Chapter 13
Application of Chitosan Nanostructures Embedded Composite Materials in Cancer Therapy

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Abstract Chitosan is a naturally occurring polymer formed from the chitin found in the shells of many different animals, including shrimp, crabs, and squid. Weak organic acids dissolve their amino groups. It is capable of binding to both physiologically active chemicals and metal ions. Chitosan and its derivative biomaterials have recently piqued the interest of biomedical researchers due to their unusual biological features. Non-toxicity, biodegradability, biocompatibility, immunostimulating, anticancer, antibacterial, and antimicrobial activity are the most important qualities of chitosan in the biomedical field. Encapsulating and delivering various substances improves water solubility, stability, and permeability into cells and helps manage the release of these molecules, particularly in medical and pharmaceutical applications. It can be used to treat and prevent a variety of illnesses more efficiently. It is also used in textile, food, agriculture, cosmetics, and other industries. Chitosan nanostructures integrated into composite materials are among the most recent types of nanomaterials being researched. Although using chitosan alone may be insufficient to result in an adequate antibacterial effect for a variety of purposes, combining chitosan with other active substances such as metals, drugs and natural compounds in nanosystems is a common strategy for increasing its application potential. These specific nanoparticles are actively being researched and developed. The authors will dwell deeper and look into one particular use of composite materials with embedded chitosan nanostructures in clinical cancer in this chapter. Chitosan has a number of

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roles in the management of malignancy. Chitosan can be used in both diagnostic and treatment. Many cancers, including lung, brain, and colon tumors, can be managed using composite materials with incorporated chitosan nanostructures.

13.1 Introduction

Chitosan (CAS 9012-76-4) is a natural polymer derived from chitin, which can be found in shrimp shells, crab shells, and squid cores, among other places, having amino groups that are soluble in dilute organic acids (Fig. 13.1). It has a strong affinity for metal ions and physiologically active compounds. Chitosan has numerous applications at the moment. Because of chitosan's many unique features, including its non-toxicity, biocompatible (biocompatibility), biological degradability (biodegradability), and does not pose any environmental risks [1] Chitosan has been known as a natural material for over a century, but its application has not been extensively investigated. In 1975, a global gathering of scientists to research the features of this chemical revealed the fundamental qualities of chitosan. Scientists have researched chitosan and found that it is a positively charged material that may trap certain lipids that are negatively charged [1]. Japan conducted the first chitosan study in biological wastewater treatment. Chitosan has since been used in a variety of industrial applications. In 1859, Professor C. Rouget developed chitosan by boiling chitin in a strong solution of potassium hydroxide, resulting in a material having qualities distinct from chitin. It is soluble in dilute organic solutions, and Hoppe-Seiler termed it "chitosan" in 1894 [1–3].

Chitin, one of the most common natural polysaccharides on the planet, is largely used in the deacetylation process to generate chitosan [3]. Chitosan is a bioactive polymer with a wide range of uses due to its beneficial properties such as antibacterial activity, non-toxicity, ease of modification, and biodegradability [3]. Chitosan is an extract derived from shrimp or crab shells, as previously stated. As a result, it is regarded as a significant natural product. When you separate proteins and minerals, you generate chitin, which is a natural dietary fiber [4, 5]. It makes people feel full and aids in the burning of extra fat. Furthermore, it possesses a mesh-like structure that may absorb 8–10 times its weight in fat or fat in the digestive tract. The fat cannot be absorbed by the body. However, it will be eliminated with feces [4, 5].

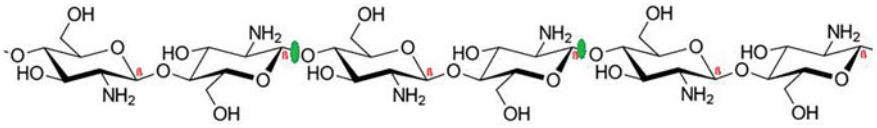

Fig. 13.1 Chitosan. In the picture, three monomers of the molecule are shown, the green dot is the intermolecular bond

Chitosan has been advocated as a dietary supplement that can aid in weight management and blood cholesterol reduction. Numerous chitosan products are widely available in pharmacies and health food stores worldwide [5]. Chitosan is a polycationic (+) fibrillar biopolymer with cellulose-like characteristics that form films with negatively charged surfaces. Chitosan is not highly hydrolyzed by digestive enzymes in humans, but there may be some limited digestion of chitosan due to bacterial flora and general enzymes. Chitosan's positively charged tertiary amino group ($-NH_3^+$) strongly binds negatively charged molecules in the stomach [5]. As a result of its interactions with anionic carboxyl groups of fatty and bile acids, chitosan inhibits the emulsification of neutral lipids (such as cholesterol and other sterols) and decreases fat absorption from the gastrointestinal system [5]. Chitosan is currently one of the most readily accessible dietary supplement products on the market (Fig. 13.2).

Even if employing chitosan by itself might not be sufficient to provide a suitable biomedical application, more research and development are still required. The new technique for material modification to increase the biological application is difficult. A novel biomedical application in medicine is the use of composite materials with incorporated chitosan nanostructures. It is already used in a number of medical specialties, including clinical oncology. Multiple functions of chitosan are involved in the treatment of cancer. Both diagnostic and therapeutic uses for chitosan are possible. Composite materials with chitosan nanostructures integrated can be used to treat a variety of malignancies, including lung, brain, and colon tumors. For biomedical professionals, knowledge of the use of chitosan nanostructures embedded composite materials in clinical cancer is new and not well discussed. The authors will continue to summarize, go into more detail, and address the use of composite materials with embedded chitosan nanostructures in cancer therapy in this chapter.

Fig. 13.2 Example of chitosan food supplementation product. The pictures are some famous locally available products in Southeast Asia

13.2 Chitosan Nanostructures Embedded Composite Materials

Chitosan is made by deacetylating chitin, which is plentiful in nature. Chitosan is created by alkaline deacetylating chitin, an abundant polymeric by-product of natural biosynthesis found primarily in crustaceans. It is available in both a simple, unstructured structure and a microcrystalline structure [5]. The difficulty of chitosan to dissolve in water and the majority of organic solvents greatly limits the variety of applications in which it can be employed [2]. Chitosan is a polycationic (+) fibrillar biopolymer with cellulose-like characteristics that form films with negatively charged surfaces [6]. Human digestive enzymes do not considerably hydrolyze chitosan, but there may be a small amount of limited chitosan digestion caused by bacterial flora and general enzymes [6].

Chitosan's positively charged tertiary amino group ($-NH_3^+$) strongly binds negatively charged molecules in the stomach [6]. As a result of interacting with the anionic carboxyl groups of fatty and bile acids, chitosan inhibits the emulsification of neutral lipids (such as cholesterol and other sterols) and decreases fat absorption from the gastrointestinal system [6]. Chitosan is a low-cost, natural, and biodegradable biopolymer. Chitosan is gaining popularity as a nanocomposite matrix due to its innovative properties for a wide range of applications [7]. There are numerous current alternative methods for creating embedded or coated nanoparticles, as well as shaping techniques that have been used (three-dimensional printing, electrospinning), and the burgeoning applications for nanocomposites in areas such as corrosion prevention, tissue engineering, and medicine [7].

Chitosan and its derivative biomaterials have recently attracted a lot of attention in the biomedical arena due to their unusual biological properties. Chitosan's most significant biological properties are non-toxicity, biodegradability, biocompatibility, immunostimulating, anticancer, antibacterial, and antimicrobial activity [8]. Chitosan's biodegradability was established in vitro and in vivo by dividing macromolecules into smaller monomer parts [8]. Living cells can interact with chitosan and its enzymatic degradation products without damage to their health, indicating that chitosan is biosafe. Chitosan can reduce chain oxidation by screening free radicals, lowering cholesterol absorption, and acting as an antibiotic and antibacterial agent against a variety of bacteria and fungi [8]. Only a few of the variables that are reported to affect the antibacterial activity of chitosan and its derivative biomaterials are the degree of deacetylation, molar weight, pH, the presence of metal cations, pKa, and the kind of bacterium [8].

Encapsulating and delivering various chemicals enhances water solubility, increases stability, increases permeability into cells, and can manage the release of these molecules, particularly in medical and pharmaceutical applications. It can be used to treat and prevent a variety of disorders. It's also useful in cosmetics, food, agriculture, textiles, and other industries [1, 2]. Chitosan nanostructures incorporated in composite materials are a novel type of nanomaterial that is being explored extensively [1, 2]. Incorporating this biopolymer with other active substances such as

medicines, metals, and natural compounds in nanosystems is a typical technique for increasing its application potential, even if chitosan alone may not create an effective antibacterial effect to fulfill diverse goals [9, 10]. Chitosan has been altered by nitration, alkylation, sulphonation, phosphorylation, xanthation, Schiff's base generation, acylation, hydroxylation, and graft copolymerization [10].

It has been established that composite materials containing chitosan nanostructures have biomedical applications. Numerous studies have been published on the use of antibacterial drugs to treat infections. Among the suggested mechanisms for the intrinsic anti-pathogenic properties of chitosan-based biomaterials include interactions with microbial nucleic acids, chelation of microbial structures, and electrostatic interactions between cationic chitosan and negatively charged pathogenic cell surfaces [11, 12]. The nanostructured composite biopolymeric nanostructure demonstrates the required properties for delayed and regulated drug release [11, 12]. Nanoparticle-based medication formulations have been shown to be useful in the treatment of difficult ailments. A quick search of the major scientific publication databases reveals an astounding number of papers on nanoparticles designed for drug delivery purposes. Because of their inherent physicochemical diversity and configurable functionality, polymer particles and capsules are suitable candidates for modern pharmacology. This allows for more effective loading and encapsulation of various medicines (including genetic components, proteins, growth factors, and cells), as well as triggerable or programmed release mechanisms [11, 12]. There are numerous studies and developments on those specific nanomaterials at the moment.

13.3 Application of Chitosan in Biomedicine

Among the various qualities of chitosan are its water solubility, stimulus responsiveness, biocompatibility, biodegradability, and antibacterial activities [10]. As previously stated, chitosan is an extract obtained from shrimp or crab shells. As a result, it is recognized as an important natural product. Chitin, a natural dietary fiber, is produced when proteins and minerals are separated [4, 5]. It makes people feel full and promotes fat burning. It also has a mesh-like structure that can absorb 8–10 times its own weight in fat or fat in the digestive tract. Fat cannot enter the bloodstream and must be removed by feces [4, 5]. Chitosan has been promoted as a dietary supplement that can help with weight loss and cholesterol lowering. Several chitosan preparations can be found in pharmacies [1]. Because of its biodegradability, biological compatibility, antibacterial and antioxidant activity, and high safety, chitosan has a wide range of uses [3, 4]. Fibers, gels, films, sponges, nanoparticles, or beads could all be used. The numerous biological activities of chitosan and its derivatives are being extensively explored in order to broaden the application sectors in a wide range of disciplines. Chitosan's natural properties are mainly dependent on its solubility in water and other solvents. Chitosan oligosaccharides with low polymerization degrees are gaining popularity in pharmaceutical and medical applications due to their reduced viscosity and higher water solubility than chitosan [13].

Furthermore, for a variety of applications, chitosan can be turned into scaffolds, fiber meshes, nanoparticles, nanovehicles, nanocapsules, nanoparticles, and three-dimensional printed scaffolds [10]. Because nanocomposites interact with cells faster than bulk or micron-sized substrates or scaffolds, nanoparticles contained in chitosan matrices have been shown to have higher biological activity [10]. Chitosan-based nanomaterials have sparked substantial interest in a wide range of biological applications because of their particular chemical properties, such as desired biodegradability, compatibility, and non-toxicity. Chitosan is a biomaterial that can be used to construct extracellular tissue matrixes in tissue engineering [8]. It can be used to carry drugs to the brain as well as a number of therapeutic chemicals for the eyes, such as proteins, genes, and medications used to treat visual system disorders. Another medicinal purpose is its use in hemodialysis and renal failure [8]. Chitosan is frequently used as a delivery vehicle for active compounds and drugs [8], as well as in gene and cancer therapy, biosensor monitoring, and bioimaging. The authors aim on summarizing and explaining the specific use of chitosan nanostructures embedded composite materials in clinical cancer in this chapter.

13.4 Chitosan Nanostructures Embedded Composite Materials in Cancer Therapy

Chitosan has been widely employed in a variety of biomedical applications, including wound dressing as an antibacterial agent [8], medication delivery as a nano-sized carrier to target tumor tissue while impacting normal tissue locations slightly, gene transfer, hemodialysis, and dentistry [8]. Chitosan can be utilized on its own or in combination with other polymers, active agents, and metallic nanocomposites. Chitosan-based nanoparticles have a high permeability and retention impact, as well as the potential to cause apoptosis, which limits tumor cell proliferation [8]. Larger particles must be phagocytosed before being taken up by receptor-mediated endocytosis, which can only take up particles as small as 100–200 nm [8]. Chitosan has various applications in clinical oncology. The two major goals of using chitosan nanostructures embedded composite materials in cancer therapy are diagnostic and therapeutic (Table 13.1) (Fig. 13.3). The application for diagnostic purposes entails the use of chitosan nanostructures implanted in composite materials to aid in illness investigation via clinical laboratory or clinical imaging approaches. The use of chitosan nanostructures implanted composite materials for therapeutic purposes is typically associated with anticancer drugs and the mediation process. Dual application, theranostics, is also possible in some situations. It has been confirmed that the new chitosan nanostructures implanted in composite materials are quite useful for cancer management.

As previously stated, there are numerous current studies on the use of chitosan nanostructures implanted in composite materials for cancer therapy. The applications

Table 13.1 Application of chitosan nanostructures embedded composite materials in cancer therapy

Purposes	Examples
Diagnostic purpose	Diagnostic assay Biosensor Nanoimaging diagnosis Theranostics
Therapeutic purpose	Drug formulation Drug delivery system Magic bullet and cancer targeting Tissue engineering and regenerative repair Photothermal cancer therapy Theranostics

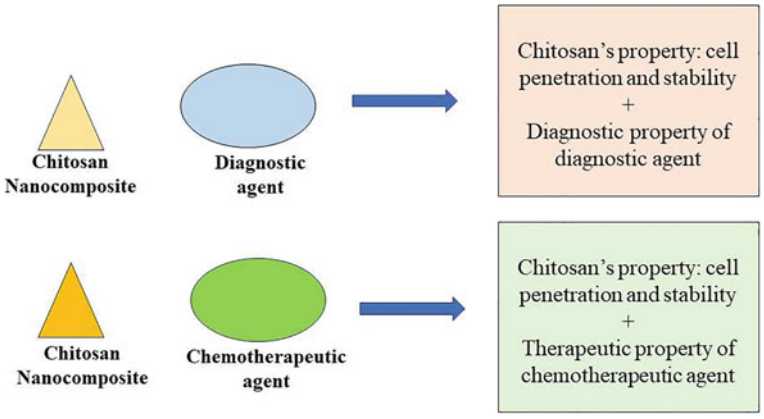

Fig. 13.3 Schematic diagram showing application of chitosan nanostructures embedded composite materials for diagnostic and therapeutic purposes in cancer therapy

of chitosan nanostructures embedded composite materials for cancer treatment will be listed below.

13.4.1 Drug Formulation

Chitosan nanoparticle composites can be made by utilizing ultrasonics to encourage consecutive precipitation; these composites can then be tested for their atomic-scale microstructure, surface charge, drug release properties, and anti-cancerous activity. For instance, Glavas-Dodov et al. [14] presented 5-Fluorouracil in topical liposome gels for anticancer treatment. A study by Glavas-Dodov et al. examined the in vitro drug release characteristics of liposome gels containing the antineoplastic agent 5-fluorouracil [14]. According to this study, hydrogels released liposomes

more quickly than those implanted in chitosan-structured vehicles [14]. According to Glavas-Dodov et al. research, the liposomes served as reservoir systems for the continuous distribution of the drug that was encapsulated and the drug released from them followed the Higuchi diffusion model [14].

13.4.2 Drug Delivery System

Building multifunctional microspheres for remotely controlled drug release requires a careful selection of composite materials and production methods. Chitosan nanostructure-infused composite materials may be employed in drug delivery systems and may support the idea of remote-control release. This is helpful in the treatment of cancer. Chitosan was combined with the inorganic nanomaterials, graphene oxide and Fe_3O_4 and electro-sprayed to create homogenous microspheres with very small dimensions for anti-cancerous purposes, according to the Li et al. publication [15]. The anti cancer medication doxorubicin was then administered to the microspheres via an adsorption or embedding technique [15]. The findings demonstrated that the presence of Fe_3O_4 causes the microsphere to respond to magnetic fields, and the addition of graphene oxide increases the drug loading capacity [15]. The results also demonstrated that the quick stimuli-responsive release of doxorubicin may be easily controlled by using NIR irradiation due to the considerable photothermal conversion of Fe_3O_4 and graphene oxide [15]. Another extrinsic mechanism for the release of doxorubicin was ultrasonic stimulation [15]. In a different investigation, Tamoxifen, a crucial anticancer medication, was added to MCF-7 and cancer cell cultures and examined for antiproliferative activity by Rossi et al. [16]. Tamoxifen was also embedded in sodium alginate microparticles from Kelco and Fluka. According to Rossi et al., the formulation of the microparticles may improve selective toxicity based on the alginate used; changes in the chemical alginate composition can greatly increase anticancer drug activity and minimize anticancer drug toxicity [16].

13.4.3 Tissue Engineering

Tissue loss could be an issue in some malignancies. An intriguing medical therapeutic strategy is the use of composite materials with embedded chitosan nanostructures for tissue engineering and regeneration. Using a combination of tissue flap, nanotherapeutic, silk fibroin, and chitosan scaffold, Gupta et al. reported on the healing and regeneration of a resected tumor defect [17]. The scaffold-emodin nanoparticle composites were developed and examined for drug entrapment and release, mechanical strength, and efficacy against breast cancer cells in vitro and in vivo in an animal tumor model [17]. The amount of entrapment was determined by the composition of the scaffold and the emodin loading concentration when emodin nanoparticles were

implanted in silk fibroin and chitosan scaffolds [17]. Gupta et al. discovered that tumors treated with emodin-loaded silk fibroin and chitosan scaffolds had decreased presence and size as well as equal regeneration of new tissue as compared to untreated tumors [17]. However, there was no discernible difference in tumor size across the in vivo test groups.

A quick-prototyped tissue engineering scaffold with an embedded multicomponent matrix for regulated drug release was reported in a different study by Chen et al. [18]. By using freeze-drying manipulation, a quick prototype macroporous polycaprolactone scaffold was implanted into a porous matrix made of nanoclay, -tricalcium phosphate, and chitosan [18]. By adjusting the kind and amount of each component, Chen et al. theorized that the scaffold might be used therapeutically in reconstructive surgery after bone tumor removal and in other tissue engineering applications that need local sustained drug release [18].

13.4.4 Photothermal Therapy

In clinical oncology, photothermal therapy is a novel and intriguing treatment option for cancer. Chitosan nanostructures can be integrated into composite materials for this specific function. Due to their inherent localized and controlled release properties, hydrogels are excellent drug or nanoparticle delivery systems. In particular, the use of hydrogels for the delivery and release of photoresponsive drugs or nanoparticles is gaining popularity [19]. In a recent study by Xia et al. [19], meso-tetrakis(1-methylpyridinium-4-yl) porphyrin (TMPyP) was enclosed in an injectable hydrogel comprised of glycol chitosan and dibenzaldehyde-terminated telechelic poly (ethylene glycol).

Xia et al. found that the hydrogel's reduced self-quenching action resulted in a markedly increased fluorescence intensity of TMPyP [19]. The TMPyP-hydrogel system's extraordinary anticancer efficacy and great fluorescence emission property, according to Xia et al., advance the development of imaging-guided photodynamic treatment [19]. A novel iodinated chitosan-backboned conjugate was created and synthesized by Lim et al. in a distinct study to create self-assembled biopolymeric nanoparticles with better singlet oxygen production and biological advantages [20]. According to this work, the self-assembled nanoparticles with biocompatible, positively charged, and tumor-homing properties have a high tumor targetability both in vitro and in vivo due to their glycol chitosan-surfaced exterior [20]. The intra-particle heavy-atom effect also helps them produce singlet oxygen more effectively [20]. When using composite materials with chitosan nanostructures for photothermal therapy, theranostics is occasionally integrated with a diagnostic strategy [21]. A notable example is the study by Liao et al. on gold/magnetic core–shell hybrid nanoparticles for targeting and imaging-guided photothermal treatment [21].

13.4.5 Theranostics

The words "therapeutics" and "diagnostics" are the roots of the term "theranostics." For cancer theranostics, composite materials incorporating chitosan nanostructures can be employed (Table 13.2). Several new nanocomposites have been reported for this purpose [21–25]. Table 13.2 compiles key reports on these issues.

Many intriguing applications of the chitosan nanostructures embedded composite materials for cancer therapy have been reported. The authors will provide a summary of a few significant reports here.

13.4.5.1 Lung Cancer

The cells that line the airways in the lungs are most frequently impacted by the malignant illness known as lung cancer. It is the main factor behind cancer related fatalities in both men and women. Small cell and non-small cell lung cancer are the two most common kinds. These two categories are handled and grown in quite different ways. One of the most prevalent malignancies in the world is this one. This form of cancer typically advances to an advanced stage and is highly lethal.

It has been proposed that implanted composite materials with chitosan nanostructures may have pharmacological uses for the treatment of lung cancer. Guo et al. [26] reported inhalable microspheres for 2-methoxyestradiol that had chitosan-coated PLGA nanoparticles. Guo et al. [26] used soluble excipients as the matrix for the respirable MS with poly(d, l-lactide-co-glycolide) nanoparticles for 2-methoxyestradiol. According to Guo et al. [26], microspheres matrix, respirable embedding poly(d,l-lactide-co-glycolide) nanoparticles have significant potential as an inhalation agent for targeted, extremely effective, and secure therapy of lung cancer. They also noticed that 2-methoxyestradiol markedly boosted cytotoxicity in experimental animals' lungs without obviously causing inflammation. Even if there is still no proof of the successful use of composite materials with embedded chitosan nanostructures for cancer therapy, the in vitro examination confirms the viability. The study by Sachdev et al. [25] provides the finest illustration of the advantages of using composite materials containing chitosan nanostructures as theranostics.

13.4.5.2 Brain Cancer

A lethal tumor, brain cancer has a high fatality rate. Brain cancer treatment is still not effective. The new hope for brain cancer is anotherapy application. Implanted composite materials with chitosan nanostructures have been theorized to have pharmacological effects on the therapy of brain cancer, just like they do for lung cancer. Kutlu et al. reported on an in vitro experiment. Double the effectiveness of brain tumor therapy with chitosan scaffold-PLGA nanoparticles [27].

Table 13.2 Some reports on applied chitosan nanostructures embedded composite materials as theranostics

Authors	Details
Liao et al. [21]	The hybrid particles are composed of gold shells on chitosan (CTS) and magnetic nanoparticles implanted in poly (methyl methacrylate) (PMMA) cores (-Fe_2O_3 @PMMA/CTS@Au), according to a study by Liao et al. [21]. The -Fe_2O_3@PMMA/CTS@Au particles, according to Liao et al.'s analysis can act as a multifunctional anti-tumor theranostic nanoplatform [21]. This new platform can be the model for magnetically targeted thermophototherapy [21]
Fernández-Álvarez et al. [22]	The development of stealth (maghemite/PLGA)/chitosan (core/shell)/shell nanocomposites with potential uses for combined MRI and hyperthermia against cancer was described by Fernández-lvarez et al. in their report [22]. In vivo magnetic resonance imaging investigations and ex vivo histological analyses of iron deposits, according to Fernández-lvarez et al., suggested the usefulness of chitosan to give the nanocomposites long-circulating capabilities, delaying nanoparticle detection by the mononuclear phagocyte system [22]
Ghoshal et al. [23]	Ghoshal e al. reported on targeting Wnt canonical signaling by recombinant sFRP1 bound luminescent Au-nanocluster embedded nanoparticles in cancer theranostics [23]
Dutta e al. [24]	Dutta et al. [24] described bimetallic silver nanoparticle-gold nanocluster embedded composite nanoparticles for cancer theranostics. According to Dutta et al. [24], by using chitosan as a template, the bimetallic system has been turned into composite nanoparticles that can be easily transported into malignant cells. According to the result reached by Dutta et al. [24], the synthetic composite nanoparticles benefit from the combinatorial properties of the metals present at two separate nanoscale levels, enabling both the killing and bioimaging of cancer cells
Sachdev et al. [25]	The easy development of a hydrogel formulation based on chitosan that contains highly fluorescent carbon dots and is loaded with the model anticancer medication 5-Fluorouracil was the focus of Sachdev et al. [25]. This study found that the developed particle treated cells' induction of apoptosis was demonstrated by modifications in cell cycle patterns and the identification of distinctive apoptotic bodies using field emission scanning electron microscope [25]. Studies on specific apoptotic gene expression shed more light on the molecular process that causes apoptosis [25]. According to Sachdev et al. analysis, hydrogels' ability to combine fluorescent carbon dots with chemotherapeutic drugs opens up new possibilities for their possible usage in cancer theranostics [25]

In this study, poly-lactic-co-glycolic acid (50:50) nanoparticles containing the anticancer drug 5-fluorouracil were made using the emulsion-solvent evaporation method [27]. Then, during fabrication, the scaffold was infused with the antivascularization medication bevacizumab and the nanoparticles by freeze-drying and embedding, respectively [27]. According to Kutlu et al. [27], the chitosan scaffold containing 100 g of 5-fluorouracil and bevacizumab has the ability to prevent the growth of malignancies in in vitro conditions. In a different study, Shamsipour et al. successfully created core/shell chitosan-poly ethylene oxide–carbon quantum dots/carboxymethyl cellulose-polyvinyl alcohol nanofibers utilizing coaxial electrospinning as a biodegradable polymeric implant for the local administration of temozolomide [28]. When temozolomide is combined with quantum dots embedded in chitosan, it is shown that the cytotoxicity of cancer cells is boosted [28].

13.4.5.3 Colon Cancer

Colon cancer is another lethal cancer that has a high mortality rate. Treatment for colon cancer is still ineffective. The use of anotherapy is the new treatment option for brain cancer. Implanted composite materials with chitosan nanostructures may have pharmacological effects on the treatment of colon cancer, similar to what has happened with lung and brain malignancies. As shown in Table 13.3 [29–32], there are a number of intriguing findings on the use of composite materials with chitosan nanostructures for colon cancer therapy (Table 13.3).

13.4.5.4 Ovarian Cancer

A serious malignancy in females is ovarian cancer. The aberrant abdominal mass is how this cancer typically manifests. Surgery is the mainstay of ovarian cancer treatment, which is followed by chemotherapy. The fifth leading cause of cancer-related mortality and the ninth most prevalent cancer in women, ovarian cancer kills more people than any other malignancy of the female reproductive system. The use of composite materials with embedded chitosan nanostructures for the management of ovarian cancer is recorded in the literature, just like it is for the treatment of other cancers. For the treatment of ovarian cancer, Chandran et al. investigated the possible use of drug-loaded nanocomposite pectin scaffolds [33]. To extend the half-life of the drug and provide localized therapy for ovarian cancer, Chandran et al. proposed the use of a highly porous, biomimetic, and implantable pectin scaffold embedded with gemcitabine-loaded fibrin nanoconstructs [33]. The controlled and sustained release of the chemokine from the scaffold structure was thoroughly examined in vitro under various pH conditions in this study [33]. When examined with mammalian cell lines, Chandran et al. discovered that the composite scaffolds were highly biocompatible

Table 13.3 Reports on using composite materials with incorporated chitosan nanostructures applied in colon cancer therapy

Authors	Details
Ullah et al. [29]	The delivery of calcium alginate beads with specified targeting for colon cancer was described by Ullah et al. in their paper on folate-modified chitosan 5-flourouraci nanoparticles [29]
Vijayakumar et al. [30]	Marine originated polysaccharide laminarin embedded zinc oxide (ZnO) nanoparticles and their based chitosan-capped ZnO nanocomposites were the subject of a report by Vijayakumar et al. [30]. The green synthesis of chitosan-capped ZnO nanocomposites and laminarin-embedded ZnO nanoparticles is discussed in the current work [30]. Additionally, the assessment of their in vivo (Zebrafish embryo) toxicity, phytotoxicity, and in vitro cytotoxicity was described [30]
Hosseinzadeh et al. [31]	Chitosan-pluronic nanoparticles were used to deliver the anticancer drug gemcitabine orally, according to Hosseinzadeh et al. [31]. Based on an in vitro examination of a colon cancer cell line, a cytotoxicity assay of gemcitabine-loaded nanoparticles revealed an increase in the cytotoxicity of the drug if it was compared to the naïve drug alone [31]
Cao et al. [32]	With the aid of oral nanomotor-enabled mucus traversal and tumor penetration, Cao et al. reported on targeted sono-immuno-chemotherapy for colon cancer [32]. This study employed silk fibroin and chondroitin sulfate to construct mesoporous manganese oxide-based nanomotors that systematically dual-functionalize their surfaces and allow passing of mitochondrial sonosensitizers into the physical mesopores [32]

[33]. According to Chandran et al., implanted "therapeutic wafers" made of nanocomposite Pectin scaffolds loaded with a particular chemokine can be utilized to divert metastatic cancer cells and increase the survival rate of ovarian cancer patients [33].

13.4.5.5 Breast Cancer

Breast cancer is a dangerous female malignancy. This malignancy often presents as an abnormal breast lump. Chemotherapy is the second line of defense in the fight against breast cancer after surgery. Just like it is for the treatment of other malignancies, the use of composite materials with embedded chitosan nanostructures for the management of breast cancer is documented in the literature. Tamoxifen, a common breast cancer treatment drug, was added to MCF-7 and Vero cultures in a study by Rossi et al., and its antiproliferative effects were assessed both alone and when embedded in sodium alginate microparticles made with sodium alginate from Kelco and from Fluka [16]. According to the alginate used, Rossi et al. determined that microparticle formulation may improve selective toxicity: variations in the chemical composition of the alginate can significantly alter both drug activity and toxicity [16].

13.4.5.6 Gastric Cancer

A significant gastrointestinal malignancy is gastric cancer. When this cancer is initially diagnosed, it is typically advanced. The use of composite materials with embedded chitosan nanostructures for the management of stomach cancer is recorded in the literature, just like it is for the treatment of other malignancies. The fabrication process used in the study by Wang et al. to create magnetic cores involved the coprecipitation of Fe^{2+} and Fe^{3+}. The magnetic nanoparticles were then covered in layers of chitosan. Next, using sodium citrate as a natural reducing agent, magnetite-gold composite nanoparticles with spherical forms and diameters between 20 and 30 nm were created [34]. Fe_3O_4@CS/AuNPs showed the best cytotoxicity effects when applied to the HCT 116 cell line, according to Wang et al. According to Wang et al., the current nanoparticles may one day be employed to treat various gastroduodenal tumors, particularly gastric cancer [34]. Chang et al. reported on a novel exceptionally sensitive fluorescence sensor for the magnetic separation-based detection of microRNA that is based on composite nanoparticles of lucigenin, chitosan, and silicon [35]. A good linear relationship between the fluorescence intensity sensitizing value and the target miRNA concentrations was achieved when the difference in fluorescence intensity increased along with the target DNA/miRNA concentration [35]. In order to directly detect let-7a in human gastric cancer cell samples without the use of an enzyme, a label, or any other immobilization, Chang et al. came to the conclusion that a new fluorescence analysis method had been developed using lucigenin/chitosan/SiO_2 composite nanoparticles as a DNA hybrid indicator [35].

Another study by Rizwan et al. reported the creation of a new organosoluble and pro-angiogenic chitosan derivative through the reaction of chitosan with triethylorthoformate and 1,3-dimethylbarbituric acid [36]. In a study by Rizwan et al., it was discovered that the novel derivative had no adverse effects on gastric cancer cells when tested for cytotoxicity and apoptosis [36].

13.4.5.7 Liver Cancer

Another common cancer is liver cancer. Alcoholism and chronic viral hepatitis are linked to it. The fight against liver cancer is still ineffective. The hope is that a novel anticancer medicine will be developed for the treatment of liver cancer. Similar to how it is used to treat other cancers, the use of composite materials containing embedded chitosan nanostructures for the management of liver cancer is documented in the literature. The core–shell type Fe_3O_4 nanoparticle (Ag/CS-Agar@Fe_3O_4) was described by Cai et al. in a unique Ag NPs-fabricated chitosan-agarose composite [37]. Ag/CS-Agar@Fe_3O_4 nanocomposite was shown by Cai et al. to be an effective chemotherapeutic agent against the lung and hepatocellular cancer cells [37]. A targeted drug delivery system was developed by functionalizing graphene oxide (GO) with carboxymethyl chitosan (CMC), fluorescein isothiocyanate, and lactobionic acid (LA) in a different study by Pan et al. [38]. According to Pan et al.,

the composite containing LA demonstrated the ability to specifically promote cell death in malignant cells, but the LA-free homologue was inactive in this situation [38]. According to Pan et al. analysis, the modified GO materials provide excellent prospects for use in drug new delivery systems to target malignancy [38]. In a different study by Huang et al., the positively charged HTCC-OREC nanocomposites and the negatively charged sodium alginate were immobilized on cellulose nanofibrous mats using the layer-by-layer (LBL) technique [39]. The intercalated nanocomposites were made using organic rectorite and N-(2-hydroxyl) propyl-3-trimethyl ammonium chitosan chloride, respectively [39]. According to Huang et al.'s research, the produced nanofibrous mats significantly inhibited the growth of human hepatoma cells [39]. Based on the numerous clinical examples provided, it is possible to infer that composite materials with embedded chitosan nanostructures might be suitable for the treatment of liver cancer.

13.4.5.8 Leukemia

Instead of a solid tumor, leukemia is a cancer of the white blood cell. The primary therapeutic approach for treating leukemia is chemotherapy. The use of composite materials with embedded chitosan nanostructures for the management of liver cancer is recorded in the literature, much like how it is used to treat other malignancies. ZnO-TiO_2-chitosan-farnesol nanocomposites (NCs) were studied for their synergistic antitumor potential against leukemia MOLT-4 cells by Elderdery et al. [40]. According to Elderdery et al., this is a novel method for enhancing the properties of ZnO-TiO_2-chitosan-farnesol composites and synergistically exhibiting anticancer activities in human leukemic cancer cells [40].

13.5 Conclusion

Chitosan is derived from chitin, a naturally occurring polymer present in several kinds of animal shells, including those of shrimp, crabs, and squid. Its amino groups are soluble in weak organic acids. Both chemical compounds having physiological activity and metal ions can be successfully bound by it. Due to their distinctive biological properties, Chitosan and its derivative biomaterials have recently attracted a lot of interest in the biomedical field. Some of chitosan's most crucial properties in the biomedical sector include its non-toxicity, biodegradability, biocompatibility, immunostimulating, anticancer, antibacterial, and antimicrobial activity. Encapsulating and delivering different chemicals enhances their water solubility, stability, permeability into cells, and capacity to control the release of these molecules, particularly in medical and pharmaceutical applications. It aids in the better treatment and prevention of numerous diseases. It can also be used in textile, food, agricultural, cosmetic, and other industries. An in-depth study is currently being carried

on the newest types of nanomaterials, such as the chitosan nanostructures found in composite materials. Chitosan is often combined with other active chemicals, including medicines, metals, and natural compounds, in nanosystems to increase its potential for application, even if employing chitosan alone might not be sufficient to generate an acceptable antibacterial effect to fulfill a range of purposes. These particular nanoparticles are the subject of current research and development. The authors have tried to include details about one particular use of composite materials with integrated chitosan nanostructures in clinical cancer. The development of numerous new chitosan-based nanomaterials has shown promise in the treatment of various malignancies. Future effective cancer treatments may be made possible by the implanted composite materials utilized in cancer therapy that incorporate chitosan nanostructures.

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