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Nanocarrier for the treatment of liver cancer

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Abstract-

Liver cancer is the world's greatest disease burden. Chronic infection with hepatitis B or hepatitis C viruses is a well-known risk factor and most influential determinant for HCC. Though various drugs acting via different mechanism of action are present in the market as conventional formulations for the treatment of liver cancer but they face substantial challenges regarding their bioavailability, low solubility and associated adverse effects whichgreatly limit their therapeutic efficacies. Various studies exhibit that nanocarriers can significantly increase the drug bioavailability and increase solubility. The present review provides exploring nanoformulations for liver cancer therapy. Nanotechnology has been observed for the enhanced delivery of many therapeutic agents, including drugs & genes.

Certainly liposomes & nanoparticles equipped with homing devices for the targeting of receptors over-expressed on the hepatic tissue enhanced the treatment of various liver diseases. Chemotherapy minimizes the side effects by restricting the amount of drug reachingthe rest of the body. Hepatic artery infusion or chemo given directly into the hepatic artery is regional chemotherapy that can be used for liver cancer. Future prospective for particulate nanocarriers in drug delivery for liver cancer includes chemotherapy and various nanocarriers that are mentioned in this review.

Keywords: Liver Cancer, Anticancer, Nanoformulation, b-catenin, Therapies

INTRODUCTION

Cancer is a complex disease which has a variety of factors interacts over a wide range of spatial and temporal scales with huge datasets relating to the different scales available. Therefore, these data do not always reveal the mechanisms underpinning the observed phenomena [1]**.** The ability of cancer cells to grow and their failure to respond to the usual controls on such proliferation are common features, but they evade cell death and most have no limits on their ability to replicate beyond the limits imposed by telomere length in normal cells. They are able to stimulate the formation of blood vessels to ensure a stable supply of oxygen and nutrients, and to invade normal tissues, subverting the normal processes within those tissues [2]. Cancer is popularly known as deadly disease, the rate of endurance of cancer-stricken patients has not risen remarkable over the last 30 years [3]. The gene expression outlines the multiple tissue samples and by comparing the genes of normal tissue with the diseased tissue, one can obtain disease pathology. The main challenge is to differentiate between cancerous gene expression in tumor cells and the gene expression in normal, non-cancerous tissues [4]. Various types of cancer along their symptoms, treatments and cell line are listed in table 1.

LIVER CANCER

The world's greatest disease burden is cancer. Hepatic cancer is the leading cause of cancer deaths in Asia and Africa. Chronic infection with hepatitis B or hepatitis C viruses is a well-known risk factor and most influential determinant for hepatocellular carcinoma (HCC). Authority of hepatitis virus infections has academic been well accepted through screening of donated blood for hepatitis B virus (HBV) and hepatitis C virus (HCV), use of disposable needles & syringes, and passive/active immunization opposed to HBV with HB immunoglobulin (HBIG) and HB vaccine. HBV plays the vital role in most Asian countries with hepato carcinogenesis, but in Japan around 80% of HCC cases are connected to HCV [25].

HCC report for 90% of all cases of liver cancer, with approx 800,000 new cases per year. The numberis more in Asia and Sub-Saharan Africa due to the high occurrence of hepatitis B virus (HBV) infection. Unlike other cancers, the main risk factors of HCC are well defined and include viral hepatitis (B and/or C), alcohol abuse, and non-alcoholic fatty liver disease in patients with metabolic syndrome and diabetes. Other cofactors of HCC progress, such as aflatoxin B1 and tobacco, grow the incidence of the disease if other common risk factors are present. The second most common liver cancer is intrahepatic cholangiocarcinoma (ICCA), with the highest incidence in Southeast Asia (30-40 cases/10^5 inhabitants) and low incidence in Western countries (fewer than 5 cases/10^5 inhabitants). Even so, steady increases in incidence have been reported [26].

HCC is one of the fatal cancers due to its complication, reoccurrence after surgical resection, metastasis and heterogeneity. Now a day's cancer nanotechnology has got awesome observation for the treatment of various cancers including HCC. The passive and active targeting are proceeding at a constant rate. Survey the on-going efficacy is to increase the tumor cell reaction of chemotherapy. It shows the best opportunities and challenges seen by nanotechnologies in current HCC therapy, where personalized medicine is progressively becoming the base. This review is used to increase our design and development of nanotechnology for treatment of HCC [27]. Figure 1 shows various treatment, symptoms and mortality of Global Burden Disease (GBD) study of liver cancer.

HCC is evaluated to be the fifth most common cause of cancer-related death worldwide and the fifth most common cancer diagnosis. Roughly 600,000 people grow HCC worldwide each year, with approximately 80% of cases being described in developing countries, where the occurrence of hepatitis is high. Liver cancer is

one of few cancers whose incidence is rising in developed countries. Roughly 17,000 new cases of HCC are diagnosed yearly in the USA, and the yearly incidence of HCC is approximately 50,000 in Europe. The recommended treatment of HCC include: loco regional therapies, surgical resection, orthotropic liver transplantation (OLT), radiofrequency ablation (RFA), percutaneous injection therapy and trans arterial chemo embolization (TACE), which usually apply to patients with early-to intermediate stage HCC according to the Barcelona Clinic Liver Cancer (BCLC) staging system [28].

HISTORY

IN 1986, report on incidence of cancer in the United States from 1950 to 1982 revealed that some 40 years of cancer research, centered primarily on treatment, had failed to reverse a long, slow increase in mortality. Now we update that analysis through 1994. Our analysis begins with 1970, both to provide some overlap with the previous article and because passage of the National Cancer Act of 1971 marked a critical increase in the magnitude and vigor of the nation's efforts in cancer research [32].

In humans, the event of cancer rises exponentially in the final decades of life, peak in a lifetime risk of 1 in 2 for men and 1 in 3 for women. This dramatic age-dependent extend cancer risk is charged largely by a marked grow in epithelial carcinomas from ages 40 to 80 years, as against to cancers of mesenchyme or haematopoietic origin [33].

Cancer is a chronic disease extending for many years before clinical signs are evident. The study of professional cancer in man, started with Sir Percival1 Pott's admits of chimney sweeps' cancer in 1775, the exhaustive laboratory investigations of experimental carcinogenesis during the past 40 years agree in exhibiting the long time lag between the first application of a carcinogenic stimulus or emergence of clinical neoplasia. Histologically unrecognizable lesions and lumps mark prominent stages in neoplasia, but they poorly reflect more basic biologic changes in reactivity and behavior that control the course of neoplasia [34].

Cancer is the second main source of death in the world behind cardiovascular diseases. Half of men and one third of women in the United States shall develop cancer during their lifetimes. Now a day millions of cancer people increase their life due to timely identification and treatment. The word cancer come from a Greek words Karakinos to express carcinoma tumor by a physician Hippocrates (460–370 B.C), but he was not the first to uncover this disease. Some of the earliest proof of human bone cancer was establish in mummies in ancient Egypt and in prehistoric manuscripts dates about 1600 B.C. The world's oldest reported case of breast cancer come from ancient Egypt in 1500 BC and it was noted that there was no treatment for the cancer, only palliative treatment. On the report of inscriptions, surface tumors were surgically separated in a similar manner as they are bringing out today [35].

HCC has a high occurrence rate in sub–Saharan Africa and Southeast Asia, but a low occurrence rate in the United States and Europe, with an age-standardized occurrence rate of 5.3/100,000 (men) and 1.9/ 100,000 (women) in the United States. However, it has been evaluated that 30–45% of HCC patients in the United States are connected to HBV or HCV infection. Other risk factors that have been alliance with HCC infections in the United States may include diabetes mellitus, alcohol consumption, and cigarette smoking. The family history of liver cancer and HCC could be described by clustering of HBV infection among members of the same family. However, a family history of HCC in European populations is likely to be independent of chronic infection with HBV [36].

HCC is the most recurrent histologic type of primary liver cancer. More than 75% cases of worldwide & 85% cases in developing countries have been associated to HBV & HCV, both of which rise the risk of HCC by roughly 20-fold. Other risk factors for HCC are age, male gender, heavy alcohol drinking, tobacco smoking, cirrhosis, and some scarce monogenic syndromes. HBV and HCV transmission among family members, jointly shared environmental risk factors, may be responsible for familial accumulation of liver cancer. Familial clustering of HCC has been occurred mostly in eastern Asia, where HBV infection is very common [37].

Risk factors of liver cancer include HBV, HCV, cirrhosis, heavy alcohol drinking, tobacco smoking and some rare monogenic syndromes. Out of these factors, HBV and HCV infections play the main roles in liver carcinogenesis. Liver cancer has been clustered within families, which may be due to genetic and/or environmental risk factors which are related to chronic HBV infection within families. A number of heritable factors may contribute to the risk of liver cancer, along with the environmental factors. A hospital-based case-control study of mainly Caucasian individuals described a link between family history of liver cancer & risk of HCC in those without HBV or HCV infection, suggesting an independent genetic effect [38].

HCC is diagnosed roughly a half-million people worldwide, pre-dominantly in Africa and Southeast Asia, where hepatitis B is mostly abundant. In the United States about 7% of adults use alcohol, which is 5 times greater than the occurrence of hepatitis C. Based on the strong alliance of alcohol with cancer, Recently, an International Agency for Research on Cancer working group assumed alcoholic beverages as "carcinogenic to humans," due to strong association of alcohol with cancer which is related to incident of malignant tumors of the oral cavity, pharynx, larynx, esophagus, liver, colorectum, and female breast. Alcohol react synergistically in case of chronic liver disease, such as hepatitis C, hepatitis B, and fatty liver disease, some lifestyle choices, such as smoking & obesity, to raise the risk of HCC in these disease states [39].

In 2018, liver cancer was the sixth most common neoplasm and the fourth main cause of cancer death with approximately 841000 incidences and 781000 mortalities worldwide. As compared to the all-other countries combined in the world, China report for

almost half of all recently diagnosed cases (46.7%) and liver cancer deaths (47.2%) annually. The heavy load causes increased risk factors for liver cancer including chronic hepatitis, alcohol consumption and family history of liver cancer. Hepatitis virus infections are the main causing factors for liver cancer, and it has been evaluated by our group that HBV is accountable for 44% and 54% of liver cancer cases worldwide and in China respectively, & HCV is responsible for 21% and 18%. In 2006, the occurrence of hepatitis B surface antigen (HBsAg) in China among younger than 60-year-olds was 7.2%, & occurrence of HCV antibody was 0.43%. Evidence showed that family aggregation causes liver cancer and its risk factors. Having family history of liver cancer was closely related with liver cancer risk by two to three folds, exposed that this disease is either due to genetic inheritance or due to environmental exposures or due to both [40].

In 2018 various cancer (number of new cases) and (number of death cases) occur (figure 2) like liver cancer (841,080) number of death (781,631) lung cancer (2,093,876) number of death (1,761,007) breast cancer (2,088,849) number of death (626,679) prostate cancer (1,276,106) number of death (358,989) stomach cancer (1,033,701) number of death (782,685) pancreas (458,918) number of death (432,242) kidney cancer (403,262) number of death (175,098) [41]. Incidence & mortality cases of various cancers as per report 2019 are listed in figure 3 and 4 respectively.

HCC the leading form of primary hepatic carcinoma is the most common cancer sources of death in many countries. HCC is a dominant malignancy for almost 50% of the cases dying within the 1st year of diagnosis. The maximum incidence cases are found in East Asia & Sub-Saharan and Western Africa with male:female ratio of more than 2:1. It is evaluated that over 2 billion people worldwide have been infected with HBV and over 360 million have chronic infection [43].

Liver cancer is the fifth most important cancer in the world (564 000 or 5.6% of incidence cases) but, because of the very poor prediction, the number of deaths is almost the same (549 000), the 3rd most common cause of death due to cancer. 81% cases happen in the less developed countries. The maximum incidence occurs in western & central Africa, eastern & south-eastern Asia & in Melanesia. Incidences are very low in developed countries, except for Japan, and somewhat increased incidence in some southern European countries [44]. Comparison of incidence and mortality of different types of cancer as per 2020 and 2021 are listed in table 2.

Hepatic carcinoma is the 3rd most common cause of death due to cancer worldwide and arise at a rate of 3% to 4% in patients with liver disease. Hepatocellular carcinoma generally occurs in the patients of chronic liver disease & cirrhosis. HCV & HBV & hereditary hemochromatosis are directly related to HCC, while HCC linked to other primary liver diseases is connected to the development of cirrhosis. These other primary hepatic diseases that cause development to cirrhosis involve non-alcoholic steatohepatitis, autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC) & α 1-antitrypsin (A1ATD) deficiency. Some drugs and toxins also cause the progression of HCC. The rise of incidence in these primary liver diseases is nearly doubled the age-adjusted incidence rate of hepatic carcinoma in the United States (US) in recent decades [47].

HCC is the 5th most common cause of cancer and the 2nd most common source of carcinoma-related mortality worldwide in men. A regularly rising tendency of HCC incidence and mortality has been noticed in USA and many European countries. In USA, incidence o f HCC increases by 4.5% yearly, which is the most fast growing cause of deaths due to cancer as per the report. In most of the cases of liver cancer, it is associated with liver cirrhosis, mostly due to chronic HBV & chronic HCV infections & heavy alcohol drinking. Chronic HBV infection is the leading cause of HCC worldwide and the main causing factor for HCC spread in eastern Asia & sub- Saharan Africa, while chronic HCV infection is the main risk factor in U.S.A. and Europe [48].

In liver disease induced by oxidative stress (alcoholic & non-alcoholic fatty liver & steatohepatitis, drug and chemically-induced hepatic toxicity) the antioxidant medicines suchas silymarin is the main therapeutic drug of choice. It can be revealed in part by good composition of food, in part by use of free radical scavengers such as the marketed silymarin products. Recently many researchers have been reported that shows beneficial effect of silymarin not only in chronic liver diseases induced by oxidative stress, but also in viral-induced chronic hepatitis and in primary liver cancer. Chronic hepatitis and liver cirrhosis are the main causing factors of HCC [49].

In the United States there has been a notable rise in the number of cases of HCC during the last 20 years. Primary intrahepatic malignancy (HCC and Cholangio carcinoma) was the 8th most usual malignancy in the US during the last 2 decades, with a death rate of 3.5 per 100,000. The recent rush in incidence of hepatic carcinoma in the US has been assigned to raise rates of HCV infection. Most HCCs appear along with known basic cause for chronic liver disease. However, 20%-25% of HCCs in Western countries happen with no known cause for basic liver disease or cryptogenic cirrhosis. Hypothyroidism has been connected with non-alcoholic steatohepatitis (NASH) as per the report [50].

In the USA, there are about 3.5 million people who have a persistent HCV infection. Many infected people with chronic hepatitis C remain asymptomatic for decades after contracting the infection because it is a slowly progressing disease. The long-term difficulty of infection is significant and includes cirrhosis, hepatic cancer, and hepatic fibrosis. Today, asymptomatic people become infected before HCV was recognised in 1989 as the main agent of chronic "non-A non B" hepatitis. The incidence of HCV associated cirrhosis and HCC has been increasing as this group ages and is predicted to reach a peak over the next ten years due to the fact that the risk of disease increases with the length of infection. The five-year survival rate of individuals with liver cancer further compounds the effects of such increases in the prevalence

of HCC [51].

The maximum incidence rates of liver cancer were noticed in Eastern Asia, South- Eastern Asia, Northern Africa and Southern Africa, with China considering for about 50% of all cases. About 80% of all primary liver cancer is considered as HCC. The hygiene of liver cancer is affect by that of basic liver diseases such as viral hepatitis. The uncontrolled alcoholic liver disease, obesity and diabetes show to have the possible to appear as major causes for liver cancer. Hang on the success of the control of risk factors, the hygiene of liver cancer in Korea may change [52].

Liver cancer new cases range from over 100/100,000 per year in Africa and Asia to less than 4/100,000 per year in Europe & US. Over the past century, there has been a significant influx of Asian immigrants into the US, particularly among the Japanese, Chinese, Vietnamese. Studies of residents who are Chinese and Japanese of the US showed that while both Asians were native-born and Asians born in the US died more often from liver cancer. The mortality rate among US Whites is typically higher than the proportion of Asian immigrants. A death certificate statement due to liver cancer is often inaccurate [53].

Activation of Wnt/β-catenin pathway been noticed in at least 1/3 of hepatic carcinoma & a notable number of these have mutations in the β-catenin gene. The effective difference of this pathway provides a novel technique to cure HCC. Regulating FH535 could prevent target genes from being activated by the b-catenin pathway, stop the formation of liver cancer stem cells (LCSC), and stop the spread of hepatic carcinoma cell lines. They state that FH535 inhibits the growth of LCSC and HCC lines in a dose-dependent manner and correlates with a decrease in the proportion of cells in the S phase. Remark of two prominent b-catenin targets, Cyclin D1 and survivin, is decreased by FH535 [54].

Kaempferol causes autophagy in a concentration & time-dependent manner in HepG2 or Huh7 cells, which was revealed by the notable rise of autophagy-related genes. Inhibition of autophagy pathway, by 3-methyladenine or Atg7 siRNA, strongly decreases kaempferol induced apoptosis. They assumed that kaempferol can induce autophagy via endoplasmic reticulum stress pathway. The kaempferol induced hepatocarcinoma cell death via CHOP autophagy signaling pathway, kaempferol may show a likely chemo preventive agent for patients with hepatic carcinoma [55].

Other 20 healthy subjects were taken as the control group. The serum AFP statement of hepatic tissue PI3K & Akt gene mRNA statement were pointed. The replica HepG2 has a solid utterance of AFP gene that was used. PCR & Western blot & other ways were used to regard the intracellular PI3K & Akt protein levels. Contrast with control group, cirrhosis group, the serum AFP levels in HCC group notable rise and the tissue PI3K & Akt mRNA expression also notably increase. HepG2 cells were arbitrating using AFP, where PIK & Akt protein statement notably rise. After action of AFP monoclonal antibodies or LY294002 obstacle, the PIK & Akt protein statement in HepG2 cell was necessary reduced ($P<0.05$). AFP can assist the spread of hepatoma cells via activation of PI3K/Akt signaling pathway [56].

Liver cancer stem cells (CSCs) cause tumorigenesis, progression, recurrence, drug resistance of HCC. miR-365 was down regulated in HCC and inhibited HCC cell proliferation. The function of miR-365 in CSCs cells is unclear. It is observed a significant decrease of miR-365 expression in CD133 or EpCAM-positive liver CSCs and in CSC-enhanced hepatoma spheres. Up-regulated of miR-365 inhibited liver CSC expansion by obstructing the dedifferentiation of hepatoma cells and lower the self-renewal capacity of liver CSCs. Overexposure of miR-365 in hepatoma cells down regulated the RAC1 mRNA and protein expression. RAC1 also could enhance the growth of liver CSCs. The special RAC1 inhibitor EHop-106/RAC1 over expression destroy the variation in liver CSC comparable and self-renewal capacity between miR-365 overexpose hepatoma cells & control cells, that shows RAC1 needed in miR-365 suppressed hepatic CSCs expansion. It is down regulated in hepatic CSCs & hinders the HCC cells dedifferentiation and hepatic CSCs growth by directing RAC1 signaling [57].

The nuclear receptor Farnesoid X receptor (FXR) is considered to be tumor suppressor in liver tissue. FXR might control the mTOR/S6K signaling pathway. It is revealed by changing the expression level of FXR in liver cancer cells. Over expression of FXR inhibits the proliferation of cells & causes cell cycle arrest, which rises by the mTOR/S6K inhibitor rapamycin. FXR up regulation also increases the suppression of cell growth by rapamycin. Down regulation of FXR causes the opposite effect. It is observed that ectopic expression of FXR in SK-Hep-1 xenografts suppresses tumor growth and decreases expression of the phosphorylated protein S6K. Our data give the first evidence that FXR inhibits growth of human liver cancer cells via the suppression of the mTOR/S6K signaling pathway. FXR expression may be used as biomarker of individualized mTOR suppressor therapy assessment for liver cancer patients [58].

Liver cancer is most heterogeneous and causes deregulation of several signaling pathways. Wnt/β-catenin pathway is always up regulated in HCC and it is required in carrying out of tumor initiating cells, drug resistance, tumor progression, and metastasis. Some selective drugs are developed to target components of the β-catenin pathway with anticancer activity but only a few of them have reached phase 1 clinical trials. β-catenin pathway is used for maintenance in hepato carcinogenesis and liver cancer stem cell. Evaluation is done to see the role of small molecules targeting the Wnt/β-catenin pathway with important application for treatment of liver cancer [59].

Myricetin hinder the development of HCC via apoptosis by inhibiting PAK1, a downstream effector of Ras signaling via harmonize repeal of MAPK/ERK and PI3K/AKT and their ensuing signaling Wnt/b-catenin pathway. The gene expression discloses that binding of myricetin to PAK1 causes retardation of the hallmarks of hepatocellular cancer. The docking survey provided

compelling proofs that myricetin adheres to the druggable pocket of PAK1 thereby down regulating the progression of HCC. Consequently, myricetin that block oncogenic transcription causes caspase-mediated apoptosis which is a promising agent for cancer chemoprevention [60].

Available Therapeutics

HCC has one of the weakest predictions for survival as it is poorly responsive to both conventional chemotherapy and mechanism-directed therapy. It is having a lack of therapeutic concentration in the tumour tissue coupled with the extreme toxic off-site effects reveal by these compounds. The best wrapping for holistic therapy for HCC requires three components: a potent therapeutic, a logically designed drug delivery vehicle to enhance the target site concentration of the drug, and a surface ligand that can permit a greater propensity to internalization by tumor cells compared to the parenchyma. We revealed a library carrying hundreds of compounds against HCC cells and found the natural product, triptolide, to be more powerful than sorafenib, doxorubicin, daunorubicin, which are the present standards of therapy. The potential clinical use of triptolide is very less due to poor solubility & high toxicity. We formulated tumor pH-sensitive nanoformulated triptolide coated with folate for the treatment of HCC that up regulated the folate receptor. The triptolide alone can prevent disease spread, but at the cost of significant toxicity [61].

FOLFOX is a combined regimen of folinic acid (FnA/FOL), fluorouracil (5-Fu/F) & oxaliplatin (OxP, OX), which is used in the treatment of HCC. Present development of nano delivery systems showed enhancing anticancer efficacy and helps in reducing side effects of FOLFOX. Nano-Folox causes OxP-mediated immunogenic cell death (ICD)-associated antitumor immunity, which importantly suppressed tumor growth in the orthotropic CRC mouse model when administrated in combination with free 5-Fu. A Nanoformulation (termed Nano-FdUMP) carry FdUMP (5-Fu active metabolite) was newly synthesized by using nano precipitation method which is used along with Nano-Folox for the treatment of HCC. Synergistic efficacy was attained in HCC mouse models. Combination of Nano-Folox/Nano-FdUMP and anti-PD-L1 antibody significantly suppressed HCC [62].

The sorafenib (sfb) Nano formulation made from a clinically safe polymer PEG-b-PLA improved the bioavailability and effectiveness in HCC therapy. NP-sfb could be usefully internalized by HCC cells, including HepG2, Hepa1-6, and H22, and could stop their proliferation. The in vivo study showed the superiority of the nano formulation compared with free drugs. NP-sfb showed a notably improved therapeutic effect at the same dose or even much lower injection dose. Mechanistic studies revealed that NP-sfb not only inhibited tumor angiogenesis and tumor cell proliferation as a TKI inhibitor but also reprogrammed the immunosuppressive microenvironment of HCC by exhaust tumor intrusion of myeloid cells and macrophages and raise the intrusion of cytotoxic T-lymphocytes. It is effectual approach to enhance the therapeutic effect of sfb for HCC therapy [63]. Table 4 indicates various anticancerous drugs used in HCC with their mechanism of action and route of administration.

The most of patients with liver cancer die in 1 year due to poor patient compliance. HCC is medically treated by chemotherapy along with surgery. The anticancer drugs have more toxicity & less specificity, causes systemic toxicity & severe complexity. To control the severe complexity of carcinoma chemotherapy on normal tissues, tumor targeting drug delivery systems need to be explored, which provides the impulsion to grow targeted therapies to attain higher efficacy with minimal side effects. The nanostructures can be used as good drug carriers, show advantages of good solubility and high drug encapsulation efficiency, high cellular uptake and desirable pharmacokinetics that are accumulated at the tumor site due to increased permeability and retention (EPR) effect with the goal to reduce toxic effects on healthy tissues while maintaining antitumor efficacy [64].

Kaempferol, quercetin, Myricetin were considered as the potential curative flavonoids in some types of cancers. The main goal of cancer treatment had been to stop the direct induction of cancer cell proliferation by the MAPK/Erk signalling pathway. In this study, total Erk1/2 protein expressions were compared to the anti-proliferative effects of these three flavonoids on human hepatocellular carcinoma cell (HepG2) and baby hamster kidney cells (BHK-2) [65].

Myricetin inhibits the proliferation of human hepatoma HepG2 cells and to induce G2/M phase arrest. The basic mechanisms of myricetin action have yet to be disclosed. The study was to find out the molecular mechanisms of cell cycle arrest due to myricetin in HepG2 cells. The MTT assays revealed that exposure of HepG2 cells to myricetin induce G2/M phase arrest. Western blot survey revealed that myricetin enhanced the protein levels of the p53/p21 cascade, and reduced the Cdc2 and cyclin B1 protein levels in HepG2 cells. Myricetin therapy helps in the up regulation of Thr14/Tyr15 phosphorylated (inactive) Cdc2 & p27, and the down regulation of CDK7 kinase protein, CDK7-mediated Thr161 phosphorylated (active) Cdc2 [66].

Oxidative DNA damage & its repair in primary rat hepatocyte cultures was explored for 4 hr of incubation with the toxic iron chelate, ferric nitrilo triacetate (Fe-NTA), in the presence or absence of the strong flavonoid myricetin. Seven DNA base oxidation results were evaluated in DNA by gas chromatography mass spectrometry in fixed ion monitoring mode. This was confirmed by RNA blot analysis of DNA polymerase β gene expression which was elicited by myricetin in a dose-dependent manner. These constitute a novel & native mechanism of cytoprotection by myricetin against iron-induced genotoxicity via stimulation of DNA repair action. The iron-induced DNA damage & inefficient repair in hepatocytes could be linked to genotoxicity and most likely to hepato carcinogenesis; transition of this activity in vitro by myricetin might be

pertinent in further precaution of liver cancer obtained from iron overload pathologies [67].

Autophagy is a preserved biological event that conserve cellular homeostasis through the clearing of damaged cellular parts under cellular stress & offers the cell building blocks for cellular survival. Deviation in autophagy causes many human pathologies, dementia, cardiovascular diseases, leishmaniosis, influenza, liver diseases & cancer like HCC. Present treatment plan with liver cancer patients show variable victory rates and fewer prognoses due to their drug resistance and toxicity. The patho physiological devices are targeted during the growth of anti-liver cancer drugs. Plant polyphenols causes angiogenesis & metastasis in liver cancer via involvement of many intracellular signals & low the risk against HCC [68].

For many flavonoids, the connection between low in vivo bioavailability and strong pharmacological activity is still unclear. Analysis of the changes in the gut microbiota caused by flavonoids is a promising strategy for offering helpful hints to clarify the mechanism of action. Here, we examine the impact of myricetin supplementation on rats' nonalcoholic fatty liver disease (NAFLD) caused by a high-fat diet (HFD) and study the relationships with the gut microbiota using high-throughput analysis. Myricetin's anti-NAFLD actions are linked to changes in the composition of the gut micro biome. Through adjustments to the gut microbiota that are connected to faecal butyric acid and protection of the gut barrier function, myricetin lowers hepatic lipid production and inflammation. This study might make it easier to understand how flavonoids with low bioavailability work [69].

Current treatments are poorly tolerated and ineffective in people whose HCC could not be discovered early. Therefore, the urgent need for effective alternative medicines. Diethylnitrosamine (DEN) was used as an initiator and 2-acetylaminofluorene (2-AAF) as a promoter in this work to cause HCC. Hepatocytes and mitochondria from rat liver were extracted, and factors relating to apoptotic signalling were then examined in the mitochondria and cellular levels [70]. Different herbal compounds used in treatment for hepatic carcinoma are listed in table 3.

Flavonoids, is a class of polyphenols mainly exist in food and medicine, have great pharmacological effects. Basic effects of flavonoids include anti-oxidative, anticancer, and anti-inflammatory effects etc. They have low bioavailability that limits their clinical application; due to their intestinal absorption and metabolism. The field of medicine and the traditional technology of drug delivery do not attain the aim of high efficiency, stability and targeting. Nanoparticles are used as drug delivery porter which is good to improve the stability of drugs, widen the time of drug action & to increase drug efficacy & decrease adverse reactions [89].

A common class of naturally occurring polyphenolic chemicals known as flavonoids has recently gained prominence as anticancer medications. Dietary flavonoids do not have a strong anticancer effect because of their poor solubility, quick metabolism, and rapid absorption. Nanocarriers enhance bioavailability of flavonoids. The anticancer properties of flavonoid nanoparticles was estimated by in-vitro and in-vivo study. The potential anticancer activity was done mostly on HepG2 hepatic carcinoma cells & melanoma cells [90].

Low water solubility and bioavailability of many natural compounds are their main limitations, which are severely restricting their development as active medicinal components. Table 5 indicates various drugs which are used in hepatic carcinoma along with their limitations. Myricetin is a nutritional supplement that risen the energy level & vitality of the body. It is noted that myricetin has poor water solubility and stability, which limits its use as an antioxidant and useful food additives for hydrophilic foods. Additionally, the issue affects the pharmaceutical industry as well because formulation is tough to finish. The majority of investigations showed that myricetin could be obtained in salt forms, suggesting a potential improvement in solubility [91].

Clinical use of myricetin is restricted due to its pharmacodynamics properties. Many researchers worked on varieties of plan to raise the solubility and resulting bioavailability of this compound. Use of myricetin as an anti-cancer treatment is constrained by its poor bioavailability, and water solubility, also toxicity profile of myricetin against normal cells needs to be investigated. Although there are further methods to improve its distribution and bioavailability, such as HP-β-CD/myricetin inclusion and encapsulated form, new techniques need to be developed to optimize the pharmacokinetics and improve the administration to increase its potential for therapeutic use [92].

The less concentration of myricetin has some effect on the ability of HepG2 cell proliferation but a high concentration of myricetin could inhibit cell proliferation notably. Furthermore, we discovered that myricetin administration elevated the expression of the autophagy biomarker LC3-II, and that this effect appeared to be dose-dependent. Myricetin could trigger the production of autophagosomes, as evidenced by the enhanced punctuate distribution of GFP-LC3 following a 24-hour treatment. Because autophagy is a dynamic process, we had to look at the autophagic flux to understand how myricetin affected the entire autophagic process as a whole [93].

For many flavonoids, the connection between low in vivo bioavailability and strong pharmacological activity is still unclear. Here, we examine the impact of myricetin supplementation on rats with nonalcoholic fatty liver disease (NAFLD) brought on by a high-fat diet (HFD) and study the relationships with the gut microbiota using high-throughput analysis. The results of faecal microbiota transplantation and 12-week myricetin administration show that myricetin considerably slows the progression of NAFLD [94].

Due to poor water solubility, 50% of medicines given orally have limited therapeutic efficacy. Natural phytochemicals have shown promise in the treatment and/or prevention of a number of illnesses, including hepatitis, diabetes, cancer, and arthritis. Most

phytochemicals struggle with issues including poor water solubility and poor metabolic stability, which restricts their application in clinical settings [95].

The buccal mucosa typically functions as a barrier restricting the permeability of released active component because the oral mucosa is generally thought to be more permeable than skin (eg, large molecules). Lipophilic medications normally follow transcellular transport across the lipid bilayer, whereas hydrophilic substances and big or highly polar molecules typically follow paracellular transport. Its lipophilic characteristics, extremely low aqueous (AQ) solubility, and extensive metabolism, which provide poor bioavailability and pharmacokinetic profiles, restrict its usage. In order to improve the solubilization and distribution of Gen for various therapeutic applications, such as antioxidant and cancer chemoprevention, nanoscale vehicles have therefore lately been created and explored [96].

However, their use in the food and medical industries is quite constrained because of their susceptibility to environmental factors and low bioavailability. These restrictions can be removed by using nanoformulations, which are effective drug delivery system (DDS). This will increase the pharmacological effects of polyphenols. Although the fundamental obstacle to the use of polyphenolic chemicals is removed by putting them onto nanoparticles, there are still worries about their toxicological safety once they have entered the human body [97].

A common class of naturally occurring polyphenolic chemicals known as flavonoids has recently gained prominence as anticancer medications. Unfortunately, the anticancer potential of dietary flavonoids is insufficient due to their poor solubility, quick metabolism, and absorption. By using nanocarriers, flavonoids' bioavailability can be increased. The majority of research examining flavonoid nanoparticles' anticancer abilities is preclinical. By boosting the anti-tumor effect or lowering the systemic toxicity of the pharmaceuticals, flavonoid nanoparticles can also support the anti-tumor effect of medicines used in cancer therapy [98].

Application of nanotechnology to natural products is a rapidly growing field. The delivery of natural chemicals in the treatment of cancer and other chronic human diseases benefits greatly from the use of nanotechnology. The bioavailability, targeting, and controlled-release features of natural compounds can be improved by the addition of nanoparticles. Only a few reviews with constrained scopes have, to our knowledge, been published on nanotechnology focused on natural products [120].

Out of many strategies nanocarrier systems have been widely developed globally for the efficient delivery of lipophilic nutraceuticals. Nanocarriers have a number of benefits due to their small size, including increased aqueous solubility, increased residence time in GI tract regions, improved physicochemical stability in GI tract, increased intestinal permeation, controlled release in GI tract, intracellular delivery, and transcellular delivery. It should be taken into account that nanocarriers used in food systems or oral administration systems must be stable in food formulations, non-toxic, biodegradable, and suitable to various food processing systems [121].

Nanotechnology-based drug delivery systems such as liposomes, dendrimers, niosomes, nanocrystal solutions, polymeric nanoparticles developed to minimise systemic side effects and improve patient compliance. Increased active absorption, which results in improved bioavailability, is a notable benefit of nanotechnology. Table 6 shows different types of nanocarriers of liver cancer with their outcomes. An alternate release mechanism is provided by pH-responsive nanomaterials, which rely on the acidic conditions inside tumour and inflamed tissues (pH 6.8) and cellular compartments such endosomes (pH 5.5–6) and lysosomes (pH 5.5–6) (pH 4.5–5.0) [122].

Nanoformulations have been extensively studied for use in medicine delivery. These make use of nanomaterials that range in size from 1 to 100 nm. Nanoparticle-incorporated compounds are superior in terms of their solubility, effectiveness, safety, and pharmacokinetics because of their small size and large surface area. The use of nanoformulations for the delivery of lipophilic drugs and/or active compounds offers a number of advantages, including enhanced intestinal absorption and protection from gastrointestinal degradation, longer systemic circulation, and regulated drug release. These, in turn, increase the bioavailability and boost the effectiveness of medicines or active pharmaceutical ingredients that are taken orally [123].

A nanoformulation enhances various features like solubility, oral bioavailability, permeability, stability and efficacy of drugs etc. [124]. Nanoparticles and nanocarriers range in size from 1 to 100 nm. In addition to increasing their bioavailability, phenolic compounds can be loaded onto nanoparticles to protect and release active ingredients in a regulated manner. For the transport of polyphenolic chemicals, numerous nanoparticles have been created recently, including liposomes, phospholipid complexes, niosomes, protein-based nanoparticles, micelles, emulsions, and metal nanoparticles [125].

The solubility and chemical stability issues with therapeutic molecules that have been reported and utilised to treat cancer can be resolved with the aid of nanoparticles. Free therapeutic pharmaceuticals can be incorporated into nanoparticles to give them unique benefits such enhanced bioavailability, site-specific targeting, controlled release, reduced side effects, and increased therapeutic efficacy to cure cancer and its unfavorable side effects [126].

Any cancer-targeted drug delivery system must be able to destroy every cancer cell while having the least amount of negative impact on healthy cells. Large drug doses are currently used in conventional approaches to treat cancer cells; however this ultimately results in unfavorable side effects. The two difficulties listed above could potentially be lessened via nanoformulation [127].

The drawbacks of traditional drug delivery systems, such as limited bioavailability, multidrug resistance, and non-specificity, have been hopefully solved by nanotherapeutics. These nanoformulations are discovered to have greater proximity and fewer side effects. The

ability of the nanoparticles to target tumour cells specifically enhances the specificity and effectiveness of cancer therapy modalities, improving patient response and survival. A stronger pharmacological response and more favourable clinical outcome for patients may result from the merging of phytotherapy with nanotechnology in the clinical context. [128]. Figure 5 shows different types of nanocarriers used in treatment of hepatocarcinoma (HCC) [129-130].

Nanocarriers in Liver Cancer Magnetic nanoparticle-

These are generally used as drug carriers owing to their biodegradability, biocompatibility & super-paramagnetic properties, which allow them for magnetic resonance imaging (MRI) detection. The lead of MNPs include their large surface area, small particle size, magnetic response, high coupling capacity, high volume ratio & ability to deliver a high amount of anticancer drug at the surface. Magnetic nanoparticles itself are used as the active component of Ferro fluids, recording tape, flexible disk recording media, as well as biomedical materials & catalysts. There are various property of materials collected of magnetic nanoparticles are both like intrinsic properties of the particles & the interactions between particles.

Doxorubicin loaded porous magnetic nanoclusters (PMNCs) with lipiodol

Dox pMNCs 0.5 ml (0.2 mg Dox, 1.4 mg pMNCs) & Dox within iodinated oil 0.5 ml (0.2 ml of Dox-iopamidol, 0.3 ml of Lipiodol) were infused near hepatic arteries to target liver tumors in a rabbit. Dox-pMNC lipidol showed significantly higher apoptosis rate (74.1%) than Dox-pMNCs group (56.2%) and Dox lipiodol (61.8%). The advanced uptake & longer retention of Dox pMNCs administered with lipiodol produced higher apoptosis levels. The results show the assist release of Dox pMNCs can be notably increase by lipiodol that raise retention. The MRI & histological assay revealed that the long-term drug release & retention of Dox-pMNCs within iodinated oil notably improved hepatic carcinoma cell death.

FA conjugated magnetic nanoparticles (MNs) of sorafenib

FA-conjugated PEGylated PLGA NPs have pH dependent (acidic medium) carry drug release mainly in cancer cells. The cellular uptake potential goes into BEL7402 HCC cell lines & found that FA-PLGA- MNP shows notably more uptake than non-conjugated NP or pure drug. FA-PLGA-MNP – (IC_{50} value 0.84 µg/ml) successfully moderates the cancer cell proliferation & has raised the anticancer efficacy than that of free drug (IC_{50} value 2.35 µg/ml) or non-targeted one (IC_{50} value 2.48 µg/ml). The multifunctional nanoparticles are the best to improve the therapeutic response in hepatic carcinoma.

Polymeric Nanoparticle

These polymers offer main advantages including protection of the contents against degradation, controlled release of the therapeutic agents & enhancement of the site-specific delivery. The structure of polymeric vehicles can be alter with functional groups include PEG moieties & targeting agents to improving the delivery of the drug & gene cargos to tumors. Many polymers with different chemical properties have showed for co-delivery of cytotoxic drugs/other curing agents (e.g. chemosensitizers, differentiation-inducing and neovasculature disruption agents). This type of NPs are made of synthetic polymers (e.g. dendrimers), poly (dl-lactide co-glycolide) (PLGA), poly (ethylenimine) (PEI), poly (l-lysine) (PLL), poly (ethylene glycol) (PEG), polymeric micelles and natural polymers (e.g. chitosan (CS)

Nanogels Carriers

Nano gels are potential polymeric Nano particulate systems having excellent biomedical applications that offer time-controlled compound delivery as well as active drug targeting. Nanogels known for their more drugs loading capacities & controlled release regulated by diverse complex densities of the polymers used in the preparation of the nanogels that affect the swelling characteristics of nanogels. The spherically shaped nanogels are nanometer sort (10s-100s of nm i.e., upto about 700 nm).

Erythrocyte-loaded pravastatin CNG carriers for therapy of HCC

Chitosan nanogels (CNG) are best carriers for carcinoma targeting quickly remove from circulation by reticuloendothelial system (RES). To control this problem formulated erythrocytes loaded pravastatin chitosan nanogels. Pravastatin chitosan nanogels show negative zeta potential, rising of haemolysis, marked phosphatidyl serine exposure and stomatocytes shape in comparison to control unloaded erythrocytes (PR–CNG).Moreover the pravastatin chitosan nanogels show 36.85% of entrapment ability, 66.82% of cell recovery & release persistent to that of hemoglobin over 48 h, pravastatin chitosan nanogels decreased cells viability of HepG2 cells line by 28% in comparison to unloaded erythrocytes (UER). The pravastatin chitosan nanogels are good drug carriers to target hepatic carcinoma.

Docetaxel (DTX)-loaded polydopamine nanoparticles

DTX-loaded Nano formulations were prepared using polydopamine as surface modifying agent. This Nanoformulation was also contained D-a-tocopherol PEG-1000 succinate poly (lactide) (pD-TPGS-PLA/NPs) as a target agent for liver cancer cells. The In vitro studies showed TPGS-PLA/NPs (126.5 ± 7.2 nm), pD-TPGS-PLA/NPs (205.2 ± 8.3 nm) &Gal-pD-TPGS-PLA/NPs (209.4 ± 5.1 nm) have common free profiles of DTX. DTX-loaded Gal-pD- TPGS-PLA/NPs (25 µg/ml) reticent the extension of HepG2 cells & show higher potency than TPGS-PLA/NPs (2.5 µg/ml), pD-TPGS-PLA/NPs (12.5 µg/ml) & a marketed DTX formulation (Taxotere®). The In vivo shows that giving DTX-loaded Gal-pD-TPGS- PLA/NPs (10 mg/kg DTX) are able to reduce the size of hepatoma markedly in BALB/c nude mice. The results show best drug delivery system targeting hepatic carcinoma.

Liposomes

The size of liposomes ranges from 5-200 nm, announce to

encapsulate hydrophilic/ lipophilic drugs in the aqueous phase or bilayer membrane phase by using the different parts of vesicles& the liposomes were in shows in the field of DDS. The small size, chemotherapeutic agents, such as doxorubicin, vincristine, gemcitabine or cisplatin, have unfavorable pharmacokinetics & a suboptimal bio distribution, represent as short blood half-life. Liposomes as a carrier have advantages like high biocompatibility, less immunogenicity, protection of the drugs or active groups, prolongation of drug half-life, reducing toxicity & more efficiency etc.

SF/GD co-loaded liposomes

The sorafenib & gadolinium co-loaded liposomes (SF/Gd-liposomes) was to enhance the bad water solubility of sorafenib & advance its bio distribution .Solubility of SF in SF/Gd- liposomes was indicative to improvement from 0.21 to 250 µg/mL when contrast to single formulation. So the SF/Gd-liposomes to be the best nanocarriers for in vivo visualization of diagnosis as well as for therapy of HCC.

Metallic Nanoparticle

Metallic NPs have special property due to their different chemical & physical properties that make different from other NPs. Silver & gold NPs are widely used as most often as metallic NPs due to their biocompatibility. Metallic nanoparticles have absorbed scientist are now heavily employ in biomedical sciences & engineering. They are a basis of interest because of their vast potential in nanotechnology.

Gold Nanoparticle

Colloidal gold as well-known as gold nanoparticles, is a suspension (or colloid) of nanometer sized particles of gold. The colloidal solution again an intense red colour (for particles lower than 100 nm) or a dirty yellowish colour (for larger particles). These interesting optical properties of these gold nanoparticles are due to their special interaction with light.

Silver Nanoparticles

Silver nanoparticles have a particle size btw 1-100 nm in size. Gold nanoparticles, ionic silver have a long history & were at first used to stain the glass for yellow. Besides it appear that ionic silver, the right quantities, is good in treating wounds. The silver nanoparticles are now exchanging silver sulfadiazine as an effective agent in the therapy of wounds. Besides the attractive physiochemical properties these nanomaterials have shown tolerable attention in biomedical imaging using SERS. Actually the surface Plasmon resonance & large effective scattering cross-section of individual silver nanoparticles make them ideal candidates for molecular labelling. More targeted silver oxide nanoprobes are currently being developed.

SM5-1 conjugated gold nanoparticles (AuNPs)

SM5-1 (monoclonal antibody) used for targeted treatment of liver cancer proper to its capability of arresting cell growth & inducing apoptosis. The (Au- SM5-1 NPs) were developed & evaluated for HCC via in vitro & in vivo method. 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- & 24-day post-treatment, properly by bioluminescent intensity evaluation method. The antitumor efficacy of AuSM5-1NP was also assessing in orthotropic HCC mice models. The results act 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 3-dimensional reconstruction result the orthotropic tumor shows that Au- SM5-1 NPs notably restrict tumor growth contrast with SM5-1alone. The data shows nano drug delivery for HCC therapy.

Silver nanoparticles of the red seaweed aqueous extract

Silver nanoparticles (AgNPs) used aqueous extract of Pterocladiella capillacea, it work as a reducing & stabilizing agent. These AgNPs were assess using UV-VIS spectroscopy, Fourier transform infrared spectroscopy, TEM & energy dispersive analysis (EDX). Silver nanoparticles were assess for cytotoxic activity in HepG2 cell line cultured in Dulbecco's Modified Eagle medium supplemented with 10% fatal bovine serum, 1% antibiotic & antimycotic solution & 2 mM glutamine. Biosynthesion of AgNPs was of 11.4 ± 3.52 nm in size. The AgNPs show strong cytotoxic activity against the human hepatocellular carcinoma (HepG2) cell line in a dose dependent manner at 5 µg/ml.

Nanoemulsion

Occasionally found that nanoemulsion penetrates easily through rough skin. The effect of nanoemulsion minimizes the additional utilization of special penetration rise which manage for incompatibility of formulation. Nanoemulsion formulation is the stable alternate for the liposomes & vesicle type of delivery systems. Nanoemulsion formulation administered by many routes of body. There is various reported evaluation which support the administration of nanoemulsion formulation through parenteral, oral, topical, nasal & ocular route. Formulations may be used to improvement the bioavailability of bad water soluble drug by developing oil in water type of nanoemulsion.

Silymarin nanoemulsion

Silymarin nanoemulsion (NEs) was produced for by mouth against human liver cancer without felling of normal cells. Nanoemulsion was produced using Sefsol 218 (5.8% v/v) as oil phase, Kolliphor RH40 & PEG 400 (Smix; 2:1; 28.99% v/v) as surfactant & co-surfactant, while distilled water (65.22% v/v) was used as aqueous phase by aqueous titration method. Mean particles size of silymarin NEs were 21.24 ± 0.291 nm & the polydispersity index was 0.104 ± 0.016. Silymarin nanoemulsion show better drug release (97.75%) profile compared to conventional silymarin suspension that is LimarinVR. The AUC of improved silymarin NEs was found to be 308.51 ± 4.23 mg/mL which was 8-fold superior than marketed suspension (37.43 ± 2.89 mg/mL) & 17-fold better than standard suspension (17.82 ± 7.32 mg/mL). The silymarin NEs (0.2 mg/mL) reduced the cell viability to 89.83% ($p<0.05$) as contrast with control & it produced cytotoxic effect in HepG2 cell line but no effect on normal cells (Chang liver cells). Silymarin NEs show a notable raise in ROS intensity in dose dependent manner that

were 121.43, 156.77 and 195.53% at 0.5, 1 &2.5 mg/mL concentration, properly of NEs compared with untreated cells [131-149].

CONCLUSION AND FUTURE PROSPECTIVE

Cancer is popular as a deadly disease. The rate of endurance of cancer-stricken patients has risen remarkable above the last 30 years. There are various symptoms (Poor appetite, Anorexia, Weight loss) etc., treatments (Liver transplantation, Surgical resection) etc and cell lines (HepG2, SMMC-7721) etc of liver cancer. Nanotechnology has been observed for the enhanced delivery of many therapeutic agents, including drugs & genes. Certainly liposomes & nanoparticles equipped with homing devices for the targeting of receptors over-expressed on the hepatic tissue enhanced the treatment of various liver diseases. Chemotherapy is used for liver cancer. There is various pathway used in treatment of HCC like Wnt/b-catenin pathway, Autophagy pathway, mTOR/S6K signalling pathway etc. It includes various available therapeutics of HCC in herbal therapeutics like (Phyllanthus, Silymarin, Glycyrrhizin, and Liv 52) and apart from herbal therapeutics it includes (Cetuximab, Cisplatin, Doxorubicin, Epirubicin, and Erlotinib) and so on. These therapeutics include various limitation mostly drug having low bioavailability, low solubility or less logP value mostly in drug whose dosage form is in tablet/capsule & nanoformulation overcome all these limitations that's why nanotechnology is a promising approach in resolving several constraints of liver cancer. There are various nanocarriers used in liver cancer (metallic, magnetic, nanoemulsion, liposomes, dendrimers, miscelle NPs), these carriers include many drugs that used in therapy of HCC like (metallic NPs include red seaweeds, SM5-1 conjugated), (Magnetic NPs include doxorubicin loaded, folate conjugated), (Liposomes include sorafenib & gadolinium) and so on. Advances in therapeutic application for cancer management are increasing day-by-day. Exploring nanocarrier for cancer therapeutics is increasing. Besides enhancing delivery of existing drugs, these nanocarriers in the future can enhance the therapeutic index of biotech drugs also. These types of approaches will open new vistas and are more effective than conventional based therapy due to high bioavailability and less side effects.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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