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A Review of Innovative Nanoparticle Based Approaches for the Treatment of Liver Cancer

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ABSTRACT

Background: Hepatocellular carcinoma (HCC) is the most prevalent type of liver cancer with poor prognosis. Various drugs have been used to inhibit cancer cell proliferation, angiogenesis, and induce tumor cell apoptosis. However, drugs resistance, poor solubility, reduced bioavailability, restricted their clinical applications. Therefore, there is a need to develop novel therapeutic approaches based on nanoparticles (NPs) to enhance targeted drug delivery and improve therapeutic efficacy of HCC. **Method:** In this review, we retrieved already published data on nanoparticles-based vaccines, from PubMed, Google Scholar, Cochrane Library, and Science Direct. **Results:** These results indicate significant role of NPs based anti-cancer vaccines for the treatment of HCC or liver cancer. NPs based cancer vaccines compared to conventional liver cancer treatment showed lesser side effects, increased safety, minimum risk to normal body cells, reduced tumor growth, and enhanced delivery of anti-cancer drugs using NPs. **Conclusion:** Based on the literature, the study concluded that NPs based anti-cancer liver vaccines can provide better alternative to traditional liver cancer treatments like liver resection, liver transplantation, chemotherapy, and radiotherapy.

Keywords: Nanoparticles; NPs; Liver cancer; Vaccines; treatment; HCC

INTRODUCTION

Cancer is the leading cause of death worldwide. It is anticipated to reach 28.4 million new cancer incidences and 16.4 million deaths by 2040 [1]. Hepatocellular carcinoma (HCC) is the prevalent type of liver cancer accounting for 800,000 deaths every year globally [2]. The global burden of HCC is rapidly increasing due to limited clinical effectiveness of traditional treatment approaches such as surgery, chemotherapy, and radiotherapy [3]. According to Lurje *et al.,* the outcome of the HCC treatment largely depends on the stage of HCC and other comorbidities. For example, local radiofrequency has showed desirable patient outcomes in the early stage compared to late-stage HCC. Liver transplantation, palliative treatment including chemoembolization, and supportive care are treatments for late-stage HCC [4].

Generally, there are six treatments for liver cancer; liver resection, liver transplantation, radiotherapy, transcatheter arterial chemoembolization (TACE), and chemotherapy [5]. However, tumor recurrence, undesirable side effects, killing of normal body cells, poor aqueous solubility of the drugs, and multi-drug resistance are predominant limitations related to HCC management [6]. HCC conventional treatment has 62-80% 5-year recurrence probability of tumor recurrence [7]. Supportive care may lead to multi drug resistance and poor clinical outcomes [8]. An HCC patient survival rates have not increased sufficiently and has

reduced sensitivity to chemotherapeutic agents. Therefore, there is a need to develop novel liver cancer therapeutic strategies such as cancer vaccines, nanoparticles (NPs), and immunotherapies.

The nature of the nanomaterials (such as gold nanoshells and nanorods) and the imaging modalities for drug administration, tumor-specific targeting, and target site visualization are some of the distinctive characteristics of NPs. The typical size range of NPs is 1-100 nm or 100-200 nm (spherical NPs) [9].

The advancements in nanotechnology have provided novel and effective therapeutic possibilities to overcome the current HCC treatment limitations. A growing number of nanotherapeutics, nanodiagnostics, nano drug delivery system (DDS) has recently reached the clinical stage. Nanotechnology and cancer immunology have been exploited to develop new liver cancer treatments based on the NPs feature to phagocytose and reverse the phenomenon of local tumor immune suppression [10].

In comparison with traditional vaccines, NPs based cancer vaccines are delivered by optimizing physiochemical properties of nanomaterials and encapsulating them with immunostimulatory materials in order to achieve desirable immune levels [11]. NPs based DDS can provide high target to non-target ratio of drug release [12]. NPs are generally produced by using polypeptides, folded or unfolded form in the aqueous solution [13]. Another nanotechnology-based approach for HCC treatment is nanotheranostic. This approach utilizes biocompatible NPs efficient enough to provide HCC diagnosis and targeted drug delivery [14].

According to Khalifehzadeh & Arami., three lipid calcium phosphate NP based DNA immunotherapeutic vaccine carriers such as phosphorylated adjuvants, CpG, 2'3'cGAMP, and 5'pppdsRNA can reduce liver metastasis [15]. mRNA-based cancer vaccines encapsulated in lipid ligand nanoparticles (LNPs) are targeted, safe, and easy to manufacture with few technical challenges such as intrinsic instability of mRNA vaccines. mRNA based cancer vaccines delivered using NPs are used to overcome this technical challenge [16, 17]. In view with this, nanodrug DDS offer relatively less HCC multi drug resistance, increased chemotherapy sensitivity, and targeted cancer cells apoptosis [18]. In this review we identified the role of NPs-based vaccines for treating liver cancer that could be used as a novel strategy for treating HCC.

MATERIALS AND METHODS

PubMed, Google Scholar, Cochrane Library, and Science Direct were used to search all the relevant studies published during the last 15 years (January 2009 to February 2024). The following search key terms were used while searching for relevant studies; Nanoparticles; "NPs", "Liver cancer", "Vaccines", "treatment", and "HCC". After excluding duplicates, citations in the abstract form, and non-English citations, titles and abstracts of full research paper were screened for their relevancy and defined as original research focusing on the topic "nanoparticles drug delivery system for liver cancer".

RESULTS

Nanoparticles based Vaccines for HCC

The countries that most frequently utilize NP-based vaccines and DDS for treating liver cancer are China, Japan, and the USA. The most commonly used types of NP-based vaccines and DDS include lipid nanoparticles, poly(lactic-co-glycolic acid) nanoparticles (PLGA-NPs), targeted sorafenib, and doxorubicin (DOX) delivery via nanomaterials. A total of thirty-four studies investigated the role of NP-based vaccines and DDS in enhancing anti-tumor activity (Table 1). Table 1: Summary of study findings evaluated.

Table 1: Summary of studies included in the review

Sr. No.	Study Design	Country	Model	Nanotechnology	Results	Ref.
1.	Clinical study	China	mouse	RNA LNP	Induced anti-tumor activity for HCC growth	19
2.	Experimental study	China	Female mouse	OX40L	Increased CD4+ and CD8+ T cells	20

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3.	Clinical study	China	Mouse	Spleen-targeted neoantigen DNA vaccine	Efficient liver cancer immunotherapy	21
4.	Clinical study	Netherlands	Mouse	Nanovaccines	Effectively targeted liver cancer cells	22
5.	Clinical study	USA	Mouse	Lambda-phage vaccine	Improved anti-tumor activity	23
6.	Clinical study	Japan	Mouse	Amphiphilic poly (γ-glutamic acid) NPs	Improved anti-tumor activity	24
7.	Experimental study	USA	Guinea pigs	PEG NPs	Induced anti-tumor activity for HCC growth	25
8.	Clinical study	China	Mouse	Virus like silicon NPs vaccine	Increased CD4+ and CD8+ T cells	26
9.	Clinical study	China	Mouse	Bio-CS NPs	Effectively targeted liver cancer cells	27
10.	Clinical study	China	Mouse models	FA-modified chitosan nanoparticles	Reduced growth of tumor cells	28
11.	Clinical study	China	Mouse models	HepM-PLGA	Efficient drug delivery	29
12.	Experimental study	China	Mouse	DOX loaded with TATp - MSN complex	Efficient drug delivery	30
13.	Systematic review	Iran	-	AuNPs	Significant anticancer mechanism against HepG2 cells	31
14.	Clinical study	China	Mouse	DOX/Curcumin-NPs	Improved cytotoxic activity	32
15.	Experimental study	China	Rats	Silybin NPs	Enhanced drug efficacy and safety	33
16.	Experimental study	China	Mouse	ILNPs	Improved cytotoxic activity	34
17.	Clinical study	China	Mouse	NPs based HCC vaccines	Potent NP based vaccine	35
18.	Experimental study	China	42 HCC patients	Targeted NPs sorafenib delivery	Efficiently target tumor sites	36
19.	Experimental study	China	Mouse	PLGA-NPs	Efficient oral anticancer drug delivery	37
20.	Experimental study	Japan	Mouse	2DG-PLGA-NPs	Improved cytotoxic activity	38
21.	Experimental study	USA	Mice	RNA NPs DDS	Efficiently target tumor sites	39
22.	Experimental study	USA	Mouse	NPs based vaccines	Reduced liver tumor growth	40
23.	Experimental study	France	Mouse	NPs vaccines	Potent NP based vaccine	41
24.	Clinical study	USA	Mouse	NPs based adjuvants	Potent NP based vaccine	42
25.	Clinical study	China	Mouse	NPs based pill	Efficiently target tumor sites	43

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26.	Clinical study	China	Rabbits	TAE and HGFK1 NPs	Reduced liver tumor volume	44
27.	Clinical study	Saudi Arabia	Mouse	PEGylated PLGA NCs with siRNA	Inhibit HCC progression	45
28.	Clinical study	China	Mouse	DOX-HA-Cyst-GA NPs	Enhanced cytotoxic potential	46
29.	Clinical study	Egypt	Mouse	hepatocyte-targeted NPs	Enhanced cytotoxic potential	47
30.	Clinical study	China	Mouse	injectable hydrogel NC with self-assembled TAK-981 and BSA NPs.	Improved anti-tumor response	48
31.	Clinical study	China	Mouse	antigen-capturing nanoplatform with mannose	Improved ICB immunotherapy against HCC	49
32.	Clinical study	China	Mouse	pH sensitive nanoplatform, LDHs-siRNA	Blocked intracellular immune checkpoints	50
33.	Clinical study	China	Mouse	P53 mRNA-based nanomedicine targeting CXCR4 combined with anti-PD-1 therapy	Improved immune global reprogramming of TME	51
34.	Clinical study	China	Mouse	HCC chemotherapy drug nanocarrier, homotypic, HepM-PLGA	Reduced liver tumor volume	52

LNP, lipid nanoparticle; OX40L, Oxford ligand encapsulated with LNPs; PEG, Polyethylene glycol; Bio-CS, biotinylated chitosan; FA, Folate; HepM-PLGA, HepG2 poly lactic-co-glycolic acid; DOX. Doxorubicin; TATp, TAT peptide; MSN, mesoporous silica nanoparticle; AuNPs, gold nanoparticles; ILNPs, Ionizable lipid nanoparticles ILNPs; PLGA-NPs, poly (lactic-co-glycolic acid nanoparticles); 2DG-PLGA-NPs, 2-deoxy-D-glucose (2DG)-encapsulated poly (lactic-co-glycolic acid) nanoparticles; HepM-PLGA, HepG2 poly lactic-co-glycolic acid; TME, tumor microenvironment; LDHs, layered double hyrodixides; BSA, bovine serum albumin; NC, nanocomposite; HA-Cyst-GA, hyaluronic acid-glycyrrhetinic acid conjugate; siRNA, short interfering RNA; NCs, nanoconjugates; TAE, Transaerterial embolization; HGFK1, peglated-H1/ Human HGF a-chain;

NPs based vaccines have the potential to reduce tumor growth, induce desired anti-tumor immunity, and deliver and release drugs at the targeted cells. A literature review conducted by Alhalmi *et al.,* in India indicated that challenges facing traditional chemotherapy have been overcome by the emerging nanotechnological approaches [53].

NPs based liver vaccines to induce anti-tumor activity and improve T-cell cancer immunotherapy

Cancer is a systemic genetic disease characterized by changes in numerous functional and compositional properties of the immune system [54]. Immunity levels are affected by various factors such as complex tumors, host, and its environment. These factors supervise the efficacy and timing of anti-tumor activity [55]. Tumors resist immune attack via various phenomenon such as restricting antigen recognition and producing T cell exhaustion [56]. T cells play a crucial role in improving cancer immunotherapy. Activation of cytotoxic T lymphocytes (CTLs), generally, includes two step process. Firstly, T cell receptors (TCRs) use antigen-presenting cells (APCs) presented on major histocompatibility complex (MHC) molecules to bind to tumor-derived peptides [57]. This interaction generates an antigen specific T cell response. Secondly, T cell activation signal mediated by the CD28-B7 interaction catalyzes the complete activation of cytotoxic T cells. This initiation enables them to target and remove cancer cells presenting antigens in the body [58,59,60]. An experimental study was conducted among four-to-six-week-old female H22 tumors bearing mice by Deng *et al.,* The results of the study demonstrated that in vivo intratumoral injection of Oxford ligand encapsulated with lipid nanoparticles (OX40L) showed increased CD4+ and CD8+ T cells among mice with OX4OL group compared to control group (mean tumor size of OX40L group = 472.52 mm^3, control group = 1265.71 mm^3 after 14^{th} day of intratumoral OX40L injection, CD4+ and CD8+ T cells in OX40L group; 23.7%, 24.4% and control group = 11.9%, 12.5%, respectively [20]. Similar findings were also reported in a systematic review carried out by Lin *et al.,* [61]. Wu *et al.,* reported that DNA vaccine encapsulating polymeric NPs prevent tumor regression and induce long-term tumor immunological memory (T-cell

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immune response = 379.000 ± 19.21) [62]. Dolen *et al.,* evaluated the role of nanovaccines using invariant natural killer T (Inkt) and revealed that nanovaccines co-delivering iNKT cells optimally produce anti-tumor response. Zhang *et al.,* conducted clinical study on mice models and found that RNA lipid nanoparticles (LNPs) effectively induced anti-tumor activity for HCC growth (zeta potential of LNPs and RNA LPNs = 29.97 ± 0.61 mV and 42.03 ± 0.43 mV, respectively [19].

In a clinical study conducted in China, Hu et al. evaluated the use of folate (FA)-modified chitosan nanoparticles as a biological carrier for delivering the mouse interferon-induced protein-10 (mIP-10) gene to activate chemoattractant cytotoxic T cells. They indicated that it substantially decreased myeloid-derived suppressor cells (MSDC) ($p < 0.01$), increased tumor-specific interferon-γ responses ($p < 0.01$), reduced growth of tumor cells ($p < 0.01$), prolonged survival of mice ($p < 0.05$), increased cell apoptosis ($p < 0.01$) in the mouse spleen, local tumor, and bone marrow [28]. A clinical study carried out by Zhao *et al.,* in China revealed improved cytotoxic activity and reduced inhibitory concentration $(IC)_{50}$ in HepG2 cells ($(IC)_{50}$ in HepG2 = 3.1mg/mL, $(IC)_{50}$ in L02 cells = 3.1). DOX/Curcumin-NPs compared to free DOX and DOX NPs showed reduced cytotoxicity in L02 cells (DOX-NPs and DOX/Cur-NPs cytotoxicity = 2:1, 1:1, 1:2, respectively) [32].

Another clinical study conducted by Mezghrani *et al.,* intracellularly delivered DOX drug combined with hyaluronic acid-glycyrrhetinic acid conjugate (HA-Cyst-GA) NPs (loading capacity = 33.9%) and showed that NPs faster release of DOX and enhanced cytotoxic potential compared to non-responsive control (cytotoxic potential = 5.750, 9.33 and 10.23 µg/mL, respectively) [46]. Similar findings were also reported in a clinical study by Nasr *et al.,* exploring hepatocyte-targeted NPs against HCC in mouse models [47]. Liu *et al.,* constructed an injectable hydrogel nanocomposite (NC) with self-assembled TAK-981 and bovine serum albumin (BSA) NPs. The study found that TAK-981 NC combined with immune checkpoint blockade (ICB), PD-L1 blockade therapy stimulated DCs and cytotoxic lymphocyte mediated anti-tumor response to further prevent incomplete radiofrequency ablation (iRFA) in residual liver tumor ($p< 0.01$) [48]. These findings were similar with the clinical study conducted by Xiao *et al.,* exploring the potential of antigen-capturing nanoplatform modified with target ligand, mannose to overcome ICB hurdle in thermal ablation therapy against HCC [49].

Lu *et al.,* developed a pH sensitive multifunctional nanoplatform on layered double hyrodixides (LDHs) combined with siRNA. The study showed that siRNA suppressed the expression of H22 tumor cells, blocked the intracellular immune checkpoints; NR2F6 and PD-L1 by silencing NR2F6 genes, and increased systemic antitumor immunity by producing interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α) [50]. P53 mRNA-based nanomedicine targeting CXCR4 combined with anti-PD-1 therapy in HCC showed improved immune global reprogramming of tumor microenvironment (TME) and ICB in a clinical study conducted by Xiao *et al.,* [51].

NP based approaches to reduce liver tumor volume

Tumor nano vaccines (NVs) use NPs to carry tumor antigens and immunomodulators to establish a targeted immune response against a particular tumor [19]. These NP based vaccines are ideal to inhibit tumor growth and provide the body with protecting immune surveillance [63]. The goal of NVs is to enhance antitumor immune response and inhibit the rapid growth of tumor cells [64]. They do so by delivering tumor antigens and NVs adjuvants initiate antigen presenting cells (APCs). This triggers a strong antitumor response which induces long term immune memory. The NVs induced immune memory plays a pivotal role in suppressing tumor growth, recurrences, and metastasis [65,66].

Cany *et al.,* first reported the reduced liver tumor growth up to 65% using alpha-fetoprotein (AFP) in an autochthonous HCC model [41]. Another clinical study conducted by Liu *et al.,* developed an HCC chemotherapy drug nanocarrier, homotypic HepG2 poly lactic-co-glycolic acid (HepM-PLGA). The result of the study found that doxorubicin drug carried by nanocarrier showed efficient drug delivery to the tumor lesion and decreased tumor volume by 90% ($p<0.01$) [52]. Similarly, a clinical study conducted by Gao *et al.,* on 42 New Zealand rabbits developed the combination of transaerterial embolization (TAE) and peglated-H1/ Human HGF a-chain (HGFK1) NPs. The results of the study found reduced tumor volume, decreased protein expression levels of CD31, CD90, and Ki67, increased apoptosis of HepG2 cells, and improved survival rates of rabbits ($p < 0.05$) [44]. Another clinical study conducted by Khan *et al.,* used PEGylated PLGA nanoconjugates (NCs) combined with silencing specific gene, short interfering RNA (siRNA). The study revealed exceptionally reduced levels of tumor size, increased DNA fragmentations, and prominent modulation of factors such as caspase-3, Bax and Bcl-2 that significantly inhibit HCC progression ($p < 0.01$) [45].

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DISCUSSION

HHC has poor prognosis and remains asymptomatic in its early stage which leads to late diagnosis. Its pathological complexities and late diagnosis often reflect the challenges of HCC medical therapy [68]. These challenges may include multidrug resistance, immune checkpoints, tumor microenvironment (TME), ineffective drug selectivity against cancer, clinical side effects, cardiotoxicity [69]. NP drug delivery can overcome different challenges of traditional treatments strategies [70]. The emergence of modifiable structural design of NP drug delivery platforms can improve targeted drug delivery to the tumor location [71]. This also minimizes severe clinical side effects of the cancer drugs and provides improved patient safety [72]. They also enhance drug sensitivity and availability by delivering higher local drug concentrations to the tumor region via mechanism of enhanced permeability and retention (EPR) [73]. Nano-vaccines have improved the overall ability of chemotherapeutic drugs to kill the liver cancer cells under hypoxic environment. They do so by enhancing the immunogenic TME and inducing a robust cytotoxic T-cells immune response.

In a study conducted by on murine models exploring the therapeutic efficacy of bio-NP lambda phage-based vaccines for the treatment of liver cancer [22]. Yang *et al.,* developed ionizable lipid-based mRNA delivery system to treat HCC with increased protein expression and effective delivery of HCC drug delivery to hepatocytes [34]. Similar findings exploring the role of NPs based liver cancer vaccines were demonstrated in various clinical studies conducted in the USA [23,24,25,40,74,75].

A clinical study was conducted by Su., among 42 HCC patients (experimental group = 18 cases with combination therapy of targeted nanodrug delivery for sorafenib, control group = 24 cases with non-drug delivery of sorafenib). The study revealed that experimental group compared to control group demonstrate higher disease control rate (DCR), reduced incidence rate of adverse reaction ($p > 0.05$, $p < 0.05$, respectively) [36]. Similar findings were also reported in a clinical study conducted by Ding *et al.,* evaluating the drug delivery efficiency of doxorubicin (DOX) loaded with TAT peptide (TATp)-mesoporous silica nanoparticle (MSN) complex (TLS11a-LB@TATp-MSN/DOX) for the treatment of liver cancer [76]. A literature review was conducted by Ladju *et al.,* in Indonesia found that nanotheranositic platforms can provide better alternative treatments for the effective and safe clinical HCC management and drug delivery [77]. Similar findings were also reported [12, 78-80].

A systematic review comprising of 20 papers was conducted by Barabadi *et al.,* in Iran. The results of the study concluded that green synthesized gold nanoparticles (AuNPs) (below 100nm in diameter) utilized for the treatment of hepatic cancer cells demonstrated significant anticancer mechanism against HepG2 cells [31]. An experimental study conducted by Zhang *et al.,* found that silybin NPs compared to silybin demonstrated enhanced drug efficacy and safety (entrapment efficiency = 88%, mean diameter of NPs = 216 nm, zeta potential = -15 mV, reduction of liver nodules = 93%) [33]. Ellipilli *et al.,* reported ligand-displaying-exosomes using RNA nanotechnology demonstrated high drug delivery efficiency with reduced toxicity on mice xenograft to treat liver cancer [39]. Similar findings were also reported in clinical studies conducted by Sasaki *et al.,* using 2-deoxy-D-glucose (2DG)-encapsulated poly (lactic-co-glycolic acid) (PLGA) NPs, Ma *et al.,* using oral (PLGA) based NPs, Kong *et al.,* with sorafenib NPs DDS, Gorbet *et al.,* Sun *et al.,* developing organic and inorganic NPs investigated in clinical and preclinical cancer immunotherapeutic [37-38, 81-83].

NPs-based liver cancer vaccines developmental challenges

There are several challenges associated with development of NPs based anti-cancer vaccines and DDS [84]. These challenges mainly include lack of regulatory standards in terms of maintaining its various parameters sensitive to minor variations. NPs are complex 3D structures demanding detailed design; engineering orthogonal and manufacturing analysis processes [85-87]. This is a crucial step to ensure a consistent NPs based anti-cancer vaccine product with desirable physiochemical properties, pharmacokinetics profile, and biological characteristics [81, 88].

Limitations of the study and future perspectives

The limitations of this review include small number of studies conducted at clinical level on human subjects with different study designs on this innovative technique. Less number of systematic reviews and meta-analysis on NPs efficacy in terms of tumor size reduction, targeted drug delivery, and enhanced anti-tumor activity were also identified as limitations of this study. Therefore, a continued development of clinical trials, systematic reviews, and meta-analysis research including human subjects with liver cancer focused on NPs based liver cancer vaccines clinical applicability combined with NPs based DDS to improve oncological outcomes.

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Conclusion

This article provides a comprehensive review of the development, effectiveness, and challenges of NP-based liver cancer vaccines and drug delivery systems (DDS). The study found that, compared to conventional liver cancer treatments, NP-based vaccines and DDS demonstrated reduced tumor size, increased cytotoxicity of CD4+ and CD8+ T cells, enhanced anti-tumor immunity (IFN-γ and TNF-α), improved immune checkpoint blockade (ICB) therapy, efficient targeted drug delivery to tumor sites, and reduced systemic toxicity.

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Disclosures

The authors declare that they have no conflicts of interest.

Consent

This manuscript does not involve any animal or human subject, that's why do not need any consent.

Author contributions

MR, performed the literature search, wrote the draft of the manuscript, and supervision, performed the literature search. NK, MR, NA performed the literature search, wrote the draft of the manuscript.

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