BioGecko

Vol 12 Issue 03 2023

ISSN NO: 2230-5807

Concise review on strategies of nanomedicine targeting to hepatocytes

Anil Kumar[1]*, Raghwendra Waghmode[2], Vaishnavi Nalawade[3], VipulSansare[4]

[1]Faculty of Pharmaceutical Sciences and Nursing Vivekanand Global University, Jaipur, Rajasthan, 303012, India.

[2]Faculty of Pharmacy, Krishna VishwaVidyapeeth, Karad, Maharashtra, 415539, India..[3]Department of Pharmacognosy, Indira Institute of Pharmacy, Sadavali, Maharashtra, 415804, India.

[4]Department of Pharmaceutics, Dnyandeep College of Pharmacy, Boraj, Khed, Maharashtra, 415709, India.

Address for correspondence: rxanilgodara29@gmail.com

Abstract

Liver disease especially liver cirrhosis is major cause of death in India. The major causative factor responsible for liver cirrhosis is chronic alcohol consumption. Numerous drugs have been approved for management of liver cirrhosis. However, these drugs suffers with common limitations like limited solubility, off-target distribution and poor bioavailability. The nanotechnology domain has solved many drawbacks associated with conventional delivery of drugs. Numerous scientific experts have attempted to load drugs in nanocarriers. Various nanocarriers like liposomes, nanoparticles, lipid nanoparticles, nanostructured lipid carriers and niosomeshave been evaluated for delivery of liver protective drugs. Furthermore, the nanocarriers can be surface modify with liver targeting ligand for better delivery of drugs directly at liver cellular level. The receptors like carbohydrate receptors, lactobionic acid receptors and asioglycoprotein receptors have been utilized targeting of drug loaded nanocarriers to hepatocytes. Thus current book chapter represent liver targeting concept with nanocarriers by highlighting various recent investigations.

Keywords: Liver targeting, liver diseases, Hepatocytes, Nanomedicines, Nanoparticles

Introduction

Liver diseases are worldwide major causes for morbidity and mortality. Liver cirrhosis is a significant cause of global health burden, with more than one million deaths [1]. The viral hepatitis, metabolic disorders, malnutrition, alcohol abuse, or autoimmune diseases are causes of chronic liver injury and subsequent complications such as liver cirrhosis or hepatocellular carcinoma. Novel nanocarrier based drugs delivery may overcome many of the hurdles of conventional drug delivery systems, because they bear the advantage of enabling a cell targeted drug delivery based on binding to a specific surface receptors. Cell-specificity increases the drug concentration at the defective/diseased cell or tissue, while reducing toxicity to normal cells. This is an important feature of nanocarriers, since many common drugs have limited efficacy because their concentration at the target site is too low. The use of drug loaded nanocarriers for management of liver diseases has been reported in many literatures.

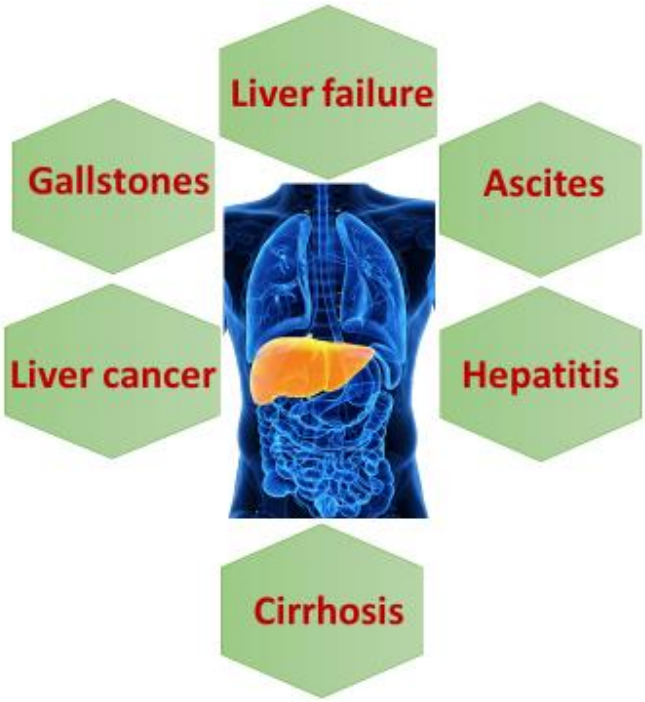

Figure 1 Overview of hepatic diseases.

Mechanism of liver injury

The etiology and mechanisms of liver injury is complex, many factors contribute in liver injury. The mitochondrial dysfunction due to variety of chemicals results in release of excessive amount of reactive oxygen species leading to hepatic cells injury[2]. The accumulation of bile salts inside the liver due to the hepatocyte injury promotes liver damage. Two important pathways may be responsible for toxicity – direct hepatotoxicity and adverse immune reactions[3]. These reactive metabolites interact with cellular macromolecules like proteins, lipids and nucleic acids which result in lipid peroxidation, DNA damage, protein dysfunction and oxidative stress. In most of the cases, hepatotoxicity is generally initiated by the bioactivation of drugs into chemically reactive metabolites. Ethanol metabolism results in protein conjugation, free radical generation and lipid peroxidation. Ethanol plays an important role in methionine metabolism leading to liver injury.

Recently, it has been reported that hepatocellular injury is because of the inflammatory cells that have been attacked by the stressed hepatocytes. The inflammatory response is mediated by cytokines, mainly interleukin-1b (IL-1b) and tumour necrosis factor-a (TNF-a). The elevated level of these cytokines induces liver injury[4].

Four major types of cells involve in liver injury

While development of effective nanocarrier based system for hepatocellular targeting, it is necessary to understand the types of cells involved in liver injury and types of receptors overexpressed on the same[5]. Hepatocytes as the major parenchymal cells, and on the three major non-parenchymal cell types hepatic stellate cells (HSC), macrophages, and Liver sinusoidal endothelial cells (LSEC) are critically involved in liver disease and thus might be potential cellular targets for drug loaded nanocarriers. Hepatocytes perform essential functions of the liver such as protein synthesis and storage, carbohydrate turnover,

synthesis of bile salts, phospholipids, and cholesterol. During liver disease, hepatocytes undergo apoptosis are replaced with ECM, a process involved in liver fibrogenesis.

HSC are located in the perisinusoidal space (the area between the sinusoids and hepatocytes). In healthy liver HSC store vitamin A and secrete a limited amount of ECM proteins. During the course of liver disease, HSC differentiated into highly proliferative myofibroblasts, which produces large amounts of ECM proteins such as collagen type I and III. The production of collagen leads to an excess production of hepatic connective tissue, termed fibrosis, and eventually reduction in liver functionality.

Macrophages are also responsible for injury and progression of liver disease. The predominant macrophages of the liver are the Kupffer cells (KC). In a normal healthy liver, the KC function as immune sentinels that activate other cells and components of the immune system upon pathogenic threats.

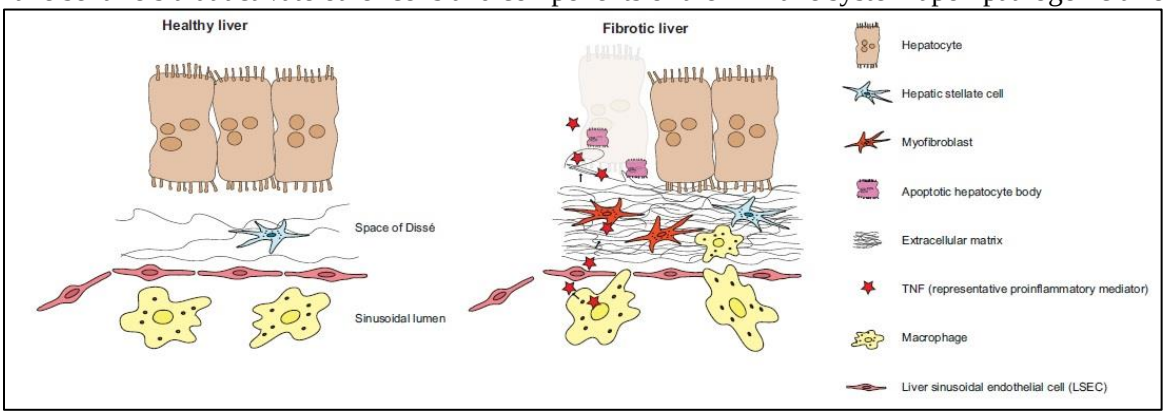

Figure 2 Four major types of cells under healthy and fibrotic condition [5].

LSEC constitute about half of the nonparenchymal cells of the liver. Under normal conditions, healthy LSEC protects the activation of HSC and can even deactivate activated HSC. Upon liver injury, LSEC undergoes capillarization. Following their capillarization, LSEC lose their fenestrations and enable macrophages and other immune cells to infiltrate the space of Disse.

Liver cell targeting using nanomedicine

Liver targeting of drug loaded nanocarriers minimize off-target distribution of drug in other highly perfused organs and allow selective delivery of delivery of drug at cellular levels, which consequently increase accumulation of drug in hepatic cellular level and increase therapeutic efficacy of drug[4]. Numerous landmark investigations proved efficacy of nanocarrier mediated liver targeting in treatment of various disease conditions associated with liver. Numerous strategies have put forwarded by many scientific experts for targeting of drug loaded nanocarriers to liver cells[6][7].

Surface anchoring of targeting ligand on nanocarriers is acceptable and widely used strategy for liver targeted drug delivery[8]. Many scientific experts have utilized various targeting ligands for liver targeting. Few prominent and successful ligands are represented below.

Galactosylated and mannosylated ligand

Carbohydrates like galactose and mannose are well known targeting ligands for targeting of asialoglycoprotein receptors on hepatocytes. The carbohydrates like galactose and mannose can specifically interacts with asialoglycoprotein receptors which are expressed on the cell membrane on hepatocytes, thus can be possibly utilize for targeting of drug loaded nanocarriers to hepatocytes [8]. The mannose or galactose can be surface anchored on drug loaded nanocarrier by surface coating of preformed nanocarriers. Many scientific experts have utilized these carbohydrates as targeting ligand for hepatocytes specific delivery of drug loaded nanocarriers. The major outcomes of hepatocytes targeting using these ligands are highlighted in below figure.

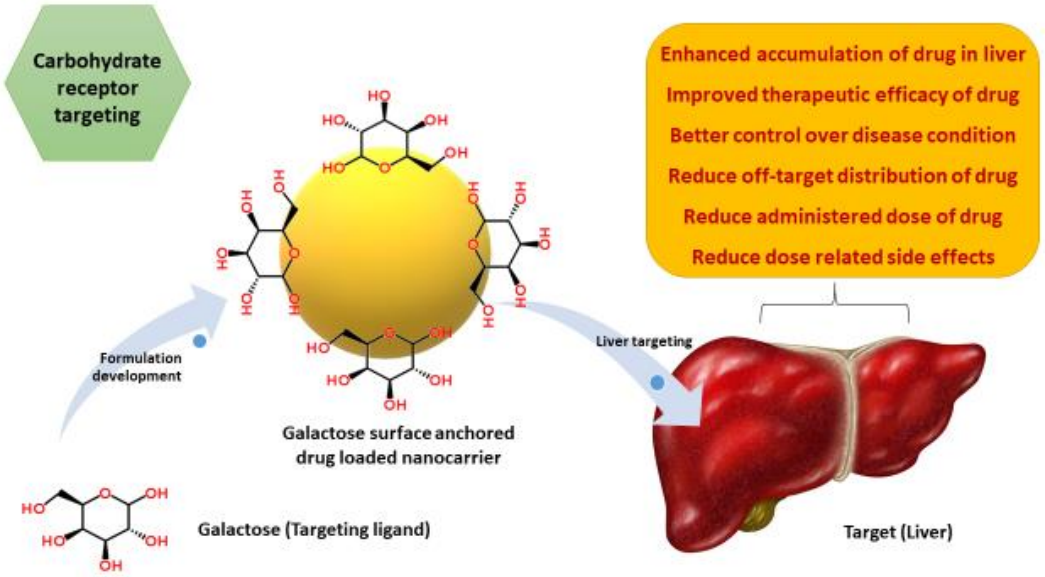

Figure 3 Diagrammatic representation of liver targeting using galactose ligand.

Yike et al., 2018 [9]have utilized galactosylated nanoparticles for targeted delivery of curcumin in hepatocellular carcinoma. A novel moiety was used for the selective targeting of (DOX) which showed that the galactosylated nanoparticles have high liver-targeting potential.

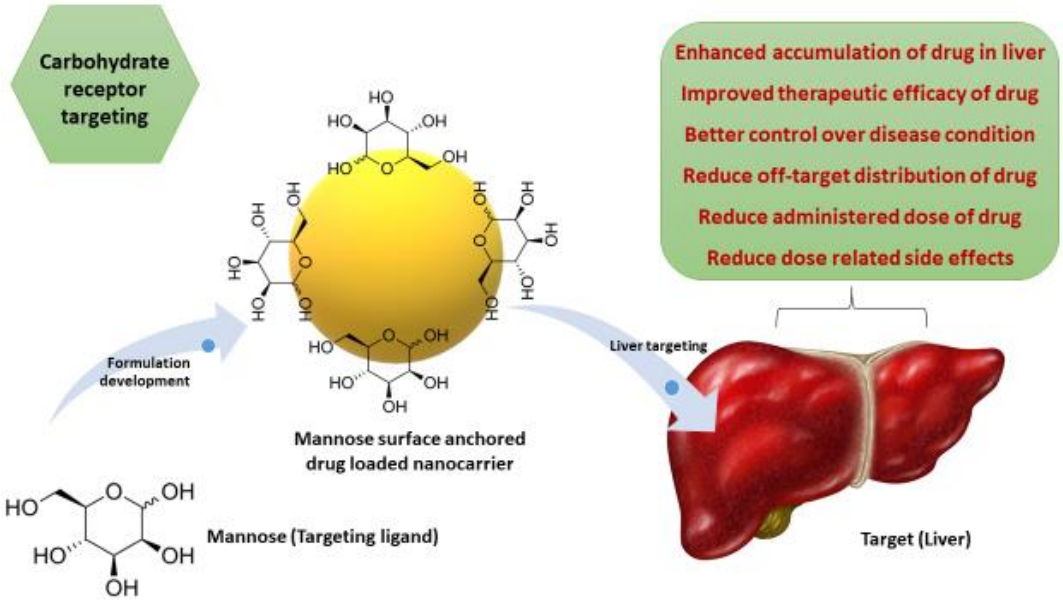

Figure 4 Diagrammatic representation of liver targeting using mannose ligand.

Raposo et al., 2020[10] have designed galactose conjugated PLGA nanoparticles for the specific delivery of doxorubicin to human hepatoma cellular carcinoma cells (Hep G2). For specific delivery of drug encapsulated polymer containing nano sized particles, the chemical moiety is required. The chemical moiety act as targeting carrier which is responsible for directing nanoparticles specifically at liver cancer cells and minimize distribution of particles in health cells. The carbohydrate i.e. galactose and sterylamine were effectively utilized for formation of targeting carrier. The formed carrier then chemically joined with

polymer and polymeric nanocarriers were designed for encapsulation of anticancer active. The designed nanoparticles were exhibited spherical morphology with better particle size as well as anticancer active encapsulation. The cancerous cells killing potential of designed anticancer active loaded nano sized particles were proved using cytotoxicity studies. Thus carbohydrate receptor targeting is a promising tool for specific delivery of active, especially anticancer active at affected cells.

Lactobionic acid ligand

Lactobionic acid is molecule derived by oxidization of lactose. Chemically, it contains galactose molecule in its chemical structure. Thus, lactobionic acid also bind with asialoglycoprotein receptors expressed on hepatocytes. Lactobionic acid surface conjugated nanoparticles can specifically accumulate in hepatocytes on parenteral administration.

Naqvi et al., 2019 [11] have fabricated lactobionic acid conjugated quercetin loaded silica nanoparticles for hepatocytes targeting. Authors have demonstrated a significant hepatoprotective effect of nanoparticles compared to free quercetin against cyclophosphamide-induced hepatotoxicity in animal models.

Du et al., 2016 [12] attempted to deliver lamivudine loaded polymeric nanoparticles to hepatocytes. The authors reported synthesis of lactobionic acid and chitosan conjugate. The synthesized conjugate was then incorporated in nanoparticles for delivery of lamivudine. The lactobionic acid conjugated nanoparticles reported to accumulate with better concentration in hepatic cells compared to unconjugated nanoparticles. The more accumulation of nanoparticles on conjugation with lactobionic acid could be due to targeting potential of nano sized particles.

Li et al., 2009 [13] formulated lactobionic acid conjugated Pluronic containing micelles for liver targeted delivery of silybin. Lactobionic acid- Pluronic conjugate was synthesized using esterification reaction and micelles of this conjugate was prepared. The formulation of micelles showed increased dissolution of silybin compared to free silybin. In addition to this, the lactobionic acid conjugated micelles showed significantly better accumulation in liver compared to free drug.

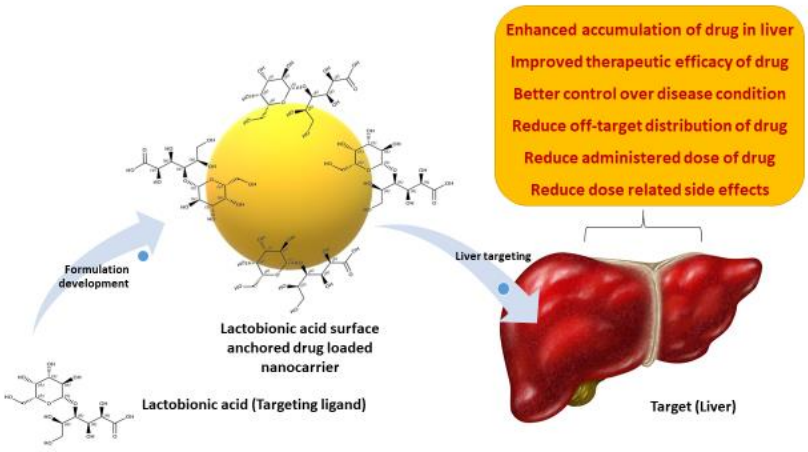

Figure 5 Diagrammatic representation of liver targeting using lactobionic acid ligand.

Mehan et al., 2021 (Mehan et al., 2021)formulated lactobionic acid decorated polyphosphazene containing nanoparticles for liver targeting of antimalarial primaquine. The lactobionic acid modified nanoparticles showed enhanced uptake in HepG2 cell compared to conventional nanoparticles. In addition to this, lactobionic acid modified nanoparticles was revealed safe with lesser toxicity to liver tissues.

Wang et al., 2021 [15]designed lactobionic acid surface conjugated polymeric nanoparticles for liver targeting of methotrexate. The cell line study revealed enhanced uptake of lactobionic acid surface conjugated nanoparticles in liver carcinoma cells.

Glycyrrhetinic acid ligand

The glycyrrhizin (GL) and glycyrrhetinic acid (GA) are major chemical constituents of liquorice. These are mainly used as anti-inflammatory, antiallergic, antigastric, antihepatitis and antihepatotoxic effects. It has reported that there are specific binding sites for both GL and GA on the hepatocytes. Thus these ligands can be used to target drug loaded nanocarriers to hepatocytes. Lin et al., 2008 [16]have formulated prepared glycyrrhizin modified chitosan nanoparticles and reported glycyrrhizin conjugate nanoparticles were accumulated more in the rat hepatocytes by ligand receptor interaction as compared to that of conventional nanoparticles of chitosan. It was also reported the 3.3-fold higher uptake hepatocytes uptake of glycyrrhetinic acid modified liposomes than that of unmodified one[1].

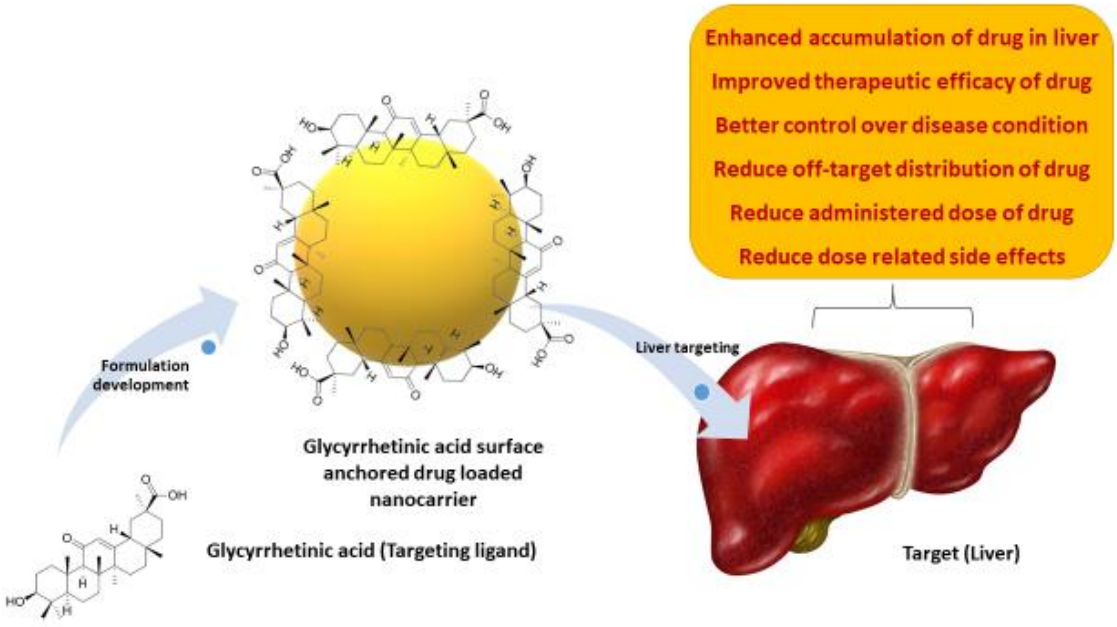

Figure 6 Diagrammatic representation of liver targeting using glycerrhetinic acid ligand.

Qin et al., 2010 [17]formulated glycyrrhetinic acid surface modified nanoparticles using ionic gelation technique for liver targeted delivery of doxorubicin in management of liver carcinoma. The formulated nanoparticles exhibited enhanced uptake in human liver carcinoma cells. In addition to this, the glycyrrhetinic acid modified nanoparticles showed more accumulation in liver compared to other organ in animal studies.

Wen-Wen et al., 2015 [18]fabricated glycyrrhetinic acid surface anchored albumin nanoparticles for delivery of doxorubicin at liver cellular level. The resulting spherical nanoparticles revealed better uptake in liver cancer cell line compared to unconjugated nanoparticles. In addition to this, biodistribution studies in animals showed greater accumulation of glycyrrhetinic acid modified nanoparticles in liver tissues compared to unconjugated nanoparticles.

Conclusion

Liver targeting is challenging task for formulation scientist due to complicated cellular structure and lack of cellular receptors. The receptors overexpressed on surface of hepatocytes in liver injury conditions are promising target for targeting of drugs to liver. Various scientific investigators have attempted to target drug loaded nanocarriers to liver cells through various receptors like carbohydrate receptors, lactobionic acid receptors and asioglycoprotein receptors. The active targeting of drugs to liver cells through these receptors results in increase in accumulation of drugs in liver cells which can possibly manage liver

disease conditions in better way. Thus, active targeting of drugs to liver cells like hepatocytes could be viable and promising strategy for delivery of hepatoprotective drugs.

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