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ROLE OF NANOPARTICLES IN TREATMENT OF HEPATOCELLULAR CARCINOMA

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ABSTRACT

Cancer is a disease characterized by uncontrolled proliferation of body cells. Hepatocellular carcinoma (HCC) is one of the most common malignant tumors worldwide. There are many treatment strategies available for hepatocellular carcinoma but there are several limitations of traditional surgery and radiation therapy and chemotherapy that results into failure and poor prognosis. In recent years, the development and advances of nanotechnology has brought new hope for the diagnosis and treatment of HCC. This article reviews the development of nanoparticles used for detection, diagnosis and treatment of hepatocellular carcinoma due to their large specific surface area and unique optical, electronic and magnetic properties. Moreover, research have shown that after Nanoparticle based therapy including nano-carriers can achieve active targeting effect, which improves the efficacy of chemotherapeutic drugs and decreases their side effects.

KEYWORDS: Hepatocellular carcinoma, Nanoparticles, prognosis, drug targeting.

The field of nanotechnology has been growing at an incredible skyrocketrate.The Targeted delivery of anti-cancer agents has been recently drawing more attention, especially with the ongoing advances in nanotechnology. The definition of nanotechnology varies, but according to the National Nanotechnology Initiative (NNI) it definesbasically all about understanding, manipulating and manufacturing matters into nanoscale, typically within the range of 1–100 nm although a slight increase in dimensions is still acceptable.[1] Nanotechnology provides alternative solutions to old problems and fresh insights into challenging issues in multiple fields such as medicine, environment, agriculture, electronics, industrial and commercial usage.[2] The matchup between nanotechnology and cancer research has led to the evolving field of what is now known as "cancer nanotechnology", which might be just the key for cancer treatment. In this context, nanotechnology offers innovative set of tools needed to design and synthesize drug delivery vehicles that can carry sufficient drug loads, efficiently cross physiological barriers to reachtarget sites, and safely and sustainably cure disease. Cancer nanotechnology seeks to characterize the interaction of nanoscale devices with cellular and molecular components specifically related to cancer diagnosis and therapys.[3] Nanoparticles (NPs) are miniscule, solid particulates in the size range of 1–100 nm, where an anticancer agent is either entrapped in the core, adsorbed on the surface or both.[4] The potential of using NPs for delivery of anticancer drugs is massive and can be applied to various areas of medicine. Small sized particles possess large surface area and hence, increase the dissolution properties of antineoplastic agents that have poor solubility. NPs can be tailored to reach specific tumor site by modulation of their size, surface characteristics, and particle charge.[5,6] Delivery of anticancer agents in the form of nanoparticles also ensures reduction in the therapeutic dosage and frequency due to the controlled release properties of the nanosystems. Additionally, nanoparticulate drug delivery systems reduce the unwanted toxicities associated with antitumor agents and prevent the degradation of drug molecules.[6] NPs can prove to be very effective in treating cancer by bypassing all the physical and biological obstacles that typically hinder the conventional drugs. A wide range of NPs have been modified for targeted drug delivery to HCC. The structure of the nanoparticle is pivotal to determine forms of cargo loading, such as dissolution, encapsulation, or adsorption. NPs used for the treatment of HCC are usually classified based on their chemical structure, as organic; mainly macromolecular in structure, or inorganic such as metal and ceramic NPs. Given the surface properties of the NPs and functional groups of the targeting agents, NPs' surface can be modified by specific targeting ligands, mostly via covalent bonding, to achieve the desired therapeutic efficacy.[7]

Nanoparticles for hepatocellular carcinoma

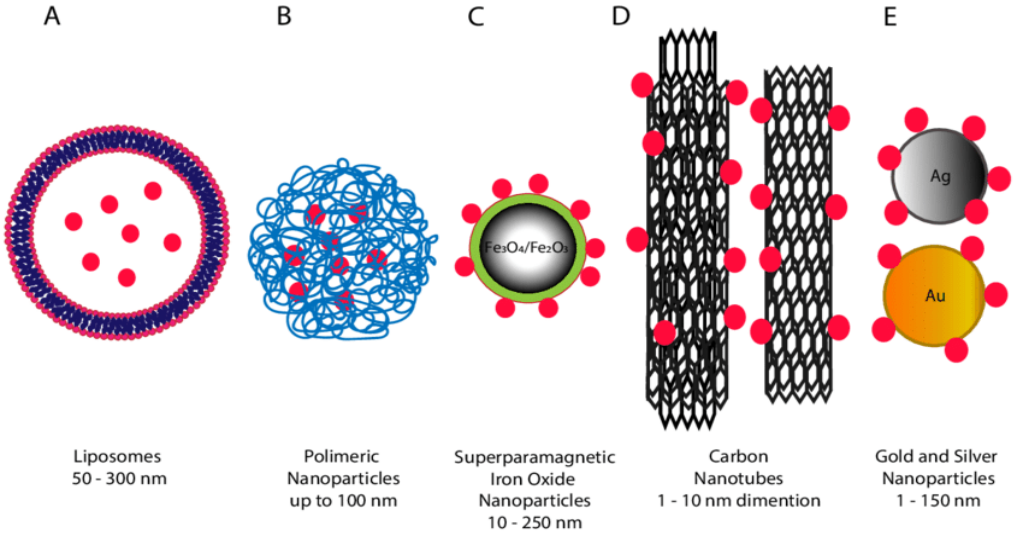

Figure 1: Example of nanocarrier system for HCC.

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Lipidbased nanoparticles

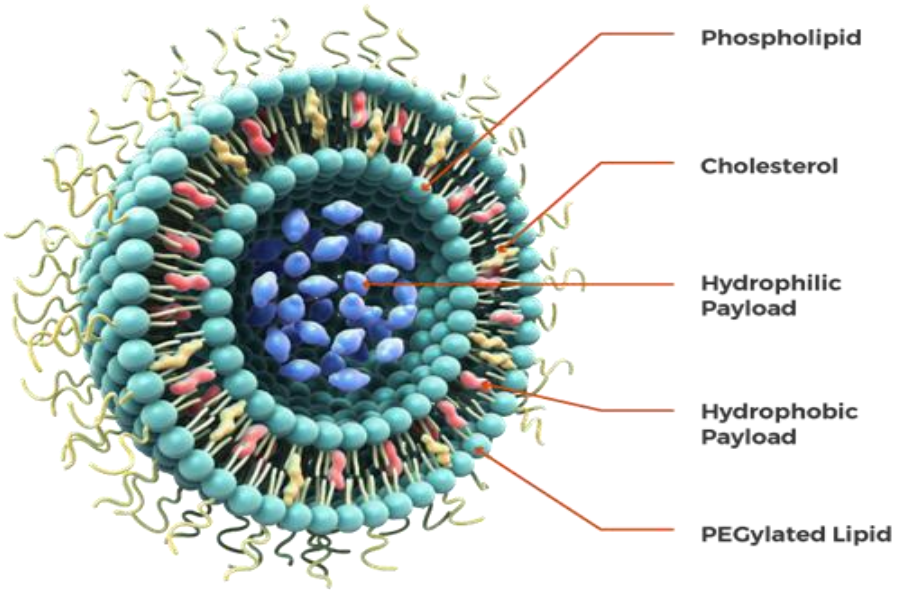

Figure 2: Lyposome drug delivery system.

Liposomes, micelles, and polymersomes are nanoscale lipid-based vehicles. Preclinical and clinical models using these nanoscale platforms have been documented well over the past several decades. These lipid-based vehicles have been used primarily for increasing the solubility of hydrophobic chemotherapeutics and for limiting drug toxicity. However, several problems exist with these traditional vehicles, including nonspecific uptake by the RES, rapid clearance, and instability, all of which have limited the therapeutic potential of these vehicles. Novel preparations of these compounds recently have been developed with the objective of overcoming some of those limitations. Liposomes coated with PEG, so-called stealth liposomes, have increased bioavailability significantly because of reduced, nonspecific RES uptake.[8] Liposomes are the most studied delivery systems due to the biocompatibility and biodegradability that they present. The main components of these nanoparticles are phospholipids, which are organized in a bilayer structure due to their amphipathic properties.[9]

Solid Lipid Nanoparticles (SLN)

SLNs represent a relatively new colloidal drug delivery system, composed of physiological lipids that remain in a solid state at both room and body temperature. These particles are in the size range of 50–1000 nm. The solid lipid used forms a matrix material for drug encapsulation

and include mono-, di- or triglycerides, fatty acids and complex glyceride mixtures. This matrix is stabilized by a mixture of surfactants or polymers. SLNs have significant advantages, such as site-specific targeting, physical stability over a long period, possibility of controlled release of both lipophilic and hydrophilic drugs, protection of labile drugs, low cost, ease of preparation and nontoxic.[10]

Nanostructured Lipid Carriers (NLC)

NLCs represent a second generation of lipid-based nanocarriers, developed from SLN, which comprise a combination of solid and liquid lipids. This system was developed in order to overcome the limitations of SLNs; hence, NLCs have higher drug loading capacity, and could also avoid drug expulsion during storage by avoiding lipid crystallization due to the presence of liquid lipids in the NLC formulation. While SLNs are composed of solid lipids, NLCs are a mixture of solid and liquid lipids, such as glyceryltricaprylate, ethyl oleate, isopropyl myristate and glyceryldioleate.[11]

5-(Fluorouracil)FU-loaded cubosomes and PTX-loaded NLCs have been used in hepatocellular carcinoma treatment. On the one hand, 5-FU-loaded cubosomes prevent the drug from its rapid enzymatic degradation, increasing its accumulation in the liver. On the other hand, paclitaxel PTX-loaded NLCs improve the effect of the commercial formulation Intaxel®, benefitting its accumulation and permanence in plasma.[12] In addition, a system constituted by sorafenib and SPIONs co-loaded in SLNs has been developed as a dual treatment against HepG2 cells.[13] Furthermore, new nanoformulations are being developed and tested to increase the available antitumor strategies against Liver cancer.

Antioxidant-derived nanoparticles (nano-antioxidant)

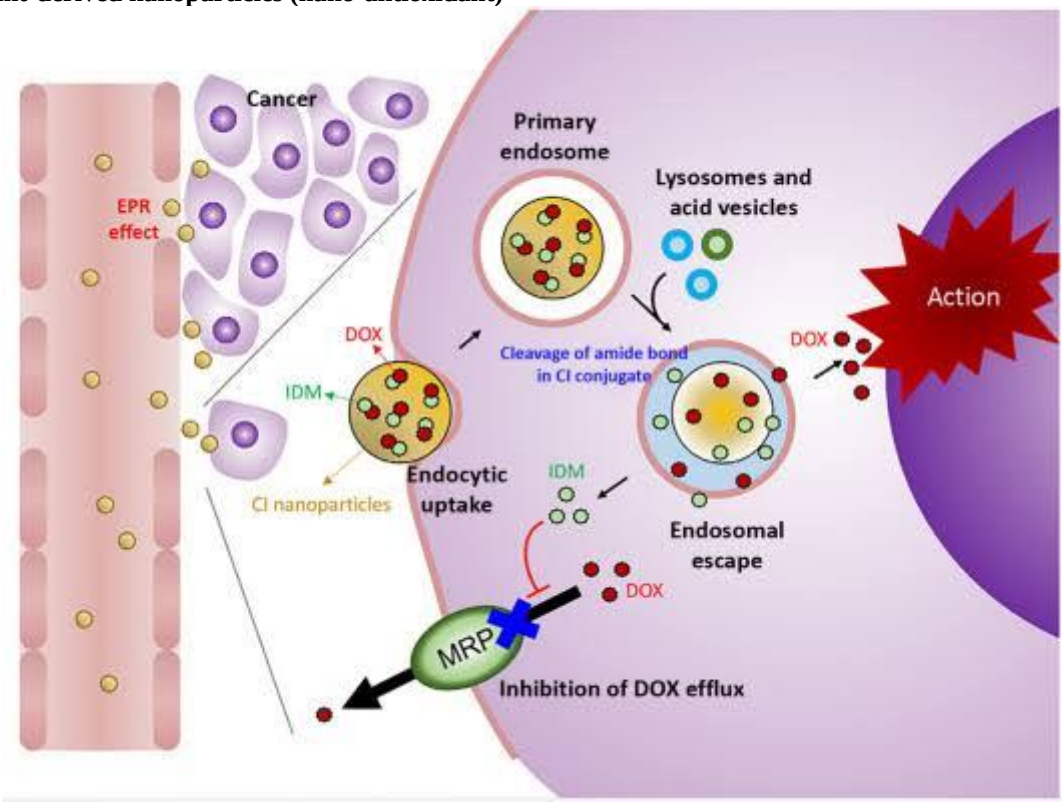

Figure 3: Nanocarrier-mediated antioxidant delivery for liver diseases.

The use of nanocarriers can improve the biological delivery of antioxidants and have documented therapeutic potential. In particular, the incorporation of antioxidants into nanoparticles can increase their bioavailability, improve targeting to the desired tissues or receptors, and provide controlled release of compounds over an extended period of time. However, because most reported nanocarriers are synthetic (i.e. polymers, lipids, inorganic metals, etc.) and do not possess intrinsic therapeutic efficacy, long-term application of these nanocarriers is associated with concerns regarding their degradation, elimination, and toxicity in humans. Furthermore, nanocarriers typically have low drug-loading capacities (typically below 10% for drugs), and this significantly reduces their accumulation in the tumor hence diminishing their therapeutic efficacy. Therefore, self-carrying Nano-antioxidant delivery systems that do not require the use of inner carriers could be seen as a paradigm shift in the therapeutic modality of liver diseases.[14]

some studies showed pomegranate fruit and flower extracts to exhibit free-radical scavenging properties, playing a role in hepatoprotection and prevention of liver

injury.[15] Some studies found that Pomegranate emulsion (PE) is able to counter dietary carcinogen diethyl nitrosamine (DENA)-induced rat hepatocarcinogenesis. After PE treatment (1 or 10 g/kg), striking chemo-preventive results were demonstrated by reduced incidence, number, multiplicity, size and volume of hepatic nodules, all precursors of HCC. PE also alleviated DENA-induced hepatic lipid peroxidation and protein oxidation, and elevated protein and messenger RNA expression of the Nuclear factor erythroid 2-related factor 2 (Nrf2).[16]

An in vivo and in-vitro study was conducted by Pandey P et al., wherein, Rutin (a natural flavonoid, possessing antioxidant and anticancer properties) loaded poly(lactic co-glycolic acid) PLGA NPs were used. DEN induced rats had liver nodules and the hepatic tissue was decolorized, characteristic of liver cancer. DEN induced rats treated with Rutin exhibited improvement in physiology and color while as Rutin PLGA NPs manifested mild decolorization and complete absence of nodules. These results conclude that Rutin PLGA NPs were successful in treating DEN induced HCC in rats. Rutin PLGA NPs also had considerable effect on hepatic, non-hepatic, antioxidant enzymes, inflammatory mediators and haematological parameters.[17]

Polysaccharides-derived nanoparticles

These are naturally occurring polymers with excellent biocompatibility and multifunctionality that allows further structural development to be loaded with various types of drugs. Examples include Chitosan and Dextran; Chitosan (CS) is a natural linear biopolyaminosaccharide, derived from alkaline deacetylation of chitin. It has been found to be the second most abundant biopolymer in nature, behind cellulose.[18]

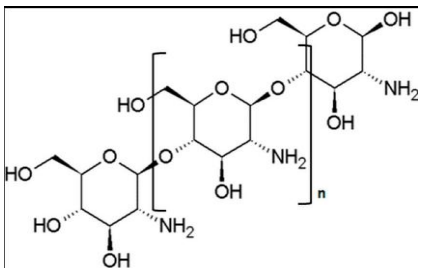

Figure 4: Chemical structure of chitosan.

Yang et al. prepared chitosan nanoparticles (average particle size of about 175 nm, chitosan with deacetylation degree of 93%) loaded with 125I-labeled 5-iodo-20 –deoxyuridine.[19] It was found that Nanomaterials the nanoparticle accumulation was significantly higher in HCC cells HepG2 than in normal liver cells HL-7702. In vivo animal experiments were carried out on Male New Zealand white rabbit VX2 liver tumor. According to the authors, the way by which the drug loaded chitosan nanoparticles come into the tumor is mainly represented by passive targeting. These experiments showed that the internal irradiation obtained by drug loaded nanoparticles, induced significant cell apoptosis and enhanced DNA-damage in rabbit hepatocellular tumors, with respect 125I-labeled 5-iodo-20 -deoxyuridine infusion at the same dose. Hydroxycamptothecin (HCPT) loaded chitosan nanospheres (average size of about 330 nm) were prepared using the membrane emulsification technique.[20] HCPT is an alkaloid isolated from the Camptotheca acuminate in China. It shows anticancer activity although the clinical application is limited owing to its water-insolubility. SEM images showed that drug loaded nanospheres have spherical morphology with a size of 200–300 nm. The nanospheres exhibited in vitro an initial burst effect followed by a sustained HPCT release of more than 15 days. An anti-tumor ability was observed towards human hepatoma (HepG2) cells. In vivo study was carried out by injecting subcutaneously intra-tumor, the drug loaded HCPT nanoparticles into mice bearing HepG2 tumor and put into evidence that the nanoparticles reduced tumor weight and growth rate. CD147 antibody was coupled with α-hederin loaded chitosan nanoparticles by Zhu et al.[21]

Metallic nanoparticles

Metallic nanoparticles have different physical and chemical properties while in the nanoscale than those in their bulk.[22] Most metallic nanoparticle studies have been focused on gold and silver nanoparticles due to their biocompatibility.[23]

Ma X et al, found thatSM5-1 (monoclonal antibody) can be used for targeted therapy of hepatocellular carcinoma due to its capability of arresting cell growth and inducing apoptosis. The SM5-1-conjugated gold nanoparticles (Au- SM5-1 NPs) were developed and evaluated for HCC via in vitro and in vivo techniques. SRF/ FA-PEG-PLGA NP [Poly (lactic-co-glycolic acid)] effectively inhibited the colony forming ability indicating its superior anticancer effect. The tumor suppression rates of Au-SM5-NPs for subcutaneous tumor in mice were 40.10 ± 4.34, 31.37 ± 5.12, and 30.63 ± 4.87% on 12, 18 and 24 day post-treatment, respectively by bioluminescent intensity evaluation technique. The antitumor efficacy of AuSM5-1NP was also evaluated in orthotropic HCC mice models The results represented that the inhibition rates of Au- SM5- 1NPs can reach up to 39.64 ± 4.87% on day 31 of post-treatment in tumor-bearing mice. After all three-dimensional reconstruction outcomes of the orthotopic tumor revealed that Au-SM5-1 NPs significantly inhibited tumor growth compared with SM5-1alone. This result suggested that the developed Au- SM5-1NPs has greater potential as an antibody based nano drug delivery for HCC therapy.[24]

Silver nanoparticles of the red seaweed aqueous extract for cytotoxicity in HepG2 cell line Kassas HY et al prepared Green synthesis of silver nanoparticles (AgNPs) using aqueous extract of Pterocladiellacapillacea, it acts as a reducing and stabilizing agent. These AgNPs were evaluated using

UV-VIS spectroscopy, Fourier transform infrared (FT-IR) spectroscopy, TEM and energy dispersive analysis (EDX). Silver nanoparticles were evaluated for cytotoxic activity in HepG2 cell line cultured in Dulbecco's Modified Eagle medium supplemented with 10% fetal bovine serum, 1% antibiotic and antimycotic solution and 2 mM glutamine. The biosynthesized AgNPs were of 11.4 ± 3.52 nm in size. The AgNPs showed potent cytotoxic activity against the human hepatocellular carcinoma(HepG2) cell line in a dose dependent manner. 5 lg/mL of AgNPs significantly inhibited the cell lines.[25]

Magnetite nanoparticles (MNPs)

Magnetite nanoparticles (MNPs) are particularly useful drug carriers due to their biocompatibility, biodegradability and superparamagnetic properties. In fact, their superparamagneticbehaviour is widely exploited in magnetic resonance imaging (MRI).[26] Because of their large surface area-to-volume ratio, high quantity of anticancer agents can be loaded onto the surfaces of MNPs. When administered into patients, these therapeutic agents are released from MNPs at the cancer site by passive or active targeting, thereby offering the possibility of minimizing the side effects.[27]

large-poremesoporous silica nanoparticles (LPMSNs) with an expanded pore size are capable of better mass transfer, diffusivity and permeability, and have been used to encapsulate large +biomolecules and small nanoparticles into their pores.[28] Xiaoqin Chi *et al*fabricate a novel type of magnetic LPMSNs (M-LPMSNs) with a core-shell structure. Loading of pH-responsive nanoparticles composed of nickel arsenite complexes into the pores of M-LPMSNs and further surface modification with methoxypolyethylene glycol (mPEG) or a cell-targeting ligand folic acid (FA) furnish the multifunctional arsenite-based nanomedicines. These nanomedicines could achieve controlled release of Aresenic Trioxide in acidic environments and effectively kill liver cancer cells. In vivo experiments with mice further demonstrate their curative ability for H22 solid tumors and imaging capacity for monitoring via MRI.A new type of multifunctional nanomedicines based on LPMSNs was constructed. These nanodrugs that permit controlled release and targeted delivery of arsenite, show their excellent curative ability against solid tumors and outstanding imaging capacity for monitoring during therapy. LPMSNs-based nanomedicines could serve as a promising targeted treatment for hepatocellular carcinoma and would enlighten the construction of more versatile nanoplatforms based on LPMSNs.[29]

Silica nanoparticles

Silica nanoparticles have been explored for various biomedical applications. Crystalline silica NPs were found toxic since they were found to induce chronic obstructive pulmonary disease.[30] Alternatively, amorphous silica NPs were commonly used for biomedical applications, especially for controlled drug delivery and multimodal imaging.[31] Niu Y et al reported that Nano-SiO2 treatment induced significant G1 cell cycle arrest relative to the controls in HepG2 cell lines . The G1 checkpoint is strictly regulated by cyclindependent kinase inhibitors, such as p21. The mRNA expression of p21 significantly increased in HepG2 treated with Nano-SiO2. By contrast, the mRNA expression of cyclin D1, a cyclin that associates with and functions as a regulatory subunit of CDK4/6, decreased in HepG2 cells treated with Nano-SiO2. This trend of expression of p21 and cyclin D1 was also demonstrated at the protein level by western blot assay. The results of study, together with previous reports, demonstrate that Nano-SiO2 exhibits a potential cytotoxic effect on HCC cells, regardless of whether the cancer cells are resistant to cisplatin, 5FU, Taxol, and sorafenib or not.[32]

Dendrimers

Dendrimer are highly branched synthetic macromolecules that are fabricated in a stepwise manner using units of branched monomer producing dendrimers with nearly monodisperse; homogeneous size distribution features. These features are considered advantageous, considering the counterpart polymeric molecules that are polydisperse and mostly hyperbranched.[33,34] The typical architectural structure of dendrimers includes the central core, branched monomers and surface functional groups where the branched units are organized around the central core in a layer-wise fashion, each layer is called generation.[35]

Recently, therapeutic dendrimers as a new type of efficient chemotherapy drugs have been reported. Zhang and coworkers designed the bioinspiredtryptophanrich peptide dendrimers (TRPDs) as a chemotherapy drug for efficient tumor treatment. The tryptophan-rich dendrimeric structures of TRPDs significantly induced supramolecular interactions with DNA. Most importantly, TRPDs showed excellent cytotoxicity against various tumor cells by strong membrane permeability and prominently disturbed the cell cycle.[36] Further experiment showed that the TRPDs also restrained the proliferation and boosted apoptosis of cancer cell in vivo. Shao and coworkers reported a polyacylthioureadendrimer G4 polyacylthiourea (PATU), which had inherent potent anticancer activity and the absence of cytotoxicity in mice. The anticancer activity of G4 PATU in vivo was from the exhaust of bioavailable copper, the subsequent suppression of angiogenesis and cell proliferation. Remarkably, compared to DOX, this dendrimer could efficiently inhibit multidrug resistance (MDR) and tumor metastasis, with no-cytotoxin induced side effects.[37]

REFERENCES

1. F. Sanchez, K. Sobolev, Nanotechnology in concrete–a review, Constr. Build. Mater, 2010; 24(11): 2060–2071.
2. E. Hood, Nanotechnology: looking as we leap, Environ. Health Perspect, 2004; 112(13): 2A740–9.

3. H. Yuan, F. Liu, X. Li, Y. Guan, M. Wang, Applications of nano-drug delivery systems in interventional-targeted for hepatocellular carcinoma: a review, Chin. J. Hepatobiliary Surg, 2018; 24(6): 427–430.
4. V.J. Mohanraj, Y. Chen, Nanoparticles-a review, TJPR, 2006; 5(1): 561–573.
5. O. Kayser, A. Lemke, N. Hernandez-Trejo, The impact of nanobiotechnology on the development of new drug delivery systems, Curr. Pharm. Biotechnol, 2005; 6(1): 3–5.
6. M. Gu, X. Wang, T. Boon, T.L. Hooi, D.G. Tenen, E.K.-H. Chow, Nanodiamond based platform for intracellularspecific delivery of therapeutic peptides against hepatocellular carcinoma, Adv. Therap, 2018; 1(8): 1–10.
7. D. Ghosh, S.T. Choudhury, S. Ghosh, et al., Nanocapsulatedcurcumin: oral chemopreventive formulation against diethylnitrosamine induced hepatocellular carcinoma in rat, Chem. Biol. Interact, 2012; 195(3): 206–214.
8. Sahoo SK, Labhasetwar V. Nanotech approaches to drug delivery and imaging. Drug Discov Today, 2003; 8: 1112– 1120
9. Yingchoncharoen P, Kalinowski DS, Richardson DR Lipid-Based Drug Delivery Systems in Cancer Therapy: What Is Available and What Is Yet to Come.Pharmacol Rev, 2016 Jul; 68(3): 701-87.
10. Mydin R.B.S.M.N., Moshawih S. Nanotechnology: Applications in Energy, Drug and Food. Springer; Cham, Switzerland Nanoparticles in Nanomedicine Application: Lipid-Based Nanoparticles and Their Safety Concerns, 2007; 227–232.
11. Obeid M.A., Tate R.J., Mullen A.B., Ferro V.A. Lipid-Based Nanoparticles for Cancer Treatment. Elsevier Inc.; Amsterdam, The Netherlands, 2018.
12. Nasr M., Ghorab M.K., Abdelazem A. In vitro and in vivo evaluation of cubosomes containing 5-fluorouracil for liver targeting. *Acta Pharm. Sin. B.*, 2015; 5: 79–88.
13. Grillone A., Riva E.R., Mondini A., Forte C., Calucci L., Innocenti C., de Julian Fernandez C., Cappello V., Gemmi M., Moscato S., et al. Active Targeting of Sorafenib: Preparation.
14. PE, Zhang L. Nanocarrier-mediated antioxidant delivery for liver diseases. Theranostics, 2020; 10(3): 1262-1280.
15. Celik I, Temur A, Isik I. Hepatoprotective role and antioxidant capacity of pomegranate (Punicagranatum) flowers infusion against trichloroacetic acid-exposed in rats. *Food ChemToxicol*, 2009; 47: 145–9.
16. Bishayee A, Bhatia D, Thoppil RJ, Darvesh AS, Nevo E, Lansky EP. Pomegranate-mediated chemoprevention of experimental hepatocarcinogenesis involves Nrf2-regulated antioxidant mechanisms. *Carcinogenesis*, 2011; 32: 888–96.
17. P. Pandey, M. Rahman, P.C. Bhatt, S. Beg, et al., Implication of nano-antioxidant therapy for treatment of hepatocellular carcinoma using PLGA nanoparticles of rutin, Nanomedicine, 2018; 13(8) 849–870.
18. D.W. Lee, H. Lim, H.N. Chong, W.S. Shim, Advances in chitosan material and its hybrid derivatives: a review, Open Biomater. J., 2009; 1(1).
19. Yang, C.; Zhu, R.; Wan, J.; Jiang, B.; Zhou, D.; Song, M.; Liu, F. Biological effects of irradiating hepatocellular carcinoma cells by internal exposure with 125I-labeled 5-Iodo-20 -Deoxyuridine-chitosan drug loading nanoparticles. Cancer Biother. Radiopharm, 2014; 29: 395–402.
20. Han, J.; Hou, Z.Q.; Wang, Y.G.; Guo, X. Synthesis and evaluation of hydroxycamptothecin encapsulated chitosan nanospheres for the treatment of liver cancer technology in cancer research and treatment. Technol. Cancer Res. Treat, 2015; 14: 111–117.
21. Zhu, R.; Zhang, C.-G.; Liu, Y.; Yuan, Z.-Q.; Chen, W.-L.; Yang, S.-D.; Li, J.-Z.; Zhu, W.-J.; Zhou, X.-F.; You, B.-G.; et al. CD147 monoclonal antibody mediated by chitosan nanoparticles loaded with α-hederin enhances antineoplastic activity and cellular uptake in liver cancer cells. Sci. Rep, 2015; 5: 17904.
22. S. Horikoshi, N. Serpone, Microwaves in Nanoparticle Synthesis, Wiley-VCH, Weinheim, 2013.
23. K.K. Comfort, E.I. Maurer, L.K. Braydich-Stolle, S.M. Hussain, Interference of silver, gold, and iron oxide nanoparticles on epidermal growth factor signal transduction in epithelial cells, ACS Nano, 2011; 5(12).
24. Ma X, Hui H, Jin Y, et al. Enhanced immunotherapy of SM5-1 in hepatocellular carcinoma by conjugating with gold nanoparticles and it's in vivo bioluminescence tomographic evaluation. Biomaterials, 2016; 87: 46–56.
25. Kassas HY, Attia AA. Bactericidal application and cytotoxic activity of biosynthesized silver nanoparticles with an extract of the red seaweed Pterocladiellacapillacea on the HepG2 cell line. Asian Pac J Cancer Prev, 2014; 15: 1299
26. R.A. Revia, M. Zhang, Magnetite nanoparticles for cancer diagnosis, treatment, and treatment monitoring: recent advances, Mater. Today, 2016; 19(3): 157–168.
27. M. Mahdavi, M. Ahmad, M. Haron, F. Namvar, B. Nadi, M. Rahman, J. Amin, Synthesis, surface modification and characterisation of biocompatible magnetic iron oxide nanoparticles for biomedical applications, Molecules, 2013; 18(7): 7533–7548.
28. Knezevic NZ, Durand JO Large pore mesoporous silica nanomaterials for application in delivery of biomolecules Nanoscale, 2015; 7: 2199-209.
29. Chi X, Zhang R, Zhao T, et al Targeted arsenite-loaded magnetic multifunctional nanoparticles fortreatment of hepatocellular carcinoma.

Nanotechnology, 2019 April 26; 30(17): 175101. PMID: 30654348.
30. E. Meijer, H. Kromhout, D. Heederik, Respiratory effects of exposure to low levels of concrete dust containing crystalline silica, Am. J. Ind. Med, 2001; 40(2): 133–140.
31. I.Y. Kim, E. Joachim, H. Choi, K. Kim, Toxicity of silica nanoparticles depends on size, dose, and cell type, Nanomed. Nanotechnol. Biol. Med, 2015; 11(6): 1407–1416.
32. YuexiangNiu, Engong Tang and Qingan Zhang, Cytotoxic effect of silica nanoparticles against hepatocellular carcinoma cells through necroptosisinduction. Toxicol Res, 2019. PMID: 32153770.
33. A. Nazemi, E.R. Gillies, Dendritic surface functionalization of nanomaterials: controlling properties and functions for biomedical applications, Braz. J. Pharm. Sci., 2013; 49: 15–32.
34. E.R. Gillies, J.M. Frechet, Dendrimers and dendritic polymers in drug delivery, Drug Discov. Today, 2005; 10(1): 35–43.
35. F. Aulenta, W. Hayes, S. Rannard, Dendrimers: a new class of nanoscopic containers and delivery devices, Eur. Polym. J., 2003; 39(9): 1741–1771.
36. Zhang X, Zhang Z, Xu X, et al. Bioinspired therapeutic dendrimers as efficient peptide drugs based on supramolecular interactions for tumor inhibition. AngewChemInt Ed, 2015; 54: 4289–4294.
37. Shao S, Zhou Q, Si J, et al. A non-cytotoxic dendrimer with innate and potent anticancer and anti-metastatic activities. Nat Biomed Eng, 2017; 1: 745–757.