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LIVER SPECIFIC TARGETED DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

Hepatic diseases square measure turning into one in every of the few diseases that can't be effectively cured because of some reasons though numerous receptors existed within the liver. Currently, many passive targeting delivery systems are utilized in the drug/gene delivery for the treatment of internal organ diseases. More significantly, completely different measures would be taken in unison to the desired cell that was lesioned or dysfunctioned via interaction between orienting ligands and target receptors therefore on improve accumulation of medication within the target cell and to cut back nonspecific toxicity towards alternative cells or organs. Many serious liver diseases affecting millions of people world-wide cannot be treated despite many efforts which warrant a search for new therapeutic strategies. Potent medicine might not be effective enough *in-vivo* or exhibit adverse effects and increased delivery into the target cells could improve this considerably. We aim to summarize the offered choices for drug delivery to the various intrahepatic cell-types.

KEYWORDS

Liver targeted drug delivery, Hepatic disease and Nonspecific toxicity.

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INTRODUCTION

From the previous few years, hefty advances are created within the development of plant-based liver protecting medication largely thanks to their lesser toxicity and a multi-factorial approach to restoring health, seeking equilibrium between mind, body, and surroundings and putting a larger stress on the three-d components of health than on pathology alone. Alongside medication, phytomedications have progressively been prescribed for the treatment of variety of diseases. However,

phytotherapeutics desires a scientific approach to deliver the parts in an exceedingly sustained manner thus on increase patient compliance and avoid recurrent administration. This may be achieved by planning novel drug delivery systems (NDDS) for flavoring constituents, additionally to the medication already out there within the market. Novel drug delivery systems not solely cut back the recurrent administration (due to its sustained-release properties) to beat insubordination however conjointly facilitate to extend the therapeutic worth by reducing toxicity, increasing the bioavailability, stability, and target ability to a particular cell or organ (due to its subcellular size). For an extended time, flavoring medicines weren't thought-about for development as novel formulations due to the dearth of scientific justification and process difficulties, like standardization, extraction, and identification of individual drug parts in advanced polyherbal systems. However, fashionable phytopharmaceutical analysis solves the scientific desires for flavoring drugs as in fashionable medicine, which supplies manner for developing novel formulations like nanoparticles, microemulsions, matrix systems, solid dispersions, liposomes, and solid macromolecule nanoparticles. However, for delivery to specific cell variety of liver, novel medication delivery system for flavoring medication still desires some modification like attaching of matter or targeting moiety which is able to acknowledge and act with specific cell variety of liver. Within the gift review, we tend to enumerate all the strategies for attaching targeting moiety to delivery system and various factors that might be taken into consideration whereas planning NDDS for liver cell which is able to be of vast importance in close to future. The review elucidates the importance of delivery of each the medication and flavoring medications to the liver thus on guarantee sure-fire treatment outcomes.

Morphological Study of Liver

Before discussing the various strategies of targeting, it's necessary to know the morphology of liver (especially tube-shaped structure supply) and molecular scale of the target tissue so as to style a novel drug delivery system rationally. The liver engages various metabolic, medicine, and endocrine functions. It receives blood (oxygenated and deoxygenated) from the gut and heart via the vena portae and arterial blood vessel, severally. Blood circulates through a permeable discontinuous capillary network term as the sinusoids to reach the central and hepatic veins. The sinusoids are small blood vessels (5 to 10μm wide) between the radiating rows of hepatocytes having fenestrations of size 100–150 nm (depending on the type of animal species). They allow almost unrestricted passage of plasma components to the perisinusoidal space, where the cords of parenchyma cells called as hepatocytes are situated. Inside the sinusoid capillaries, the Kupffer cells square measure chargeable for vegetative cell activity of the liver[1,2].

LIVER

The liver, Associate in Nursing organ solely found in vertebrates, detoxifies varied metabolites, synthesizes proteins, and produces organic chemistry necessary for digestion[3]. In humans, it's situated within the right higher quadrant of the abdomen, below the diaphragm. Its different roles in metabolism embrace the regulation of polyose storage, decomposition of red blood cells and also the production of hormones[4]. The liver is an adjunct exocrine gland that produces bile, Associate in Nursing base-forming compound that helps the breakdown of fat. Bile acids in digestion via the emulsification of lipids. The gallbladder, a small pouch that sits just under the liver, stores bile produced by the liver[4]. The liver's highly specialized tissue consisting of mostly hepatocytes regulates a wide variety of high-volume organic chemistry reactions, together with the synthesis and breakdown of tiny and complicated molecules, many of which are necessary for normal vital functions[5]. Estimates regarding the organ's total number of functions vary, but textbooks generally cite it being around 500[6]. Terminology related to the liver often starts in hepat- from ἡπατο-, the Greek word for liver. There is presently no thanks to atone for the absence of liver perform within the

long run, although liver dialysis techniques can be used in the short term. Artificial livers are yet to be developed to promote long-term replacement in the absence of the liver. As of 2017, liver transplantation is that the solely possibility for complete liver failure.

Function of liver

The various functions of the liver area unit applied by the liver cells or hepatocytes. The liver is believed to be answerable for up to five hundred separate functions, sometimes together with alternative systems and organs. Currently, there's no artificial organ or device capable of reproducing all the functions of the liver. Some functions will be applied by liver chemical analysis, associate degree experimental treatment for liver failure.

Blood supply

The liver receives a twin blood provide from the internal organ vein and internal organ arteries. The internal organ vein delivers some seventy fifth of the liver's blood provide, and carries blood drained from the spleen, epithelial duct, and its associated organs. The internal organ arteries provide blood to the liver, accounting for the remaining quarter of its blood flow. Oxygen is provided from each sources; some 1/2 the liver's gas demand is met by the internal organ vein, and [*fr1] is met by the internal organ arteries[7].

Biliary flow

The biliary tract comes from the branches of the digestive fluid ducts. The biliary tract, additionally referred to as the biliary tree, is that the path by that digestive fluid is secreted by the liver then transported to the primary a part of the little intestine, the duodenum. The digestive fluid created within the liver is collected in digestive fluid canaliculi, tiny grooves between the faces of adjacent hepatocytes. The canaliculi radiate to the sting of the liver lobe, wherever they merge to make digestive fluid ducts. Within the liver, these ducts are termed intrahepatic bile ducts, and once they exit the liver they are considered extra hepatic. The intrahepatic ducts eventually drain into the proper and left viscus ducts, that exit the liver at the cross fissure, and merge to make the common epithelial duct. The cystic duct from the gallbladder joins with the common hepatic duct to form the common bile duct[8].

Synthesis

The liver plays a serious role in sugar, protein, amino acid, and macromolecule metabolism. The liver performs many roles in sugar metabolism: The liver synthesizes and stores more or less 100g of polyose via glycogenesis, the formation of polyose from aldohexose. When required, the liver releases glucose into the blood by performing glycogenolysis, the breakdown of glycogen into glucose. The liver is additionally to blame for gluconeogenesis, which is the synthesis of glucose from certain amino acids, lactate or glycerol. Adipose and liver cells produce glycerol by breakdown of fat, which the liver uses for gluconeogenesis[9].

The liver is to blame for the mainstay of super molecule metabolism, synthesis as well as degradation. It is additionally to blame for an outsized a part of organic compound synthesis. The liver plays a job within the production of curdling factors similarly as red somatic cell production. Some of the proteins synthesized by the liver include coagulation factors I (fibrinogen), II (prothrombin), V, VII, VIII, IX, X, XI, XIII, as well as protein C, protein S and antithrombin. In the trimester craniate, the liver is the main site of red blood cell production. By the thirty second week of gestation, the bone marrow has almost completely taken over that task. The liver could be a major website of production for thrombopoietin, a compound protein endocrine that regulates the assembly of platelets by the bone marrow.

Breakdown

The liver is chargeable for the breakdown of endocrine and different hormones. The liver breaks down haematoidin via glucuronidation, facilitating its excretion into gall. The liver is chargeable for the breakdown and excretion of the many waste merchandise. It plays a key role in breaking down or modifying harmful substances (e.g., methylation) and most medicinal products in a process called drug metabolism. This generally leads to toxication,

when the metabolite is more toxic than its precursor. Preferably, the toxins ar conjugated to avail excretion in gall or excreta. The liver breaks down ammonia into urea as part of the urea cycle, and the urea is excreted in the urine[9].

Liver diseases and its treatments

Different types of liver diseases are hepatitis B virus (HBV) infections, liver fibrosis, hepatocellular carcinoma, liver cirrhosis, choleostasis, acute liver failure, nonalcoholic fatty liver disease (NAFLD) and alcoholic liver disease. Hepatitis B Virus (HBV) Infection: Hepatitis B virus infection is a major global public health problem. HBV infection accounts for five hundred 000 to one.2 million deaths each year and is the 10th leading cause of death worldwide. Approximately 2 billion people who have been infected worldwide, more than 350 million are chronic carriers of HBV. Approximately 15-40% of infected patients can develop liver disease, liver failure, or hepatocellular carcinoma (HCC). HBV is a highly contagious DNA virus that is transmitted through parenteral or mucosal exposure to infected blood, serous fluids and other body fluids such as seminal and vaginal fluids. Common routes of infection embody perinatal transmission (from Associate in Nursing infected mother to baby throughout birth), unsafe needle sharing, intromission practices and sexual contact[9,10]. Chronic HBV infection is divided into three major phases based on virus-host interactions: immune tolerant, immune clearance and inactive carrier phases[11]. The U.S. Food and Drug Administration (FDA) approved anti-HBV drugs can be broadly categorized as interferons (IFN-α2b and pegylated IFN-α2a), nucleoside (lamivudine, entecavir and telbivudine) and nucleotide (adefovir and tenofovir) analogs[12].

Liver fibrosis

Liver pathology is outlined because the increase of excessive quantity of animate thing matrix, conjointly called connective tissue, within the liver parenchyma[13]. Liver pathology is that the final pathway for many chronic disease and is that the main reason for enhanced mortality in affected patients. The extent of liver pathology displays nice individual variation, even when dominant for age (at infection), gender factors. Thus, host genetic factors ar doubtless to play a vital role within the method of liver scarring[14]. Loss of viscus functions, ascites, malignant hypertension with AN enhanced risk for musculature varices and HCC ar among the foremost serious complications that are typically fatal. As activation of the viscus radial cells (HSCs) is that the central event in fibrogenesis, numerous candidate medicine together with rennin-angiotensin system inhibitors, IFN-γ, peroxisomal proliferator activated receptor (PPAR)-γ ligands, pirfenidone, colchicine and flavouring medicines that have incontestable potential in inhibiting HSC activation, proliferation and albuminoid synthesis are projected for the treatment of liver pathology. Additionally, antioxidants like E, silymarin, phosphatidylcholine and S-adenosyl-L-methionine have conjointly been investigated for cover against aerophilic stress which will induce viscus injury and fibrogenesis[15,16].

Hepatocellular carcinoma (HCC)

Hepato-cellular malignant neoplastic disease (HCC) is that the most frequent primary malignancy of the liver and ac- counts for as several as one million deaths annually worldwide. In some components of the planet it's the foremost common kind of internal malignancy and also the commonest explanation for death from cancer. El-Serag and Mason I even have delineate a rise of concerning eightieth within the incidence of HCC within the us over the past 20-30 years and it's calculable that or so fifteen,000 new cases occur annually[17]. HCC usually happens within the environment of long standing liver diseases like chronic hepatitis B or C virus infections, alcoholic liver disease and non-alcoholic steatohepatitis, the character of that follows a definite geographical distribution[18,19]. In the early stages of HCC, the illness is doubtless curable by surgical surgery, liver transplantation and nonsurgical native ablation techniques like connective tissue alcohol injection and radiofrequency ablation (RFA). Patients with advanced HCC will be treated by typical general

therapy agents like antibiotic, cisplatin and 5-fluorouracil, sorafenib used alone or together[20-22].

Cholestatic Liver Diseases

Cholestasis (reduced duct excretion) is another well-known reason behind liver pathology. Cholestasis triggers the proliferation of the cholangiocyte lining of the intrahepatic and extrahepatic bile duct systems through a complex regulatory milieu that involves both autocrine and paracrine factors[23]. Cholestasis i.e., blockage of bile flow, is due to either intrahepatic disorders such as cystic fibrosis, granulomatosis or drug side effects. In Cholestasis, the bile canaliculi are enlarged, the fluidity of the canalicular cell membrane is decreased (cholesterol embedding, bile salt effect), their brush border is deformed (or totally absent) and the function of the cytoskeleton, including canalicular motility, is disrupted[24]. The dihydroxy bile acid, ursodeoxycholic acid (UDCA), is increasingly used for the treatment of chronic cholestatic liver diseases.

Liver cirrhosis

Cirrhosis of the liver refers to scarring of the liver which ends in abnormal liver perform as a consequence of chronic liver injury. Cirrhosis could be a leading reason behind sickness and death within the u. s. The most common causes of cirrhosis are excess alcohol use, chronic infection with hepatitis viruses (such as hepatitis B and hepatitis C), cirrhosis can be caused by other conditions including malady} disease, inherited disorders, drug-induced injury, bile duct disorders and autoimmune diseases. A large portion of patients (up to 20%) do not have an identifiable cause for cirrhosis this is known as cryptogenic cirrhosis[25]. Two goals within the management of salaried liver disease are:

1. Treatment of the underlying liver disease (e.g., hepatitis C or B, alcohol, non-alcoholic steatohepatitis), and;
2. Prevention or early diagnosis of the complications of cirrhosis.

Acute Liver Failure

Acute liver failure (ALF) could be a rare condition during which fast deterioration of liver perform leads to altered thought and coagulopathy in antecedently traditional people. U.S. estimates are placed at approximately 2,000 cases per year[26]. The most distinguished causes embrace drug induced liver injury, viral hepatitis, autoimmune liver disease and shock or hypo perfusion; many cases (~20%) have no discernible cause[27]. Acute liver failure usually affects young persons and carries a high morbidity and mortality. The causes of chronic liver failure that is accompanied by fibrosis (cirrhosis) of the liver are; inflammation, chronic persistent viral hepatitis; alcohol abuse, the most common cause in susceptible patients, facet effects of medicine like, folic acid antagonists and phenylbutazone. Liver transplant is the best way to manage the liver failure[28].

Nonalcoholic Fatty Liver Disease (NAFLD)

NAFLD and its subtype, Non-Alcoholic Steatohepatitis, or NASH, are sometimes seen in people with metabolic syndrome (MS) or its parts like fatness, type- a pair of polygenic disease (DM), dyslipidemia, and internal secretion resistance. NASH rarely manifests as inflammation and/or apoptosis/ necrosis only, more often than not it is also accompanied by liver fibrosis[29]. It refers to the accumulation of fat, mainly triglycerides, in hepatocytes so that it exceeds 5% of the liver weight. Treatment strategies for NAFLD have revolved around;

1. Identification and treatment of associated metabolic conditions such as diabetes and hyperlipidaemia;
2. Improving insulin resistance by weight loss, exercise, or pharmacotherapy;
3. Using hepatoprotective agents such as antioxidants to protect the liver from secondary insults.

Alcoholic Liver Disease

Excessive and chronic alcohol consumption is a crucial determinant of liver pathology and cirrhosis of the liver. The process of the breakdown of ethanol produces two profibrotic agents, acetaldehyde and reactive oxygen species (ROS)[16]. Alcoholic liver diseases are often grouped into three histological stages of ALD: fatty liver or easy

steatosis, alcoholic infectious disease, and chronic hepatitis with hepatic fibrosis or cirrhosis. These latter stages may also be associated with a number of histological changes including the presence of Mallory's hyaline, mega mitochondria, or perivenular and perisinusoidal fibrosis. Fatty liver develops in regarding ninetieth of people WHO drink quite sixty g/day of alcohol, however may additionally occur in people WHO drink less[14]. Treatment approaches includes inhibition of growth mortification issue, inhibitor medical aid, stimulation of liver regeneration, and stimulation of collagen degradation.

Drug targeting

Drug targeting is that the ability of the drug to accumulate within the organ or tissue by selection and quantitatively, freelance of the positioning and strategies of its administration. Ideally, under such conditions, the local concentration of the drug at the disease site(s) should be high, while its concentration in other non-target organs and tissues should be below minimal level to prevent any negative side-reactions[30].

The following advantages of drug targeting are:

1. Drug administration protocols may be simplified;
2. Drug quantity required to achieve a therapeutic effect may be greatly reduced;
3. The cost of therapy reduced;
4. Drug concentration in the required sites can be sharply increased without negative effects on non-target compartments. The same is, for the great extent, true for the use of many diagnostic agents.

Currently, the idea of cure includes a coordinated behavior of 3 components:

- Drug
- Targeting moiety and
- Pharmaceutical carrier used to multiply the number of drug molecules per single targeting moiety.

Pharmaceutical carriers include soluble polymers, microcapsules, microparticles, cells, cell ghosts, lipoproteins, liposomes, and micelles. All of them can be made targeted in one way or another.

The recognition of the target will occur on the amount of an entire organ, on the level of certain cells specific for a given organ, or even on the level of individual elements characteristic of those cells, such as cell surface antigens. The most universal kind of target recognition is that the recognition on the molecular level, based on the fact that every organ or tissue certain compounds (antigens) can be found that are specific just for the organ of interest. For victorious targeting, another compound can be used as a transporting unit, which is capable of the specific interaction with the specific target component (for example, a monoclonal antibody against the target antigen). Basing on this principle, numerous systems for drug targeting have been constructed capable of the delivery of pharmaceuticals to the variety of tissues and organs. Currently, the complete set of targeting protocols is beneath development that has many alternative approaches to targeted drug delivery. Not necessarily these approaches involve the use of specific targeting moieties. In sure cases numerous physical principles and/or some physiological options of the target is also used for a victorious targeting of prescribed drugs and pharmaceutical carriers.

Principal schemes of drug targeting currently investigated in various experimental and clinical settings include,

1. Direct application of the drug into the affected zone (organ, tissue)
2. Passive accumulation of the drug through leaky vasculature (tumors, infarcts, inflammation)
3. Physical targeting based on abnormal pH and/or temperature in the target zone, such as tumor or inflammation (pH and temperature-sensitive drug carriers)
4. Magnetic targeting of drugs attached to paramagnetic carriers under the action of external magnetic field
5. Use of vector molecules possessing high specific affinity toward the affected zone.

Liver targeting

The liver is a critical target tissue for drug delivery because many fatal conditions including chronic hepatitis, enzyme deficiency, and hepatoma occur in hepatocytes. In general, liver targeting systems employ passive trapping of microparticles by reticuloendothelium or active targeting based on recognition between hepatic receptor and ligand-bearing particulates[31].

Passive targeting refers to NP transport through leaky tumour capillary fenestrations into the tumour interstitium and cells by passive diffusion or convection or additionally refers to the buildup of nanoparticles therapeutics at a selected body web site thanks to sure anatomic or pathophysiological options[33]. The liver sinusoids are extremely specialised capillaries characterised by,

1. The presence of 100-200 nm fenestrations along the endothelial wall and;
2. Absence of basal lamina. As a results of these characteristics, speedy and passive liver accumulations are oftentimes ascertained with nanoparticles medicine following blood vessel (i.v) administration.

Following general administration, the process size properties (typically < 200nm in diameter) of nanoparticles medicine greatly facilitates passive liver targeting within the absence of serious self-aggregation or aggregation with liquid body substance proteins as it allows for their extravasations through the slightly larger sinusoidal fenestrations. This effectively builds up a high local concentration of nanoparticles therapeutics in the space of Disse, where diffusion to the various liver cell types can occur. Interestingly, evidence has also suggested a chance for deformable nanocarriers of up to four hundred nm to extravasate through the sinusoid epithelial tissue fenestrations via a mechanism of forced extrusion, possibly aided by transient interactions with the sinusoidal endothelial cells[34]. In HCC, passive accumulation of nanoparticle medicine within the liver may be achieved by EPR result that was 1st delineated by Matsumura and Maeda in 1986[35].

The EPR effect can be observed in almost all human cancers with the exception of hypovascular tumors like prostate cancer or pancreatic cancer. For such a passive targeting mechanism to work, the size of the nanoparticles must be controlled to avoid uptake by the reticuloendothelial system and #40; RES and #41. The EPR effect stems from distinctive features of the tumor microenvironment including:

1. Leaky tumor vasculature brought about as a consequence of the rapid and incomplete tumor angiogenesis to meet the elevated demands for oxygen and nutrients, leading to enhanced permeability and extravasation of macromolecules,
2. Impaired lymphatic drainage, which favors the retention of nanoparticles therapeutics in the tumor tissues[36].

As the size of the gap junction between endothelial cells is reported to vary between 400 and 600 nm, nanoparticles therapeutics are therefore expected to be extremely efficient at extravagating from the tumor microvasculature to result in a high local tumor interstitial concentration. Indeed, the EPR effect has been credited with the selective deposition and targeting of zein nanoparticles (ZP) encapsulated 5-fluorouracil in HCCs following intravenous injection. In these studies, the drug loaded ZPs could be efficiently targeted at the liver by intravenous delivery observed in patients with liver cancer[37].

The method and site of administration of nanoparticles therapeutics are also known to influence distribution patterns within the liver. In the area of gene delivery, for instance, hydrodynamic injections of naked DNA led to increased accumulations of DNA in the livers of rodents as the increased intrahepatic pressure results in a transient increase in the diameter of the sinusoidal fenestrate to cause a leakage of DNA-containing solutions from hepatic sinusoids into the space of Disse[38].

Active targeting

The specific delivery of the therapeutic system to the pathological cell sort permits for the

capitalization of the therapeutic effects of the payload and conjointly minimizes unwanted facet effects on normal liver cells resulting from non-specific cellular uptake. The diverse physiological functions of the human liver ar achieved through the precise activities of assorted cell varieties, together with the non-parenchymal curved epithelium cells (SECs), Kupffer cells (KCs), hepatic stellate cells (HSCs) and the predominant parenchymal hepatocytes. In liver fibrosis, HSCs are considered to be the main target for therapeutic interventions due to their major roles in the secretion and maintenance of copious amounts of extracellular matrix (ECM) in response to various biochemical stimuli produced by the injured hepatocytes, SECs and KCs. Hepatocytes, on the other hand, are implicated in the development of HBV infections and HCC and therefore, are being targeted for the treatment of these diseases. As each of the two liver cell types has distinct morphologies, physiological activities and pathoanatomical characteristics that are reasonably established, unique targeting opportunities of therapeutics by ligand-mediated approaches to the HSCs and hepatocytes are abound.

Drug targeting to Hepatic stellate cells (HSCs)

The 5 main methods create the utilization of options of the pathological development of liver pathology that's initiated by the activation, proliferation and also the resulting transformation of HSCs into myofibroblasts. Activated HSCs are known to have upregulated expression of mannose-6-phosphate/ insulin-like growth factor II (M6P) receptors to facilitate the activation of the cytokine, transforming growth factor β (TGF-β), which stimulates collagen production by HSCs[39]. Capitalizing on this phenomenon, the direct conjugation of M6P via a short peptide linker to a N-(2- hydroxypropyl) methacrylamide (HPMA) copolymer showed a majority uptake (80%) by the HSCs in dimethylnitrosamine (DMN)-induced liver fibrotic rats[40]. To exploit native interaction between albuminoid kind VI receptors and its matter, researchers have covalently attached a cyclic octapeptide C*GRGDSPC* (C* denotes the cyclizing cysteine residues) to the lysine groups of human serum albumin (HSA) and observed selective internalization by activated rat HSCs[41]. A further modification was created to the amide by work amino acid with essential amino acid (C*GRGDSPK*) so as to switch the less stable cyclizing disulfide (—S—) bond with a additional stable peptide bond (—NH—CO—) in the latter, without adversely influencing targeting efficacy[42,43]. Receptors for platelet-derived growth factors (PDGFs), which mediate many of the HSC responses to cytokines, are generally upregulated during liver injury. Expression of the PDGF receptor type, in particular, is acquired at high levels during the myofibroblastic transformation of HSC[44]. The scavenger receptors (ScRs) present on HSCs act as an alternative endocytotic uptake route for nanoparticle therapeutics, particularly for the HSA-based therapeutic systems due to their polyanionic nature[45,46].

Drug targeting to Hepatocytes

Targeting to the asialoglycoprotein receptor (ASGP-R) is the most universally employed method to enhance clathrin mediated endocytotic uptake of nanoparticle therapeutics by hepatocytes. This approach takes advantage of the innate binding affinity of the ASGP-R to a broad range of molecules exposing galactose and N-acetyl-galactosamine residues, such as asialoorosomucoid, asialofetuin (AF), sterylglucoside, lactose and poly-(N-ρ-vinylbenzyl-O-β-Dgalactopyranosyl-[1- 4]-D-glucosamine (PVLA) for target in to hepatocytes. In polymeric systems, the most commonly seen approach is through coupling of lactobionic acid or lactose to the nanocarrier through carbodiimide chemistry, with the ultimate product retentive purposeful sucrose moieties. L. Li and his cluster has recently synthesized a series of amphiphilic polycarbonate-based copolymers bearing supermolecule pendant chains as targeted drug carriers and located considerably higher uptake of antibiotic (DOX)-loaded galactose-containing micelles by the ASGP-R positive HCC cell line HepG2 compared to the ASGP-R negative HEK293 cell line[47]. The specificity of galactose-mediated

uptake of the DOX-loaded nanoparticles by HepG2 was evidenced by the inhibition by AF in a dose-dependent manner. Interestingly, although the conjugation of most galactose-bearing moieties to the polymer backbone occur at the 1-position of the pyranose ring, Li and his co-workers results demonstrated that the ASGP-R can recognize galactopyranosides appended at the 6-position. Simultaneous expression of ASGP-Rs in normal hepatocytes and HCC cells, however, could restrict the clinical applicability of this class of receptors for targeting purposes. In fact, studies have discovered a decrease in ASGP-R expression in HCC, particularly in the poorly differentiated state[47,48]. Suggesting that the normal hepatocytes may internalize the nanoparticle therapeutics to a greater extent compared to their diseased counterparts. The tumor levels of the galactosylated poly (HPMA)-DOX is nevertheless substantially higher than the background levels, implying that the galactose moiety does provide some form of targeting, albeit with lower specificity, to the tumors. The carboxylic acid metabolism and sterol storage perform of the liver is another avenue that has been explored to reinforce hepatocyte uptake of nanoparticle medical specialty. For example, linoleic acid, an essential polyunsaturated fatty acid that is taken up by hepatocytes via its putative plasma membrane transporter 53 has been used to drive the uptake of self-assembled super paramagnetic iron oxide nanoparticles-loaded chitosan-linoleic acid/DNA complexes by hepatocytes for imaging and gene delivery purposes[48]. Additionally, various liposomes containing apolipoprotein A-I (apo A-I), the major protein of the high-density lipoprotein (HDL), have exploited the natural mechanism of uptake of HDL cholesteryl ester via the class B type I scavenger receptor, CLA-1 (human) or SR-BI (rat) to enhance internalization in the hepatocytes[49]. Besides the frequently over expressed cell surface receptors such as transferrin, folate and epidermal growth factor receptors in solid tumors, other ligand mediated targeting strategies have also exploited natural hepatic invasion mechanisms by protozoa through the use of acetyl-CKNEKKNKIERNNKLKQPP-amide to bind to heparin sulfate proteoglycans on the hepatocyte surface[50] and the use of pre-S1, a hepatitis B infectious agent envelope supermolecule sequence celebrated to mediate virus entry into hepatocytes[51]. In addition, the internal organ glycyrrhizin (GL) receptors have additionally been targeted through GL surface modifications[52].

Liposomes

Liposomes are small vesicles composed of unilamellar or multilamellar phospholipid bilayers enclosing an aqueous space. Soluble drugs can readily be incorporated into this aqueous space and lipophilic drugs can be incorporated into the lipid bilayers. Elimination from the circulation is dependent on the lipid composition, charge, and size of the liposomes. Common liposomes such as neutral and negatively-charged liposomes, are however, primarily cleared by the phagocytotic processes of the cells of the reticuloendothelial system and #40; RES and #41; the KCs having the greatest responsibility for this process. It has been shown for instance that the targeting of cytostatic agents such as adriamycine to tumours is associated with loss of KC function, thereby contributing to the immune suppressed status of patients. The high kHz uptake has been astonishingly under-exploited in drug targeting approaches to treat liver diseases[53]. Liposomes have been used for the targeting of anti-Leishmania drugs[54] and immunomodulators[55] and have greatly increased the efficacy of these drugs in Leishmania infections and metastatic tumor growth, respectively. Hepatocytes selective targeting of liposome can be achieved through introduction of cells recognizing ligands on the liposomal surface. There is saccharose receptor on the surface of hepatocytes that acknowledges the galactosyl residues of desilated body fluid glycoproteins. So, galactose-terminated compound such as asialofetuinlactosylceramide have been used as the ligand on liposomes for targeting to hepatocytes[56]. M. Hashida and his co-workers synthesized the galactosylated liposomes for hepatocyte targeting and elucidate the connection

between the movements of galactosylated liposomes[57]. The glycyrrhizin derivative is also used as the ligand on liposome for targeting to hepatocytes. H. Kiwada and his co-workers developed the glycyrrhizin changed cyst for hepatocyte targeting[56]. PEG liposomes, also called stealth liposomes because when modifying the SUV liposome membrane by adding polyethylene glycol can markedly reduce the interaction of the vesicles with the stationary macrophages in the liver and spleen after i.v. application and this increases the circulation half-time. Pohlen *et al*, prepared the 5-flurouracil enclosed in Stealth Liposome for the treatment of Liver Metastases[58]. Nanoparticles (NPs): Biodegradable nanoparticles (NPs) are effective drug delivery devices. Various polymers are employed in drug delivery analysis as they will effectively deliver the drug to a target web site and therefore increase the therapeutic profit, whereas minimizing facet effects[59]. The controlled unleash (CR) of pharmacologically active agents to the precise web site of action at the therapeutically best rate and dose program has been a significant goal in planning such devices. Liposomes are used as potential drug carriers rather than standard indefinite quantity forms attributable to their distinctive blessings that embrace ability to guard medication from degradation, target the drug to the site of action and reduce the toxicity or side effects[60]. However, developmental work on liposomes has been limited due to inherent problems such as low encapsulation efficiency, rapid leakage of soluble drug within the presence of blood parts and poor storage stability. On the opposite hand, polymeric NPs offer some specific advantages over liposomes. For instance, NPs help to increase the stability of drugs/proteins and possess useful CR properties. Nanoparticles typically vary in size from ten to a thousand nm. In the NPs drug is dissolved, entrapped, encapsulated or attached to a NPs matrix and depending upon the method of preparation, nanoparticles, nanospheres or nanocapsules can be obtained. For targeting of polymeric nanpoarticle to liver various ligands such as folic acid and asialoglyco proteins, galactosyl residues, glycyrrhizin derivative, have been introduced into drug carriers. C. Li *et al* designed albumen nanoparticles with surface modification by saccharose residues to realize the effectively targeting delivery of Oridonin into carcinoma cells[61]. Ping *et al*, conjugated glycyrrhizin (GL) to the surface of chitosan nanoparticles (CS-NPs), prepared by an ionic gelation process 58. These nanoparticles were developed for a drug delivery system targeting the liver through a specific interaction between GL and hepatocytes. The cellular uptake of GL-CS-NPs was dependent on incubation time and dose of nanoparticles, suggesting that internalization of these nanoparticles into hepatocytes was mostly mediated by a ligand receptor interaction. Liang *et al*, ready Paclitaxel-loaded poly (γ-glutamic acid)-poly (lactide) nanoparticles as a targeted drug delivery system for the treatment of carcinoma and that they studied, the distribution of the particle size, the letter potential, the drug loading content and also the drug loading potency of the ready nanoparticles, and their unleash profile and toxicity on HepG2 cells (a carcinoma cell line) were investigated *in vitro*[62]. Additionally, bio-distributions of the prepared nanoparticles were studied *in vivo* in normal mice and hepatoma-tumor-bearing nude mice. Q. Wang *et al,* developed Norcantharidin-associated galacto-sylated chitosan nanoparticles for hepatocyte-targeted delivery and confirm its targeting characteristics[63].

Polymeric micelles

Polymeric micelles have recently emerged as a completely unique promising mixture carrier for the targeting of poorly water soluble and amphiphilic medicine. Polymeric micelles square measure significantly additional stable than wetter micelles and might solubilize substantial amounts of hydrophobic compounds in their inner core. Due to their hydrophilic shell and tiny size they often exhibit prolonged circulation times *in vivo* and might accumulate in tumoral tissues. Polymeric micelles also used in liver targeting, Yang KW and his co-worker designed Diammoniumglycyrrhizinate (DG)-loaded

conventional PIC micelles (mPIC micelles) and lactose-modified PIC micelles (Lac-PIC micelles) and they found that Lac-PIC micelles might deliver additional weight unit to liver than mPIC micelles[64].

Phytosomes

The term "Phyto" suggests that plant whereas "some" suggests that celllike. The phytosome structures contain the active ingredients of the standardized plant extract or its constituents bound to phospholipids, mainly phosphatidylcholine producing a lipid compatible molecular complex. Phytosomes have improved pharmacokinetic and medical specialty parameter that in result will well be utilized in the treatment of the acute and chronic disease of ototoxic metabolic or infective origin or of degenerative nature. It can also be used in anti-inflammatory activity as well as in pharmaceutical and cosmetic compositions[65]. Phytosomes are prepared by reacting the herbal extract in an aprotic solvent like dichloromethane, dioxane and ethyl acetate with the phospholipid such as phosphatidylcholine, phosphatidylethanolamine or phosphatidyiserine dissolved in the same solvent. After solubilization has been completed, the complex compounds are isolated by removing the solvent under vacuum, by freeze drying or by precipitation with non-solvents such as n-hexane. Thus, the obtained complexes are lipophilic in character and soluble in a polar and aprotic solvent, in which the individual components of the complex are normally insoluble[66]. The phytosome method has conjointly been applied to several standard seasoner extracts together with ginkgo, grape seed, hawthorn, milk thistle, green tea, and ginseng. The flavonoid and terpenoid components of these herbal extracts lend themselves quite well for the direct binding to phosphatidylcholine[67]. Ravarotto *et al,* reported silymarinphytosome show better antihepatotoxic activity than silymarin alone and can provide protection against the toxic effects of aflatoxin B1 on performance of broiler chicks[68].

Medications

There are so many drugs and chemicals that are used to cure the liver diseases and in treatment of injury to the liver. Probably the best-known medication that can damage the liver is acetaminophen, also known as Tylenol®. However, medications wont to treat sleep disorder, nail plant, high sterol, high blood pressure, cancer, seizures, pain, infections and lots of alternative conditions place associate excessive strain on the live[69].

Table No.1: Ligand Mediated Approaches for Liver Targeting

S.No	Liver cell type	Cellular target	Targeting ligand	References
1	Hepatic stellate cells	Mannose – 6 –phosphate receptor	Mannose-6-phosphate	44
		Type VI collagen receptor	Cyclic RGD	45, 46, 47
		PDGF receptor	PDGF	48
		Scavenger receptor class A	Human serum albumin	49, 50
2	Hepatocytes	Asialoglyco protein receptor	Galactoside	51, 63, 67
			Galactosamine	68
		Plasma membrane fatty acid binding protein (Putative)	Linoleic acid	54
		Scavenger receptor class B type I	Apolipoprotein A-I	55
		Heparan sulfate	Acetyl CKNEKKNKIERNNKLKQPP-amide	56
		IL-6-receptor and/or immunoglobulin A binding protein (Putative)	Pre-S1	57
		Glycyrrhizin receptors	Glycyrrhizin	58, 62

RGD: Arg-Gly-Asp; PDGF: platelet-derived growth factor.

Table No.2: liver targeting drug carriers

S.No	Carriers	Model drug	Polymers/ lipids	Method
1	Liposome	30-stearyl glycyrrhizin	HEPC,CH	Ether Injection
		Probucol	DSPC, CH	Ether Injection
2	Nanoparticles	Oridonin	BSA	Desolvation
		Adriamycine	Chitosan	Ionic gelation
		Antifibrotic drug	HAS	Desolvation
		Paclitaxel	γ-PGA-PLA	Emulsion/solvent evaporation
		Norcantharidin 5-fluorouracil	Chitosan Zein	Ionic gelation Phase separation
3	Polymeric micelles	Diammoniumglycyrrhizinate	Chitosan	-
4	Phytosome	Silymarin	Phospholipids	Solvent evaporation

HEPC: Hydrogenated egg phosphatidylcholine; CH: cholesterol
DSPC: Distearoylphosphatidylcholine; γ-PGA-PLA: poly (γ-glutamic acid)-poly (lactide)
BSA: Bovine serum albumin; HSA: Human serum albumin.

Table No.3: Allopathic medicine can also induce hepatotoxicity[70]

Chemical	Consequence
Acetaminophen	Cytochrome P-450-2E1 generates a toxic metabolite NAPQI and this produces hepatic necrosis.
Amoxicillin	Moderate rise in SGOT and SGPT level, hepatic dysfunction including jaundice, hepatic cholestasis and acute cytolytic hepatitis.
Chlorpromazine	Infectious hepatitis with laboratory features of obstructive jaundice.
Ciprofloxacin	Cholestatic jaundice elevated SGPT, SGOT and alkaline phosphatase level.
Diclofenac	Elevation of ALT and AST level, liver necrosis, jaundice and fulminant hepatitis.
Erythromycin	Increased level of SGPT, SGOT, hepatocellular and/or cholestatic hepatitis with or without jaundice.
Fluconazole	Elevated transaminase level, hepatitis, cholestasis and fulminant hepatic failure
Isoniazid	Elevation of serum transaminase level, severe and fatal hepatitis
Oral contraceptives	Intrahepatic cholestasis with pruritus, jaundice, benign neoplasm, rarely neoplasm of the liver and hepatic vein occlusion.
Rifampin	Hepatitis, hyperbilirubinemia and cholestasis.

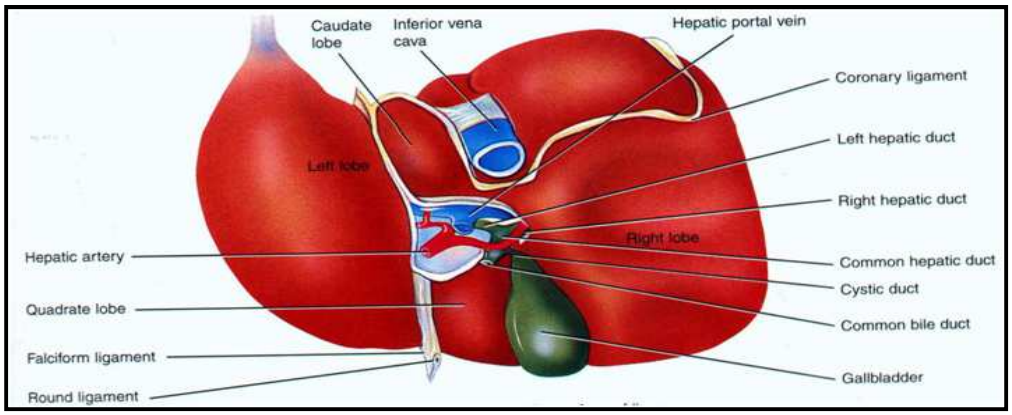

Figure No.1: Liver anatomy and physiology

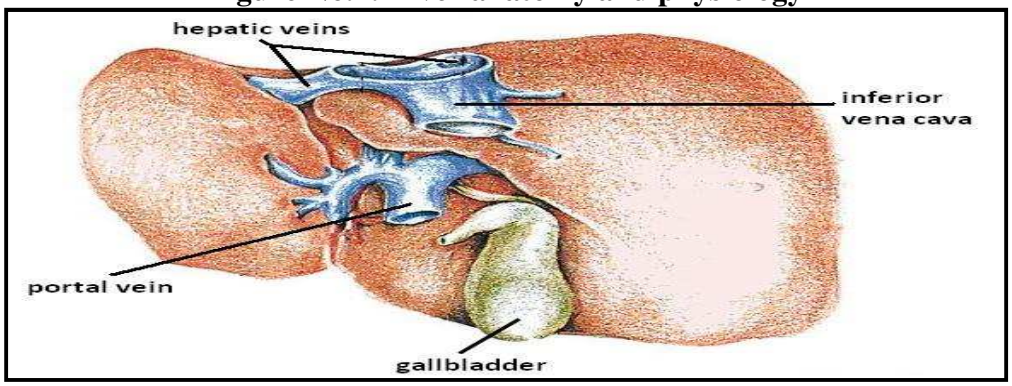

Figure No.2: Liver Veins

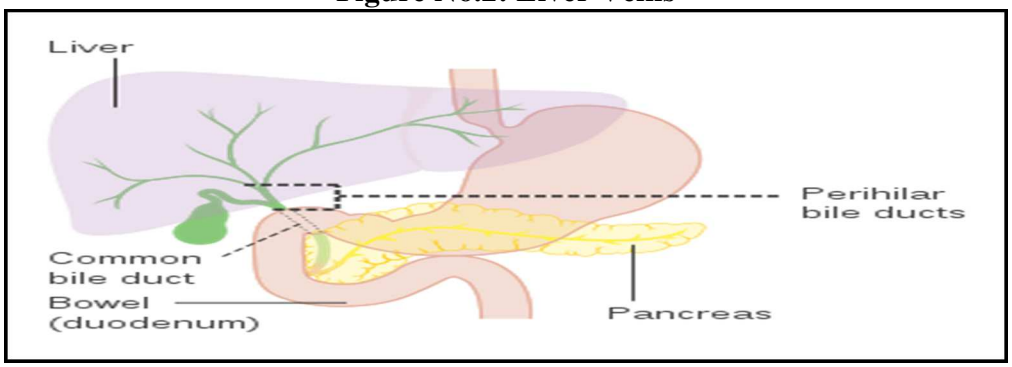

Figure No.3: Bilary Tract

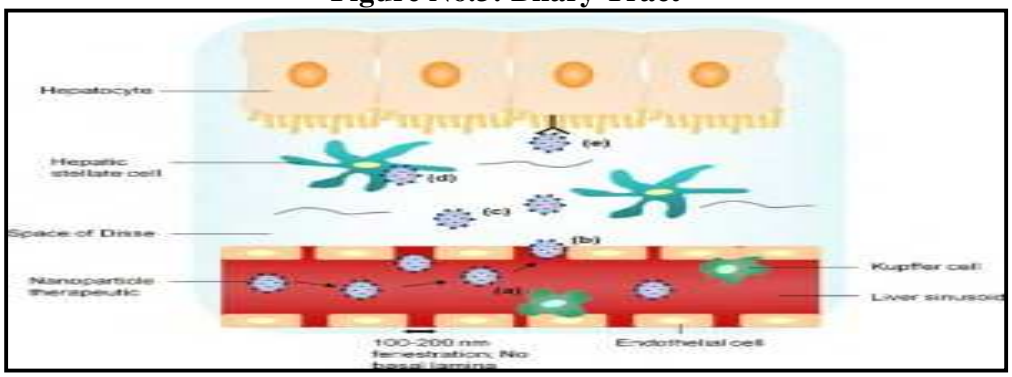

Figure No.4: Passive and Active Liver Targeting Strategies of Nanoparticles Therapeutics[32]

CONCLUSION

Targeted drug delivery will be an extremely fascinating strategy to boost the therapeutic outcome, with considerably weakened cyanogenic side-effects compared to ancient therapy. Previously most studies were supported conjugating carriers or medicine with targeting ligands, like antibodies and sugars. The recent methods use web site specific drug carriers like antibodies, peptides, natural and changed or artificial polymers. Beside these, prodrugs area unit|are} investigated that are designed to cleave in a very site-specific manner. Some prodrugs gain cell specificity whereas others gain specificity by victimization cell-specific surface receptors (e.g., steroid transporter) that facilitate prodrug transport into liver cells. Till nowadays only a few delivery systems area unit marketed as liver targeted drug delivery system.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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