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Systematic Review

Nanoparticles Combining Gene Therapy and Chemotherapy as a Treatment for Gastrointestinal Tumors: A Systematic Review

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Abstract: Gastrointestinal cancer is one of the greatest challenges for biomedical research, accounting for one-quarter of diagnoses and one-third of deaths nowadays, due to the existence of drug resistance mechanisms that prevent therapeutic efficacy in advanced stages. Nanotechnology has been shown to be an effective strategy for the evasion of this phenomenon, and gene silencing by siRNA makes it possible to decrease the expression of certain genes involved in chemoresistance and tumor progression. Our review analyzed studies published during the last 5 years that combined siRNA gene inhibition and chemotherapy as treatment of different gastrointestinal tumors. This review was carried out by searching PubMed, SCOPUS and WoS databases, where 49 articles were finally selected. The results showed that simultaneous encapsulation of siRNA targeting different genes involved in cancer and chemotherapy were more effective at the preclinical level compared to the administration of both treatments individually. The cytotoxic effect was generated through increased induction of apoptosis derived from the dysregulation of chemoresistance-related pathways, producing a decrease in tumor volume and an increase in survival of mice in in vivo assays. Therefore, the combination of both therapies in the same nanoformulation appears to be an interesting therapeutic strategy for the treatment of gastrointestinal tumors.

Keywords: nanotechnology; gastrointestinal cancer; siRNA; chemotherapy

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1. Introduction

Gastrointestinal cancer, one of the most common diseases worldwide, has become one of the greatest challenges in medicine and biomedical research [1], with a rising incidence of 151,030 new cases in 2022, but most patients are diagnosed at the late stages of the disease when the tumor cells do not fully respond to therapy. In fact, 50% of patients were already at an advanced stage of metastasis at the time of diagnosis [2] due to the lack of distinctive clinical signs, such as the inexistence of specific markers or symptoms for it, which made its treatment very difficult [3]. Among the neoplasms included in the group of gastrointestinal cancers, we can highlight colorectal cancer, which the literature has emphasized in recent years due to its high recurrence and mortality. Other neoplasms included are esophagus, stomach, liver, pancreas and biliary tract [4]. One of their main problems is the ineffective therapy used nowadays in advanced metastatic cancers due to the existence of several resistance mechanisms that hinder the application of these conventional treatments [5]. In addition, most of the drugs and their combinations generate unwanted side effects in the patient such as 5-fluorouracil cardiotoxicity or oxaliplatin neurotoxicity [6]. Currently, treatment has evolved greatly by integrating procedures such as immunotherapy against specific tumor receptors such as HER2 [7] and focusing on immune checkpoints targeting programmed cell death ligands, such as PD-L1 [2]. T

cells with chimeric antigen receptors [8] and targeted therapies for much more effective individualized treatments, e.g., CRISPR/CAS9 gene-editing, or tumor vaccines [9], were also used, but still with limitations due to outcome variability between patients.

To alleviate the disadvantages, the alternative of using nanoparticles, i.e., structures of less than 100 nm, has emerged as a vehicle element, which has the capacity to increase therapeutic efficacy and reduce toxicity. This is due to the unspecified activity of anticancer agents through specific targeting of the tumor tissue using antibodies or specific binding molecules [10].

Recently, the use of siRNA together with other chemotherapeutics has emerged as a new therapy against tumor development by suppressing the expression of specific genes associated with tumor progression in different cancer cell models, achieving a considerable cell proliferation and migration reduction. In preclinical models, reduced angiogenesis, metastasis and tumor growth compared with individual treatments were observed, obtaining an interesting synergic effect when these two therapies are used together. Despite having a solid preclinical success in some experimental models, these treatments did not have a demonstrable clinical impact due to several factors. Among them, we could highlight the rapid degradation of these siRNAs by RNAases present in the serum of the bloodstream of the patient or the side effects that may be produced by these therapies due to the non-specificity of action. In addition, the inability of these drugs to passively penetrate the cell membrane and the dense and irregular structure of the extracellular matrix (ECM) may render these therapies ineffective. Finally, unencapsulated administration of these therapies may result in macrophage-assisted hepatobiliary excretion and renal clearance, in addition to generating immunogenicity due to the administration of these siRNAs [11–13].

siRNA could be protected and directed by its encapsulation in nanoparticles, optimizing their applicability and overcoming their intrinsic limitations such as lack of specific tumoral direction in vivo or the difficulty of crossing the cell membrane and controlling immunogenicity [13]. It is common to incorporate antitumor chemotherapeutics into treatment to maximize their effect in a reciprocal way, and the use of siRNA in nanoparticles can mediate chemosensitivity and enhance the effects of the drug, and even reprogram the tumor microenvironment [12,14–19]. A wide variety of nanoparticles have also been used for the delivery of these molecules, ranging from polymeric nanoparticles [11] to liposomes [20], to optimize their use in different tumor types and clinical situations.

This systematic review aims to convey the most recent advances in the use of siRNA in nanoparticles for tumor therapy in gastrointestinal cancer, addressing their possible joint use with chemotherapeutics to optimize their efficiency.

2. Materials and Methods

2.1. Study Eligibility

The purpose of this systematic review was to analyze the most recent and relevant information from studies focusing on siRNA-loaded nanoparticles for cancer therapy against gastrointestinal cancer, using another chemotherapeutic, drug or therapy in a complementary and synergistic manner, for example, to increase the chemosensitivity of cancer cells to a particular drug to which they were initially resistant. This review was conducted following the criteria set out in the PRISMA guidelines [21] and it was registered in the OSF database (osf.io) on 12 June 2024. The registration information can be accessed through the following link: https://doi.org/10.17605/OSF.IO/TV7KZ (accessed on 26 July 2024).

2.2. Inclusion Criteria

The systematic review included all scientific publications in article form found in the PubMed, Scopus and Web of Science databases published between 2019 and 2024 and which included, as a fundamental topic, the use of siRNA-carried nanoparticles in gastrointestinal cancer, in any of its subtypes, in combination therapy with other chemotherapeutics or

therapeutic elements to achieve a synergistic effect, reduce chemoresistance or any other effect contemplated in the review.

2.3. Exclusion Criteria

Studies were excluded from the systematic review based on whether they lacked any of the fundamental concepts that were addressed in this study, such as the use of nanoparticles, the use of siRNA or the type of cancer, as they had to have all the requirements to be considered in the study. In addition, studies withdrawn from databases, reviews or book chapters were excluded from the study.

2.4. Data Sources

For the bibliographic search, the electronic databases Pubmed, SCOPUS, and Web of Science were used. The established medical subject heading (MeSH) terms for the search in Pubmed were integrated by: ((((“Colorectal Neoplasms”[MeSH Terms] OR “Gastrointestinal Neoplasms”[MeSH Terms] OR “Esophageal Neoplasms”[MeSH Terms] OR “Intestinal Neoplasms”[MeSH Terms] OR “Stomach Neoplasms”[MeSH Terms] OR “Cecal Neoplasms”[MeSH Terms] OR “Duodenal Neoplasms”[MeSH Terms] OR “Ileal Neoplasms”[MeSH Terms] OR “Jejunal Neoplasms”[MeSH Terms] OR “pancreatic neoplasms”[MeSH Terms] OR “liver neoplasms”[MeSH Terms] OR ((“colon*”[Title/Abstract] OR “colorectal”[Title/Abstract] OR “gastric*”[Title/Abstract] OR “liver”[Title/Abstract] OR “pancreas*”[Title/Abstract] OR “Gastrointestinal”[Title/Abstract] OR “esophageal*” [Title/Abstract] OR “intestinal*”[Title/Abstract] OR “stomach*”[Title/Abstract] OR “cecal*”[Title/Abstract] OR “duodenal*”[Title/Abstract] OR “ileal*”[Title/Abstract] OR “jejunal*”[Title/Abstract]) AND (“cancer*”[Title/Abstract] OR “tumor*”[Title/Abstract] OR “tumour*”[Title/Abstract] OR “neoplasm*”[Title/Abstract] OR “carcinoma*”[Title/Abstract]))) AND (“rna, small interfering”[MeSH Terms] OR “interfering rna small”[Title/Abstract] OR “short interfering RNA”[Title/Abstract] OR “small interfering RNA”[Title/Abstract] OR “shRNA”[Title/Abstract]) AND (“nanoparticles”[MeSH Terms] OR “nanoparticles” [Title/Abstract]) AND (“antineoplastic agents”[MeSH Terms] OR “agents anticancer”[Title/Abstract] OR “agents antineoplastic”[Title/Abstract] OR “agents antitumor”[Title/Abstract] OR “Anticancer Agents”[Title/Abstract] OR “Antineoplastic Drugs”[Title/Abstract] OR “Antineoplastics”[Title/Abstract] OR “Antitumor Agents”[Title/Abstract] OR “Antitumor Drugs”[Title/Abstract] OR “Cancer Chemotherapy Agents”[Title/Abstract] OR “Cancer Chemotherapy Drugs”[Title/Abstract] OR “Chemotherapeutic Anticancer Agents”[Title/Abstract] OR “Chemotherapeutic Anticancer Drug”[Title/Abstract] OR “chemotherapy agents cancer”[Title/Abstract] OR “chemotherapy drugs cancer”[Title/Abstract] OR “drugs antineoplastic”[Title/Abstract] OR “drugs antitumor”[Title/Abstract] OR “drugs cancer chemotherapy”[Title/Abstract] OR “chemotherapy”[Title/Abstract])) NOT “review” [Publication Type]) NOT “systematic review”[Publication Type]) AND (2019:2024[pdat]).

This search formula was subsequently adapted to the SCOPUS and WoS databases for the corresponding systematic searches. All bibliographic information extracted from the searches was stored in the bibliography software Mendeley Reference Manager 2.120.0 (Elsevier, Amsterdam, The Netherlands).

2.5. Study Selection

The selection of included studies was performed in duplicate. J.R.-C. and F.Q. found the relevant literature using the search formula above. Subsequently, the titles and abstracts were observed to select those articles that met the established inclusion criteria. Subsequently, a complete reading of the texts was carried out, selecting for the elaboration of this review those articles that possessed the information sought.

2.6. Data Extraction

The data obtained following a thorough analysis of the selected articles included in the review were presented in different tables indicated in the manuscript. This included information about the type of nanoparticle, the type of gastrointestinal cancer, the siRNA target, the co-therapy drug, whether in vitro and in vivo assays were employed, and the results obtained.

3. Results

3.1. Study Description

After conducting the bibliographic search in the PubMed, SCOPUS, and Web of Science databases, a total of 140 articles were obtained. Subsequently, 44 duplicate articles were excluded and, once analyzed by title and abstract, another 32 articles were excluded, leaving 64 selected. Likewise, 15 of the 64 articles did not meet the inclusion criteria or had low-quality values. Therefore, a total of 49 articles were finally included in the present systematic review. All the data concerning the search are represented in the flow diagram in Figure 1.

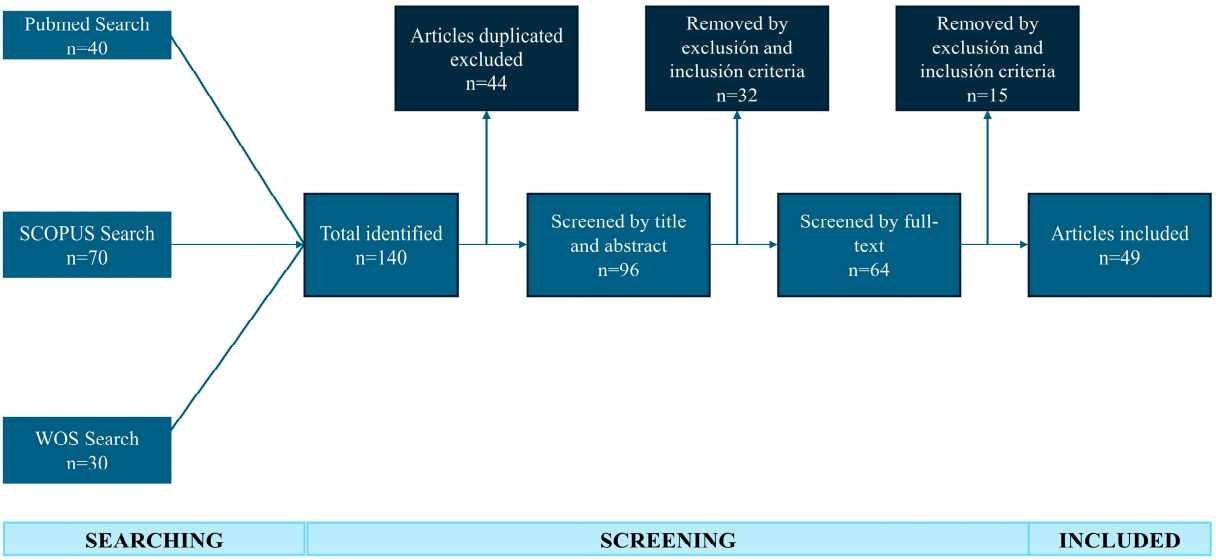

Figure 1. Flow diagram that represents the articles included in the systematic review.

3.2. Nanoparticles for Colorectal Cancer Treatment

Most of the studies included the chemotherapeutic oxaliplatin (OXA) as co-therapy with siRNA. A study performed by Zhou et al. (2022) used DAN nanoparticles as the main nanoplatform, assisted by DOTAP and integrated by PEG5k-b-PLGA11k. This research combined this drug with a siRNA targeting ATP7A, which correlated with oxaliplatin resistance in colorectal cancer (CRC) by reducing the intracellular concentration of the drug. The results of this study were exceptional with an improvement in sensitivity for oxaliplatin and reversed chemoresistance of cancer cells with 40% differential cellular viability between the control and the treated cells. In addition, in an in vivo assay these NPs reduced the tumor volume with the synergic therapy by 96.66% compared to the free OXA [22].

Another study performed by Huang et al. (2023) used OXA as co-therapy with the patient's own endocytic primary exosomes loaded with siRNA against CCDC80, which is associated with liver metastasis and CRC chemoresistance. This treatment produced an 85% apoptosis compared to the individualized treatments in cells. Furthermore, xenograft tumor volume was drastically reduced by up to 70% compared to the free drug [23].

Huang et al. (2022) employed a polyamidoamine (PAMAM) dendrimer modified with methoxylpolyethylene glycol (mPEG) and complexed OXA simultaneously with siRNA against ASPN, which promotes chemoresistance by regulating the Wnt/β-catenin signaling

pathway and ABC transporters. It achieved a 25% cell viability reduction gap between the synergic treatment and the one without siRNA in resistant lines. In in vivo assays, it achieved an 80% reduction in tumoral volume and a 5-fold reduction in tumor weight between oxaliplatin alone and synergic treatment [24].

A study by Hu et al. (2022) used oxaliplatin administered individually with silencing therapy (siLDHA) in a cationic polymeric nanoparticle. In this study, a xenograft tumor volume reduction of up to 33.33% was achieved between synergic treatment and OXA alone. It inhibited the M2-like polarization of tumor-associated macrophages (TAM), which was observed in the CD206 population where it was reduced to only 15–26% of the total versus 35% for the single drug [25].

In addition, Huang et al. (2019) developed cationic lipid-assisted nanoparticles, made of biocompatible block copolymers of poly (ethylene glycol) and block-poly (lactic-co-glycolic acid), to carry an siRNA against IDO1 combined with the drug OXA. This protein was involved in the generation of the immunosuppressive microenvironment by inducing apoptosis of cytotoxic T lymphocytes. This therapy achieved a differential reduction of 65.9–70.4% in the size of in vivo tumors treated with synergistic therapy compared to individual treatments, drastically inhibited primary tumor growth and organ metastasis, and increased the percentage of central memory T and effector memory T cells by up to 1% and 3% in tumor site $CD4^+$ T cells, respectively [26].

Other studies incorporated another drug (simvastatin), like the study carried out by Liu et al. (2023) that used ZIF-8 framework nanoparticles coated with PCBMA (carboxybetaine methacrylate) and siRNA targeting x-CT. This was a protein of the anti-cystine/glutamate carrier system, related to ferroptosis. This nanoformulation produced a reduction of 70% in cell viability in vitro, between synergic treatment at the highest concentration and ZIF-8 alone, and a 6-fold and 10-fold reduction in tumor volume and tumor weight, between synergic treatment and ZIF-8 alone, respectively [27]. On the other hand, Ling et al. (2021) developed polymeric nanoparticles, with DSPE-PEG2k on the shell. It was loaded with siRNA against PD-L1 and encapsulated the drugs carboplatin and digitoxin simultaneously. With this treatment, the IC_{50} of the analyzed cell lines decreased by 67% with the synergistic complete therapy (5.7 ± 1.7 μM) compared to treatments without digitoxin (8.4 ± 4.4 μM). Furthermore, the survival of the mice treated with the synergistic therapy was better (20–24 more days), reducing the overall toxicity and increasing the immunogenicity, reducing the macrophage polarization by 30% [28].

In addition, Manoochehri et al. (2022) employed cationic liposomes, carrying siRNA against COL1A1 pro-α 1 chains of type I collagen of the extracellular matrix associated with poor prognosis in cancer development. The combination with the drugs oxaliplatin and 5-fluoflouracil, co-incorporated after treatment with free-form siRNA, enhanced the antitumor effect of chemotherapy drugs and reversed chemoresistance. The inhibition of COL1A1 was better in the synergic treatment compared to the individual one. Furthermore, the authors observed a 5-fold and 3-fold IC_{50} reduction with the synergic treatment compared to free 5-FU and OXA, respectively [29].

It is also worth highlighting the study carried out by Jia et al. (2023) that employed a polymeric nanocomplex, loaded with siRNA against CCAT1 and Fru. Fru is the vascular endothelial growth factor receptor inhibitor, and it is used as a chemotherapeutic to inhibit epithelial–mesenchymal transition and increase drug chemosensitivity to exert antitumor and antiangiogenic effects. With this treatment, the co-loaded nanocomplex reduced the cell migration and viability ratio to almost half that of the untreated control and 20–30% that of the individualized treatments. Tumor volume was reduced by almost 1500 mm^3 [30].

Two of the studies analyzed incorporated doxorubicin (DOX) simultaneously with siRNA in the same nanovector. Shen et al. (2023) used poly (lactic-coglycolic acid) nanoemulsion, targeting cancer-associated fibroblasts via N-cadherin capped aptamer (NC3S) and carrying siRNA against HGF (hepatocyte growth factor) to facilitate drug entry into the CAF-induced tumor microenvironment and regulate it [31]. The clonogenicity with this treatment was reduced by up to 200% compared to the untreated control, and the in vivo

tumor weight was reduced by up to almost 50% and tumoral volume to 75% with the complete treatment compared to the individual treatments.

In addition, the study carried out by Salehi Khesht et al. (2021) employed chitosan lactate nanoparticles functionalized by the HIV-1-derived TAT peptide, which greatly increases the rate of cell penetration, and hyaluronate (linkage to CD44). This treatment reduced the side effects of DOX, stimulated anti-tumor immune responses and reduced the DOX IC_{50} from 1097 to 451 nM. In in vivo assays, the tumor growth was reduced by 200% in the NP compared with the chemotherapeutic, with increased granzyme B, IFN-γ, and IL-17 secretion and decreased IL-4 and IL-10 levels [32].

In addition, Zou et al. (2021) encapsulated docetaxel combined with RelA siRNA treatment in cyclodextrin nanoparticles PEGylated and linked to a target of the folate receptor. In this study, a 95% cytotoxicity in tumor cell viability was achieved with the synergistic treatment in vitro and a 75% reduction in tumor volume between the synergic full treatment and the individual chemotherapeutic agent and siRNA [33]. On the other hand, Chen et al. (2020) produced NPs encapsulating Cu^{2+} ions, which catalyze reactions with glutathione, converting H_2O_2 to ^{-}OH. In addition, they encapsulated siRNA against VEGF (siVEGF). The combined therapy increased the survival rate of mice with xenografts to 80% after 40 days of treatment, 55% more than the best result with individualized therapies without gene silencing. The $CD4^+$ and $CD8^+$ T-cell population increased by up to 5-10% compared to incomplete therapy without gene silencing [34].

Ray et al. (2020) used a combination of doxorubicin (DOX) and aspirin together with siRNA-Bcl2 co-administered in the same nanoformulation. Within this treatment, the simultaneous administration of DOX, aspirin and siRNA, at an effective concentration of 10 µg/mL overall, achieved greater in vitro cell viability decline in cancer lines compared to the individual drugs. Furthermore, in vitro cellular uptake of the co-therapy improved 6-fold compared to the control, and G2/M arrest was higher in the synergistic therapy 2.5- and 3.6-fold over the individual drugs [35]. Meanwhile, Meng et al. (2022) used paclitaxel as a co-therapy with siRNA against PD-L1, with the aim of inducing anti-tumor immunity. This study achieved a 45% reduction in cell viability in the synergic treatment compared to the nanoparticle alone. Also, in an in vivo xenograft model, the therapy induced a strong antitumor immunity with synergic treatment with a 66% reduction in tumor volume compared to the treatment with the chemotherapeutic agent alone [36].

Another study performed by Chen et al. (2023) used the FuOXP (combination of 5-FU and OXA) prodrug encapsulated in an amphiphilic polymer (PMBOP), with a 1-octadecene lipid motif as a nanocarrier, with a hydrophobic core and surface coating and a mixture of chondroitin sulfate (natural ligand for CD44) and PEG (polyethylene glycol). This system co-delivers an siRNA against Xkr8, which is associated with tumor immunosuppression. This strategy achieved a 17% increase in caspase-3 levels compared with the full treatment and produced an increase of 20% in annexin V levels compared with the prodrug treatment. The in vivo results were also interesting, producing a drastic inhibition of tumoral growth with a 15% decrease in tumor volume with the full treatment in contrast with the siRNA alone [37].

Another study performed by Shahidi et al. (2022) encapsulated regorafenib and quercetin separately through a biodegradable polymeric hybrid nanoparticle, constructed from mPEG-PCL and cationic lipid DDAB, and a shell coated with siRNA specific against a5B1. The NP treatment achieved a 20% and 55% decrease in the IC_{50} compared to the drugs regorafenib and quercetin, respectively, demonstrating the in vitro synergistic potential of these nanoplatforms [38].

The last study, carried out by Babaei et al. (2020), used camptothecin, a topoisomerase I inhibitor, in simultaneous administration with a plasmid encoding for a specific shRNA against survivin as a synergistic therapy element, both encapsulated in the same NP. This strategy showed an 80% decrease in cell viability with full synergistic therapy, twice that achieved with the free drug (40%). Moreover, the mean final tumor burden volume of the

synergistic treatment was reduced by 78.6% compared to over 40% with the no-surface-aptamer treatment and compared with the treatment with only the free drug [39].

For the treatment of colorectal cancer, many different chemotherapeutics and siRNA gene-silencing targets have been used, some of which have been reported in this systematic review. We can highlight the use of more conventional chemotherapeutics such as sorafenib, which is widely used to stop the spread of cancer cells, or newer drugs such as Cu^{2+} ions, which catalyze reactions with glutathione, converting H_2O_2 to ^{-}OH, generating a toxic response in tumor tissue. Among the gene targets silenced by siRNA, we can highlight CCAT1 or IDO1, both linked to molecular pathways involved in cell proliferation and chemoresistance. In each of the articles reviewed, strong in vitro and in vivo results were observed, significantly reducing cell viability and migration, reducing tumor volume compared to the administration of the individual treatments and even modifying the immunogenic microenvironment of the tumor. Each of these articles presents a potential preclinical therapy for the treatment of this type of neoplasm (Table 1).

Table 1. Nanoparticle-siRNA-drug strategies developed for colorectal cancer treatment.

Nanoformulation (Loading Method)	Chemotherapeutic Agent	siRNA Target	Targeting Ability	In Vitro Results	In Vivo Results	Ref.
DOTAP (double emulsion solvent evaporation technique)	OXA	ATP7A	PEGylated structure (passive)	Improved cytotoxicity compared to the free drug due to OXA sensibilization and apoptosis induction (70%).	A 96.66% reduction in tumor volume in synergic therapy compared with free OXA.	[22]
Patient endocytic primary cell-derived exosomes (transfection)	OXA	CCDC80	NS	Decreased cell proliferation and increased apoptosis induction.	The combined treatment reduced the tumor volume by 90% compared to the individual treatments.	[23]
PPO (NS)	OXA	ASPN	PEGylated structure (passive)	Cell viability reduction and 7.5-fold IC_{50} decreased reduction between the synergic treatment and the one without siRNA in resistant lines.	A 95% reduction in tumoral volume between OXA alone and synergic treatment.	[24]
PAPEI (NS)	OXA	LDHA	PEGylated structure (passive)	Inhibition of M2-like polarization of TAMs and amplified OXA-induced autophagy.	A 33.33% tumoral volume reduction between synergic treatment and OXA alone.	[25]
CLAN made of biocompatible PEG-b-PLGA and cationic lipids (double emulsion method)	OXA	IDO1	NS	Increased percentage of central memory T and effector memory T cells by up to 1% and 3% in tumor site $CD4^{+}$ T cells.	A 70.4% and 65.9% tumoral volume reduction with the synergic treatment when compared with those receiving free OXA and siIDO1, respectively.	[26]
ZIF-8 covered by PCBMA (NS)	Simvastatin	x-CT (subunit SLC7A11)	NS	Improved cytotoxicity in the combined therapy.	A 6-fold reduction in tumor volume between synergic treatment and ZIF-8 alone.	[27]
DSPE-PEG2k in the cover (microemulsion)	Digitoxin and carboplatin	PD-L1	NS	IC_{50} decreased by 1.8-fold and caspase 3/7 increased expression, inducing apoptosis.	A 4-fold reduction in tumor volume between synergic treatment and siRNA alone.	[28]
As1411 aptamer-conjugated cationic liposomes (NS)	OXA and 5-FU	COL1A1	Nucleolin AS1411 aptamer (active)	Lower COL1A1 expression, decreased cell proliferation and 5-fold and 3-fold IC_{50} reduction compared to free 5-FU and OXA.	-	[29]

Table 1. *Cont.*

Nanoformulation (Loading Method)	Chemotherapeutic Agent	siRNA Target	Targeting Ability	In Vitro Results	In Vivo Results	Ref.
PEI-PDLLA (two-time hydration method)	Fru	CCAT1	PEGylated structure (passive)	A 50% reduction in cell proliferation between the synergic treatment and Fru alone.	A 3-fold reduction and 50% inhibition rate of tumor growth in tumor volume between synergic treatment and Fru.	[30]
Nano-emulsion of PLGA with NC3S (solvent evaporation method)	Doxorubicin	HGF	Aptamer over N-Cadherin	A 5-fold reduction in the number of colonies between the combined treatment and doxorubicin alone.	In vivo tumor volume was reduced 4 times between full treatment and doxorubicin alone.	[31]
CL-TAT-HA (NS)		CD73	Hyaluronate (active) and HIV-1 derived peptide (active)	A 58.88% decrease in IC_{50} of DOX with the synergic treatment compared to doxorubicin alone.	A 64.28% reduction in tumor volume and 20% reduction in necrotic area between free chemotherapeutic and synergic treatment, with an increase in granzyme B, IFN-γ, and IL-17 secretion and a decrease in IL-4 and IL-10 levels.	[32]
CD nanoparticle modified with FA (rehydration and evaporation method)	Docetaxel	RelA	PEGylated folate structure (passive)	A 95% reduction in tumor cell viability between the full treatment and the treatment without siRNA.	A 75% reduction in tumor volume between the synergic full treatment and the individual chemotherapeutic agent and siRNA.	[33]
HLBBRT NPs (rehydration and evaporation method)	Cu^{2+} ions	VEGF	PEGylated structure (passive) and azobenzene derivative (passive)	A 30% reduction in cell viability test with the complete synergic therapy compared to control and 50% reduction in GSH levels between the complete synergic therapy and the free siRNA.	An 80% increased survival rate of mice with xenografts at 40 days compared to the non-survival of the free siRNA, content of Tregs in tumor was reduced by 81% with the synergic treatment compared to controls.	[34]
bPEI (NS)	Doxorubicin and aspirin	Bcl-2	NS	Decreased cell survival and increased apoptosis induction and ROS generation. Induction of G2/M cell cycle arrest.	Not performed	[35]
2E′ (NS)	Paclitaxel	PD-L1	NS	Increased cell cytotoxicity compared with the NP alone.	A 30% reduction in tumor volume at 20 days with the synergic treatment, increased immunoreactive phenotype in TME, as well as tumor-specific T-cell responses with an increased $CD8^+$ T cell infiltration into tumors of about 6-fold with the full treatment with respect to the chemotherapeutic agent alone.	[36]
PMBOP-CP (NS)	FuOXP	Xkr8	Lipidic motif in the polymeric structure (active)	Increased caspase-3 and annexin V levels in the combined treatment compared with the free drug.	Additional 15% decrease in tumor growth compared with the treatment with siRNA alone, increased $CD45^+$ cells by 30% and Treg cells by 20%, compared to siRNA treatment alone.	[37]

Table 1. *Cont.*

Nanoformulation (Loading Method)	Chemotherapeutic Agent	siRNA Target	Targeting Ability	In Vitro Results	In Vivo Results	Ref.
DDAB-mPEG-PCL (nanoprecipitation method)	Regorafenib and Quercetin	A5B1	PEGylated structure (passive)	Decreased the regorafenib and quercetin IC_{50} in resistant cell lines by 20% and 55%, respectively, compared with the free drugs.	Not performed	[38]
Apt-PEG@MSNR-CPT/Sur (sonication)	Camptotecine	Survivine	PEGylated (passive) and AS1411 TAT aptamer (active)	Increased cell cytotoxicity and apoptosis induction compared with the free drug.	Final tumor volume with the synergistic treatment was reduced by 78.6% compared with the free drug. Survival rate with synergic treatment was 100%, doubling the free drug.	[39]

Apt-PEG@MSNR-CPT/Sur (PEG rod-shaped mesoporous silica nanoparticle); bPEI (amphiphilic polymer with modified ramified polietilenimine); CD (amphiphilic cationic cyclodextrin); CLAN (cationic lipid-assisted nanoparticles); CL-TAT-HA (chitosan lactate nanoparticles (composed of chitin acetylation and N-acetyl-D-glucosamine (acetylated unit) and α-(1-4)-linked D-glucosamine) functionalized by HIV-1-derived TAT (trans-activating transcriptional activator) peptide and hyaluronate (HA)); DDAB-mPEG-PCL (polymeric hybrid nanoparticles built with mPEG-PCL and cationic lipid DDAB, a quercetin core); DSPE-PEG2k (polymeric with 1,2-diestearoil-sn-glicero-3-fosfoetanolamine-N-[methoxy(poliethylenglicol)-2000]); DOTAP (DAN, PEG5k-b-PLGA11k (LA/GA = 75/25)-1,2-dioleoil-3-trimetilamonio-propan); 2E′ (polyethyleneimine-acid lithocholic conjugate, with hydrophobic core and cationic surface); FA (PEGylated Folate); Fru (endothelial vascular growth factor receptor inhibitor); 5-fu (5-fluoracile); HLBBRT NPs (hypoxia-activated liposome-supported metal polyphenol gene bio-nanoreactor (azobenzene derivative) with IR780 photosensitizer as the hydrophobic part and polyethylene glycol as the hydrophilic chain); NS (non-specified); OXA (oxaliplatin); PAPEI (cationic polymer APEG-PAsp); PCBMA (carboxybetaine methacrylate); PEG-b-PLGA (poly (ethylene glycol)-block-poly(lactic-co-glycolic acid); PEI-PDLLA (polymeric nanocomplex of polyethyleneimine and poly-1,2-diesteraoil-snglicero-3-fosfoetanolamine-N-[methoxypolyethylenglicol]); PLGA (poli coglycolic-lactic acid); PMBOP-CP (polymeric amphiphilic, with hydrophobic core and a PEG and chondroitin sulfate; PPO (polyamidoamine dendrimer modified with metoxylpolyethylenglicol); ZIF-8 (Zeolitic Imidazolate-8).

3.3. Nanoparticles for Liver Cancer Treatment

Most of the studies included the chemotherapeutic DOX in conjunction with siRNA, such as the one carried out by Tian et al. (2019) that employed DSPE-PEG-PEI nanoparticles, with glycyrrhetinic acid-modified hyaluronic acid, to carry siRNA against Bcl-2. This study achieved a decrease in Bcl2 protein expression with the combination therapy. In addition, an in vivo study performed in mice with the synergistic RNAip/DOX/GH-DPP treatment produced a reduction in the tumor volume by 90% compared with the free drug [40].

On the other hand, Wu et al. (2022) employed a hydrophobic core–shell nanoparticle loaded with DOX and siTOX to increase $CD8^+$ T-cell infiltration and achieve tumor inhibition. The treatment achieved a 17% increase in apoptosis rate with the synergic treatment compared to DOX alone and a 50% reduction in relative tumor volume. Finally, the TNF-α and IFN-γ expression increased 200% and 100% compared to chemotherapeutic alone [41].

Another study employing doxorubicin is the one carried out by Yuan et al. (2023), which used a copolymeric nanoplatform loaded with DOX and siADP6. It obtained a reduction in tumoral cell viability and a higher apoptosis rate and inhibition rate of tumoral volume [42]. Furthermore, another study that used doxorubicin was performed by Leboeuf et al. (2020). They employed lipid nanoparticles co-carrying siRNA against UBR1, UBR2, UBR4 and UBR5 to induce the downregulation of cell migration and proliferation in liver cancer cells. With this strategy, a concentration of 0.25 nM of each siRNA resulted in a 70–80% decrease in in vitro expression of UBR1, UBR2, UBR4 and UBR5 after 72 h of exposure. In an in vivo assay, the nanoformulation induced a 75–90% reduction in the expression of these genes in the mice liver and reduced the tumor proliferation by up to 20%. In addition, the proportion of neutrophils, eosinophils and macrophages,

with high Ly6C content, in the livers of the in vivo model increased between 11.5 and 13.5% compared to the untreated controls [43].

Finally, Yan et al. (2020), developed pH-sensitive chitosan micelle-based nanoplatforms prepared with glycyrrhetinic acid grafts on their surface loaded with siBcl2 and DOX as a tumor inhibition strategy. Furthermore, the cotreatment increased the apoptosis rate by 8.5% compared to the double administration of the siBcl2 and DOX independently. Finally, a difference in tumor volume growth of 50% was observed between combination therapy and free drug administration, with a tumor inhibition rate of 88% [44].

The chemotherapeutic agent sorafenib was also used in the treatment of liver cancer. Chen et al. (2024) employed TAT-poly-SS-lysine-modified chitosan nanoparticles to co-deliver siPD-L1 and sorafenib. The apoptosis rate was higher in the groups treated with the complete synergistic therapy compared to the administration of the free drugs, reaching a 73% retention of the nanoplatform in the blood circulation with the synergistic therapy. Also, this combined treatment showed a better in vivo antitumor effect, with a tumor inhibition rate of 90.2 ± 3.5% compared to the untreated controls [45].

On the other hand, Younis et al. (2021) employed ultra-small lipid nanoparticles, co-loading sorafenib and siMK. The in vivo results showed a 68.33% tumoral volume reduction in vivo at the end of treatment compared to the synergistic therapy at half the concentration [46].

Furthermore, the study carried out by Chen et al. (2020) employed cytoplasmic enzyme-degradable porous biological nanospheres with hydrophobic cavity using RNA as a building block and cyclodextrin to load sorafenib and siRNA against EpCAM as a combination therapy. This study achieved a general reduction in cell viability with 90% compared to the untreated cells. In addition, the apoptosis rate increased to almost 20% compared to the free drug. In in vivo assays, the NP produced a 3-fold decrease in the tumor volume compared to the treatment using the nanoparticle and the aptamer alone [47].

In addition, Younis et al. (2019), developed pH-sensitive lipid nanoparticles modified with a SP94-targeted peptide for liver cancer cells loaded with siMK and sorafenib (SOR) as combined therapy. In this study, the IC50 for SOR + MK-siRNA decreased to 5 ± 1.50 μM, lower compared to the IC50 obtained with control SOR + siRNA at 9 ± 2.20 and with gene silencing alone at 17 ± 2.60 μM [48].

Punuch et al. (2022) encapsulated a combination of sorafenib and sunitinib through PVA-emulsified polymeric PLGA nanoparticles, co-loaded with siAFP as combination therapy against hepatocellular carcinoma. With this strategy, the cell viability with the complete combination therapy with sorafenib 2.5 μM decreased to 39.29 ± 2.72%, whereas it decreased to 44.04 ± 3.05% when combined with 5.0 μM sunitinib. Furthermore, caspase 3/7 activity increased by up to 300% with sunitinib therapy and 200% with sorafenib 5.0 μM compared to no increase with sorafenib at 2.5 μM [49].

Other studies used cisplatin as chemotherapy encapsulated in its nanoparticles. Huang et al. (2023) used a metal-organic framework nanocarrier, with a nuclear localization sequence (NLS) as the core and A54 peptide on the shell, coloaded with NOR1 shRNA. These NPs achieved a decrease in cancer cell viability of cisplatin-resistant cells of 90% in contrast to the 70% achieved with the free drug at the highest possible concentration. In the in vivo results, the group treated with the synergistic strategy showed inhibited tumor growth with an inhibition rate of 75 ± 5% [50].

Meanwhile, Li et al. (2019) developed calcium phosphate nanoparticles with an asymmetric lipid bilayer coating loaded with cisplatin and siBmi-1 as antitumor therapy. The combined treatment induced a 20% increase in cell death compared to the free drug. In the in vivo xenograft model, the group treated with the synergistic therapy achieved the greatest inhibition of tumor growth with a final volume of 380.62 ± 100.34 mm3 in contrast to 1271.69 ± 59.69 mm3 for siRNA therapy [51].

Huang et al. (2019) employed arsenic trioxide as a primary drug in Zinc arsenite NPs involved in a SiO_2 matrix to co-deliver siRNA against SHP-1. These NPs promoted

apoptosis and significantly inhibit proliferation, migration, and invasion of tumor liver cells compared to the free drugs. With this strategy, the apoptosis was increased by 39% compared to chemotherapeutic alone. In the in vivo assay, the synergistic therapy inhibited tumor growth 2.2-fold and metastasis 3.5-fold compared with individual therapies [52].

Another chemotherapeutic drug employed was Adriamycin. Zhao et al. (2020) employed NPs co-loaded with siRNA against T-type Ca^{2+} channels and Adriamycin, with the objective of decreasing intracellular Ca^{2+} concentration and increasing chemosensitivity to Adriamycin. This study achieved an 80% cell viability decrease using synergistic therapy, increasing the cytotoxic potential compared with the NP encapsulating siRNA alone. In a xenograft model, the combined therapy produced a 60% inhibition in the tumor volume compared with the NP-siRNA that did not encapsulate the drug [53].

Finally, it is noteworthy that the use of imidazole through nanoplatforms, based on spherical carboxylate metallodendrimers, encapsulated simultaneously with siRNA against Mcl-1 as combination therapy. This study achieved a promoted entry of Mcl-1 siRNA into HEPG2 cancer cells and promoted lower IC50 values compared to the free drug [54].

In liver cancer, many different chemotherapeutics and siRNA gene-silencing targets have been reported in this systematic review. We can highlight the use of conventional chemotherapeutics such as doxorubicin, widely used as a DNA intercalator to reduce the proliferation of cancer cells, or newer primary drugs such as arsenic trioxide, to promote apoptosis and proliferation reduction in tumor cells. These drugs were combined with various silencing targets such as SHP-1 or NOR1, disabling cellular pathways linked to cell proliferation and resistance (Table 2).

Table 2. Nanoparticle-siRNA-drug strategies developed for liver cancer treatment.

Nanoformulation (Loading Method)	Chemotherapeutic Agent	siRNA Target	Targeting Ability	In Vitro Results	In Vivo Results	Ref.
DSPE-PEG-PEI with hyaluronic acid modified with glicerretinic acid (dialysis)	Doxorubicin	Bcl-2	PEGylated (passive) and hyaluronate (active) structure	In vitro time-dependent sustained release, GA receptor-mediated internalization significantly increased cellular uptake efficiency, enhanced cell apoptosis and exhibited enhanced antitumor effect.	A 10-fold tumoral volume reduction between the synergic treatment and the chemotherapeutic agent alone.	[40]
FD/FM@siTOX (nanoprecipitation)	Doxorubicin	TOX	Cationic cytolytic peptide in the surface (active)	A 17% increase in apoptosis rate with the synergic treatment compared to doxorubicin alone.	A 72.73% tumoral volume reduction between the synergic treatment and doxorubicin alone, TNF-α and IFN-γ increased by 200% and 100% compared to the chemotherapeutic agent alone, respectively.	[41]
mPEG-PLys-PDPA (NS)	Doxorubicin	ADP6	PEGylated structure (passive)	A 40% cell viability reduction with synergic treatment compared to the one without siRNA and 51.31% increased apoptosis rate in contrast with the treatment without chemotherapeutic.	Not performed	[42]
Lipidic nanoparticles (micro-fluidization)	Doxorubicin	UBR1, UBR2, UBR4 and UBR5	NS	High decrease (75–90%) in in vitro expression of UBR1, UBR2, UBR4 and UBR5 and 20% decrease in cell proliferation.	Increased apoptotic rate (11.5–13.5%) compared to controls and 80% decrease in tumor volume.	[43]

Table 2. *Cont.*

Nanoformulation (Loading Method)	Chemotherapeutic Agent	siRNA Target	Targeting Ability	In Vitro Results	In Vivo Results	Ref.
pH-sensitive chitosan micelle (NS)	Doxorubicin	Bcl-2	Glycyrrhetinic acid motifs (Active)	Increased cytotoxicity compared to the administration of DOX and siRNA independently and increased apoptotic rate (34.3% vs. 25.8%) compared to the same condition.	A 55% tumoral volume reduction with the synergic full treatment compared to the chemotherapeutic agent alone, with a tumor inhibition rate of 88%.	[44]
Chitosan modified with TAT-Poli-SS-Lysine (dialysis)	Sorafenib	PD-L1	NS	Higher repression of some proliferation markers like VEGF and resistance markers like P-GP. Higher apoptosis rate.	A 73% retention of the nanoplatform in the blood circulation with the synergistic therapy and better antitumor effect, with a tumor inhibition rate of 90.2 ± 3.5%	[45]
Ultra-small lipid nanoparticles with a fusogenic cover and a selective peptide (micro-fluidization)	Sorafenib	MK	Targeting peptide SP94 in the surface (active)	Not performed	A 66.66% tumoral volume reduction between synergic full treatment and chemotherapeutic alone.	[46]
Porous biological nanospheres with a hydrophobic cavity and cyclodextrin as an adhesive with an aptamer of EpCAM (hybridation and thermal shock)	Sorafenib	EpCAM	EPCAM aptamer (active)	A 90% reduction in the cell viability and 20% apoptosis increase compared to the untreated control.	A 4-fold tumor volume reduction between full treatment and nanoparticle with aptamer alone.	[47]
pH-sensitive lipid nanoparticles consisting of a novel lipid, YSK05, modified with a targeted peptide SP94 selective for liver cancer cells (sonication)	Sorafenib	MK	Targeting peptide SP94 in the surface (active) and PEGylated structure (passive)	Decreased Sorafenib IC_{50} in the combined therapy compared to the drug alone and 27-fold higher encapsulation of the drug inside the tumoral cell.	Not performed	[48]
Polymeric PLGA nanoparticles (double emulsion method	Sorafenib and Sunitinib	AFP	PEGylated structure (passive)	A 20% cell viability reduction with the synergic treatment compared to 5.0 µM sunitinib alone, caspase 3/7 activity increased by up to 300% compared to control.	Not performed	[49]
Dual-target biomimetic nano-delivery system with a metal-organic core modified with NLS charged with DDP with A54 peptide in the cover (ultrasounds)	Cisplatin	NOR1	Nuclear location sequence (active) and A54 peptide (active)	A 20% cell cytotoxicity increase compared to the free drugs treatment.	A 75% reduction in tumor volume with the synergic treatment compared to empty nanoparticle.	[50]
Calcium phosphate (CaP) nanoparticles with asymmetric lipid bilayer coating (step-by-step precipitation)	Cisplatin	Bmi-1	Calcium phosphate structure (passive)	A 20% increase in cell cytotoxicity compared with the free drug and reduction in the Bmi-1 expression by 50%.	A 70.05% tumoral volume reduction with the synergistic therapy in contrast with the siRNA therapy alone.	[51]

Table 2. *Cont.*

Nanoformulation (Loading Method)	Chemotherapeutic Agent	siRNA Target	Targeting Ability	In Vitro Results	In Vivo Results	Ref.
ZnAsOx in a matrix of SiO_2 ("one-pot" reverse emulsification)	Arsenic trioxide	SHP-1	NS	A 39% reduction in cell viability and 20% increase in apoptosis rate with the synergic treatment compared to chemotherapeutic alone.	A 2.2-fold and metastasis 3.5-fold reduction in tumor growth and metastasis in the combined therapy compared with individual therapies and induced significant changes in different EMT markers	[52]
iRGD-targeted hybrid nanoparticles (NS)	Adriamycin	Ca^{2+} T Channels	iRGD (passive)	Higher cellular cycle arrest in G0/G1 and decrease in viability to 40% at the maximum drug concentration (20% lower than treatment with siRNA alone).	A 66.66% tumoral volume reduction with the synergic treatment compared to the one without the drug.	[53]
NHC at the periphery of the imidazolium precursors with dendriplex formation with the siRNA (NS)	Imidazole	Mcl-1	NS	Promoted entry of Mcl-1 siRNA into HEPG2 cancer cells and 15-fold IC_{50} reduction between the combined NP and the drug alone.	Not performed	[54]

ATO (arsenic trioxide); DSPE-PEG-PEI (1,2-diestearoil-sn-glicero-3-fosfoetanolamine-polietilenglicol-polieterimide); FD/FM@siTOX, (fluorinated nanoparticle with hydrophobic core); mPEG-PLys-PDPA (copolymer tri-block amphiphilic methoxy poli(ethylenglicol)-block-poly(L-lysine)-block-poly (methacrylate de 2-(diisopropil amino)ethyl)); NHC (spherical carbosilane metallodendrimers of different generations containing ruthenium (II) N-heterocyclic carbene); NS (non-specified); ZnAsOx (zinc arsenate); NLS (nuclear localization sequence).

3.4. Nanoparticles for Pancreatic Cancer Treatment

Different strategies for the treatment of pancreatic cancer have been employed among the studies analyzed in this systematic review, using different combinations of chemotherapeutics, and siRNAs targeting different aspects of the neoplasm have been encapsulated in nanoparticles.

Inside these, a great proportion of studies included chemotherapeutic gemcitabine as a co-therapy with siRNA. In this context, Norouzi et al. (2020) employed polymeric trilamellar micelles, co-loaded simultaneously with NF-kB. This treatment induced a significant increase in apoptosis and inhibition of cell migration compared with chemotherapy alone [55].

Furthermore, another study, carried out by Wang et al. (2019), employed cationic liposomes co-loaded simultaneously with gemcitabine and siMcl-1. The combined treatment induced a 40% and 27% increase in cell cytotoxicity compared with the siRNA and gemcitabine treatments alone, respectively. In addition, the tumor volume decreased by 83.33% with the complete LP-Gem-siMcl1 therapy reaching a minimum size compared to the chemotherapeutic alone and 90% with the PBS control [56]. Li et al. (2021) used a core–shell micelle-like nanocomplex based on a conjugation of cholesterol to the N-termination of short peptides and a labile dipeptide of cathepsin B (Val-Cit) to load siPCBP2 combined with gemcitabine. This was to try to reverse the accumulation of type I collagen in the tumor stroma and induce antitumor activity. It achieved a 97% reduction in PCBP2 mRNA expression with synergic treatment and decreased αCP2 and type I collagen levels by 82% and 70%, respectively, with respect to the siRNA alone. Moreover, the combination of gemcitabine and the siRNA nanocomplex induced the highest inhibition of collagen expression in the tumor in vivo with 46.8%. Also, the combined synergic therapy reduced tumoral volume by 36.66% compared to gemcitabine alone [57].

Another study employed gemcitabine co-administered independently with the gene silencing using a dextran-coated ferric magnetic nanocarrier that delivers siPD-L1 as

an anti-tumor strategy. This strategy showed a higher tumor volume decrease, with a 93.75% reduction between the synergic high-dose treatment and gemcitabine alone. The combined treatment increased the recruitment of $CD8^+$ tumor-infiltrating lymphocytes (TILs) with increased cell-mediated cytotoxicity, indicating an initiation of antitumor immune response [58].

The last study that employed gemcitabine was performed by Tang et al. (2021). They used nanoparticles with a polymeric antagonist of CXCR4 (overexpressed in pancreatic cancer) and cholesterol to deliver siPLK1 to enhance the effect of gemcitabine. This therapy achieved a synergistic effect, achieving a 30% reduction in cell viability compared with free gemcitabine. In a xenograft tumor model, this combined therapy obtained the greatest tumor weight reduction, with a 3.75-fold reduction between synergic treatment and the gemcitabine alone [59].

Other studies applied paclitaxel as the main chemotherapy. A study carried out by Yu et al. (2019) employed PEGylated liposomes to negatively regulate Bcl-2 expression. Cell viability was reduced by 35%, and the cell invasion capacity was reduced by 15% in comparison with the treatment with paclitaxel alone. Tumor volume barely increased, with a reduction difference of 75%, compared to the treatment without siRNA, paralleled by increased expression of proapoptotic caspase-3 [60].

On the other hand, Chen et al. (2023), employed a combination of 5-FU and oxaliplatin encapsulated in an amphiphilic polymer (PMBOP). It was coated with a mixture of chondroitin sulphate (natural ligand for CD44) and PEG (polyethylene glycol) that co-delivers an siRNA against Xkr8, which is associated with tumor immunosuppression. This strategy achieved a 17 and 20% increase in caspase-3 and annexin V levels with the combined treatment compared to the use of the free drugs, respectively. Also, the study obtained good results in vivo, with a 15% extra inhibition of tumoral growth with a 15% decrease in tumor volume compared to the use of siRNA alone [37].

Finally, it is noteworthy that a study that used a TGF-β receptor inhibitor, called LY2157299, encapsulated in a nanoplatform with a hydrophobic core, and a surface adsorbing siPD-L1 that acts by increasing CD8 T-cell infiltration. This combined NP produced an increased cytotoxicity (26%) compared to the use of a free inhibitor. Furthermore, the tumor volume in vivo decreased by ≈73% with the synergic full treatment compared to the chemotherapeutic alone and had a 90% reduction in tumor weight between the synergic therapy and LY2157299 alone [61].

In summary, in pancreatic cancer, we highlight the use of conventional chemotherapeutic agents, such as oxaliplatin or gemcitabine, or novel therapies, such as TGF-β receptor inhibitors. These therapies were combined with gene silencing of important targets such as PD-L1 or Xkr8, increasing the chemosensitivity of these cells to drug treatments administered in conjunction with siRNA therapy (Table 3).

Table 3. Nanoparticle-siRNA-drug strategies developed for pancreatic cancer treatment.

Nanoformulation (Loading Method)	Chemotherapeutic Agent	siRNA Target	Targeting Ability	In Vitro Results	In Vivo Results	Ref.
PCL-PEI-PEG tri-layer micelles (solvent evaporation method)	Gemcitabine	NF-kB	PEGylated structure (passive)	Reduced cell migration and increased apoptotic rate compared to chemotherapy alone.	Not performed	[55]
Cationic liposome-based system (NS)	Gemcitabine	Mcl-1	NS	Reduced cell migration compared to gemcitabine.	Decrease of 83.33% in the tumor volume with the complete LP-Gem-siMcl1 therapy compared to the chemotherapeutic alone and 90% compared with PBS control.	[56]

Table 3. *Cont.*

Nanoformulation (Loading Method)	Chemotherapeutic Agent	siRNA Target	Targeting Ability	In Vitro Results	In Vivo Results	Ref.
Nanocomplex with cholesterol conjugated core with N short-peptide end (micro-flow mixing method)	Gemcitabine	PCBP2	NS	Reduced PCBP2 expression, better intratumoral penetration and decreased collagen I level.	Reduced production of ECM, reduced tumoral volume (36.66%) compared to gemcitabine alone and 5.4-fold increased apoptosis compared to the free drug.	[57]
Magnetic ferric nanoparticle covered in dextran and reticulated with epichlorohydrin (NS)	Gemcitabine	PD-L1	NS	Not performed	Higher tumor volume decrease, with a 93.75% reduction between the synergic high dose treatment and gemcitabine alone.	[58]
PAMD-CHOL (NS)	Gemcitabine	PLK1	Cholesterol modifications in the structure (passive)	Cell migration (75%) and cell growth (30%) inhibition in the combined treatment compared with the gemcitabine alone.	A 3.75-fold reduction in tumor weight between synergic treatment and gemcitabine alone.	[59]
LH-Lip with PEG (film hydration method)	Paclitaxel	Bcl-2	PEGylated structure (passive) and incorporation of low-molecular-weight heparin (passive)	Reduced cell viability and cell invasion compared to the use of chemotherapy alone.	Reduction in tumor volume (75%) and tumor weight (50%) compared to the free drug and increased expression of proapoptotic caspase 3.	[60]
PMBOP-CP (NS)	FuOXP (5-FU + oxaliplatin)	Xkr8	Lipidic motif in the polymeric structure (active)	Reduced cell viability and increased apoptosis induction compared to the combination of the free drugs.	Decreased cell growth (15%) in the combined NP compared with the combination of the free drugs, 30% increase in CD45 cells and 20% in Tregs in the tumor sinus.	[37]
LYiClustersiPD-L1 (NS)	Inhibitor of TGF-β receptor	PD-L1	NS	Reduction of 26% in survivance of tumor cells with the complete therapy compared to the one without siRNA.	Tumor volume in vivo decreased 73% with the synergic full treatment compared to chemotherapeutic alone. This therapy decreased PD-L1 expression by 75%, and mice treated with it exhibited a strong increase in tumor-infiltrating $CD8^+$ T cells (9-fold higher) and in the expression of IFN-γ.	[61]

LH-Lip (low-molecular-weight heparin-coated liposomes); LYiClustersiPD-L1 (PCL-CDM-PAMAM, pH-responsive clustered nanoparticles with hydrophobic nuclei); NS (non-specified); PAMD-CHOL (polymeric nanoparticles modified by cholesterol); PCL-PEI-PEG (polymeric ε-caprolactone-polyethyleneimine-PEG); PMBOP-CP (polymeric amphiphilic nanoparticle, with a hydrophobic core and a PEG and chondroitin sulfate).

3.5. Nanoparticles for Gastric Cancer Treatment

Different strategies for the treatment of gastric cancer have been employed among the studies analyzed in this systematic review using different combinations of chemotherapeutics, and siRNAs targeting different aspects of the neoplasm have been encapsulated in nanoparticles.

Kumar et al. (2024) encapsulated navitoclax in combination with siRNA against Bcl-2. In this study, the combined NP increased the cytotoxicity of chemotherapy, and the synergistic treatment reduced the tumor weight on the mouse stomach reaching a minimum weight, which was negligible compared to the weight of a healthy organism's stomach. Furthermore, the individualized treatments increased the weight by 50% due

to the accumulation of tumor mass. In vitro, it achieved an increase in apoptosis rate of 2.5-fold along with a 33% decrease in the expression of Ki67, a tumor prognostic factor [62].

On the other hand, another study incorporated cisplatin employing a plasma exosome, which simultaneously carries siRNA against C-Met, which is overexpressed in a wide variety of tumors and involved in tumor proliferation, invasion, and metastasis, to enhance tumor sensitivity to cisplatin in vivo and induce antitumor activity. Through this, the cisplatin resistance was reversed, and the apoptosis rate improved by about 7% with synergistic treatment and produced a decreased cell migration. Furthermore, the tumor volume between controls and treatments showed a difference of up to 50% and 71.42% in tumor weight [63].

Furthermore, a study performed by Wu et al. (2022) used salinomycin encapsulated in cholesterol-loaded chitosan micelles carrying siRNA (siRNA@C-SAL). This nanotherapy showed enhanced cytotoxicity compared with the free drug at low concentrations with a decrease of about 55% in cell viability. In addition, the tumor volume in mice was reduced by 55.71% at the end of the study compared to the free drugs, and its weight was halved [64].

Another study employed paclitaxel, encapsulated in cationic liposomes modified with PEG to enhance in vivo circulation of the liposomes, and loaded with a siRNA capable of inhibiting APAF1. APAF1 is a protein that blocks apoptosome assembly and caspase 9/3 activation. This therapy induced a decrease in cell colony formation and an increase in apoptosis induction (5% more compared to the free drug). In addition, in a xenograft in vivo experiment, it achieved a 55% tumoral volume reduction between the complete therapy and the treatment without gene silencing and chemotherapy [65].

Wang et al. (2021), co-encapsulated arsenic oxide and a siRNA targeting Her-2 in a calcium phosphate nanoparticle, modified with PEG. The combined therapy increased the apoptosis rate by 12.1% and decreased the expression of different markers of tumor progression such as HER2, CXCR4, MMP2, and MMP9. Finally, the weight of the tumor mass in vivo was reduced by about 71.4% with the combined therapy with respect to the free drug and the number of metastases was reduced by 50% [66].

Therefore, in gastric cancer, the most widely used chemotherapeutics have been paclitaxel (conventional) together with other novel therapies such as arsenic oxide. Among the molecular targets silenced with siRNA, we find HER2 or APAF1, which are linked to chemoresistance in this type of cancer. Among the most relevant results, significant reductions in cell proliferation were shown in simultaneous treatment compared to individual treatments, in addition to a reduction in tumor growth in vivo (Table 4).

Table 4. Nanoparticle-siRNA-drug strategies developed for gastric cancer treatment.

Nanoformulation (Loading Method)	Chemotherapeutic Agent	siRNA Target	Targeting Ability	In Vitro Results	In Vivo Results	Ref.
Mucoadhesive vehicle composed of β-glucan and docosahexaenoic acid (modified solvent–antisolvent precipitation method)	Navitoclax	Bcl-2	NS	Increased cell cytotoxicity compared to the administration of the free drugs.	Reduced stomach tumor weight Reduced the tumor weight and 2.5-fold increase in apoptosis, with a 33% decrease in the expression of Ki67.	[62]
Plasmatic exosome (NS)	Cisplatin	C-Met	NS	Increased induction of apoptosis (7%) and decreased cell migration compared to the free drugs.	Tumor volume decreased by 50% compared with the untreated controls.	[63]
Cholesterol-loaded chitosan micelles with hydrophobic core (condensation and dialysis)	Salinomycin	C-Sal	Cholesterol modifications in the structure (passive)	Decreased cell viability (55%), increased apoptosis (10%) in the combined therapy compared with the free drug.	Tumor volume in mice with the full synergic treatment was reduced by 55.71% at the end of the study compared to the free drugs.	[64]

Table 4. *Cont.*

Nanoformulation (Loading Method)	Chemotherapeutic Agent	siRNA Target	Targeting Ability	In Vitro Results	In Vivo Results	Ref.
Cationic liposomes modified with PEG (condensation)	Paclitaxel	ABL	NS	Decreased clonogenicity and increased apoptotic rate compared to the free chemotherapy.	A 55% tumoral volume reduction between the complete therapy and the free drug and 5-fold decrease in tumor weight.	[65]
cRGD-PEG-DSPE (NS)	As_2O_3	HER2	NS	Improved cell growth inhibition (50%) and increased apoptosis (12.1%) compared to the administration of the free drugs.	Reduction in tumor weight (71.4%) and in metastasis (50%) compared with the free drug.	[66]

cRGD-PEG-DSPE (pH-Sensitive Nano Platform integrated by calcium phosphate and RGD(H-(D-Val)-Arg-Gly-Asp-Glu-OH) peptide modified with polyethylene glycol phosphatidylethanolamine); NS (non-specified).

3.6. Nanoparticles for Esophageal Cancer Treatment

Different strategies for the treatment of esophageal cancer have been employed among the studies analyzed in this systematic review, using different combinations of chemotherapeutic agents, and siRNAs targeting different aspects of the neoplasm have been encapsulated in nanoparticles. Among all the studies, the ones focused on esophageal cancer were the least represented.

Jun et al. (2020) employed doxorubicin co-administered simultaneously with siLPCAT in the same low lipid toxicity nanovector (EYLN). These NPs achieved excellent blood compatibility analyzed by hemolysis assay with only 2% cell lysis at the maximum concentration tested. In addition, the circulation time of the drugs increased by 20% at 72 h post-injection. Finally, a consistent in vivo antitumor effect was obtained, reaching an almost 90% tumoral volume reduction with respect to the PBS control and almost 80% with respect to the individual drugs 35 days after inoculation of the treatment [67].

The last study was carried out by Zhang et al. (2022) using the drug Adriamycin combined with siRNAs targeting MVP and Bcl-2 using a pH-sensitive nanoplatform and functionalized with an EGFR antibody. The combined therapy induced superior G0/G1 cell cycle arrest and therefore improved cell cytotoxicity. In addition, the complete synergistic therapy was the only one that reduced esophageal tumor volume in vivo to below 100 mm^3, reaching a tumoral volume reduction of 80% compared to the chemotherapeutic agent alone; the other therapies simply reduced growth [68].

Finally, in esophageal cancer, only two articles have been found that use this combination of treatments. Among the chemotherapeutic agents, we found adriamycin and DOX, which have been combined with siRNAs aimed at inhibiting LPCAT1, Bcl-2 and MVP, reducing cell proliferation capacity and tumor growth in vivo (Table 5).

Table 5. Nanoparticle-siRNA-drug strategies developed for esophageal cancer treatment.

Nanoformulation (Loading Method)	Chemotherapeutic Agent	siRNA Target	Targeting Ability	In Vitro Results	In Vivo Results	Ref.
mEYLNs (sonication)	DOX	LPCAT1	LFA-1 coating (active)	Reduced clonogenicity (66%) and cell migration (72%) compared with the individual treatments.	Significative growth, migration and metastasis inhibition, improvement in blood circulation time by 20%, 90% tumoral volume reduction with respect to the PBS control and almost 80% with respect to the individual drugs 35 days after inoculation of the treatment.	[67]

Table 5. *Cont.*

Nanoformulation (Loading Method)	Chemotherapeutic Agent	siRNA Target	Targeting Ability	In Vitro Results	In Vivo Results	Ref.
NP CEAMB (ultrasonication)	Adriamycin	Bcl-2 and MVP	Multiple histidines (active), cholesterol (passive) and epidermal growth factor receptor (EGFR) antibodies (active)	Improved cytotoxicity, drug internalization and induction of cell cycle arrest in G0/G1 phase in the combined therapy NP.	Extension of siRNA and Adriamycin blood circulation time in vivo, and improved antitumoral effect, tumoral volume reduction of 80% compared to chemotherapeutic agent alone.	[68]

DOX (doxorubicin); mEYLNs (lipidic nanovector revested with leucocyte proinflammatory membranes); NP CEAMB (multifunctional nanoparticles with a carboxymethylquitosan base and histidines, cholesterol and EGFR receptor antibodies).

4. Discussion

Among all the types of tumors included in this systematic review, colorectal cancer was the second most represented worldwide due to its relevant incidence and mortality, possessing a keen interest in the world of preclinical and clinical research. Furthermore, oxaliplatin was the most used chemotherapeutic, being one of the few drugs active on this type of metastatic cancer [69]. Other studies incorporating other relevant chemotherapeutic agents could be highlighted, such as docetaxel, a semisynthetic taxoid that has been presenting a high effectiveness in colorectal cancer in conjunction with siRNA treatment in the nanoparticle, among other relevant chemotherapeutic strategies targeting different mechanisms of colorectal cancer (Figure 2).

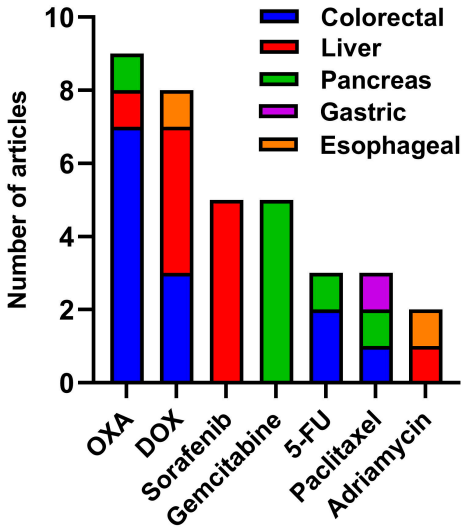

Figure 2. Main chemotherapy treatments used for each type of gastrointestinal cancer.

Liver cancer was the most represented of all those analyzed due to being third in overall mortality, and within this, doxorubicin was the most used chemotherapy, representing 33.3% of the total studies analyzed. In pancreatic cancer, the most-used drug was Gemcitabine (62.5% of the studies), while in gastric cancer, all the articles included a different chemotherapeutic regime than the rest. For example, we can find the use of Navitoclax, used as a co-therapy with siRNA against drug resistance with simultaneous delivery in the vector, as a Bcl-2 inhibitor to prevent cancer cells from growing. Meanwhile, esophageal cancer was the least studied, with only two studies included in this review. This shows the great heterogeneity of strategies employed and chemotherapeutics tested among all the studies analyzed, in addition to the fact that the use of each chemotherapeutic was

variable between each type of gastrointestinal cancer, attacking the different neoplasms in a different way according to different mechanisms and characteristics linked to each one.

The combination of siRNA and chemotherapy has been confirmed as effective for the treatment of various types of gastrointestinal cancer, showing solid in vitro and in vivo results at the preclinical level with different cancer cell lines and xenograft animal models. This demonstrates the enormous potential of these combined gene silencing and chemotherapy strategies for the treatment of not only gastrointestinal cancer in any of its forms but also any type of neoplasm, amplifying the effect of individual therapies and achieving a relevant synergistic effect, at least at the preclinical level according to the analysis in this systematic review.

Furthermore, we could mention the great diversity of siRNA targets that were developed among these studies. They focused on a wide variety of possible pathways and expressions within the tumor cell, which in many cases are under-regulated or in an aberrant state. For example, we can mention the targeting of overexpression of Bcl-2, a protein that helps control the survival or destruction of a tumor cell by preventing apoptosis and the family of which is regulated through post-translational modifications and interactions with other proteins, allowing them to serve as crucial nodal points at the intersection of multiple pathways with significant relevance to oncology [40]. These proteins regulate all major forms of cell death, including apoptosis, necrosis, and autophagy, and can modulate various cell death mechanisms. This elevated expression is observed in nearly half of all human cancers and usually results in the loss of the tumor suppressor function of these killer genes, thereby inhibiting cell death, including that induced by cytotoxic anticancer drugs. For this reason, it has become an interesting target for different strategies to induce tumoral cell death [70].

Regarding the inhibited molecular pathways, we found targets located in the same signaling pathways, in different but correlated pathways due to their cellular effects, or even targets located in independent pathways or specific protein expressions. For example, within this last subdivision, we can find COL1A1, a cancer-promoting factor whose accumulation is correlated with dysregulation of the epithelial–mesenchymal transition and tumorigenesis [29]; IDO-1, which is integrating the kynurenine pathway related to tumor neovascularization through modulating the expression of interferon-gamma (IFN-γ) and tumor immunosuppression [26]; LDHA, related to the growth and proliferation of tumor cells through the secretion of lactic acid and the activation of the epithelial–mesenchymal transition [25]; UBR, associated with the Arg/N-degron pathway, related to cell cycle control [43]; VEGF, present in its own signaling pathway for stimulating angiogenesis; PLK1, linked to the regulation of the G2/M transition and the initiation of cancer through activation of CDC25 via the PLK signaling pathway cascade, among others [59].

However, we can also exemplify cases of different siRNA targets that have an influence on the same signaling pathway. For example, si-SHP-1 [52], which influences as a multi-regulator of signals in the JAK/STAT3 signaling pathway, as well as si-Bmi-1, is involved in most signaling pathways, including JAK/STAT3, and present in the DDR pathway of ROS reduction [51]. In addition, C-Met and HGF were both associated with the activation of key oncogenic pathways such as STAT3, PI3K, or RAS, and with processes of organogenesis and metastasis. Furthermore, regarding the PI3K pathway, targets such as PD-L1 are also notable, related to immune system suppression and tumor proliferation, and associated with it, ATP7A was positively related to tumor infiltration and the detoxification of copper in tumor cells, preventing apoptosis [22]. Also, within the PI3K/AKT pathway, we can find the target PCBP2, essential in the apoptotic pathway and present in the STAT3 pathway. Finally, EpCAM was also associated with the regulation of this pathway, being linked to increased cellular proliferation and differentiation, angiogenesis, and metastasis [47,57].

In addition, HER2, related to the control of cell division and the survival of tumor cells, was also present in the mTOR pathway [35,40,44,60,62,63,68]. Noteworthy also is the Bcl-2 pathway, comprised of Bcl-2 itself, linked to the regulation of the induction of apoptosis; Mcl-1, anti-apoptotic; and MK, related to the proliferation of cancer cells and the

activation of Bcl-2, also associated with the mTOR and VEGF-A pathways. The different affected pathways and targets are represented in Figure 3.

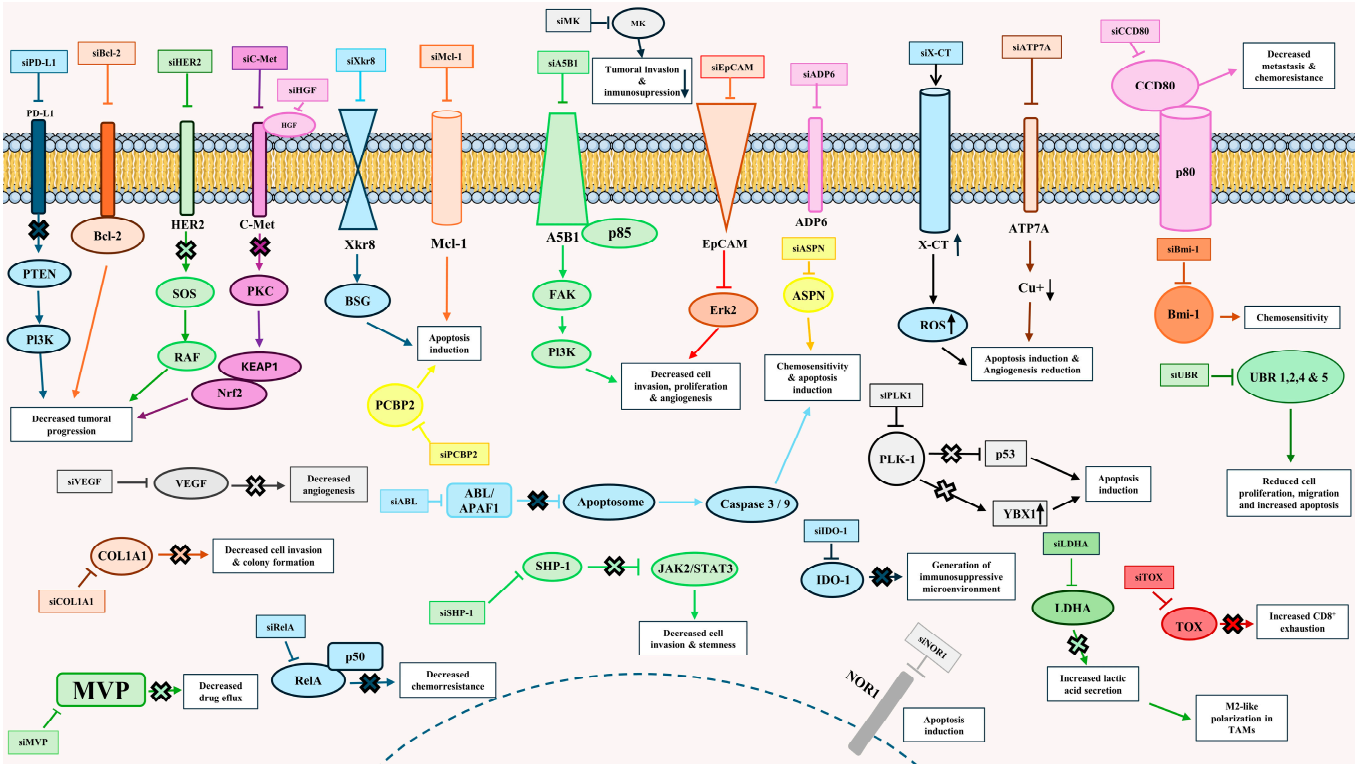

Figure 3. Different siRNA strategies and affected cellular pathways within their cancerous effects were employed among all the studies analyzed.

Treatment based on the synergistic combination of drug and gene silencing via siRNA offered a novel and promising therapeutic strategy for gastrointestinal cancers. This systematic review has elucidated its great potential, observing a wide variety of drug-siRNA and nanoplatform combinations with very promising results both in vitro and in vivo. These results were seen in the reduction in cell viability and proliferation, increased rate of apoptosis, decreased cell migration and increased chemosensitivity compared to the administration of the free drugs. Also, these therapies achieved a considerable reduction of tumor xenograft volume and weight in murine models, a reduction in angiogenesis in the introduced tumor tissue and an increase in survival.

In the different studies, the authors used a wide range of different cancer cell lines obtained from different animal models, as many of them naturally generate an insensitivity to certain drugs or artificially acquire resistance to further studies, such as HepG2-SI cells insensitive to sorafenib [45]. Also, a vast variety of in vitro and in vivo techniques were used to analyze different parameters and characteristics, e.g., immunohistochemistry and hematoxylin-eosin staining, western blot, qPCR, cell viability (calculating the IC_{50} cytotoxicity), apoptosis detection by flow cytometer and TUNEL staining, among others. In the in vivo assays, the authors analyzed in vivo biodistribution and the antitumor effect, i.e., the accumulation of the nanoparticles in the tumor. They achieved good in vitro and in vivo results and were represented in most studies.

This also showed its great applicability. All the analyzed studies were focused on a preclinical level of treatment, using murine models as in vivo elements. The next step for the development of these promising strategies is to reach the clinical phase to ensure their maximum applicability in humans and to have a real therapeutic use, not only as an antitumor element but also as a translational medical tool for a multitude of diseases.

This approach should be applicable at all levels and customizable, without patient rejection and with few side effects. Currently, there are many preclinical trials focused on the combination of gene therapy, chemotherapeutics, and nanoparticles, but they have not yet reached the level of clinical trials in humans in most cases. Therefore, few therapies containing these three elements have been approved by any regulatory agency. However, gene therapy or chemotherapeutics alone in nanoparticles, have reached the clinical phase and in many cases have been approved by the FDA or EMA. These treatments aim to overcome potential low tumor localization, low stability, and rapid elimination from the bloodstream. They show promising antitumor activities and adequate safety profiles when used individually. For example, notable siRNA anticancer nanotherapeutics include CALAA-01 for solid tumors targeting RRM2, selectively targeting transferrin receptors on the surface of tumor cells, with a completed phase I clinical trial in 2012 (NCT00689065); or DCR-MYC against hepatocellular carcinoma targeting c-Myc to inhibit cell proliferation and growth, with completed phase II (NCT02314052), among others. And as an exceptional case, we could find the use of Atu027, a novel liposomal RNA interference therapeutic targeting PKN3, to inhibit angiogenesis and tumor invasion, with completed phase Ib/IIa in 2016 combined with gemcitabine (NCT01808638) against advanced or metastatic pancreatic adenocarcinoma. The study employed two cohorts, with non-pancreatic cancer and with advanced pancreatic cancer, as one of the few studies that combined gene therapy and chemotherapy that reached the clinical phase [13,71,72].

This demonstrates the great interest in applying this strategy to translational oncology and its great potential, with an increasing trend in published articles that include these therapies, but it has become evident that there is a need to extend the studies to a clinical level as all in vivo results have been marked in a biocompatible non-human animal model context; it would also be beneficial to extend the types of gastrointestinal cancer under study, e.g., esophageal cancer, which is under-represented in the studies analyzed. Furthermore, all the studies analyzed presented a wide variety of nanoparticle-drug-siRNA combinations that employed completely different molecular strategies that generated different effects on the tumor environment and its inhibition. This proves its great potential and growing interest as one of the major anti-tumor therapies to stop the expanding incidence, prevalence and mortality of gastrointestinal cancer.

Due to its potential, siRNA-drug co-delivery systems should be further developed for possible effective clinical application. This involves several points, such as the optimization of its large-scale production or the homogenization of its physicochemical characteristics for its commercialization as an effective nanodrug. In addition to this, it is necessary to analyze which surface modifications can be made to improve its active targeting in different types of cancer or to improve its stability in blood, trying to reduce the side effects generated as much as possible. On the other hand, it would also be interesting to develop siRNA therapies that allow the activation of the immune system itself to produce an effective therapeutic effect in combination with encapsulated chemotherapy, which could improve the antitumor effect of these drugs. Once these points have been optimized, their use in different clinical trials with a larger number of control and treated individuals would lead to the possible development of effective therapies for the treatment of various gastrointestinal tumors [73–76].

5. Conclusions

The efficacy of chemotherapy in gastrointestinal tumors is limited by the different mechanisms of drug resistance. The results obtained in this review have shown that simultaneous nanoencapsulation of siRNA and chemotherapy was effective in several different gastrointestinal tumors, possessing greater efficacy in vitro and in vivo compared to free drug administration. The deregulation of several molecular pathways involved in chemoresistance and cell survival allowed increasing the sensitivity of tumor cells to the different drug treatments, generating an induction of apoptosis, a decrease in cell proliferation and migration capacity, and immune activation. This was reflected in the

results obtained in vivo, which showed a decrease in tumor volume in the mice treated with this combined therapy compared to the individual therapies, as well as an increase in their survival. Despite this, further research is needed in this field, improving biocompatibility and efficacy of the designed nanoformulations since the few clinical trials using this type of therapy are still in very early stages (phase I–II) and these therapies are of interest for effective treatment of these types of tumors.

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References

1. López, M.J.; Carbajal, J.; Alfaro, A.L.; Saravia, L.G.; Zanabria, D.; Araujo, J.M.; Quispe, L.; Zevallos, A.; Buleje, J.L.; Cho, C.E.; et al. Characteristics of Gastric Cancer around the World. *Crit. Rev. Oncol. Hematol.* **2023**, *181*, 103841. [CrossRef]
2. Kelly, R.J.; Bever, K.; Chao, J.; Ciombor, K.K.; Eng, C.; Fakih, M.; Goyal, L.; Hubbard, J.; Iyer, R.; Kemberling, H.T.; et al. Society for Immunotherapy of Cancer (SITC) Clinical Practice Guideline on Immunotherapy for the Treatment of Gastrointestinal Cancer. *J. Immunother. Cancer* **2023**, *11*, e006658. [CrossRef] [PubMed]
3. Park, W.; Chawla, A.; O'Reilly, E.M. Pancreatic Cancer: A Review. *JAMA* **2021**, *326*, 851–862. [CrossRef] [PubMed]
4. Bray, F.; Laversanne, M.; Sung, H.; Ferlay, J.; Siegel, R.L.; Soerjomataram, I.; Jemal, A. Global Cancer Statistics 2022: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J. Clin.* **2024**, *74*, 229–263. [CrossRef] [PubMed]
5. Papież, M.A.; Krzyściak, W. Biological Therapies in the Treatment of Cancer-Update and New Directions. *Int. J. Mol. Sci.* **2021**, *22*, 11694. [CrossRef] [PubMed]
6. Cheng, F.; Zhang, R.; Sun, C.; Ran, Q.; Zhang, C.; Shen, C.; Yao, Z.; Wang, M.; Song, L.; Peng, C. Oxaliplatin-Induced Peripheral Neurotoxicity in Colorectal Cancer Patients: Mechanisms, Pharmacokinetics and Strategies. *Front. Pharmacol.* **2023**, *14*, 1231401. [CrossRef]
7. Guan, W.-L.; He, Y.; Xu, R.-H. Gastric Cancer Treatment: Recent Progress and Future Perspectives. *J. Hematol. Oncol.* **2023**, *16*, 57. [CrossRef]
8. Baker, D.J.; Arany, Z.; Baur, J.A.; Epstein, J.A.; June, C.H. CAR T Therapy beyond Cancer: The Evolution of a Living Drug. *Nature* **2023**, *619*, 707–715. [CrossRef]
9. Wang, S.W.; Gao, C.; Zheng, Y.M.; Yi, L.; Lu, J.C.; Huang, X.Y.; Cai, J.B.; Zhang, P.F.; Cui, Y.H.; Ke, A.W. Current Applications and Future Perspective of CRISPR/Cas9 Gene Editing in Cancer. *Mol. Cancer* **2022**, *21*, 57. [CrossRef]
10. Rehman, U.; Parveen, N.; Sheikh, A.; Abourehab, M.A.S.; Sahebkar, A.; Kesharwani, P. Polymeric Nanoparticles-SiRNA as an Emerging Nano-Polyplexes against Ovarian Cancer. *Colloids Surf. B Biointerfaces* **2022**, *218*, 112766. [CrossRef]
11. Isazadeh, H.; Oruji, F.; Shabani, S.; Behroozi, J.; Nasiri, H.; Isazadeh, A.; Akbari, M. Advances in SiRNA Delivery Approaches in Cancer Therapy: Challenges and Opportunities. *Mol. Biol. Rep.* **2023**, *50*, 9529–9543. [CrossRef]
12. Roscigno, G.; Scognamiglio, I.; Ingenito, F.; Chianese, R.V.; Palma, F.; Chan, A.; Condorelli, G. Modulating the Crosstalk between the Tumor and the Microenvironment Using SiRNA: A Flexible Strategy for Breast Cancer Treatment. *Cancers* **2020**, *12*, 3744. [CrossRef] [PubMed]
13. Mirzaei, S.; Gholami, M.H.; Ang, H.L.; Hashemi, F.; Zarrabi, A.; Zabolian, A.; Hushmandi, K.; Delfi, M.; Khan, H.; Ashrafizadeh, M.; et al. Pre-Clinical and Clinical Applications of Small Interfering RNAs (SiRNA) and Co-Delivery Systems for Pancreatic Cancer Therapy. *Cells* **2021**, *10*, 3348. [CrossRef]
14. Jiang, L.; Qi, Y.; Yang, L.; Miao, Y.; Ren, W.; Liu, H.; Huang, Y.; Huang, S.; Chen, S.; Shi, Y.; et al. Remodeling the Tumor Immune Microenvironment via SiRNA Therapy for Precision Cancer Treatment. *Asian J. Pharm. Sci.* **2023**, *18*, 100852. [CrossRef] [PubMed]
15. Tong, F.; Zhou, Y.; Xu, Y.; Chen, Y.; Yudintceva, N.; Shevtsov, M.; Gao, H. Supramolecular Nanomedicines Based on Host–Guest Interactions of Cyclodextrins. *Exploration* **2023**, *3*, 20210111. [CrossRef]
16. Liu, L.; Xiong, M.; Rong, Q.; Zhang, M.; Zhang, X. Nucleic Acid Sensors in Vivo: Challenges and Opportunities. *View* **2023**, *4*, 20220064. [CrossRef]

17. Dai, Y.; Sun, J.; Zhang, X.; Zhao, J.; Yang, W.; Zhou, J.; Gao, Z.; Wang, Q.; Yu, F.; Wang, B. Supramolecular Assembly Boosting the Phototherapy Performances of BODIPYs. *Coord. Chem. Rev.* **2024**, *517*, 216054. [CrossRef]
18. Yan, M.; Wu, S.; Wang, Y.; Liang, M.; Wang, M.; Hu, W.; Yu, G.; Mao, Z.; Huang, F.; Zhou, J. Recent Progress of Supramolecular Chemotherapy Based on Host–Guest Interactions. *Adv. Mater.* **2024**, *36*, 2304249. [CrossRef] [PubMed]
19. Yang, W.; Zhang, W.; Chen, J.; Zhou, J. Mono-Functionalized Pillar[n]Arenes: Syntheses, Host–Guest Properties and Applications. *Chin. Chem. Lett.* **2024**, *35*, 108740. [CrossRef]
20. Jorge, A.; Pais, A.; Vitorino, C. Targeted SiRNA Delivery Using Lipid Nanoparticles. *Methods Mol. Biol.* **2020**, *2059*, 259–283. [CrossRef]
21. Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; et al. The PRISMA 2020 Statement: An Updated Guideline for Reporting Systematic Reviews. *BMJ* **2021**, *372*, n71. [CrossRef] [PubMed]
22. Zhou, Y.; Zhang, Q.; Wang, M.; Huang, C.; Yao, X. Effective Delivery of SiRNA-Loaded Nanoparticles for Overcoming Oxaliplatin Resistance in Colorectal Cancer. *Front. Oncol.* **2022**, *12*, 827891. [CrossRef] [PubMed]
23. Huang, C.; Zhou, Y.; Feng, X.; Wang, J.; Li, Y.; Yao, X. Delivery of Engineered Primary Tumor-Derived Exosomes Effectively Suppressed the Colorectal Cancer Chemoresistance and Liver Metastasis. *ACS Nano* **2023**, *17*, 10313–10326. [CrossRef]
24. Huang, C.-Z.; Zhou, Y.; Tong, Q.-S.; Duan, Q.-J.; Zhang, Q.; Du, J.-Z.; Yao, X.-Q. Precision Medicine-Guided Co-Delivery of ASPN SiRNA and Oxaliplatin by Nanoparticles to Overcome Chemoresistance of Colorectal Cancer. *Biomaterials* **2022**, *290*, 121827. [CrossRef] [PubMed]
25. Hu, L.; Huang, S.; Chen, G.; Li, B.; Li, T.; Lin, M.; Huang, Y.; Xiao, Z.; Shuai, X.; Su, Z. Nanodrugs Incorporating LDHA SiRNA Inhibit M2-like Polarization of TAMs and Amplify Autophagy to Assist Oxaliplatin Chemotherapy against Colorectal Cancer. *ACS Appl. Mater. Interfaces* **2022**, *14*, 31625–31633. [CrossRef]
26. Huang, H.; Jiang, C.-T.; Shen, S.; Liu, A.; Gan, Y.-J.; Tong, Q.-S.; Chen, S.-B.; Gao, Z.-X.; Du, J.-Z.; Cao, J.; et al. Nanoenabled Reversal of IDO1-Mediated Immunosuppression Synergizes with Immunogenic Chemotherapy for Improved Cancer Therapy. *Nano Lett.* **2019**, *19*, 5356–5365. [CrossRef]
27. Liu, H.; Yao, X.; Zhu, W.; Zhang, J.; Ma, S.; Lu, D.; Yang, W. A Functionalized Metal–Organic Framework-Based Controlled Dual-Drug Delivery System with Short Hairpin RNA and Simvastatin for Ferroptosis in Colorectal Cancer. *Adv. Ther.* **2023**, *6*, 2200356. [CrossRef]
28. Ling, X.; Han, W.; Jiang, X.; Chen, X.; Rodriguez, M.; Zhu, P.; Wu, T.; Lin, W. Point-Source Burst of Coordination Polymer Nanoparticles for Tri-Modality Cancer Therapy. *Biomaterials* **2021**, *270*, 120690. [CrossRef]
29. Manoochehri, H.; Jalali, A.; Tanzadehpanah, H.; Taherkhani, A.; Najafi, R. Aptamer-Conjugated Nanoliposomes Containing COL1A1 SiRNA Sensitize CRC Cells to Conventional Chemotherapeutic Drugs. *Colloids Surf. B Biointerfaces* **2022**, *218*, 112714. [CrossRef]
30. Jia, F.; Li, Y.; Gao, Y.; Wang, X.; Lu, J.; Cui, X.; Pan, Z.; Xu, C.; Deng, X.; Wu, Y. Sequential-Delivery Nanocomplex for Combined Anti-Angiogenesis and Gene Therapy against Colorectal Cancer. *Int. J. Pharm.* **2023**, *637*, 122850. [CrossRef]
31. Shen, W.; Yao, P.-A.; Li, W.; Gu, C.; Gao, T.; Cao, Y.; Wang, Z.; Pei, R.; Xing, C. Cancer-Associated Fibroblast-Targeted Nanodrugs Reshape Colorectal Tumor Microenvironments to Suppress Tumor Proliferation, Metastasis and Improve Drug Penetration. *J. Mater. Chem. B* **2023**, *11*, 1871–1880. [CrossRef] [PubMed]
32. Salehi Khesht, A.M.; Karpisheh, V.; Sahami Gilan, P.; Melnikova, L.A.; Olegovna Zekiy, A.; Mohammadi, M.; Hojjat-Farsangi, M.; Majidi Zolbanin, N.; Mahmoodpoor, A.; Hassannia, H.; et al. Blockade of CD73 Using SiRNA Loaded Chitosan Lactate Nanoparticles Functionalized with TAT-Hyaluronate Enhances Doxorubicin Mediated Cytotoxicity in Cancer Cells Both in Vitro and in Vivo. *Int. J. Biol. Macromol.* **2021**, *186*, 849–863. [CrossRef] [PubMed]
33. Zou, Y.; Xiao, F.; Song, L.; Sun, B.; Sun, D.; Chu, D.; Wang, L.; Han, S.; Yu, Z.; O'Driscoll, C.M.; et al. A Folate-Targeted PEGylated Cyclodextrin-Based Nanoformulation Achieves Co-Delivery of Docetaxel and SiRNA for Colorectal Cancer. *Int. J. Pharm.* **2021**, *606*, 120888. [CrossRef]
34. Chen, C.; Zhang, S.; Zhang, R.; Sun, P.; Shi, C.; Abdalla, M.; Li, A.; Xu, J.; Du, W.; Zhang, J.; et al. In Situ Tuning Proangiogenic Factor-Mediated Immunotolerance Synergizes the Tumoricidal Immunity via a Hypoxia-Triggerable Liposomal Bio-Nanoreactor. *Theranostics* **2020**, *10*, 11998–12010. [CrossRef] [PubMed]
35. Ray, L. Synergistic Anticancer Activity by Co-Delivered Nanosized Dual Therapeutic Agents and SiRNA in Colon Cancer. *J. Drug Deliv. Sci. Technol.* **2020**, *55*, 101351. [CrossRef]
36. Meng, F.; Wang, J.; He, Y.; Cresswell, G.M.; Lanman, N.A.; Lyle, L.T.; Ratliff, T.L.; Yeo, Y. A Single Local Delivery of Paclitaxel and Nucleic Acids via an Immunoactive Polymer Eliminates Tumors and Induces Antitumor Immunity. *Proc. Natl. Acad. Sci. USA* **2022**, *119*, 1. [CrossRef]
37. Chen, Y.; Huang, Y.; Li, Q.; Luo, Z.; Zhang, Z.; Huang, H.; Sun, J.; Zhang, L.; Sun, R.; Bain, D.J.; et al. Targeting Xkr8 via Nanoparticle-Mediated in Situ Co-Delivery of SiRNA and Chemotherapy Drugs for Cancer Immunochemotherapy. *Nat. Nanotechnol.* **2023**, *18*, 193–204. [CrossRef]
38. Shahidi, S.; Rostamizadeh, K.; Fathi, M.; Nedaei, K.; Ramazani, A. Combination of Quercetin or/and SiRNA-Loaded DDAB-MPEG-PCL Hybrid Nanoparticles Reverse Resistance to Regorafenib in Colon Cancer Cells. *BMC Complement. Med. Ther.* **2022**, *22*, 340. [CrossRef]

39. Babaei, M.; Abnous, K.; Taghdisi, S.M.; Taghavi, S.; Saljooghi, A.S.; Ramezani, M.; Alibolandi, M. Targeted Rod-Shaped Mesoporous Silica Nanoparticles for the Co-Delivery of Camptothecin and Survivin ShRNA in to Colon Adenocarcinoma in Vitro and in Vivo. *Eur. J. Pharm. Biopharm.* **2020**, *156*, 84–96. [CrossRef]
40. Tian, G.; Pan, R.; Zhang, B.; Qu, M.; Lian, B.; Jiang, H.; Gao, Z.; Wu, J. Liver-Targeted Combination Therapy Basing on Glycyrrhizic Acid-Modified DSPE-PEG-PEI Nanoparticles for Co-Delivery of Doxorubicin and Bcl-2 SiRNA. *Front. Pharmacol.* **2019**, *10*, 4. [CrossRef]
41. Wu, P.; Zhang, H.; Sun, M.; Mao, S.; He, Q.; Shi, Y.; Deng, Y.; Dong, Z.; Xu, Q.; Zhao, C.; et al. Manipulating Offense and Defense Signaling to Fight Cold Tumors with Carrier-Free Nanoassembly of Fluorinated Prodrug and SiRNA. *Adv. Mater.* **2022**, *34*, e2203019. [CrossRef]
42. Yuan, Y.; Wang, Y.; Huang, H.; Tao, S.; Huang, J. Fine-Tuned Polymer Nanoassembly for Codelivery of Chemotherapeutic Drug and SiRNA. *Macromol. Biosci.* **2023**, *23*, e2200529. [CrossRef] [PubMed]
43. Leboeuf, D.; Abakumova, T.; Prikazchikova, T.; Rhym, L.; Anderson, D.G.; Zatsepin, T.S.; Piatkov, K.I. Downregulation of the Arg/N-Degron Pathway Sensitizes Cancer Cells to Chemotherapy In Vivo. *Mol. Ther.* **2020**, *28*, 1092–1104. [CrossRef]
44. Yan, T.; Zhu, S.; Hui, W.; He, J.; Liu, Z.; Cheng, J. Chitosan Based PH-Responsive Polymeric Prodrug Vector for Enhanced Tumor Targeted Co-Delivery of Doxorubicin and SiRNA. *Carbohydr. Polym.* **2020**, *250*, 116781. [CrossRef]
45. Chen, Y.; Jiang, Z.; Yan, Z.; Liu, J.; Lai, Y.; Li, L.; Lin, X.; Lin, J. A Codelivery System Loaded with PDL1-SiRNA and Sorafenib Enhances the Therapeutic Effect of Sorafenib on Hepatocellular Carcinoma via TAT-Poly-SS-Lysine Modified Chitosan. *Int. J. Biol. Macromol.* **2024**, *263*, 130162. [CrossRef]
46. Younis, M.A.; Khalil, I.A.; Elewa, Y.H.A.; Kon, Y.; Harashima, H. Ultra-Small Lipid Nanoparticles Encapsulating Sorafenib and Midkine-SiRNA Selectively-Eradicate Sorafenib-Resistant Hepatocellular Carcinoma in Vivo. *J. Control. Release* **2021**, *331*, 335–349. [CrossRef] [PubMed]
47. Chen, X.; Chen, T.; Zhang, L.; Wang, Z.; Zhou, Q.; Huang, T.; Ge, C.; Xu, H.; Zhu, M.; Zhao, F.; et al. Cyclodextrin-Mediated Formation of Porous RNA Nanospheres and Their Application in Synergistic Targeted Therapeutics of Hepatocellular Carcinoma. *Biomaterials* **2020**, *261*, 120304. [CrossRef] [PubMed]
48. Younis, M.A.; Khalil, I.A.; Abd Elwakil, M.M.; Harashima, H. A Multifunctional Lipid-Based Nanodevice for the Highly Specific Codelivery of Sorafenib and Midkine SiRNA to Hepatic Cancer Cells. *Mol. Pharm.* **2019**, *16*, 4031–4044. [CrossRef]
49. Punuch, K.; Wongwan, C.; Jantana, S.; Somboonyosdech, C.; Rodponthukwaji, K.; Kunwong, N.; Nguyen, K.T.; Sirivatanauksorn, V.; Sirivatanauksorn, Y.; Srisawat, C.; et al. Study of SiRNA Delivery via Polymeric Nanoparticles in Combination with Angiogenesis Inhibitor for The Treatment of AFP-Related Liver Cancer. *Int. J. Mol. Sci.* **2022**, *23*, 12666. [CrossRef]
50. Huang, Y.; Kou, Q.; Su, Y.; Lu, L.; Li, X.; Jiang, H.; Gui, R.; Huang, R.; Nie, X.; Li, J. Combination Therapy Based on Dual-Target Biomimetic Nano-Delivery System for Overcoming Cisplatin Resistance in Hepatocellular Carcinoma. *J. Nanobiotechnol.* **2023**, *21*, 89. [CrossRef]
51. Li, M.; Zhao, P.; Fan, T.; Chen, Y.; Zhang, X.; He, C.; Yang, T.; Lee, R.J.; Khan, M.W.; Raza, S.M.; et al. Biocompatible Co-Loading Vehicles for Delivering Both Nanoplatin Cores and SiRNA to Treat Hepatocellular Carcinoma. *Int. J. Pharm.* **2019**, *572*, 118769. [CrossRef]
52. Huang, Y.; Zhou, B.; Luo, H.; Mao, J.; Huang, Y.; Zhang, K.; Mei, C.; Yan, Y.; Jin, H.; Gao, J.; et al. ZnAs@SiO(2) Nanoparticles as a Potential Anti-Tumor Drug for Targeting Stemness and Epithelial-Mesenchymal Transition in Hepatocellular Carcinoma via SHP-1/JAK2/STAT3 Signaling. *Theranostics* **2019**, *9*, 4391–4408. [CrossRef]
53. Zhao, J.; Wen, B.; Tan, Z.; Li, X.; Zhang, X. IRGD-Targeted Hybrid Nanoparticles Reverses Multi-Drug Resistant to Effectively Combat Liver Cancer. *J. Drug Target.* **2020**, *28*, 1063–1070. [CrossRef]
54. Rodríguez-Prieto, T.; Michlewska, S.; Hołota, M.; Ionov, M.; de la Mata, F.J.; Cano, J.; Bryszewska, M.; Gómez, R. Organometallic Dendrimers Based on Ruthenium(II) N-Heterocyclic Carbenes and Their Implication as Delivery Systems of Anticancer Small Interfering RNA. *J. Inorg. Biochem.* **2021**, *223*, 111540. [CrossRef]
55. Norouzi, P.; Amini, M.; Dinarvand, R.; Arefian, E.; Seyedjafari, E.; Atyabi, F. Co-Delivery of Gemcitabine Prodrug along with Anti NF-KB SiRNA by Tri-Layer Micelles Can Increase Cytotoxicity, Uptake and Accumulation of the System in the Cancers. *Mater. Sci. Eng. C* **2020**, *116*, 111161. [CrossRef] [PubMed]
56. Wang, Y.; Gao, F.; Jiang, X.; Zhao, X.; Wang, Y.; Kuai, Q.; Nie, G.; He, M.; Pan, Y.; Shi, W.; et al. Co-Delivery of Gemcitabine and Mcl-1 SiRNA via Cationic Liposome-Based System Enhances the Efficacy of Chemotherapy in Pancreatic Cancer. *J. Biomed. Nanotechnol.* **2019**, *15*, 966–978. [CrossRef] [PubMed]
57. Li, Y.; Zhao, Z.; Lin, C.-Y.; Liu, Y.; Staveley-OCarroll, K.F.; Li, G.; Cheng, K. Silencing PCBP2 Normalizes Desmoplastic Stroma and Improves the Antitumor Activity of Chemotherapy in Pancreatic Cancer. *Theranostics* **2021**, *11*, 2182–2200. [CrossRef] [PubMed]
58. Yoo, B.; Jordan, V.C.; Sheedy, P.; Billig, A.-M.; Ross, A.; Pantazopoulos, P.; Medarova, Z. RNAi-Mediated PD-L1 Inhibition for Pancreatic Cancer Immunotherapy. *Sci. Rep.* **2019**, *9*, 4712. [CrossRef] [PubMed]
59. Tang, S.; Hang, Y.; Ding, L.; Tang, W.; Yu, A.; Zhang, C.; Sil, D.; Xie, Y.; Oupický, D. Intraperitoneal SiRNA Nanoparticles for Augmentation of Gemcitabine Efficacy in the Treatment of Pancreatic Cancer. *Mol. Pharm.* **2021**, *18*, 4448–4458. [CrossRef]
60. Yu, Q.; Qiu, Y.; Chen, X.; Wang, X.; Mei, L.; Wu, H.; Liu, K.; Liu, Y.; Li, M.; Zhang, Z.; et al. Chemotherapy Priming of the Pancreatic Tumor Microenvironment Promotes Delivery and Anti-Metastasis Efficacy of Intravenous Low-Molecular-Weight Heparin-Coated Lipid-SiRNA Complex. *Theranostics* **2019**, *9*, 355–368. [CrossRef]

61. Wang, Y.; Gao, Z.; Du, X.; Chen, S.; Zhang, W.; Wang, J.; Li, H.; He, X.; Cao, J.; Wang, J. Co-Inhibition of the TGF-β Pathway and the PD-L1 Checkpoint by PH-Responsive Clustered Nanoparticles for Pancreatic Cancer Microenvironment Regulation and Anti-Tumor Immunotherapy. *Biomater. Sci.* **2020**, *8*, 5121–5132. [CrossRef] [PubMed]
62. Kumar, R.; Afrin, H.; Bhatt, H.N.; Beaven, E.; Gangavarap, A.; Esquivel, S.V.; Zahid, M.I.; Nurunnabi, M. Mucoadhesive Carrier-Mediated Oral Co-Delivery of Bcl2 Inhibitors Improves Gastric Cancer Treatment. *ACS Appl. Mater. Interfaces* **2024**, *16*, 305–317. [CrossRef] [PubMed]
63. Zhang, Q.; Zhang, H.; Ning, T.; Liu, D.; Deng, T.; Liu, R.; Bai, M.; Zhu, K.; Li, J.; Fan, Q.; et al. Exosome-Delivered c-Met SiRNA Could Reverse Chemoresistance to Cisplatin in Gastric Cancer. *Int. J. Nanomed.* **2020**, *15*, 2323–2335. [CrossRef] [PubMed]
64. Wu, C.; Zhang, Y.; Li, F.; Bei, S.; Pan, M.; Feng, L. Precise Engineering of Cholesterol-Loaded Chitosan Micelles as a Promising Nanocarrier System for Co-Delivery Drug-SiRNA for the Treatment of Gastric Cancer Therapy. *Process Biochem.* **2022**, *120*, 265–274. [CrossRef]
65. Wang, Q.; Chen, C.; Xu, X.; Shu, C.; Cao, C.; Wang, Z.; Fu, Y.; Xu, L.; Xu, K.; Xu, J.; et al. APAF1-Binding Long Noncoding RNA Promotes Tumor Growth and Multidrug Resistance in Gastric Cancer by Blocking Apoptosome Assembly. *Adv. Sci.* **2022**, *9*, e2201889. [CrossRef]
66. Wang, Q.; Tian, Y.; Liu, L.; Chen, C.; Zhang, W.; Wang, L.; Guo, Q.; Ding, L.; Fu, H.; Song, H.; et al. Precise Targeting Therapy of Orthotopic Gastric Carcinoma by SiRNA and Chemotherapeutic Drug Codelivered in PH-Sensitive Nano Platform. *Adv. Health Mater.* **2021**, *10*, e2100966. [CrossRef]
67. Jun, Y.; Tang, Z.; Luo, C.; Jiang, B.; Li, X.; Tao, M.; Gu, H.; Liu, L.; Zhang, Z.; Sun, S.; et al. Leukocyte-Mediated Combined Targeted Chemo and Gene Therapy for Esophageal Cancer. *ACS Appl. Mater. Interfaces* **2020**, *12*, 47330–47341. [CrossRef]
68. Zhang, X.; Wang, M.; Feng, J.; Qin, B.; Zhang, C.; Zhu, C.; Liu, W.; Wang, Y.; Liu, W.; Huang, L.; et al. Multifunctional Nanoparticles Co-Loaded with Adriamycin and MDR-Targeting SiRNAs for Treatment of Chemotherapy-Resistant Esophageal Cancer. *J. Nanobiotechnol.* **2022**, *20*, 166. [CrossRef]
69. Raymond, E.; Chaney, S.G.; Taamma, A.; Cvitkovic, E. Oxaliplatin: A Review of Preclinical and Clinical Studies. *Ann. Oncol.* **1998**, *9*, 1053–1071. [CrossRef]
70. Yip, K.W.; Reed, J.C. Bcl-2 Family Proteins and Cancer. *Oncogene* **2008**, *27*, 6398–6406. [CrossRef]
71. Schultheis, B.; Strumberg, D.; Santel, A.; Vank, C.; Gebhardt, F.; Keil, O.; Lange, C.; Giese, K.; Kaufmann, J.; Khan, M.; et al. First-in-Human Phase I Study of the Liposomal RNA Interference Therapeutic Atu027 in Patients with Advanced Solid Tumors. *J. Clin. Oncol.* **2014**, *32*, 4141–4148. [CrossRef] [PubMed]
72. Hattab, D.; Gazzali, A.M.; Bakhtiar, A. Clinical Advances of SiRNA-Based Nanotherapeutics for Cancer Treatment. *Pharmaceutics* **2021**, *13*, 1009. [CrossRef] [PubMed]
73. Sabio, R.M.; Meneguin, A.B.; Ribeiro, T.C.; Silva, R.R.; Chorilli, M. New Insights towards Mesoporous Silica Nanoparticles as a Technological Platform for Chemotherapeutic Drugs Delivery. *Int. J. Pharm.* **2019**, *564*, 379–409. [CrossRef] [PubMed]
74. Mirzaei, S.; Gholami, M.H.; Hashemi, F.; Zabolian, A.; Hushmandi, K.; Rahmanian, V.; Entezari, M.; Girish, Y.R.; Kumar, K.S.S.; Aref, A.R. Employing SiRNA Tool and Its Delivery Platforms in Suppressing Cisplatin Resistance: Approaching to a New Era of Cancer Chemotherapy. *Life Sci.* **2021**, *277*, 119430. [CrossRef]
75. Gandhi, N.S.; Tekade, R.K.; Chougule, M.B. Nanocarrier Mediated Delivery of SiRNA/MiRNA in Combination with Chemotherapeutic Agents for Cancer Therapy: Current Progress and Advances. *J. Control. Release* **2014**, *194*, 238–256. [CrossRef]
76. Chen, M.; Dong, C.; Shi, S. Nanoparticle-mediated SiRNA Delivery and Multifunctional Modification Strategies for Effective Cancer Therapy. *Adv. Mater. Technol.* **2021**, *6*, 2001236. [CrossRef]

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