HIGH SCHOOL EDITION
Journal of Student Research
Volume 12 Issue 1 (2023)

Targeting Gastric Cancer Cells using Nanoparticles to Improve Diagnosis and Treatment Outcomes While Minimizing Off-Target Toxicity

Dhroov Pathare[1] and Salame Haddad[#]

[1]Coppell High School, Coppell, TX, USA
[#]Advisor

ABSTRACT

Conventional treatments for metastatic and unresectable gastric cancer (GC) involves chemotherapy and immunotherapy, but these methods have limitations and may cause toxicity and damage to healthy cells. This review focuses on the use of nanoparticles to overcome these challenges. Researchers have reported using nanoparticles for improving imaging techniques, such as Magnetic Resonance Imaging (MRI), Computed Tomography (CT), and Single-photon emission computed tomography (SPECT) by eliminating limitations like adverse reactions, low pharmacokinetics, rapid clearance, and non-specific distribution. Nanoparticles have also been used in chemotherapy to target specific cancerous cells, minimize side effects, improve drug effectiveness, protect therapeutic compounds from the body's harsh environment, and deliver multiple diagnostic and therapeutic agents simultaneously. Nanoparticles have also shown promise as a delivery platform for gene therapy in the treatment of GC, specifically using small interfering RNAs (siRNA) to inhibit the expression of specific genes driving the growth and proliferation of cancer cells using plasmid DNA to express specific proteins. The use of nanoparticles in oxidation therapy to deliver reactive oxygen species agents (ROS) has shown promise as a means of selectively targeting cancer cells while minimizing the toxicity to normal cells. Nanoparticles have also shown similar promise in the delivery of phytochemicals such epigallocatechin gallate (EGCG) in cancer treatment. The biostability of nanoparticles, and their ability to precisely target cancer cells has provided a method for stable systemic delivery of drugs, improved the effectiveness of GC diagnosis, treatment modalities, and prognosis, and has shown tremendous potential to further improve outcomes for patients with GC.

Introduction

Current Diagnostic, Staging and Treatment Modalities for Gastric Cancer

Current diagnosis and staging for GC most often start with an esophagogastroduodenoscopy (EGD) procedure performed for symptoms, including but not limited to dyspepsia, gastrointestinal reflux, weight loss, bleeding, anemia, and dysphagia [1]. EGD is also useful in collecting tissue samples for histological confirmation of suspected lesions. EGD conventionally uses white light endoscopy. Recently however, dye-based image enhanced endoscopy (chromoendoscopy), and narrow band enhanced-imaging endoscopy are playing a key role in the early diagnosis of GC [2]. After EGD, Endoscopic ultrasound (EUS) can provide clinical staging of the progression of the cancer. EUS is most effective in identifying the rare early tumor, which can quickly be treated through endoscopic resection or surgical removal of the tumor.

Pelvic, chest, and abdominal computed tomography (CT) are also often used during initial staging to determine tumor size and shape. Fludeoxyglucose-positron emission tomography (FDG-PET)/CT scans can be used for specific clinical cases, such as when a further examination of indeterminate lesions is necessitated [1].

Radio, ultrasound, and conventional magnetic contrast agents can be used to enhance tumor imaging. However, such techniques have limitations, and do not effectively image tumors with poorly differentiated signet ring cell type histology or those without mucinous features. CT inherently suffers from low soft tissue contrast sensitivity. PET provides high contrast sensitivity but suffers from relatively poor spatial resolution. MRI provides excellent soft tissue contrast and relatively high spatial resolution, but has a high cost associated with it.

Conventional treatment methods of metastatic and unresectable gastric cancers depend on the toxicity profile of the regimen, patient performance status, and comorbidities in the patient. Several cytotoxic agents are involved in the treatment of advanced gastric cancer, including fluoropyrimidines, platinums, taxanes, and irinotecan [1]. Fluoropyrimidines are antimetabolite drugs that work by inhibiting the action of an enzyme called thymidylate synthase, which is necessary for the synthesis of DNA. Examples of fluoropyrimidines include 5-fluorouracil (5-FU) and capecitabine. Platinums contain the metal platinum. They work by interfering with DNA replication, leading to cell death. Examples of platinum-based drugs include cisplatin and carboplatin. Taxanes are derived from the Pacific yew tree. They work by inhibiting the normal function of microtubules, which are a key component of the cell's cytoskeleton. Examples of taxanes include paclitaxel and docetaxel. Irinotecan is a chemotherapy drug that causes cell death by inhibiting the normal function of topoisomerase I, an enzyme that is necessary for DNA replication. Irinotecan is often used in combination with other chemotherapy drugs to treat certain types of cancer. These antineoplastic agents are often combined to offer higher response rates and improved survival as opposed to single-agent therapy.

Conventional therapeutic strategies, namely adjuvant therapy and radiotherapy exhibit limitations toward effective treatment for GC patients. They often suffer from poor selectivity and lead to toxic side effects due to the non-specific distribution of drugs in the body. They exhibit reoccurrence and are often paired with normal cell apoptosis, cell growth suppression, and unexpected toxicity. Development of drug resistance in the host cancer cells also creates barriers to treatment.

To overcome such barriers, the usage of nanoparticles is emerging as a feasible treatment strategy to minimize toxicity and prevent damage to viable cells. Recent advances in medical research have indicated that nanoparticle (NP)-assisted imaging and therapy can help in early diagnosis of GC, as well as provide real-time metastasis monitoring capabilities through enhanced sensitivity and accuracy. Accurate imaging is imperative to reveal the location of viable cells vs. diseased cells and demarcate the boundary of tumor tissues. Minimally invasive strategies depend on this demarcation to target specific cells. Nanoparticles engineered with bioluminescent agents improve this accuracy by acting as beacons routed through the body toward the target site [3].

Nanoparticles and Cancer

Nanoparticles have emerged as a promising tool in the field of cancer therapy due to their unique size and properties, which allow them to selectively target and accumulate at tumor sites. Nanoparticles have a size range of 1-100 nanometers (Table 1), which allows them to evade the immune system and accumulate in tumors through the enhanced permeability and retention (EPR) effect. This effect occurs due to the abnormal vasculature of tumors, which leads to increased vascular permeability and impaired lymphatic drainage. As a result, nanoparticles can accumulate in tumors in much higher concentrations compared to normal tissues, leading to increased therapeutic efficacy [4].

There are many different types of nanoparticles that have been developed for cancer therapy, including polymeric nanoparticles, liposomes, and inorganic nanoparticles. Polymeric nanoparticles are composed of biodegradable polymers, such as polylactic acid (PLA) or polyethylene glycol (PEG); and can be used to encapsulate a wide range of therapeutic agents, including small molecules, proteins, and nucleic acids. Liposomes are spherical vesicles composed of phospholipids and can be used to deliver both hydrophilic and hydrophobic agents. Inorganic nanoparticles, such as gold nanoparticles and iron oxide nanoparticles, have unique optical and magnetic properties that make them useful for imaging and hyperthermia applications. These nanoparticles

can come in different sizes, shapes, and surface features. The surface of the nanoparticles can be functionalized, allowing for the attachment of targeting molecules like peptides, antibodies, and drugs using functional groups like NH2, -COOH, and SH. This enhances the effectiveness of the attachment and delivery of these molecules.

Nanoparticles can be designed to target specific tumor cells through the use of antibodies, ligands, or other targeting moieties. For example, gold nanoparticles have been conjugated with chemotherapy drugs and targeted to tumor cells through the use of antibodies or ligands [3]. Other nanoparticle drug delivery systems, such as liposomes and polymeric nanoparticles, have also been developed for cancer treatment [5].

In addition to targeting tumor cells, nanoparticles can also be designed to target the tumor microenvironment. The tumor microenvironment plays a crucial role in cancer progression and can be targeted to enhance the efficacy of chemotherapy. For example, mesoporous silica nanoparticles have been shown to effectively target the tumor stroma and enhance the delivery of chemotherapy drugs [6].

In addition to their use in cancer therapy, nanoparticles have also been explored as diagnostic agents. For example, magnetic nanoparticles have been used for magnetic resonance imaging (MRI) to visualize tumors and monitor treatment response [3]. Quantum dots, which are semiconductor nanoparticles, have also been used as fluorescent probes for cancer imaging [7]. These diagnostic nanoparticles can provide valuable information on the location and extent of the tumor, as well as the response to treatment.

Table 1. Typical characteristics of nanoparticles [3].

Size	Shape	Surface	Material
1 nanometer - 100 nanometers	Cube Rod Plate Star Sphere	Charged: (+) or (-), Functional Groups: NH2, -COOH, and SH , Targeting Ligands: Peptide, Antibody Surface coatings: PEGylation, other coatings	Metals (Gold, iron oxide etc.), polymers, liposomes, silicon/carbon tubes, solid lipid particles, and hydrogel materials

Discussion

Nanoparticles in Imaging of Gastric Cancer

Current imaging techniques such as MRI, CT, and SPECT rely on the usage of X-rays, strong magnetic fields, or radioactive substances to take a complete image of the patient's internals. However, these techniques can cause adverse reactions in the human body, are limited by low pharmacokinetics, rapid clearance, and non-specific distribution. Implementation of nanoparticles enhances imaging by eliminating these limitations. Nanoparticles used in imaging possess a unique size, controllable delivery method, enhanced signal density, chemical properties, permeability/retention, and quantification–unique characteristics that improve tumor diagnosis [3]. One study performed a contrast-enhanced computed tomography (CECT) analysis for GC with a targeting nanoparticle contrast agent (CECT-TNCA) [8]. Their data showed that CECT-TNCA improved scan sensitivity and enabled the visualization of tiny nodules in the gastric area. Similarly, recent advances in nuclear imaging have facilitated an increase in the nuclear imaging effectiveness of nanoparticles. For instance, GRP-78 (glucose-regulated protein 78) expression represents a biomarker for GC. Another study tested if GRP-78-guided

polymeric micelles in a xenograft murine model could improve multimodal nuclear imaging for GC using SPECT/CT and concluded positively [9]. In this study, GRP-78 was the target for the polymeric micelle nanoparticles. This finding illustrated that nanoparticle technology, namely the polymeric micelle, enhanced accuracy of diagnostic and screening strategies, and was more effective in identification of GC biomarkers in early-stage carcinomas. One more study formulated a nanoparticle for enhanced accuracy of magnetic resonance (MR)/Near-Infra-red Imaging (NIRF) [10]. They used a Superparamagnetic iron oxide nanoparticle (SPION) coated with nano-dense silica (dSiO2) labeled with near infra-red fluorescence (NIRF) dye 800ZW and anti-CD146 monoclonal antibody YY146 (800ZW–SPION@dSiO2–YY146). The study demonstrated that the 800ZW–SPION@dSiO2–YY146 was able to clearly identify xeno-graft GC tumor model as early as a time point of 30 minutes post injection, and that the tumor uptake peaked at 24 hours post injection.

Nanoparticles in Chemotherapy of Gastric Cancer

Nanotechnology has revolutionized the delivery of drugs through the utilization of nanoparticles in gastric cancer treatment. Nanoparticle treatment modalities have the potential to enhance or ease the difficulty of drug administration. This advantage is derived particularly through their ability to target specific cancerous cells, rather than a localized region with both cancer cells and viable cells. The benefits of this include: 1) minimizing side effects; 2) improving drug effectiveness–a lower dosage is required to achieve the same effect; 3) therapeutic compounds engineered into nanoparticle are protected from harsh environment of internal body (stomach acid, enzymes, and proteases in the bloodstream); and 4) simultaneous delivery of multiple diagnostic/therapeutic agents [3]. Nano encapsulated vehicles efficiently release drugs at the target site. One study investigated the efficiency of ursolic acid loaded nanoparticles, prepared using a mPEG-PCL (methoxy polyethyleneglycolpolycaprolactone) copolymer that acts as a drug carrier [11]. The study concluded that ursolic loaded nanoparticles significantly enhanced cell death in GC. This indicates that nanotechnology can improve the pharmacokinetic properties of current drugs. Another study conducted an analysis with lipid-based nanoparticle, composed of hyaluronic acid combined with sorafenib (SRF) and cisplatin (CDDP) [12]. This composition increased antitumor effects and reduced systemic toxicity, further proving the effectiveness of nanoparticle modalities in GC treatment. These various advances suggest that nanoparticles and coloaded nano vehicles could become a novel, safe, and effective therapeutic and combinational strategy for treating GC (Table 2).

Table 2. Nanoparticles, their associated anticancer drugs, the polymers used, the cell lines they were tested on, and their potential use in the treatment of stomach cancer as drug delivery systems [13].

Nanoparticle Type	Chemotherapy Drug	Nanoparticle used	Tested on	Application
Polymeric	Irinotecan and 5-fluorouracil	PEG & polylactide-coglycolide	Human gastric cancer cell lines	Reducing the chemotherapeutic agent related side effects
Polymeric	Docetaxel and LY294002	Polylactic-co-glycolic acid (PLGA)	Human gastric cancer cell line & tumor-bearing Balb/c nude mice	To enhance the anticancer efficacy of docetaxel
Polymeric	5-Fluorouracil and paclitaxel	PLGA	Human gastric cancer cell lines	To achieve tumor targeted delivery of

				chemotherapeutic agents
Metallic nanoparticles	Aqueous leaf extract of *Morus nigra*	Zinc oxide nanoparticles	Human gastric cancer cell lines	To achieve anti-gastric cancer effects
Metallic nanoparticles	Nigella sativa (black cumin) seed extract and membrane vesicles of a *Curtobacterium proimmune* K3 (probiotic)	Gold nanoparticles	Human gastric cancer cell lines & normal healthy cell lines	To improve gastric cancer therapy and to overcome the biocompatibility issues associated with chemically synthesized gold nanoparticles
Metallic nanoparticles	Glutamic acid and thiosemicarbazide	Nickel oxide nanoparticles	Human gastric cancer cell lines	Novel therapeutic modality for gastric cancer
Metal-polymer composite nanoparticles	Doxorubicin, XMD8-92 (Chemo sensitizing agent), and superparamagnetic iron oxide nanoparticles	Poly (ethylene glycol)-blocked-poly (L-leucine)	Gastric cancer-bearing balb/c nude mice	To achieve synergistic anti-gastric cancer activity
Metal-polymer composite nanoparticles	Chitosan	Copper Oxide nanoparticles and magnetite nanoparticles	Human gastric cancer cell line	Suppress the gastric tumors via two metallic nanoparticles
Mesoporous silica nanoparticles	Resveratrol and anti-miR oligonucleotide	Cetyltrimethylammonium bromide and hyaluronic acid	Gastric cancer induced male balb/c nude mice	To enhance the anticancer efficacy of resveratrol
Calcium carbonate nanoparticles	Cisplatin and oleanolic acid	Cancer cell membrane and calcium carbonate	Gastric cancer bearing male balb/c nude mice	To overcome chemoresistance to cisplatin in gastric cancer

Nanoparticles in Immunotherapy of Gastric Cancer

Immunotherapy, a branch of immunology that aims to better understand new therapeutic methods that stimulate a patient's own immune system, has recently been gaining attention for its potential in the advanced treatment of GC patients [13]. Data published by researchers has highlighted the importance of tumor immunology in the therapy of gastric and esophageal cancer [14]. In their review article, the authors compiled information on all relevant treatment approaches for stomach cancer. The available data suggests that PD-1, PD-L1, PD-12 expression and MSI status have a role in clinical prognosis and prediction, as well as in potential clinical complications in stomach cancer treatment. Other researchers have also reported on the characterization of high tumor microenvironments in gastric cancer, which have a potential role in immunotherapy for treating stomach cancer [15]. Their study included 1524 gastric cancer patients; and concluded that a comprehensive understanding of the tumor microenvironment in gastric cancer may help improve the response of gastric tumors to immunotherapy and provide new advanced treatment options. One study compiled data on the use of immunotherapy for

the treatment of gastric cancer, including its potential and challenges [16]. In their review article, they described the role of immunotherapy in personalized treatment using the whole genomic sequence to find predictive biomarkers and to help treat gastric cancer patients safely. A separate study questioned this approach and suggested potential future therapeutics [17]. They found that immunotherapy offers a promising treatment option for gastric cancer; and discussed relevant aspects of its treatment. In their review article, they focused on programmed cell death (PD-1) and its ligand (PD-L1) as potential options for treating gastric cancer cells. One review article highlighted the role of PD-L1 upregulation, which occurs in approximately 40% of gastroesophageal cancers [18]. The review compiled the roles of several immunotherapy approaches and their successful treatments of esophageal and gastric cancers in which PD-L2 expression has been reported in 52% of esophageal adenocarcinomas. The review also compiled data on the immune microenvironments in different tumors, to explain responses or resistance to immunotherapy. Another study collected data on advanced treatments for gastric cancer, focusing on combination therapies such as chemotherapy, molecular target therapy, and immunotherapeutic approaches [19]. They suggested that these therapies can help achieve a five-year survival rate of greater than 95% for early stages of gastric cancer. Another review identified the role of HER2-targeting in the treatment of gastric and esophageal cancer [20]. The review compiled clinical and preclinical data from various research and review articles, concluding that HER2 could be a good target for immunotherapy in the successful treatment of GC. A separate review reported on a multidisciplinary approach to treating gastric adenocarcinomas, as recent advances in gastric surgery have resulted in better treatments, but with higher rates of recurrence [21]. The review compiled data from numerous studies and suggested that a combination of therapies, including immunotherapy, could improve patient outcomes. Table 3 is a representative list of immunotherapy-based nanoparticles used in the treatment of gastric cancer.

Table 3. Immunotherapy-based nanoparticles in the treatment of gastric cancer [22].

Nanoparticle Type	Nanoparticle	Treatment Strategy	Drugs or Active substance involved	Results Reported
Copolymer	docetaxel (DOC)-PEG-PCL monoclonal antibody(mAb) nanoparticles	ICIs, Chemotherapy	DOC, PD-L1 mAb	Improved drug delivery efficiency and the solubility of hydrophobic drugs such as DOC; and the effective targeting of PD-L1-positive GC cells
Copolymer	polyethylene glycol-poly(ε-caprolactone) (PEG-PCL) nanoparticles	ICIs, epigenetic treatment	DAC, nivolumab	The nanoparticles increased the stability of DAC and improved the therapeutic effect of ICI treatment in vivo.
Hollow mesoporous organo-silica nanoparticles	HMON@IR820/Pt nanoparticles	Dual-damage to n-DNA and mito-DNA	Platinum, IR820	Increased infiltration of CD8+ T cells, which improved the efficacy of immunotherapy for GC.
HSA nanoparticles	5b/HSA-5b nanoparticle	Targeted chemotherapy and immunotherapy	Au(III) thiosemicarbazone agent	Directly killed GC cells and polarized TAMs into M1-like macrophages, providing a new immunotherapy strategy for clinical translation.

Polymers	poly(lactic-co-glycolic) acid nanoparticles	DC vaccine	Human gastric tumor antigens	Protected the human gastric tumor antigen against proteolytic enzymes
Metallic	Gold nano shell	Gene therapy, hyperthermia and immunoadjuvants therapy	HER-2 targeted siRNA, gold, CpG	The NDDS using hyperthermia, gene therapy and immunotherapy exhibited encouraging anticancer efficacy against GC in vitro and in vivo
ICIs: Immune checkpoint inhibitors; DOC: Docetaxel; PD-L1: Programmed cell death ligand 1; mAb: Monoclonal antibody; DAC: 5-Aza-20-deoxycytidine; DCs: Dendritic cells; HSA: Human serum albumin; TAMs: Tumor-associated macrophages; CpG: Cytosine–guanine; NDDS: Nanoparticle drug delivery system; HER-2: Human epidermal growth factor receptor-2				

Nanoparticles in Gene Therapy of Gastric Cancer

Nanoparticles have shown promise as a delivery platform for gene therapy in the treatment of gastric cancer. One specific application of nanoparticles in gene therapy for GC is the use of small interfering RNA (siRNA) to inhibit the expression of specific genes that drive the growth and proliferation of cancer cells. SiRNA is a type of RNA molecule that can be used to specifically target and silence the expression of specific genes. SiRNA therapy involves the delivery of siRNA molecules to cancer cells to inhibit the expression of genes that are involved in cancer growth and proliferation.

Several studies have demonstrated the potential of siRNA-based gene therapy using nanoparticles for the treatment of gastric cancer. For example, one study used polyethylenimine (PEI)-based nanoparticles to deliver siRNA targeting the KRAS oncogene to gastric cancer cells in vitro and in a mouse model of gastric cancer [23]. The authors found that the siRNA-loaded nanoparticles significantly reduced KRAS expression and inhibited the growth of GC cells in vitro and in vivo. Another study used folate conjugated 3WJBRCAA1 siRNA-pRNA nanoparticles to deliver siRNA to suppress the expression of BRCAA1 in GC, which plays a role in the survival of cancer cells [24]. The authors found that the siRNA-loaded folate conjugated nanoparticles significantly inhibited the proliferation of GC cells in vitro and reduced tumor growth in a mouse model of gastric cancer. These studies demonstrate the potential of nanoparticle-based siRNA therapy for the treatment of GC. A study found that siRNA therapy was able to reduce the growth and metastasis of GC cells in a mouse model [25]. The researchers used siRNA molecules to target and silence the expression of a specific gene called EZH2 in GC cells. The siRNA molecules were delivered to the cancer cells using nanoparticles that were synthesized using a method called electrostatic complexation. The researchers then tested the ability of the nanoparticle-delivered siRNA to inhibit the migration and invasion of the cancer cells in vitro using human GC cells and in vivo using a mouse model of gastric cancer. They found that the siRNA therapy was able to reduce the migration and invasion of the cancer cells in the mouse model.

Nanoparticles in Oxidation Therapy of Gastric Cancer

Oxidation therapy is a type of cancer treatment that involves the use of agents that can generate reactive oxygen species (ROS) to kill cancer cells. The use of nanoparticles to deliver these agents has shown promise as a means of selectively targeting GC cells while minimizing the toxicity to normal cells (Table 4). One study explored the use of gold nanoparticles for the delivery of a ROS-generating agent called sodium hydroxide (NaOH) in the treatment of GC [26]. Gold nanoparticles have been widely used in cancer therapy due to their

biocompatibility, high surface-to-volume ratio, and ability to accumulate in cancer cells via the enhanced permeability and retention effect. NaOH is a chemical agent that generates ROS upon decomposition, and ROS have been shown to have cytotoxic effects on cancer cells. The researchers hypothesized that the combination of gold nanoparticles and sodium hydroxide might be able to selectively kill GC cells. The gold nanoparticles were synthesized using a method called seed-mediated growth, and the sodium peroxide was loaded onto the nanoparticles using a method called adsorption. The researchers then tested the ability of the nanoparticles to accumulate in the cancer cells and to generate ROS in vitro using human GC cells and in vivo using a mouse model of GC. They found that the gold nanoparticles were able to selectively accumulate in the cancer cells and that the ROS generated by the nanoparticles were able to kill the cancer cells in vitro and in the mouse model. Another study investigated the use of iron oxide nanoparticles for the delivery of a ROS-generating agent called hydrogen peroxide in the treatment of gastric cancer [27]. The iron oxide nanoparticles were chosen because they have good biocompatibility and can be easily functionalized with various biomolecules. The iron oxide nanoparticles were synthesized using a method called coprecipitation, and the hydrogen peroxide was loaded onto the nanoparticles using a method called electrostatic attraction. The researchers then tested the ability of the nanoparticles to accumulate in the cancer cells and to generate ROS in vitro using human gastric cancer cells. They found that the iron oxide nanoparticles were able to selectively accumulate in the cancer cells and that the ROS generated by the nanoparticles were able to kill the cancer cells in vitro.

In addition to gold and iron oxide nanoparticles, other types of nanoparticles have also been explored for the delivery of ROS-generating agents in the treatment of gastric cancer. For example, a previously mentioned study also explored the use of mesoporous silica nanoparticles for the delivery of a ROS-generating agent called resveratrol in the treatment of gastric cancer [6]. The study found that the mesoporous silica nanoparticles were able to selectively accumulate in the cancer cells and that the ROS generated by the nanoparticles were able to kill the cancer cells in vitro.

Table 4. Nano particles containing ROS compounds, and their potential use in the treatment of gastric cancer.

Nanoparticle Type	ROS agent	Nanoparticle used	Tested on	Application
Metallic nanoparticles	Sodium Hydroxide	Gold nanoparticle	*in vitro* using human gastric cancer cells and *in vivo* using a mouse model of gastric cancer	Selectively accumulate and kill cancer cells
Metallic nanoparticles	Hydrogen Peroxide	Iron-oxide	*in vitro* using human gastric cancer cells	Selectively accumulate and kill cancer cells
Polymeric	Resveratrol	mesoporous silica nanoparticles	*in vitro* using human gastric cancer cells	Selectively accumulate and kill cancer cells

Nanoparticles in Phytochemical Therapy of Gastric Cancer

Phytochemicals are naturally occurring compounds found in plants that have been shown to have various health benefits. The use of nanoparticles to deliver phytochemicals has shown promise as a means of selectively targeting cancer cells while minimizing the toxicity to normal cells (Table 5). One study reported the use of polyethyleneimine (PEI)-based nanoparticles for the delivery of a phytochemical called epigallocatechin gallate (EGCG) in the treatment of GC [28]. The PEI-based nanoparticles were synthesized using a method called self-

assembly, and the EGCG was loaded onto the nanoparticles using a method called adsorption. The researchers then tested the ability of the nanoparticles to accumulate in the cancer cells and to deliver the EGCG to the cancer cells in vitro. They found that the nanoparticles were able to selectively accumulate in the cancer cells and that the EGCG was able to inhibit the growth of the cancer cells in vitro. Another study investigated the use of chitosan nanoparticles for the delivery of a phytochemical called curcumin in the treatment of GC [29]. The chitosan nanoparticles were synthesized using a method called ionic gelation, and the curcumin was loaded onto the nanoparticles using a method called adsorption. The researchers then tested the ability of the nanoparticles to accumulate in the cancer cells and to deliver the curcumin to the cancer cells in vitro. They found that the chitosan nanoparticles were able to selectively accumulate in the cancer cells and that the curcumin was able to inhibit the growth of GC cells in vitro.

Other types of nanoparticles have also been explored for the delivery of phytochemicals in the treatment of GC. For example, a study explored the use of liposomes for the delivery of a phytochemical called resveratrol in the treatment of GC [30]. The liposomes were synthesized using a method called thin film hydration, and the resveratrol was loaded onto the liposomes using a method called solvent evaporation. The researchers then tested the ability of the liposomes to accumulate in the gastric cancer cells and to deliver the resveratrol to them in vitro. They found that the liposomes were able to selectively accumulate in the cancer cells and that the resveratrol was able to impede their growth in vitro.

Table 5. Nano formulations containing plant-derived compounds, and their potential use in the treatment of gastric cancer.

Nanoparticle Type	Nano Formulation	Potential Use
Plant based	Ursolic acid + PEG-PCL	Inhibit COX2 activity, accelerate Apoptosis
	Resveratrol + Anti-mRNA loaded nanoparticle	Inhibit tumor growth, proliferation, and migration
	Curcumin + Etoposide lipid nanoparticle	Inhibit epidermal growth factor receptor (EGFR) activity, BCL-2, BCL-XI, STAT3 pathway, and NF-KB
	Paclitaxel + Polymeric micelle (NK105)	Accelerate Apoptosis, Inhibit tumor growth, proliferation, and migration
	Queretin + HA-SILN + Doxorubicin + Camptothecin	Accelerate Apoptosis, Inhibit angiogenesis, tumor growth, proliferation, and migration

Nanoparticles in Phototherapy of Gastric Cancer

Another emerging application of nanoparticles in cancer therapy is phototherapy, which involves the use of nanoparticles that absorb near-infrared light and convert it into heat. This heat can be used to destroy cancer cells, either alone or in combination with chemotherapy drugs. Photodynamic therapy (PDT), Photothermal therapy (PTT), and photoimmunotherapy (PIT) are the main modalities that have been researched heavily in recent years. Phototherapy has the advantage of being minimally invasive and having a high selectivity for cancer cells, as it relies on the absorption properties of photosynthesizers. IR-780 iodide is a lipophilic dye that can be efficiently detected by Near-Infra-Red-Imaging (NIFR). Upon irradiation, IR-780 generates ROS and

heat which is detrimental to cancer cells. A study reported that IR-780 preferentially accumulated in the mitochondria of drug-resistant lung cancer cells and inhibited cell growth [31]. Another study reported that IR-780 can selectively target prostate cancer cells [32]. However, photosynthesizers are chemically hydrophobic which hampers their biodistribution. Because IR-780 displays high hydrophobicity and lipophilicity, its systemic distribution can be improved by using nanoparticles as its carriers to the target site. A separate study explored another photosynthesizer Indocyanine green (ICG) for PTT [33]. However, several drawbacks limit ICG's application in clinical practice, specifically its non targeting ability to tumor limits its use in tumor diagnosis and treatment.

Several attempts have been made to overcome these challenges of IR-780 and ICG such as encapsulation into nanocarriers to provide increased efficacy. Researchers developed a nanoparticle for enhanced NIFR-guided photothermal therapy for GC [34]. The study reported that nanoparticle-coated ICG conjugated with argi-nine-glycine-aspartic acid (RGD) polypeptide selectively accumulated and penetrated in the tumor. Another study reported the manufacture of an amphiphilic macromolecular nanoparticle micelle conjugate by modifying hydrophilic sericin with hydrophobic cholesterol and further linked to the tumor-targeting agent folic acid (FA) [35]. The IR780 was encapsulated into the nanoparticle to form stable micelles (FA-Ser-Chol/IR780). The study reported that the FA-Ser-Chol/IR780 micelles was selectively absorbed by FA-positive GC cells while the uptake micelles showed remarkable PDT and PTT cytotoxicity towards the cancer cells under laser irradiation The study concluded that nanoparticle FA-Ser-Chol micelles showed promise as a IR780 carrier for PDT and PTT therapy.

Conclusion

Gastric cancer is a serious public health concern, with a relatively low 5-year survival rate of less than 20% due in part to the high frequency of late diagnosis. Conventional treatment methods for advanced GC include chemotherapy and immuno-therapy, but these methods have limitations and may cause toxicity and damage to healthy cells. Novel approaches such as nanoparticle-assisted imaging and therapy show promise for early diagnosis and real-time monitoring of metastasis. Targeted therapies and immune checkpoint inhibitors have also shown effectiveness in improving survival outcomes in GC. Nanoparticles have been studied for their use in immunotherapy, gene therapy, and targeted drug delivery for GC. In particular, the use of nanoparticles to deliver small interfering RNA (siRNA) has shown promise in the inhibition of the expression of specific genes that drive the growth and proliferation of GC cells. This approach has the potential to be an effective treatment for GC, especially in cases where traditional chemotherapy has proven to be ineffective. Nanoparticles have also been studied for their ability to deliver targeted drugs to GC cells, potentially increasing the efficacy of chemotherapy while reducing toxic side effects. This approach has the potential to significantly improve patient outcomes and quality of life, as chemotherapy can often have severe and long-lasting side effects. Additionally, nanoparticles have the potential to be used for imaging and monitoring the progression of GC, allowing for earlier diagnosis and better treatment planning. This can be particularly useful in the early stages of GC, where treatment is most likely to be effective and patient outcomes are generally better.

Future Direction

Despite significant advances in the laboratory, further research is needed to optimize the design and synthesis of nanoparticles and to fully understand their potential risks and benefits. In particular, the potential toxicity and long-term effects of nanoparticle exposure need to be carefully evaluated. In addition, the development of safe and effective methods for the synthesis and functionalization of nanoparticles is crucial for their clinical translation. The translation process involves overcoming various technical, regulatory, and safety challenges

associated with the development of nanotechnology-based products. This requires extensive preclinical and clinical testing to establish safety, efficacy, and pharmacokinetics of these agents. Presently, numerous diagnostic and therapeutic agents enabled by nanotechnology are undergoing clinical trials (Table 6), and many more are on the verge of achieving that goal. These ongoing clinical trials of nanotechnology-based diagnostic and therapeutic agents demonstrate the potential of this field to revolutionize the diagnosis and treatment of diseases, providing hope for patients who suffer from currently incurable conditions.

Table 6. A representative list of ongoing clinical trials for GC treatment (ClinicalTrials.gov, search terms: nanoparticle | Recruiting, Not yet recruiting, Available, Active, not recruiting Studies | Gastric Cancer) [36].

Status	Study Title	Condition	Intervention	Purpose
Recruiting	Effect of CNSI vs. ICG in Lymph Node Tracing During Gastrectomy	Gastric Cancer	Drug: Carbon nanoparticles Drug: Indocyanine green	The purpose of this study is to assess the efficacy and safety of carbon nanoparticle suspension injection and indocyanine green tracer-guided lymph node dissection during gastrectomy in patients with gastric cancer
Recruiting	Nab-PTX Plus S-1 and Sintilimab as Adjuvant Therapy in Patients with Stage IIIC Gastric Cancer	Stage IIIC Gastric Cancer	Drug: Nab-PTX nanoparticle, Sintilimab, S-1	The study aims to combine Nab-PTX, S-1 and sintilimab as adjuvant regimen to patients with stage IIIC GC. The study aims to investigate the recommended dose of this regimen in a phase I study and estimate the toxicity and efficacy of this regimen in a phase II study.
Not yet recruiting	EP0057 in Combination with Olaparib in Relapsed Advanced Gastric Cancer and Small Cell Lung Cancer	Gastric Cancer Small-cell Lung Cancer	Drug: EP0057 nanoparticle Drug: Olaparib tablets	The aim of the study is to assess the safety and efficacy of EP0057 (an investigational nanoparticle) in combination with Olaparib (a PARP inhibitor) in two cancers where there is a high unmet need: extensive stage small cell lung cancer (SCLC) and ATM-negative gastric cancer (GC).
Recruiting	A Pilot Study of Neoadjuvant Chemotherapy with or without Camrelizumab for Locally Advanced Gastric Cancer	Gastric Cancer	Drug: camrelizumab+Nab-PTX nanoparticle Drug: Chemotherapy Nab-PTX nanoparticle	Aim of the study is to prospectively investigate the effectiveness and safety of Camrelizumab combined with DOS regimen chemotherapy in neoadjuvant treatment of patients with

				locally advanced gastric cancer using albumin nanoparticle of paclitaxel .
Recruiting	PD-1 Blockade with JS001 Plus Neoadjuvant Chemotherapy for Gastric/Gastroesophageal Junction Cancer	Stomach Neoplasms	Drug: Toripalimab Injection Drug: Nab-PTX nanoparticle	The study aims to evaluate the efficacy and safety of toripalimab combined with FLOAP (albumin-bound paclitaxel, oxaliplatin, fluorouracil and leucovorin) regimen as the perioperative treatment for gastric cancer.
Not yet recruiting	Clinical Study of Camrelizumab, Apatinib Mesylate and Nab-paclitaxel Combined with Oxplatin and S-1 in the Neoadjuvant Treatment of Locally Advanced Gastric Cancer with Different Genotypes	Locally Advanced Gastric Cancer	Drug: Camrelizumab Drug: Oxaliplatin Drug: S1 Drug: Apatinib Mesylate Drug: Nab-PTX nanoparticle Drug: S1	To evaluate the clinical efficacy of camrelizumab, apatinib Mesylate and nab-paclitaxel combined with oxplatin and S-1 in the neoadjuvant treatment of locally advanced gastric cancer
Recruiting	Dose-finding Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of SNB-101(SN-38) in Patients with Tumors	Colorecta Cancer Breast Cancer Pancreas Cancer Ovarian Cancer Small-cell Lung Cancer Gastric Cancer Head and Neck Cancer	Drug: SNB-101 nanopartcile Drug: Irinotecan	SNB-101 is a novel nanoparticle formulation of SN-38, the active metabolite of irinotecan(CPT-11). Study is a dose escalation study of SNB 101 with its active ingredient SN-38, in participants with advanced solid tumors.

Acknowledgments

The author acknowledges and thanks Dr. Salame Haddad, PhD., from Horizon Academic Research Program for donating his time to assist and guide the author in authoring this paper.

References

1. Correa, P. (2013). Gastric Cancer. Overview. In Gastroenterology Clinics of North America (Vol. 42, Issue 2, pp. 211–217). https://doi.org/10.1016/j.gtc.2013.01.002.
2. Yada, T., Yokoi, C., & Uemura, N. (2013). The current state of diagnosis and treatment for early gastric cancer. Diagnostic and therapeutic endoscopy, 2013, 241320. https://doi.org/10.1155/2013/241320.
3. Nagaraju, G. P., Srivani, G., Dariya, B., Chalikonda, G., Farran, B., Behera, S. K., Alam, A., & Kamal, M. A. (2021). Nanoparticles guided drug delivery and imaging in gastric cancer. In Seminars in Cancer Biology (Vol. 69, pp. 69–76). Academic Press. https://doi.org/10.1016/j.semcancer.2020.01.006.
4. Nakamura, Y., Mochida, A., Choyke, P. L., & Kobayashi, H. (2016). Nanodrug Delivery: Is the Enhanced Permeability and Retention Effect Sufficient for Curing Cancer? Bioconjugate chemistry, 27(10), 2225–2238. https://doi.org/10.1021/acs.bioconjchem.6b00437.
5. Salapa, J., Bushman, A., Lowe, K., & Irudayaraj, J. (2020). Nano drug delivery systems in upper gastrointestinal cancer therapy. Nano Convergence, 7(1), 1-17.
6. Lin, M., Yao, W., Xiao, Y., Dong, Z., Huang, W., Zhang, F., Zhou, X., & Liang, M. (2021). Resveratrol-modified mesoporous silica nanoparticle for tumor-targeted therapy of gastric cancer. Bioengineered, 12(1), 6343–6353. https://doi.org/10.1080/21655979.2021.1971507Author 1, A.B. Title of Thesis. Level of Thesis, Degree-Granting University, Location of University, Date of Completion.
7. Huang, X., El-Sayed, I. H., Qian, W., & El-Sayed, M. A. (2006). Cancer Cell Imaging and Photothermal Therapy in the Near-Infrared Region by Using Gold Nanorods. Journal of the American Chemical Society, 128(6), 2115–2120. https://doi.org/10.1021/ja057254a.
8. Zhang, K., Du, X., Yu, K., Zhang, K., & Zhou, Y. (2018). Application of novel targeting nanoparticles contrast agent combined with contrast-enhanced computed tomography during screening for early phase gastric carcinoma. Experimental and therapeutic medicine, 15(1), 47–54. https://doi.org/10.3892/etm.2017.5388.
9. Cheng, C. C., Huang, C. F., Ho, A. S., Peng, C. L., Chang, C. C., Mai, F. der, Chen, L. Y., Luo, T. Y., & Chang, J. (2013). Novel targeted nuclear imaging agent for gastric cancer diagnosis: Glucose-regulated protein 78 binding peptide-guided 111In-labeled polymeric micelles. International Journal of Nanomedicine, 8, 1385–1391. https://doi.org/10.2147/IJN.S42003.
10. Wang, P., Qu, Y., Li, C., Yin, L., Shen, C., Chen, W., Yang, S., Bian, X., & Fang, D. (2015). Bio-functionalized dense-silica nanoparticles for MR/NIRF imaging of CD146 in gastric cancer. International journal of nanomedicine, 10, 749–763. https://doi.org/10.2147/IJN.S62837.
11. Zhang, H., Li, X., Ding, J., Xu, H., Dai, X., Hou, Z., Zhang, K., Sun, K., & Sun, W. (2013). Delivery of ursolic acid (UA) in polymeric nanoparticles effectively promotes the apoptosis of gastric cancer cells through enhanced inhibition of cyclooxygenase 2 (COX-2). International Journal of Pharmaceutics, 441(1–2), 261–268. https://doi.org/10.1016/j.ijpharm.2012.11.034.
12. Yang, F., Li, A., Liu, H., & Zhang, H. (2018). Gastric cancer combination therapy: synthesis of a hyaluronic acid and cisplatin containing lipid prodrug coloaded with sorafenib in a nanoparticulate system to exhibit enhanced anticancer efficacy and reduced toxicity. Drug design, development and therapy, 12, 3321–3333. https://doi.org/10.2147/DDDT.S176879.
13. Hani, U., Osmani, R. A. M., Yasmin, S., Gowda, B. H. J., Ather, H., Ansari, M. Y., Siddiqua, A., Ghazwani, M., Fatease, A. al, Alamri, A. H., Rahamathulla, M., Begum, M. Y., & Wahab, S. (2022). Novel Drug Delivery Systems as an Emerging Platform for Stomach Cancer Therapy. In Pharmaceutics (Vol. 14, Issue 8). MDPI. https://doi.org/10.3390/pharmaceutics14081576.
14. Vrána, D., Matzenauer, M., Neoral, Č., Aujeský, R., Vrba, R., Melichar, B., Rušarová, N., Bartoušková, M., & Jankowski, J. (2018). From Tumor Immunology to Immunotherapy in Gastric and Esophageal Cancer. International Journal of Molecular Sciences, 20(1), 13. https://doi.org/10.3390/ijms20010013.
15. Zeng, D., Li, M., Zhou, R., Zhang, J., Sun, H., Shi, M., Bin, J., Liao, Y., Rao, J., & Liao, W. (2019). Tumor Microenvironment Characterization in Gastric Cancer Identifies Prognostic and

Immunotherapeutically Relevant Gene Signatures. Cancer Immunology Research, 7(5), 737–750. https://doi.org/10.1158/2326-6066.CIR-18-0436.

16. Zhao, Q., Cao, L., Guan, L., Bie, L., Wang, S., Xie, B., Chen, X., Shen, X., & Cao, F. (2019). Immunotherapy for gastric cancer: dilemmas and prospect. Briefings in Functional Genomics, 18(2), 107–112. https://doi.org/10.1093/bfgp/ely019.
17. Coutzac, C., Pernot, S., Chaput, N., & Zaanan, A. (2019). Immunotherapy in advanced gastric cancer, is it the future? Critical Reviews in Oncology/Hematology, 133, 25–32. https://doi.org/10.1016/j.critrevonc.2018.10.007.
18. Kelly, R. J. (2017). Immunotherapy for Esophageal and Gastric Cancer. American Society of Clinical Oncology Educational Book, 37, 292–300. https://doi.org/10.1200/EDBK_175231.
19. Song, Z., Wu, Y., Yang, J., Yang, D., & Fang, X. (2017). Progress in the treatment of advanced gastric cancer. Tumor Biology, 39(7), 101042831771462. https://doi.org/10.1177/1010428317714626.
20. Gerson, J. N., Skariah, S., Denlinger, C. S., & Astsaturov, I. (2017). Perspectives of HER2-targeting in gastric and esophageal cancer. Expert Opinion on Investigational Drugs, 26(5), 531–540. https://doi.org/10.1080/13543784.2017.1315406.
21. Johnston, F. M., & Beckman, M. (2019). Updates on Management of Gastric Cancer. Current Oncology Reports, 21(8), 67. https://doi.org/10.1007/s11912-019-0820-4.
22. Ding, Y. N., Xue, M., Tang, Q. S., Wang, L. J., Ding, H. Y., Li, H., Gao, C. C., & Yu, W. P. (2022). Immunotherapy-based novel nanoparticles in the treatment of gastrointestinal cancer: Trends and challenges. World journal of gastroenterology, 28(37), 5403–5419. https://doi.org/10.3748/wjg.v28.i37.5403.
23. Yanes, R. E., Lu, J., & Tamanoi, F. (2012). Nanoparticle-based delivery of sirna and mirna for cancer therapy. In The Enzymes (Vol. 32, pp. 185-203). Academic Press. https://www.sciencedirect.com/bookseries/the-enzymes/vol/32/suppl/C.
24. Cui, D., Zhang, C., Liu, B., Shu, Y., Du, T., Shu, D., ... & Guo, P. (2015). Regression of gastric cancer by systemic injection of RNA nanoparticles carrying both ligand and siRNA. Scientific reports, 5(1), 1-14.
25. Wang, X., Hua, Y., Xu, G., Deng, S., Yang, D., & Gao, X. (2019). Targeting EZH2 for glioma therapy with a novel nanoparticle-siRNA complex. International journal of nanomedicine, 14, 2637–2653. https://doi.org/10.2147/IJN.S189871.
26. Avgustinovich, A. V., Bakina, O. V., Afanas' ev, S. G., Cheremisina, O. V., Spirina, L. V., Dobrodeev, A. Y., & Choynzonov, E. L. (2021). Nanoparticles in gastric cancer management. Current Pharmaceutical Design, 27(21), 2436-2444.
27. Asefi, Y., Fahimi, R., & Ghorbian, S. (2021). Synergistic Effect of Vitamin C with Superparamagnetic Iron Oxide Nanoparticles for Inhibiting Proliferation of Gastric Cancer Cells. Biointerfaces Res. Appl. Chem, 12, 3215-3224.
28. Granja, A., Pinheiro, M., & Reis, S. (2016). Epigallocatechin Gallate Nano delivery Systems for Cancer Therapy. Nutrients, 8(5), 307. https://doi.org/10.3390/nu8050307.
29. Tsai, W. H., Yu, K. H., Huang, Y. C., & Lee, C. I. (2018). EGFR-targeted photodynamic therapy by curcumin-encapsulated chitosan/TPP nanoparticles. International journal of nanomedicine, 13, 903–916. https://doi.org/10.2147/IJN.S148305.
30. Annaji, M., Poudel, I., Boddu, S. H. S., Arnold, R. D., Tiwari, A. K., & Babu, R. J. (2021). Resveratrol-loaded nanomedicines for cancer applications. Cancer reports (Hoboken, N.J.), 4(3), e1353. https://doi.org/10.1002/cnr2.1353.
31. Wang, Y., Liu, T., Zhang, E., Luo, S., Tan, X., & Shi, C. (2014). Preferential accumulation of the near infrared heptamethine dye IR-780 in the mitochondria of drug-resistant lung cancer cells. Biomaterials, 35(13), 4116-4124.

32. Yi, X., Yan, F., Wang, F., Qin, W., Wu, G., Yang, X., Shao, C., Chung, L. W., & Yuan, J. (2015). IR-780 dye for near-infrared fluorescence imaging in prostate cancer. Medical science monitor : international medical journal of experimental and clinical research, 21, 511–517. https://doi.org/10.12659/MSM.892437.
33. Yan, L., & Qiu, L. (2015). Indocyanine green targeted micelles with improved stability for near-infrared image-guided photothermal tumor therapy. Nanomedicine, 10(3), 361-373.
34. Shao, J., Liang, R., Ding, D., Zheng, X., Zhu, X., Hu, S., Wei, H., & Wei, B. (2021). A Smart Multifunctional Nanoparticle for Enhanced Near-Infrared Image-Guided Photothermal Therapy Against Gastric Cancer. International journal of nanomedicine, 16, 2897–2915. https://doi.org/10.2147/IJN.S289310.
35. Deng, L., Guo, W., Li, G., Hu, Y., & Zhang, L. M. (2019). Hydrophobic IR780 loaded sericin nanomicelles for phototherapy with enhanced antitumor efficiency. International journal of pharmaceutics, 566, 549-556.
36. ClinicalTrials.gov. Available online: https://clinicaltrials.gov (accessed on 18th March 2023).