al., "Chitosan derivatives inhibit cell proliferation and induce apoptosis in breast cancer cells," *Anticancer Research*, vol. 31, no. 4, pp. 1321–1328, 2011.

[74] R. Huang, E. Mendis, N. Rajapakse, and S.-K. Kim, "Strong electronic charge as an important factor for anticancer activity of chitooligosaccharides (COS)," *Life Sciences*, vol. 78, no. 20, pp. 2399–2408, 2006.

[75] X. Li, J. Wang, X. J. Chen et al., "Effect of chitooligosaccharides on cyclin D1, bcl-xl and bcl-2 mRNA expression in A549 cells using quantitative PCR," *Chinese Science Bulletin*, vol. 56, no. 15, pp. 1629–1632, 2011.

[76] C. Allemani, T. Matsuda, and V. Di Carlo, "Global surveillance of trends in cancer survival 2000–14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries," *The Lancet*, vol. 391, no. 10125, pp. 1023–1075, 2018.

[77] X. Li, L. Chen, S. Luan et al., "The development and progress of nanomedicine for esophageal cancer diagnosis and treatment," *Seminars in Cancer Biology*, vol. 86, pp. 873–885, 2022.

[78] F.-L. Huang and S.-J. Yu, "Esophageal cancer: risk factors, genetic association, and treatment," *Asian Journal of Surgery*, vol. 41, no. 3, pp. 210–215, 2018.

[79] M. Choi, S. Ishizawa, D. Kraemer, A. Sasson, and E. Feinberg, "Perioperative chemotherapy versus adjuvant chemotherapy strategies in resectable gastric and gastroesophageal cancer: a Markov decision analysis," *European Journal of Surgical Oncology*, vol. 48, no. 2, pp. 403–410, 2022.

[80] T. Tsuji, S. Matsuda, M. Takeuchi, H. Kawakubo, and Y. Kitagawa, "Updates of perioperative multidisciplinary treatment for surgically resectable esophageal cancer," *Japanese Journal of Clinical Oncology*, vol. 53, no. 8, pp. 645–652, 2023.

[81] M. J. Valkema, B. Mostert, S. M. Lagarde, B. P. L. Wijnhoven, and J. J. B. van Lanschot, "The effectivity of targeted therapy and immunotherapy in patients with advanced metastatic and non-metastatic cancer of the esophagus and esophagogastric junction," *Updates in Surgery*, vol. 75, no. 2, pp. 313–323, 2023.

[82] J. J. Li, J. E. Rogers, K. Yamashita, R. E. Waters, M. Blum Murphy, and J. A. Ajani, "Therapeutic advances in the treatment of gastroesophageal cancers," *Biomolecules*, vol. 13, no. 5, p. 796, 2023.

[83] H. He, P. Zhang, F. Li, D. Liu, and K. Wu, "The role of adjuvant chemotherapy after neoadjuvant chemotherapy or chemoradiotherapy plus esophagectomy in patients with esophageal cancer: a retrospective cohort study," *Journal of Gastrointestinal Oncology*, vol. 13, no. 6, pp. 2736–2748, 2022.

[84] J. Palzer, L. Eckstein, I. Slabu, O. Reisen, U. P. Neumann, and A. A. Roeth, "Iron oxide nanoparticle-based hyperthermia as a treatment option in various gastrointestinal malignancies," *Nanomaterials*, vol. 11, no. 11, p. 3013, 2021.

[85] Z. Liu, F. Xie, J. Xie et al., "New-generation photosensitizer-anchored gold nanorods for a single near-infrared light-triggered targeted photodynamic–photothermal therapy," *Drug Delivery*, vol. 28, no. 1, pp. 1769–1784, 2021.

[86] A. Fatehi Hassanabad, R. Chehade, D. Breadner, and J. Raphael, "Esophageal carcinoma: towards targeted therapies," *Cellular Oncology*, vol. 43, no. 2, pp. 195–209, 2020.

[87] A. S. Doghish, A. A. El-Husseiny, N. M. Abdelmaksoud et al., "The interplay of signaling pathways and miRNAs in the pathogenesis and targeted therapy of esophageal cancer," *Pathology, Research & Practice*, vol. 246, Article ID 154529, 2023.

[88] Q. Liang, J. Wang, L. Zhao, J. Hou, Y. Hu, and J. Shi, "Recent advances of dual FGFR inhibitors as a novel therapy for cancer," *European Journal of Medicinal Chemistry*, vol. 214, Article ID 113205, 2021.

[89] L. Fu, C. Zhang, L. Y. Zhang et al., "Wnt2 secreted by tumour fibroblasts promotes tumour progression in oesophageal cancer by activation of the Wnt/-catenin signalling pathway," *Gut*, vol. 60, no. 12, pp. 1635–1643, 2011.

[90] S. Y. Ha, S.-Y. Yeo, Y.-H. Xuan, and S.-H. Kim, "The prognostic significance of cancer-associated fibroblasts in esophageal squamous cell carcinoma," *PLoS One*, vol. 9, no. 6, Article ID e99955, 2014.

[91] I. Gockel, C. C. Schimanski, C. Heinrich et al., "Expression of chemokine receptor CXCR4 in esophageal squamous cell and adenocarcinoma," *BMC Cancer*, vol. 6, pp. 290–297, 2006.

[92] S. J. Gros, H. Graeff, A. Drenckhan et al., "CXCR4/SDF-1α-mediated chemotaxis in an in vivo model of metastatic esophageal carcinoma," *In Vivo*, vol. 26, no. 4, pp. 711–718, 2012.

[93] N. Salazar, D. Muñoz, G. Kallifatidis, R. K. Singh, M. Jordà, and B. L. Lokeshwar, "The chemokine receptor CXCR7 interacts with EGFR to promote breast cancer cell proliferation," *Molecular Cancer*, vol. 13, pp. 198–213, 2014.

[94] M. Velasco-Velázquez, X. Jiao, M. De La Fuente et al., "CCR5 antagonist blocks metastasis of basal breast cancer cells," *Cancer Research*, vol. 72, no. 15, pp. 3839–3850, 2012.

[95] P. D. Potdar and A. U. Shetti, "Evaluation of anti-metastatic effect of chitosan nanoparticles on esophageal cancer-associated fibroblasts," *Journal of Cancer Metastasis and Treatment*, vol. 2, no. 7, pp. 259–267, 2016.

[96] O. C. Didamson and H. Abrahamse, "Targeted photodynamic diagnosis and therapy for esophageal cancer: potential role of functionalized nanomedicine," *Pharmaceutics*, vol. 13, no. 11, p. 1943, 2021.

[97] Y. Qi, J. Shen, C. Liu et al., "Modularly designed peptide-based nanomedicine inhibits angiogenesis to enhance chemotherapy for post-surgical recurrence of esophageal squamous cell carcinomas," *Nano Research*, vol. 16, no. 5, pp. 7347–7354, 2023.

[98] A. Hu, A. A. Alarfaj, A. H. Hirad et al., "Chitosan-sodium alginate-polyethylene glycol-crocin nanocomposite treatment inhibits esophageal cancer KYSE-150 cell growth via inducing apoptotic cell death," *Arabian Journal of Chemistry*, vol. 15, no. 6, Article ID 103844, 2022.

[99] C. Ji, S. Ju, D. Zhang, and J. Qiang, "Nanomedicine based N-trimethyl chitosan entangled solid lipid nanoparticle loaded with Irinotecan to enhance the therapeutic efficacy in esophageal cancer cells," *Journal of Biomaterials and Tissue Engineering*, vol. 8, no. 8, pp. 1195–1200, 2018.

[100] L.-F. Qi, Z.-R. Xu, Y. Li, X. Jiang, and X.-Y. Han, "In vitro effects of chitosan nanoparticles on proliferation of human gastric carcinoma cell line MGC803 cells," *World Journal of Gastroenterology*, vol. 11, no. 33, pp. 5136–5141, 2005.

[101] G. Arya, N. Gupta, and S. Nimesh, "Chitosan nanoparticles for therapeutic delivery of anticancer drugs," in

Polysaccharide Nanoparticles, pp. 201–230, Elsevier, Amsterdam, The Netherlands, 2022.

[102] J. D. Yang, P. Hainaut, G. J. Gores, A. Amadou, A. Plymoth, and L. R. Roberts, "A global view of hepatocellular carcinoma: trends, risk, prevention and management," *Nature Reviews Gastroenterology & Hepatology*, vol. 16, no. 10, pp. 589–604, 2019.

[103] N. Subhapradha, V. Shanmugam, and A. Shanmugam, "Chitosan nanoparticles from marine squid protect liver cells against N-diethylnitrosoamine-induced hepatocellular carcinoma," *Carbohydrate Polymers*, vol. 171, pp. 18–26, 2017.

[104] F. J. F. Coimbra, V. H. F. de Jesus, H. S. C. Ribeiro et al., "Impact of ypT, ypN, and adjuvant therapy on survival in gastric cancer patients treated with perioperative chemotherapy and radical surgery," *Annals of Surgical Oncology*, vol. 26, no. 11, pp. 3618–3626, 2019.

[105] N. Jaiswal, R. D. Chaudhari, and B. P. Chaudhari, "Understanding fundamentals of hepatocellular carcinoma to design next-generation chitosan nano-formulations: beyond chemotherapy stride," *Journal of Drug Delivery Science and Technology*, vol. 58, Article ID 101723, 2020.

[106] Z. Chen, L. Zhang, Y. Song et al., "Hierarchical targeted hepatocyte mitochondrial multifunctional chitosan nanoparticles for anticancer drug delivery," *Biomaterials*, vol. 52, pp. 240–250, 2015.

[107] S. Sihvola, L. Kuosmanen, and T. Kvist, "Resilience and related factors in colorectal cancer patients: a systematic review," *European Journal of Oncology Nursing*, vol. 56, Article ID 102079, 2022.

[108] S. Wahab, M. Y. Alshahrani, M. F. Ahmad, and H. Abbas, "Current trends and future perspectives of nanomedicine for the management of colon cancer," *European Journal of Pharmacology*, vol. 910, Article ID 174464, 2021.

[109] I. A. A. Ibrahim, A. R. Alzahrani, I. M. Alanazi et al., "Carbohydrate polymers-based surface modified nano delivery systems for enhanced target delivery to colon cancer-A review," *International Journal of Biological Macromolecules*, vol. 253, Article ID 126581, 2023.

[110] Q. Xu, L. Guo, X. Gu et al., "Prevention of colorectal cancer liver metastasis by exploiting liver immunity via chitosan-TPP/nanoparticles formulated with IL-12," *Biomaterials*, vol. 33, no. 15, pp. 3909–3918, 2012.

[111] R. Dave, R. Patel, and M. Patel, "Hybrid lipid-polymer nanoplatform: a systematic review for targeted colorectal cancer therapy," *European Polymer Journal*, vol. 186, Article ID 111877, 2023.

[112] I. Mármol, J. Quero, M. J. Rodríguez-Yoldi, and E. Cerrada, "Gold as a possible alternative to platinum-based chemotherapy for colon cancer treatment," *Cancers*, vol. 11, no. 6, p. 780, 2019.

[113] N. A. Bhaskaran and L. Kumar, "Treating colon cancers with a non-conventional yet strategic approach: an overview of various nanoparticulate systems," *Journal of Controlled Release*, vol. 336, pp. 16–39, 2021.

[114] K.-S. Nam, M.-K. Kim, and Y.-H. Shon, "Inhibition of proinflammatory cytokine-induced invasiveness of HT-29 cells by chitosan oligosaccharide," *Journal of Microbiology and Biotechnology*, vol. 17, no. 12, pp. 2042–2045, 2007.

[115] P. Rawla, T. Sunkara, and V. Gaduputi, "Epidemiology of pancreatic cancer: global trends, etiology and risk factors," *World Journal of Oncology*, vol. 10, no. 1, pp. 10–27, 2019.

[116] M. Carpelan-Holmström, S. Nordling, E. Pukkala et al., "Does anyone survive pancreatic ductal adenocarcinoma? A nationwide study re-evaluating the data of the Finnish Cancer Registry," *Gut*, vol. 54, no. 3, pp. 385–387, 2005.

[117] M. Hidalgo, "Pancreatic cancer," *New England Journal of Medicine*, vol. 362, no. 17, pp. 1605–1617, 2010.

[118] A. Jemal, M. M. Center, C. DeSantis, and E. M. Ward, "Global patterns of cancer incidence and mortality rates and trends," *Cancer Epidemiology, Biomarkers & Prevention*, vol. 19, no. 8, pp. 1893–1907, 2010.

[119] R. Shafabakhsh, B. Yousefi, Z. Asemi, B. Nikfar, M. A. Mansournia, and J. Hallajzadeh, "Chitosan: a compound for drug delivery system in gastric cancer-a review," *Carbohydrate Polymers*, vol. 242, Article ID 116403, 2020.

[120] F. Bray, J. Ferlay, I. Soerjomataram, R. L. Siegel, L. A. Torre, and A. Jemal, "Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries," *CA: A Cancer Journal for Clinicians*, vol. 68, no. 6, pp. 394–424, 2018.

[121] H. S. Lee, W. H. Kim, Y. Kwak et al., "Molecular testing for gastrointestinal cancer," *Journal of pathology and translational medicine*, vol. 51, no. 2, pp. 103–121, 2017.

[122] H. Wu, W. Wang, S. Tong, and C. Wu, "Nucleostemin regulates proliferation and migration of gastric cancer and correlates with its malignancy," *International Journal of Clinical and Experimental Medicine*, vol. 8, no. 10, pp. 17634–17643, 2015.

[123] Y. Peng, J.-J. Guo, Y.-M. Liu, and X.-L. Wu, "MicroRNA-34A inhibits the growth, invasion and metastasis of gastric cancer by targeting PDGFR and MET expression," *Bioscience Reports*, vol. 34, no. 3, Article ID e00112, 2014.

[124] Y.-I. Jeong, S.-G. Jin, I.-Y. Kim et al., "Doxorubicin-incorporated nanoparticles composed of poly (ethylene glycol)-grafted carboxymethyl chitosan and antitumor activity against glioma cells in vitro," *Colloids and Surfaces B: Biointerfaces*, vol. 79, no. 1, pp. 149–155, 2010.

[125] J.-H. Kim, Y.-S. Kim, S. Kim et al., "Hydrophobically modified glycol chitosan nanoparticles as carriers for paclitaxel," *Journal of Controlled Release*, vol. 111, no. 1-2, pp. 228–234, 2006.

[126] J. Chi, Z. Jiang, J. Qiao et al., "Antitumor evaluation of carboxymethyl chitosan based norcantharidin conjugates against gastric cancer as novel polymer therapeutics," *International Journal of Biological Macromolecules*, vol. 136, pp. 1–12, 2019.

[127] E. Zhang, R. Xing, S. Liu et al., "Vascular targeted chitosan-derived nanoparticles as docetaxel carriers for gastric cancer therapy," *International Journal of Biological Macromolecules*, vol. 126, pp. 662–672, 2019.

[128] C.-K. Lai, Y.-L. Lu, J.-T. Hsieh et al., "Development of chitosan/heparin nanoparticle-encapsulated cytolethal distending toxin for gastric cancer therapy," *Nanomedicine*, vol. 9, no. 6, pp. 803–817, 2014.

[129] X. Li, J. Feng, R. Zhang et al., "Quaternized chitosan/alginate-Fe3O4 magnetic nanoparticles enhance the chemosensitization of multidrug-resistant gastric carcinoma by regulating cell autophagy activity in mice," *Journal of Biomedical Nanotechnology*, vol. 12, no. 5, pp. 948–961, 2016.

[130] Y. H. Lin, Z. R. Chen, C. H. Lai, C. H. Hsieh, and C. L. Feng, "Active targeted nanoparticles for oral administration of gastric cancer therapy," *Biomacromolecules*, vol. 16, no. 9, pp. 3021–3032, 2015.

[131] R.-F. Song, X.-J. Li, X.-L. Cheng et al., "Paclitaxel-loaded trimethyl chitosan-based polymeric nanoparticle for the effective treatment of gastroenteric tumors," *Oncology Reports*, vol. 32, no. 4, pp. 1481–1488, 2014.

[132] J. Huo, "Effects of chitosan nanoparticle-mediated BRAF siRNA interference on invasion and metastasis of gastric cancer cells," *Artificial Cells, Nanomedicine, and Biotechnology*, vol. 44, no. 5, pp. 1232–1235, 2016.

[133] X. Zhou, L. He, M. Liang, and J. Liu, "Chitosan/PIK3CA siRNA nanoparticle-mediated PIK3CA gene interference decreases the invasive capacity of gastric cancer cells in vitro," *Nan Fang yi ke da xue xue bao= Journal of Southern Medical University*, vol. 34, no. 10, pp. 1503–1506, 2014.

[134] N. Hu, W. Li, Y. Hong et al., "A PD1 targeted nano-delivery system based on epigenetic alterations of T cell responses in the treatment of gastric cancer," *Molecular Therapy-Oncolytics*, vol. 24, pp. 148–159, 2022.

[135] G. Zheng, R. Zhao, A. Xu, Z. Shen, X. Chen, and J. Shao, "Co-delivery of sorafenib and siVEGF based on mesoporous silica nanoparticles for ASGPR mediated targeted HCC therapy," *European Journal of Pharmaceutical Sciences*, vol. 111, pp. 492–502, 2018.

[136] N. L. Kelekis, R. C. Semelka, S. Worawattanakul et al., "Hepatocellular carcinoma in North America: a multiinstitutional study of appearance on T1-weighted, T2-weighted, and serial gadolinium-enhanced gradient-echo images," *American Journal of Roentgenology*, vol. 170, no. 4, pp. 1005–1013, 1998.

[137] Y. Xu, Z. Wen, and Z. Xu, "Chitosan nanoparticles inhibit the growth of human hepatocellular carcinoma xenografts through an antiangiogenic mechanism," *Anticancer Research*, vol. 29, no. 12, pp. 5103–5109, 2009.

[138] A. Forner and J. Bruix, "The size of the problem: clinical algorithms," *Digestive Diseases*, vol. 31, no. 1, pp. 95–103, 2013.

[139] M. C. Kew, "Hepatic iron overload and hepatocellular carcinoma," *Cancer Letters*, vol. 286, no. 1, pp. 38–43, 2009.

[140] J. Balogh, D. Victor III, E. H. Asham et al., "Hepatocellular carcinoma: a review," *Journal of Hepatocellular Carcinoma*, vol. 3, pp. 41–53, 2016.

[141] D. Ban, T. Ogura, K. Akahoshi, and M. Tanabe, "Current topics in the surgical treatments for hepatocellular carcinoma," *Annals of gastroenterological surgery*, vol. 2, no. 2, pp. 137–146, 2018.

[142] G. Torzilli, J. Belghiti, N. Kokudo et al., "A snapshot of the effective indications and results of surgery for hepatocellular carcinoma in tertiary referral centers: is it adherent to the EASL/AASLD recommendations?: an observational study of the HCC East-West study group," *Annals of Surgery*, vol. 257, no. 5, pp. 929–937, 2013.

[143] S. L. Ye and R. X. Chen, "Comments on management of hepatocellular carcinoma: an update," *Zhonghua gan zang bing za zhi= Zhonghua ganzangbing zazhi= Chinese journal of hepatology*, vol. 19, no. 4, pp. 251–253, 2011.

[144] J. M. Llovet, J. Zucman-Rossi, E. Pikarsky et al., "Nature reviews disease primers," *Hepatocellular carcinoma*, vol. 2, no. 1, Article ID 16018, 2016.

[145] Y. Yang, S.-X. Yuan, L.-H. Zhao et al., "Ligand-directed stearic acid grafted chitosan micelles to increase therapeutic efficacy in hepatic cancer," *Molecular Pharmaceutics*, vol. 12, no. 2, pp. 644–652, 2015.

[146] F. M. Ghorbani, B. Kaffashi, P. Shokrollahi, E. Seyedjafari, and A. Ardeshirylajimi, "PCL/chitosan/Zn-doped nHA electrospun nanocomposite scaffold promotes adipose derived stem cells adhesion and proliferation," *Carbohydrate Polymers*, vol. 118, pp. 133–142, 2015.

[147] C. Lai, X. Yu, H. Zhuo et al., "Anti-tumor immune response of folate-conjugated chitosan nanoparticles containing the IP-10 gene in mice with hepatocellular carcinoma," *Journal of Biomedical Nanotechnology*, vol. 10, no. 12, pp. 3576–3589, 2014.

[148] J. Zhong, H.-L. Huang, J. Li et al., "Development of hybrid-type modified chitosan derivative nanoparticles for the intracellular delivery of midkine-siRNA in hepatocellular carcinoma cells," *Hepatobiliary and Pancreatic Diseases International*, vol. 14, no. 1, pp. 82–89, 2015.

[149] M. I. Shekh, J. Amirian, F. J. Stadler, B. Du, and Y. Zhu, "Oxidized chitosan modified electrospun scaffolds for controllable release of acyclovir," *International Journal of Biological Macromolecules*, vol. 151, pp. 787–796, 2020.

[150] P. Vongchan, Y. Wutti-In, W. Sajomsang, P. Gonil, S. Kothan, and R. J. Linhardt, "N, N, N-Trimethyl chitosan nanoparticles for the delivery of monoclonal antibodies against hepatocellular carcinoma cells," *Carbohydrate Polymers*, vol. 85, no. 1, pp. 215–220, 2011.

[151] Z. Jiang, J. Chi, B. Han, and W. Liu, "Preparation and pharmacological evaluation of norcantharidin-conjugated carboxymethyl chitosan in mice bearing hepatocellular carcinoma," *Carbohydrate Polymers*, vol. 174, pp. 282–290, 2017.

[152] C. Qu, J. Li, Y. Zhou et al., "Targeted delivery of doxorubicin via CD147-mediated ROS/pH dual-sensitive nanomicelles for the efficient therapy of hepatocellular carcinoma," *The AAPS Journal*, vol. 20, no. 2, pp. 34–14, 2018.

[153] M. A. D. Vente, M. Wondergem, I. van der Tweel et al., "Yttrium-90 microsphere radioembolization for the treatment of liver malignancies: a structured meta-analysis," *European Radiology*, vol. 19, no. 4, pp. 951–959, 2009.

[154] World Health Organization, *Cancer Today*, World Health Organization, Geneva, Switzerland, 2021.

[155] M. Arnold, M. S. Sierra, M. Laversanne, I. Soerjomataram, A. Jemal, and F. Bray, "Global patterns and trends in colorectal cancer incidence and mortality," *Gut*, vol. 66, no. 4, pp. 683–691, 2017.

[156] M. C. S. Wong, H. Ding, J. Wang, P. S. F. Chan, and J. Huang, "Prevalence and risk factors of colorectal cancer in Asia," *Intestinal research*, vol. 17, no. 3, pp. 317–329, 2019.

[157] H. Choukaife, S. Seyam, B. Alallam, A. A. Doolaanea, and M. Alfatama, "Current advances in chitosan nanoparticles based oral drug delivery for colorectal cancer treatment," *International Journal of Nanomedicine*, vol. 17, pp. 3933–3966, 2022.

[158] C. Yang and D. Merlin, "Lipid-based drug delivery nanoplatforms for colorectal cancer therapy," *Nanomaterials*, vol. 10, no. 7, p. 1424, 2020.

[159] Q. Tian, Y. Liu, Y. Zhang et al., "THBS2 is a biomarker for AJCC stages and a strong prognostic indicator in colorectal cancer," *J buon*, vol. 23, no. 5, pp. 1331–1336, 2018.

[160] K. Bennedsgaard, L. Ventzel, A. C. Themistocleous et al., "Long-term symptoms of polyneuropathy in breast and colorectal cancer patients treated with and without adjuvant chemotherapy," *Cancer Medicine*, vol. 9, no. 14, pp. 5114–5123, 2020.

[161] G. Duran, R. Cruz, A. R. Simoes et al., "Efficacy and toxicity of adjuvant chemotherapy on colorectal cancer patients: how much influence from the genetics?" *Journal of Chemotherapy*, vol. 32, no. 6, pp. 310–322, 2020.

[162] X. Yang and Y. Xie, "Recent advances in polymeric core–shell nanocarriers for targeted delivery of chemotherapeutic drugs," *International Journal of Pharmaceutics*, vol. 608, Article ID 121094, 2021.

[163] A. Arumov, A. Trabolsi, and J. H. Schatz, "Potency meets precision in nano-optimized chemotherapeutics," *Trends in Biotechnology*, vol. 39, no. 10, pp. 974–977, 2021.

[164] A. N. Shwter, N. A. Abdullah, M. A. Alshawsh et al., "Chemopreventive effect of Phaleria macrocarpa on colorectal cancer aberrant crypt foci in vivo," *Journal of Ethnopharmacology*, vol. 193, pp. 195–206, 2016.

[165] R. Zhao, H. Huang, B. Y. Choi et al., "Cell growth inhibition by 3-deoxysappanchalcone is mediated by directly targeting the TOPK signaling pathway in colon cancer," *Phytomedicine*, vol. 61, Article ID 152813, 2019.

[166] M. Pal, T. Muinao, H. P. D. Boruah, and N. Mahindroo, "Current advances in prognostic and diagnostic biomarkers for solid cancers: detection techniques and future challenges," *Biomedicine & Pharmacotherapy*, vol. 146, Article ID 112488, 2022.

[167] T. Armaghany, J. D. Wilson, Q. Chu, and G. Mills, "Genetic alterations in colorectal cancer," *Gastrointestinal cancer research: GCR*, vol. 5, no. 1, pp. 19–27, 2012.

[168] A. B. Lowenfels and P. Maisonneuve, "Epidemiology and risk factors for pancreatic cancer," *Best Practice & Research Clinical Gastroenterology*, vol. 20, no. 2, pp. 197–209, 2006.

[169] M. S. D. De La Cruz, A. P. Young, M. T. Ruffin, T. Mack, and I. V. Ruffin, "Diagnosis and management of pancreatic cancer," *American Family Physician*, vol. 89, no. 8, pp. 626–632, 2014.

[170] S. Mohammed, G. Van Buren 2nd, and W. E. Fisher, "Pancreatic cancer: advances in treatment," *World Journal of Gastroenterology*, vol. 20, no. 28, pp. 9354–9360, 2014.

[171] D. F. Emerich and C. G. Thanos, "Nanotechnology and medicine," *Expert Opinion on Biological Therapy*, vol. 3, no. 4, pp. 655–663, 2003.

[172] Y. Yarden, "The EGFR family and its ligands in human cancer: signalling mechanisms and therapeutic opportunities," *European Journal of Cancer*, vol. 37, pp. 3–8, 2001.

[173] J. Xiao and H. Yu, "Gemcitabine conjugated chitosan and double antibodies (Abc-GC-gemcitabine nanoparticles) enhanced cytoplasmic uptake of gemcitabine and inhibit proliferation and metastasis in human SW1990 pancreatic cancer cells," *Medical Science Monitor*, vol. 23, pp. 1613–1620, 2017.

[174] J. Zhou, J. Wang, Q. Xu et al., "Folate-chitosan-gemcitabine core-shell nanoparticles targeted to pancreatic cancer," *Chinese Journal of Cancer Research*, vol. 25, no. 5, pp. 527–535, 2013.

[175] K. I. David, L. R. Jaidev, S. Sethuraman, and U. M. Krishnan, "Dual drug loaded chitosan nanoparticles—sugar-coated arsenal against pancreatic cancer," *Colloids and Surfaces B: Biointerfaces*, vol. 135, pp. 689–698, 2015.

[176] K. S. Snima, R. Jayakumar, and V. K. Lakshmanan, "In vitro and in vivo biological evaluation of O-carboxymethyl chitosan encapsulated metformin nanoparticles for pancreatic cancer therapy," *Pharmaceutical Research*, vol. 31, no. 12, pp. 3361–3370, 2014.

[177] M. Pollak, "The insulin and insulin-like growth factor receptor family in neoplasia: an update," *Nature Reviews Cancer*, vol. 12, no. 3, pp. 159–169, 2012.

[178] K. S. Snima, R. Jayakumar, A. G. Unnikrishnan, S. V. Nair, and V. K. Lakshmanan, "O-Carboxymethyl chitosan nanoparticles for metformin delivery to pancreatic cancer cells," *Carbohydrate Polymers*, vol. 89, no. 3, pp. 1003–1007, 2012.

[179] G. Arya, M. Das, and S. K. Sahoo, "Evaluation of curcumin loaded chitosan/PEG blended PLGA nanoparticles for effective treatment of pancreatic cancer," *Biomedicine & Pharmacotherapy*, vol. 102, pp. 555–566, 2018.

[180] D. Borja-Cacho, E. H. Jensen, A. K. Saluja, D. J. Buchsbaum, and S. M. Vickers, "Molecular targeted therapies for pancreatic cancer," *The American Journal of Surgery*, vol. 196, no. 3, pp. 430–441, 2008.

[181] S. Safari, F. A. Dorkoosh, M. Soleimani et al., "N-Diethylmethyl chitosan for gene delivery to pancreatic cancer cells and the relation between charge ratio and biologic properties of polyplexes via interpolations polynomial," *International Journal of Pharmaceutics*, vol. 420, no. 2, pp. 350–357, 2011.

[182] S. Astuti, Y. Yulizar, A. Saefumillah, and D. O. B. Apriandanu, "Chitosan nanoparticles modified by polyethylene glycol as lamivudine drug delivery system," *AIP Conference Proceedings*, vol. 2242, no. 1, 2020.

[183] K. Taniuchi, T. Yawata, M. Tsuboi, T. Ueba, and T. Saibara, "Efficient delivery of small interfering RNAs targeting particular mRNAs into pancreatic cancer cells inhibits invasiveness and metastasis of pancreatic tumors," *Oncotarget*, vol. 10, no. 30, pp. 2869–2886, 2019.

[184] M. R. Zeiderman, D. E. Morgan, J. D. Christein, W. E. Grizzle, K. M. McMasters, and L. R. McNally, "Acidic pH-targeted chitosan-capped mesoporous silica coated gold nanorods facilitate detection of pancreatic tumors via multispectral optoacoustic tomography," *ACS Biomaterials Science & Engineering*, vol. 2, no. 7, pp. 1108–1120, 2016.

[185] F. Sadoughi, M. A. Mansournia, and S. M. Mirhashemi, "The potential role of chitosan-based nanoparticles as drug delivery systems in pancreatic cancer," *IUBMB Life*, vol. 72, no. 5, pp. 872–883, 2020.

[186] Z. Wang, M. Tong, X. Chen et al., "Survivin-targeted nanoparticles for pancreatic tumor imaging in mouse model," *Nanomedicine: Nanotechnology, Biology and Medicine*, vol. 12, no. 6, pp. 1651–1661, 2016.

[187] M. Tong, F. Xiong, Y. Shi et al., "In vitro study of SPIO-labeled human pancreatic cancer cell line BxPC-3," *Contrast Media and Molecular Imaging*, vol. 8, no. 2, pp. 101–107, 2013.

[188] H. Xu, Y. Wang, L. Wang, Y. Song, J. Luo, and X. Cai, "A label-free microelectrode array based on one-step synthesis of chitosan–multi-walled carbon nanotube–thionine for ultrasensitive detection of carcinoembryonic antigen," *Nanomaterials*, vol. 6, no. 7, p. 132, 2016.

[189] Q. Rong, F. Feng, and Z. Ma, "Metal ions doped chitosan–poly (acrylic acid) nanospheres: synthesis and their application in simultaneously electrochemical detection of four markers of pancreatic cancer," *Biosensors and Bioelectronics*, vol. 75, pp. 148–154, 2016.

[190] A. C. Soares, J. C. Soares, F. M. Shimizu, M. E. Melendez, A. L. Carvalho, and O. N. Oliveira Jr., "Controlled film architectures to detect a biomarker for pancreatic cancer using impedance spectroscopy," *ACS Applied Materials & Interfaces*, vol. 7, no. 46, pp. 25930–25937, 2015.

[191] S. Dobiasch, S. Szanyi, A. Kjaev et al., "Synthesis and functionalization of protease-activated nanoparticles with tissue plasminogen activator peptides as targeting moiety and diagnostic tool for pancreatic cancer," *Journal of Nanobiotechnology*, vol. 14, pp. 81–18, 2016.