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A Review on Nano Medicinal Delivery System for Hepatocellular Carcinoma

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***Abstract*: Hepatocellular carcinoma (HCC) remains the most common primary liver malignancy. Pain comprises one of the most pervasive and troubling symptom of HCC and may have severely negative effects on patient's quality of life. Furthermore, because HCC frequently arises in the setting of cirrhosis, treating pain related to this malignancy poses a clinical challenge The emergence of Nano medicine has enriched the knowledge and strategies of treating disease and especially some incurable diseases, such as cancer acquired immune deficiency syndrome (AIDS) and neurodegenerative diseases. Application of nanoparticles in medicine is in the core of Nano medicine. Nanoparticles can be used in drug delivery for improving the uptake of poorly soluble drugs, targeted delivery to a specific site, and drug bioavailability. Early diagnosis and targeted therapies for cancer can significantly improve patient's quality of life and extend patients' lives. The advantages of nanoparticles have given them a progressively important role in the Nano diagnosis and Nano therapy of common cancers to provide a reference for the further application of nanoparticles.**

***Keywords*: hepatocellular carcinoma, health-related QOL, analgesic, cirrhosis, nanoparticles, Nano diagnostics.**

1. Introduction

Hepatocellular carcinoma (HCC) has become an increasingly malignancy with regard to both morbidity and mortality, it is responsible for the third greatest number of cancerous deaths world-wide patients who are diagnosed with late- stage HCC have co-morbid liver disease, or receive certain loco- regional therapies (LRTS) may suffer great reduction in health- related quality of life. (HRQOL) interviews with HCC patients revealed fatigue, diarrhoea, skin toxicities and appetite adminishment as key factors affecting the quality of life most notably nine of the 10 patients queried also reported pain, assingning it an important ranking of >8 on a 0-10 scale. Pain has long been a significant concern for HCC patients and their clinicians; it may manifest as abdominal pain, metastatic bone pain, or in some cases, pain related to LRT (1). More than 80% of patients who develop HCC have underlying liver disease or cirrhosis (2) creating for pain management. Impaired hepatic function must be taken into account when administering pain medication since most traditional analgesics are metabolised in the liver, and normal doses or dosing frequency can precipitate negative side effects such as hepatic encephalopathy and somnolence (3). Procedure based pain control, especially for patients whose HCC has metastasized beyond the liver, has also been explored (4).

2. Etiology of HCC

Several risk factors are held responsible for the occurrence of HCC, but with varying importance levels in different regions. This disease mostly occurs in persons with a history of other liver diseases such as cirrhosis, which is the unique nature of HCC and points to the most important risk factors as hepatitis C&B as well as alcoholic and non-alcoholic fatty liver, other important risk factors are, toxic exposure to aflatoxins and vinyl chloride, diabetes mellitus, obesity, diet, hemochromatosis, Wilson's disease, type -2diabetes , haemophilia , and genetic factor (5).The overall average 5- years survival rate of HCC is estimated as 70% for the patients undergoing surgery(6).

3. Signs and symptoms of HCC

There are several staging systems for HCC which determine the course of treatment and treatment prognosis. HCC patients may show jaundice, bloating from fluid in the abdomen, easy bruising from coagulopathy, loss of appetite, unintentional weight loss, nausea, vomiting, and fatigue. Patients usually complain about right upper quadrant pain, weight loss, and deterioration of liver function in cirrhotic cases. Most symptoms are unspecific such as abdominal pain, malaise, fever, jaundice, and anorexia, ascites, haemorrhage, and encephalopathy may also occurs, but a large number of population may remain asymptomatic [7].

4. Diagnosis of HCC

HCC screening is recommended for high risk patients and the most frequent used surveillance methods are testing serum alpha- fetoproteins (AFP) and an abdominal ultrasound in 6mo intervals ultrasound is often the first imaging and screening modality which is used. In the patients with higher suspension of HCC, the best method of diagnosis involves a computed tomography (CT) scan of the abdomen using intravenous contrast agent a biopsy is not needed to confirm the diagnosis of HCC if certain imaging criteria are met. An alternative to a

CT imaging study would be magnetic resonance imaging (MRT) (8).

5. Definition of Nano medicine and applications

Nano medicine is defined as the application of nano technology to health. It exploits the improved & and often novel physical, chemical, & biological properties of materials at the nonmetric scale. Nano medicine has potential impact on the prevention, early &reliable diagnosis & treatment of disease, the main areas of Nano medicine are; delivery of pharmaceuticals, in vitro, in vivo, in vivo diagnostics including imaging; regenerative medicine; and implanted devices (9). Nano medicine has the ability to potential revolutionize or ability to screen, diagnose and treat conditions ranging from cancer to cardiovascular disease to diabetes (10). some Nano medicine drug delivery system and anti-cancer drugs are already in use many other applications are in various phases of clinical or pre-clinical testing, and, if found safe &effective, may reach the market more advanced Nano medicine products such as bio containers for medical diagnostics and cell treatment are earlier stages of development scientists are work on the following projects, among many others (11).

- Injection & genetic testing tools that are faster, more accurate and less invasive the conventional methods.
- Nano needle & pulsed laser surgery, that alters cell structures without damaging surrounding areas - targeted drug delivery systems, that transport the drug exactly where needed and monitor its effect.
- Nanotube – based bio sensing devices that provide in vivo diagnostic testing capabilities, such as tracking electrolyte & blood glucose levels.
- Gold- coated Nano particles (NPS) that destroy individual tumour cells while leaving nearby healthy cells unharmed.
- Intelligent synthetic biomaterials, that mimic body tissues and may eventually enable organ regeneration for mutations ate released in the market & are now routinely used in clinics (12).

6. Nano based drug delivery system

recently, there has been enormous developments in the field of delivery systems to provide therapeutic agent there are a number of drug delivery systems successfully employed in the still certain challenges that need to be addresses and an advanced technology need to be developed for successful delivery of drugs to its target sites. Hence the Nano based drug delivery systems are currently been studied that will facilitate the advanced system o t's or natural based active compounds to its target location for treatment of various aliments f drug delivery (13).

7. Fundamentals of nanotechnology based techniques in designing of drug

Nano medicine is the branch of medicine that utilities the science of Nano technology in the preclusion & cure of various disease using the Nano scale materials, such as biocompatible nanoparticles and Nano robots for various applications including, diagnosis, delivery, sensory, or actuation purpose in a living organism. drugs with very low solubility possess various biopharmaceutical delivery issues including limited bio accessibility after intake through mouth, less diffusion capacity into the outer membrane, require more quantity for intravenous intake and unwanted after effects preceding traditional formulated vaccination process. However, all there limitations could be overcome by the application of nanotechnology approaches in the drug delivery mechanism.

Drug designing at the Nano scale has been studied extensively and is by far, the most advanced technology in the area of nanoparticle applications because of its potential advantages such as the possibility to modify properties like solubility, drug release profiles, diffusivity, bioavailability and immunogenicity. This can consequently lead to the improvement and development of convenient administration routes, lower toxicity, fewer side effects, improved bio distribution and extended drug life cycle the engineered drug delivery systems are either targeted to a particular location or are intended for the controlled release of therapeutic agents at a particular site. Their formation involves self-assembly where in well- defined structures or patterns spontaneously are formed from building blocks. There are two ways through which nanostructures delivery drugs. Passive and self-delivery, in the former, drugs are incorporated in the inner cavity of the structure mainly via the hydrophobic effects. When the nanostructure materials are targeted to a particular sites, the intended amount of the drug is released because of the low content of the drugs which is can capsulated in a hydrophobic environment Conversely, in the later, the drugs intended for release are directly conjugated to the carrier nanostructure material for easy delivery. In this approach, the timing of release is crucial as the drug will not reach the target site and it dissociates from the carrier very quickly, and conversely, it's bioavailability & efficacy will be decreased if it is released from its Nano carrier system at the right time (14).

8. Bio polymeric nanoparticles in diagnosis, detection and imaging

The integration of therapy and diagnosis is defined as transonic and is being extensively utilized for cancer treatment. Theransotic nanoparticles can help diagnose the disease, report the location, identify the stage of the disease, and provide information about the treatment response in addition such nanoparticles can carry a therapeutic agent for the tumour which can provide the necessary concentration of the therapeutic agent via molecular and/or external stimuli. Chitosan is a Biopolymer which possesses distinctive properties with biocompatibility and presence of functional groups. It is used in the encapsulation or coating of various types of nanoparticles, thus producing different particles with multiple

function for their potential uses in the detection and diagnosis of different types of diseases. As per this research, chitosan based nanoparticles in combination with alginate and folic acid are tremendous vectors for the definite delivery of 5-ALA to the cc cells to enable endoscopic fluorescent detection cathe pain But (CB) is strongly associated with the metastatic process and is available in surplus in the pericellular areas where this process occurs; thus CB is important for the detection of metastasis. Pyu et al designed a CB – sensitive nonoprobe (cb-cnp) comprising a self-satisfied CB-CNP with a fuorogenic peptide attached to the tumour- targeting glycol chitosan nanoparticles (CNPs) on its surface Hyaluronic acid (HA) is another bio polymeric material this is a bioavailability negatively charged glycosaminoglycan, and is one of the main constituents of the extracellular matrix HA can bind to the CD44 receptor, which is mostly over articulated in various cancerous cells, through the receptor linker interaction. Thus, HA modified nanoparticles are intriguing for their use in the detection &cure of cancer the nanoparticles were systemically administered in the mice with tumour, & then, its effect was studied. This same research developed a variable thermostatic system using poly (ethylene glycol) conjugated hyaluronic acid (P-HA-NPS) nanoparticles for the colon cancer & targeted therapy. The therapeutic potential of PHA-NP was then investigated in different systems of the mice colon cancer. Another option that can be used is alginate which is a natural polymer derived from the brown seaweed and has been expansively scrutinized for its potential uses in the biomedical field because of its several favourable characteristics such as low cost of manufacture, harmonious nature less harmfulness and easy gelling in response to the addition of divalent actions (15).

9. Drug designing and delivery process and mechanism

Hyaluronic acid (a polysaccharide found in the extracellular matrix) has been used as a ligand – appended in several With the progression of Nano medicine and due to the advancement of drug discovery / design & drug delivery systems , numerous therapeutic procedures have been proposed and traditional clinical diagnostic methods n studied, to increase the drug specificity and diagnostic accuracy for instance, new routes of drug Administration are being explored, and there is focus on ensuring their targeted action in specific regions, thus reducing their toxicity and increasing their toxicity and increasing their bioavailability in the organism (16).In this context, drug designing has been a promising feature that characterizes the discovery of novel lead drugs based on the knowledge of a biological target. The advancement in computer sciences , and the progression of experimental procedures for the categorization &purification of proteins, peptides, and biological targets are essential for the growth & development of this sector (17).in addition, several studies and reviews have been found in this area, they focus on the rational design of different molecules & show the importance of studying different mechanisms of drug release (18) ;moreover, natural products can provide feasible and interesting solutions to address the drug design challenges, and can serve as an inspiration for drug discovery with desired physicochemical properties (19). Also the drug delivery systems have been gaining importance in the last few years. Such systems can be easily developed and are capable of promoting the modified release of the active ingredients in the body. For example; chenetal (20). Describe an interesting review using Nano carriers for imaging pelaz et al (21). and sensory applications and discussed the therapy effect of these system. In addition, provided on up- to- date overview of several applications of Nano carriers to Nano medicine and discussed new opportunities and challenges for this sector. Interestingly each of these drug delivery systems has its own chemical, physical and morphological characteristics, and may have affinity for different drugs polarities through chemical interactions (e.g. covalent bonds &hydrogen bonds) or physical interactions (e. g electrostatic and Vander walls interactions) as an example, Mattos et al (22).demonstrated that, the release profile of neem bark extract grafted biogenic silica nanoparticles (chemical interactions) was lower than neem bark extract- loaded biogenic silica nanoparticles. Hence, all these factors influence the interaction of Nano carriers with biological systems (23), as well as the release Kinetics of the active ingredient in the organism. Apart from this, other parameters, such as the composition of the nono carriers (e.g. organic, inorganic, and hybrid materials) and the form in which drugs are associated with them (such as core- shell system or matrix system) are also fundamental for understanding their drug delivery profile. Although there are several Nano carriers with different drug release profiles strategies are currently being formulated to improve the specificity of the nanostructures to targets regions of the organism (24), and to reduce the immunogenicity through their coating or chemical functionalization with several substances, such as polymer (23), natural polysaccharide (26), antibodies cell – membrane, and tenable surfactants, peptides (27) etc.

In some cases where drugs do not display binding and affinity with a specific target or do not cross certain barriers. (E. g blood-brain barrier or the blood- cerebrospinal fluid barrier (28). these ligand- modified Nano carriers have been used to pass through the cell membrane and allow programmed drug delivery in a particular environment. For example, Nano carriers owing promising results to boost antitumor action against the melanoma stem- like cells (29), Brest cancer cells (90), pulmonary adeno carcinoma cells (30), as well as to facilitate intravitreal drug delivery for retinal gene therapy and to reduce the immunogenicity of the formed protein corona(31). The hybrid Nano carriers are currently among the most promising tools for Nano medicine as they present a mixture of properties of different systems in a single system, thus ensuring materials with enhanced (i.e. theransotic systems) Despite this, little is known about the real mechanisms of action &toxicity of

drug delivery systems, which open opportunity for new studies. In addition, studies focusing on the synthesis of Nano carriers based on environmentally safe chemical reactions by implementing plant extracts and microorganisms have increased [32].

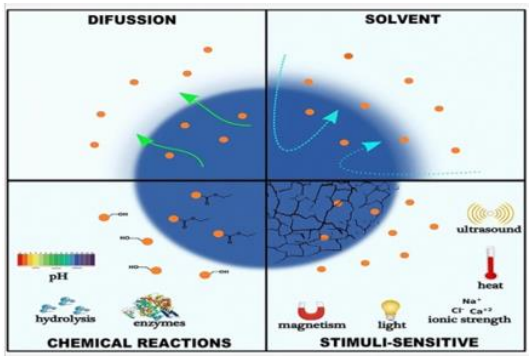

Fig. 1. Mechanisms for controlled release of drugs using different types of Nano carriers

10. Natural product based nanotechnology and drug delivery

As per the world Health Organization (who) report in developing countries, the basic needs of approximately 80% of the population are met and/ or complemented by traditional medicine (33).Currently, the scientific community is focusing on the studies related to the bioactive compounds, it's chemical composition & pharmaceutical potential of various plant species, to produce innovative active ingredients that present relatively minor side effects than existing molecules medicine (33).

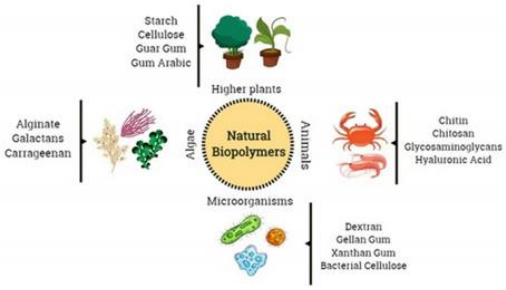

Fig. 2. Different sources of natural biopolymers

Plants are documented as a huge source of natural compounds of medicinal importance since long times & still it holds sample of resources for the discovery of new & highly effective drugs. However, the discovery of active compounds through natural sources is associated with several issues because they originate from living beings whose metabolite composition changes in the presence of stress. In this sense, the pharmaceutical industries have chosen to combine their efforts in the development of synthetic compounds (34). Several drugs that also possess natural therapeutic agents in their composition are already available commercially; their applications and names are as follows; malaria treatment (Artemotil derived from Artemisia annual, A traditional Chinese medicine plant), Alzheimer treatment (reminds, an acetyl cholinesterase inhibitor isolated from the Galan thus woronowii Losinsk) cancer treatment (Paclitaxel and it's analogues derived from the Taxus brevifolia plant, liver disease treatment (silymarin from Silybum marianum) (35). The alkaloids, flavonoids, tannins, terpenes, saponins, steroids phenolic compounds, among others, are the bioactive molecules found in plants. The scientific development of nanotechnology can revolutionize the development of formulations based on natural products. In case of the cancer disease, different organs of the body are affected, and therefore the need for the development of an alternative medicine to target the cancerous cells is the most priority among the modern researchers, however, a number of applications of Nano medicine to other aliments is also being worked on (36).

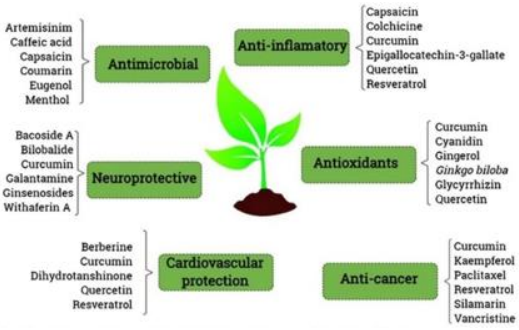

Fig. 3. Examples of natural compounds

Pharmaceutical industries have continuously sought the development & application of new technologies for the advancement & design of modern drugs, as well as the enhancement of existing ones (37) in this sense, the development of Nano technology has driven the design of new formulations through different approaches, such as driving the drug to the site of action (Nano pharmaceutical) imaging and diagnosis. (Nano diagnostic) medical implants (Nano biomaterials) & the combination diagnosis & treatment of disease (nanotheranostics) (38). In this context, it can be ascertained that the Nano- formulation offers advantages over the existing for motion if the Al is directed towards the target tissue shows increased uptake/ absorption by the cells & lower toxicity profile for the organism (39). This section is focused on berberine, cur cumin, ellagic acid, resveratrol, cur cumin &quercetin (40).Some other compounds mentioned are doxorubicin, paclitaxel And Vancomycin that also come from natural products. Nanoparticles have been synthesized using natural products. For example, metallic metal oxide & sulphide nanoparticles have been reported to be synthesized using various microorganisms including bacteria, fungi algae, yeast and so on or plant extracts (41). Presently, these natural product based material are considered as the key ingredients in the preparation & processing of new Nano- formulations because they have interesting, characteristics, such as being

biodegradable, biocompatible, availability, being renewable & presenting low toxicity (42). Gold, silver, cadmium sulfide & titanium dioxide of different morphological characteristics have been synthesized using A number of bacteria namely Escherichia coli, pseudomonas aeruginosa, bacillus subtilis & Klebsiella pneumonia (43), these nanoparticles, especially the silver nanoparticles have been abundantly studied in vitro for their antibacterial, antifungal and cytotoxicity potential due to their higher potential among all metal nanoparticles (44). The most commonly studied Nano carriers are crystal nanoparticles, liposome, Michelle's, polymeric nanoparticles, solid lipid nono particles, super paramagnetic iron oxide nanoparticles & d endrimers (45). All of these nono carriers are formulated for natural products based drug delivery. For application in cancer treatment, gupta et al (46), synthesized chitosan based nanoparticles loaded with pacltaxel (taxol) derived from Taxus brevifolia, & utilized them for treatment of different kinds of cancers. Berberine is an alkaloid from the barberry plant. Cur cumin A polyptenolic compound obtained from turmaric, have been reported to be utilized in the cure of cancers including the breast, bone, cervices, liver, lung, & prostate (47), Liposomal cur cumin formulations have been developed for the treatment of cancer (48).

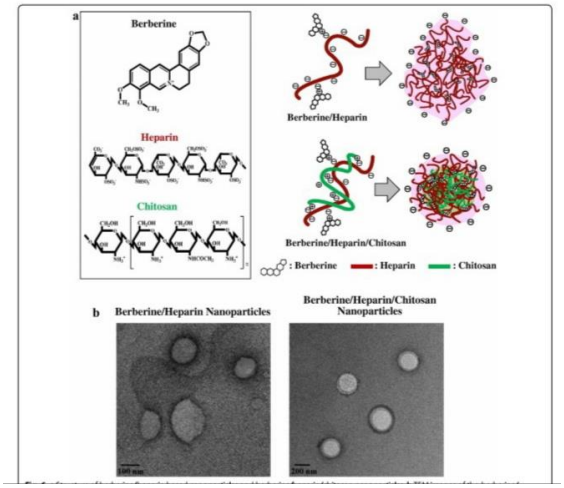

Fig. 4. a) Structure of berberine/heparin based nanoparticles and berberine /heparin /chitosan nanoparticles. b) TEM images of the berberine/heparin nanoparticles and berberine/heparin/chitosan nanoparticles (the figure is reproduced from chang et.al with required copyright permission)

11. Conclusion

The present review discusses the recent advances in Nano medicines, including technological progresses in the delivery of old &new drugs as well as novel diagnostic methodologies. A range of Nano medicinal materials, including Nano robots & Nano sensors that are applicable to diagnose, precisely deliver to targets. Initially the use of nanotechnology was largely based on enhancing the solubility, absorption, bioavailability, &controlled release of drugs. Even though the discovery of Nano drugs deals with high levels of uncertainties, and the discovery of pharmacologically active compounds from natural sources is not a favoured option today, as compared to some 50 years ago. Even though regulatory mechanisms for Nano medicines along with safety/ toxicity assessments will be the subject of further development in the future, Nano medicine has already revolutionized the way we discover and administer drugs in biological systems.

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