Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env. Pharmacol. Life Sci., Special Issue [1]2022 :71-80

Online ISSN 2277-1808
Journal's URL:http://www.bepls.com
CODEN: BEPLAD

REVIEW ARTICLE **OPEN ACCESS**

Novel Targeting Approaches in the Management of Hepatic Fibrosis: A Brief Review

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ABSTRACT

By experimentally analyzing the molecular mechanisms behind liver fibrogenesis, it is necessary to design and fabricate some vitally pertinent strategy by emphasizing on innovative therapy, which is a self-regulating process irrespective of principal investigational approach. The escalating success with the application of antiviral treatments has limited scope in the arrest or relapsing as well as re-occurrence of the hepatic fibrogenesis with associated disorder like chronic liver disease. Now- a - days, by continuous experimentation about the customary record of fibrosis degeneration, it is clear that various targeting approaches to the fibrotic tissue created a new path way along with some potent anti-fibrotic remedies. Even if , a lot of investigation was carried out to verify the fibrosis healing action of numerous new chemical entity via in vitro and in animal paradigm , not any has been carefully certified in the clinical application as well as commercially established remedy for liver fibrosis .Therefore, it is a challenge, so as to follow combinational regimen which confirms the application of double or more than two molecule as a key point in the curbing aspects of fibrosis. Besides, improvement in the existing clinical management system by the involvement of non-invasive approaches and coupling with various ligands has created a forecasting assessment in targeting the germination of fibrotic tissue. Currently, in this review, it has been taken in to account that, clinical trials along with non- invasive investigative tools extends remarkable results in controlling the reversal of fibrogenesis as well as in the diminishing of fibrosis progression.

Keywords: *Liver fibrogenesis, Anti-fibrotic therapy, chronic liver diseases, Targeted therapy and Noninvasive diagnosis.*

Received 10.02.2022 Revised 05.03.2022 Accepted 21.03.2022

INTRODUCTION

Global scenario of liver diseases revel that persistent hepatic disorders are the foremost worldwide health saddle which reports about 2 million demise of life annually [1]. Viral infections like Hepatitis B, Hepatitis C and other allied persistent liver diseases such as Non-alcoholic steatohepatitis, alcoholic steatohepatitis, autoimmune disorders and alteration in genetics are crucial pathogenic seeds in unceasing liver diseases. More ever, tissue fibrogenesis proceeds sequential development of inflammation with formation of scar in liver tissue that occupies around 45% of mortality all-inclusive [2]. Generally, inside the liver, the upgrading of fibrosis ascertains excellence of existence, including the projection of disease [3]. As a result, this rises to the most hazardous condition called hepatocellular carcinoma having greatest risk factor with increasing concentration of fibrosis associated with normal functioning of liver [4]. Moreover, hepatic encephalopathy along with hydropic decompensation with persistent blood loss causes unrelieved threshold for portal hypertension which occurs as a subsequent symptom of liver fibrosis that may be considered as a chief source of established complications [3]. Thus, as the most ending outcome of fibrosis leads to liver cirrhosis and now a day's this disease is ranked in the 11th position in the degree of fatality in the humankind [1] and also considered as 4th most recurring basis of decease in adolescents in Central Europe [5,6]. Hepatic fibrosis is defined as unremitting change in the

hepatic architecture as a consequence of endless accumulation of extracellular matrix (ECM) that leads to formation of inflammation associated scaring of tissues [7]. The pathological appearance shows injury in hepatocytes that trigger trans-differentiation of hepatic stellate cells (HSCs)due to synthesis of collagen myofibroblast as a result of viral infections associated with deposition of noxious metabolic by products and infiltration of immune cells [8, 9]. Physiologically, it is alarmed in tissue renovation which ahead momentary solution which is evenhanded by antagonizing anti-fibrotic frameworks with substantial succession in deactivation or apoptosis of myofibroblast and resolution of wounds. On the contrary, an uneven production of extracellular matrix resulted as an output of unceasing hepatic disorders assisted with a disproportion of pro-fibrogenic and anti-fibrogenic components which gives rise to unremitting organization of augmenting, contractile and transitory myofibroblasts [8, 9]. Finally this leads to formation of anti-fibrotic wound diffusing state which progress into an unconstrained fibrosis-improving stage with corresponding non-parenchymal cells together with Kupffer cells and some supplementary immune cells [10–12]. Consequently, trans-differentiation of hepatic stellate cells with activation of myofibroblast takes place as a result of apoptosis of hepatocyte and liberation of damage-associated patterns by hepatocytes which further trigger HSCs in a straight line but also support utilization and formation of lymphocytes and macrophages which also anchors HSC and activates myofibroblast with the help of pro-fibrogenic and pro-inflammatory cytokines [13, 14]. Alternatively different types of macrophage subpopulations such as matrix-metalloproteinases (MMPs) integrate fibrosis resolution [15, 16]. By viewing the molecular architecture, it is clear that, composite association of cytokine encouraging signaling pathways also instigates the pro-fibrogenic cell communications. Transforming Growth Factor Beta (TGF-β), Platelet Derived Growth Factor (PDGF), and the NLRP3-Caspase1 pathway are all involved in inflammation and beta -catenin pathway may be considered as most triggering pathways which are also responsible for activation of HSC and budding progof fibrogenesis [17–19]. The general, etiological algorithms concerned with hepatic fibrosis are framed in figure 1.

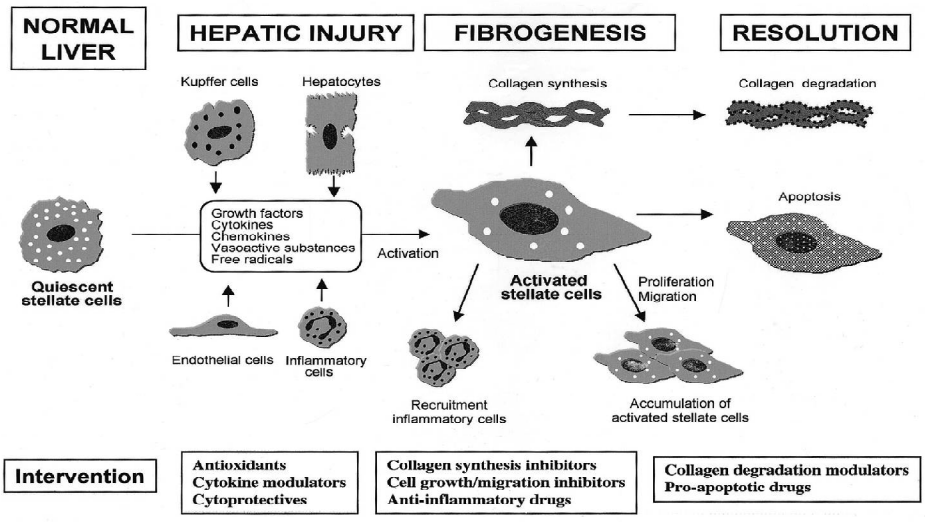

Figure1. Mechanistic Algorithm behind Germination of Liver Fibrosis

METHODOLOGY

Non-invasive Hepatic Fibrosis Diagnosis Tests

To verify the risk factor in advanced cirrhotic liver diseases with prognosis of non-alcoholic fatty liver disease, it may be supportive approach for the management of liver fibrosis. Varieties of prognostic models are also designed to categorize the type of liver fibrosis like AST (aspartate aminotransferase) /platelet ratio index (APRI), FIB-4 (Fibrosis Scoring-4), BARD score (BMI, AST-ALT in presence of Diabetes), NAFLD fibrosis score, King's score , Fibrosis index score(FI) , Enhanced Liver Fibrosis (ELF) panel, Fibro test, Fibro index, Forns Index, Fibrospect II and by using some imaging technology like Transient Elastography (Fibroscan), Acoustic Radiation Force Impulse (ARFI) Elastography, Shear Wave Elastography (SWE), and Magnetic Resonance Elastography are all examples of elastography techniques (MRE) [20].The detailed parameter in diagnosis of liver fibrosis by the implication of scoring system and imaging technology are briefly depicted in table 1 .

TABLE1: NON-INVASIVE TESTS FOR HEPATIC FIBROSIS DIAGNOSIS

Non-invasive tests for diagnosis of Hepatic Fibrosis	
Scoring system	**Imagings**
Aspartate- Aminotransferase Platelate Ratio Index(APRI)	**Transient Elastography (Fibroscan)**
1. Cut-off value is = 0.7 to detect significant hepatic fibrosis (= F2 by Metavir). 2. Has a sensitivity of 77% and specificity of 72%.	1. Cut-off value of ?8kPa has a 94% -100% negative predictive values to exclude significant hepatic fibrosis. 2. Cut-off values used to identify stages of hepatic fibrosis F = 2: 7.1 kPa F = 3: 9.5 kPa F 4: 12.5 kPa
FIBROSIS-4 Score	
1. Score = 3.25 has a positive predictive value of 82.1 % with specificity of 98.2% to confirm the existence of a significant fibrosis (F3-F4 by Metavir)	
BARD SCORE	**Acoustic Radiation Force Impulse (ARFI) elastography**
1. Score = 2 is associated with advanced fibrosis. 2. Low positive predictive value (42%) limits its utility in clinical practice.	1. Using a predictive shear stiffness of 4.24kPa , it distinguishes low (fibrosis stage 0-2) from high fibrosis stage 3-4) fibrosis stage (sensitivity of 90% and a specificity of 905).
Non-alcoholic fatty liver disease (NFS)	**Shear Wave Elastography(SWE)**
1. By using low cut-off score of -1.4555, advanced hepatic fibrosis could be excluded with high negative predictive value of 93%. 2. By applying the high cut-off score of 0.676, advanced hepatic fibrosis could be diagnosed with high positive predictive value of 90%.	1. In healthy population, liver stiffness value ranges in between 4.5-5.5kPa. 2. By using cut off values of 7.10kPa and 9.1kPa to detect F = 2and F = 3 have sensitivity and specificity of 93.8% and 52% and 93.1% and 80.8% respectively. 3. When 13kPa and 15.73kPa are used to detect F4 fibrosis, the sensitivity and specificity are 75.3 and 87.8 and 1005 and 825 respectively.
King's Score	
1. Score = 16.7 predicts cirrhosis with sensitivity 86% specificity 80% and a high negative predictive value of 96%.	
Fibrosis Index score(FI)	**Magnetic Resonance Elastography**
1. Sensitivity and positive predictive value of FI score = 3.30 for the prediction of F4 is 70.8% and 81% respectively.	1. Cut-off value of > 3.63 kPa has a sensitivity of 86% , specificity of 91% , NPV of 97% and PPV of 68% to discriminate advanced fibrosis(F3-F4) from stage F0- F2 fibrosis.
Enhanced Liver Fibrosis(ELF) panel	
1. It has 3 cut-off values. i. Value of 7.7 for exclusion of fibrosis. ii. Value of 9.8 for identification of fibrosis with sensitivity of 69% and specificity of 98% for moderate fibrosis. iii. Value of11.3 to discriminate cirrhosis with 83% sensitivity and specificity of 97%.	
Fibro Test	
1. Cut-off value of 0.30 has 90% negative predictive value for advanced fibrosis with sensitivity of 77%. 2. Cut-off values of 0.70has a 73% positive predictive value for advanced fibrosis with specificity of 98%.	
Fibrospect-II	
1. Score > 0.42 indicates presence of stage F2 to F4 fibrosis with sensitivity of 80.6% and specificity of 71.4%.	

Liver Fibrosis Therapy

There is no particular therapy for liver fibrosis because of its intricacy and related disease. Some anti-fibrotic medications can be used in the treatment of hepatic fibrosis depending on the severity. With progression, a combination of ribaverin, pegylated interferon, and ribavirin has shown to be effective in curing liver fibrosis [21]. Alcohol moderation is an approach for correcting alcohol-induced liver fibrosis that is well-organized [22]. Due to the provocation of the condition, corticosteroids are known to cure autoimmune hepatitis and acute alcoholic hepatitis [23]. Inhibitors of the renin-angiotensin system, interferon (IFN), PPAR ligands, pirfenidone, colchicines, and other pharmacological medications are often used to treat liver fibrosis. [23,24]. Combining sorafenib and a MEK inhibitor through a CXCR4 targeted nanoparticle has been shown to restrain ERK stimulation in activated hepatic satellite cells (HSCs). In a CCl4-induced murine model, it was discovered to exhibit antifibrotic effects. Targetable HSCs might be a

good way to stop fibrosis-coupled HCC from growing and progressing. It was also discovered that silibinin and siCol11 added Vitamin A adorned biocompatible micelles could be used as a secure and effective HSCs specific targeting chemogene distribution system for suppressing fibrous collagen I, and that they could be used as a unique and beneficial therapeutic treatment for liver cirrhosis. For hepatic fibrosis treatment, polypeptide pPB modified stable nucleic acid lipid nanoparticles (pPBSNALPs) were created for specifically delivering siRNAs against heat-shock protein 47 to the liver. LX2 cells and HSCs from mice absorbed more of the prepared system, according to the study. It was discovered that it boosted liver dispersion and HSC absorption in vivo. Furthermore, in mouse models with high gp46 mRNA expression, pPB SNALP exhibited a higher inhibitory impact on TAA-induced hepatic fibrosis [20].

Liver–Specific Targeting

Opsonization occurs when various carrier systems enter the circulation and interact with serum proteins in an untargeted manner; this is known as nonspecific contacts with serum proteins and membrane accumulation of antibodies or complement proteins. Alveolar mechanical entrapment and clearance of aggregates in the alveoli decrease total dosage and carrier circulation time, especially when aggregates are more than 200nm in size and have a substantial surface negative charge present. As part of the scavenger receptors, endothelial cells in the liver sinusoids may take in particles as tiny as 0.23 millimeters in vivo. Protein binding and carrier scavenging may be reduced by the incorporation of PEG moieties into the structure of RES [25]. Passive and active targeting are the most common methods of achieving an objective. Nanocarriers of a desired size and surface modification may be used to perform passive targeting. Passive targeting may be utilized to produce site-specific therapeutic delivery, which enhances the local absorption of the medication and lowers serious symptoms, such as nausea and vomiting. Nanoparticles can be coated with definite ligands, such as proteins, antibodies, carbohydrates and, peptides to promote absorption in certain liver cell types while limiting changes to other liver cell types' physiological functioning.

Passive Targeting

Nanoparticles therapies aggregate in particular body regions due to various anatomic or pathophysiological properties; this sort of targeting, termed as passive targeting, is often used [26]. There are no basal lamina and 100200nm fenestrations along endothelial wall in liver sinusoids capillaries, which distinguish them from other liver capillaries. Nanoparticles therapies may be passively accumulated due to these properties. This makes them suitable for passively targeting the liver, as particles lesser than 200 nm in width can go across slightly broader sinusoidal openings. Nano particle treatments were able to attain a high local concentration at the site of disuse, where they may be distributed to a variety of liver cell types [27]. The EPR effect, initially observed in 1986 by Matsumura and Maeda, also helps nanoparticles therapies accumulate passively in the liver. The retention of nanoparticles therapeutics in tumor tissues is favored by ruptured tumor vasculature, which results in increasing and inadequate tumor ontogenesis to accommodate the increasing need for oxygen and nutrients, resulting in greater porosity and extravasations of macromolecules and deficient lymphatic drainage [28]. With gap junction widths extending from 400 to 600nm, nano particle treatments should be particularly effective in extravagating from the tumor microvasculature, leading to significant concentrations of nano-particles in the local tumor interstitial environment [29; 30].

Active Targeting

Increased treatment efficacy and reduced negative effects can be achieved by site-specific therapeutic system delivery. SECs, KCs, HSCs, and the mostly parenchymal hepatocytes are all nonparenchymal sinusoidal endothelial cells that play a significant part in the liver's varied physiological processes. As a result of their role in secreting and sustaining significant quantities of ECM in accordance to biochemical cues provided by damaged hepatocytes, SECs, and KCs, HSCs are the major focus of treatment for liver fibrosis. Hepatocytes are the primary purpose of HBV infections and HCC [31]. Many liver illnesses, including chronic viral hepatitis, liver cirrhosis, and hepatocellular carcinoma, can be treated with targeted drug delivery systems. It is possible to lessen side effects by increasing amount of drug in target cells while decreasing drug distribution to non-target cells. To target asialo glycoprotein and mannose receptors in hepatocytes and kupffer and hepatic endothelial cells, sugar moieties are widely utilized. The use of ligands to specifically target liver cells is becoming more common.

1. Hepatic stellate cells have mannose 6-phosphate receptors, which can be targeted with the ligand mannose 6-phosphate in the diagnosis of liver cirrhosis [32, 33].
2. Vitamin A is an effective ligand for the treatment of liver illness because of retinol binding protein (RBP) receptor in fibrosis-prone hepatic stellate cells [34].
3. Hepatic satellite cells exhibit significant levels of Type VI collagen receptor and PDGF receptor, and cyclic RGD and PDGF are both employed as ligands in the therapy of liver fibrosis [35].

4. Hepatic stellate cells are targeted by human serum albumin, which is beneficial in the therapy of liver fibrosis because it activates scavenger receptor class A on these cells.
5. Hepatocytes have Asialoglycoprotein receptors. Galactoside, Galactosamine, Asialofetuin, Sterylglucoside, Lactose/lactobionic acid, PVLA. This technique is employed in the treatment of HCC as a ligand to target these receptors [36-44].
6. Scavenger receptor class B I, which are abundantly expressed in cancerous hepatocytes and hepatocytes, are targeted by apolipoprotein A I [45].
7. Linoleic acid targets plasma membrane fatty acid binding protein (Putative); these receptors can also be located on hepatocytes, and they're utilized to treat HCC. [46].
8. Acetyl-Cknekknkiernnklkqpp-amide ligand targets Glycyrrhizin receptors and Heparan sulphate receptors; both receptors are found on hepatocytes and are used to treat HCC [47].

FORMULATION STRATEGY OF LIVER TARGETING OF DRUGS

Targeting the liver is essential for most medicines to attain high hepatic levels because the liver is the main organ for absorption, detoxifying, metabolic change, and outflow of xenobiotics into bile. Consequently, most medications are swiftly eliminated from the body and have high first-pass liver clearance rates. Hepatocytes are responsible for the majority of overall hepatic intake, whereas Kupffer cells are crucial in hepatic particulate material uptake. The intended cell type is not always reached by drugs that reach the liver via covalent carrier moiety or direct entry into the liver. Drugs that build up in the liver are also affected by the pharmacokinetic considerations and macrophage-delivery system interactions addressed earlier in this chapter. In order to achieve sustained intracellular drug concentrations, it is necessary to increase drug accumulation in only one kind of cell. Target liver cells and receptors are listed in table 2, along with the ways by which these drugs might enter these cells.

TABLE2: RECEPTORS ARE FOUND ON A VARIETY OF LIVER CELLS AND CAN BE UTILIZED TO TARGET DRUGS [48]

Hepatocytes	Kupffer cells	Endothelial cells	Hepatic stellate cells
ASGP-R	Mannose or N-acetyl glucose amine R	N-acetyl glucose amine R or Mannose	IGF II R or M6P
HDL-R	Galactose particle R	Scavenger R (Class A1 and A11)	α2 macroglobulin R
LDL-R	Galactose particle R	Fc R immune complexes	Ferritin R
IgA-R	Fc R (immune complexes, opsonized material)	Matrix compound (hyaluronan fibronectin, denatured collagen PIIINP)	Uroplasminogen R
Scavenger R (Class BI)	Scavenger R (Class AI, BI, BII, MARCO CD36 and macrosialin)		Thrombin R
Transferrin R	LDL R matrix compounds (fibronectin)		RBP R matrix compounds (intregrin, collagen type VI, fibronectin CD44)
Insulin R	Complement R (C3b and C1q) LPS R α2 macroglobulin R		-

Hepatocytes are the liver's functional units in responsible of the majority of the organ's metabolic and secretory functions. The delivery system's modest size (150 nm) prevents it from being captured by phagocytic cells and enables it to permeate out of the sinusoids and onto the hepatocyte discs via the fenestrations. Pinocytosis and receptor-mediated endocytosis allow these cells to take in colloidal drug delivery systems. With a tiny delivery system, such as 50 nm, which may diffuse deeper in the area of dissemination, improved delivery (increased localization) to the parenchyma can be obtained [49-51]. Hepatocyte receptors could also be precisely targeted. The ASGP-R is a receptor that acknowledges carbohydrates with different degrees of affinity (mainly galactose and N-acetylgalactosamine) [52], is the most widely employed target. Because ASGP-R positive vesicles are carried to lysosomes by endocytosis, the rising acidic and reactive situations in organelles should be considered when following this approach. Similarly, colloidal internalisation through ASGP-R appears to have a size limit of fewer than 90 nm [53]. This restricts the carrier systems that may be provided using this route. Another option is to coat the delivery mechanism with hepatocytes that target lipoproteins before or after injection [54, 55] or in situ after injection [56, 57]. Though successful hepatocyte interaction is achievable, the versatile nature of lipoprotein receptors in multiple organs may result in nonspecific dispersion and consequent adverse consequences [58]. Finally, emphasizing on non-parenchymal liver cells might be advantageous at times

since they fulfill both good and harmful functions. Scavenging receptors have been shown to target kupffer and endothelial cells [57, 59], while linking vitamin A to the membrane of a colloidal distribution mechanism has been shown to be a useful way of achieving energetic to stellat cells, which contribute significantly in liver fibrosis [60].

Various Aspects of Formulation Development for Liver Targeting

Drug-carrier systems may be directed to liver cells via receptor ligand processes depicted in figure 2, which shows several techniques of coupling ligand molecules to drug delivery systems. Some of these are described in further detail below, and they may also be used to target herbal medications to the liver.

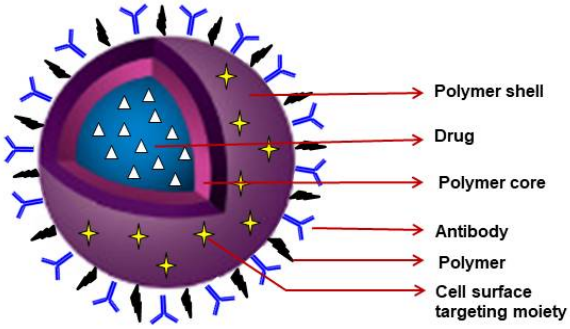

Figure2. Encapsulating a drug grafted with a targeted moiety in a drug delivery system

Figure 3 demonstrates several techniques of attaching ligands molecule to drug delivery devices.
(a) Targeting moieties are coupled on preformed nanocarriers [61-64];
(b) The procedure of connecting targeted moieties after insertion [65];
(c) The Avidin/Biotin complex works together to target certain moieties [66-70];
(d) Prior to the formulation of nanocarriers, targeting moieties are combined [71-76]

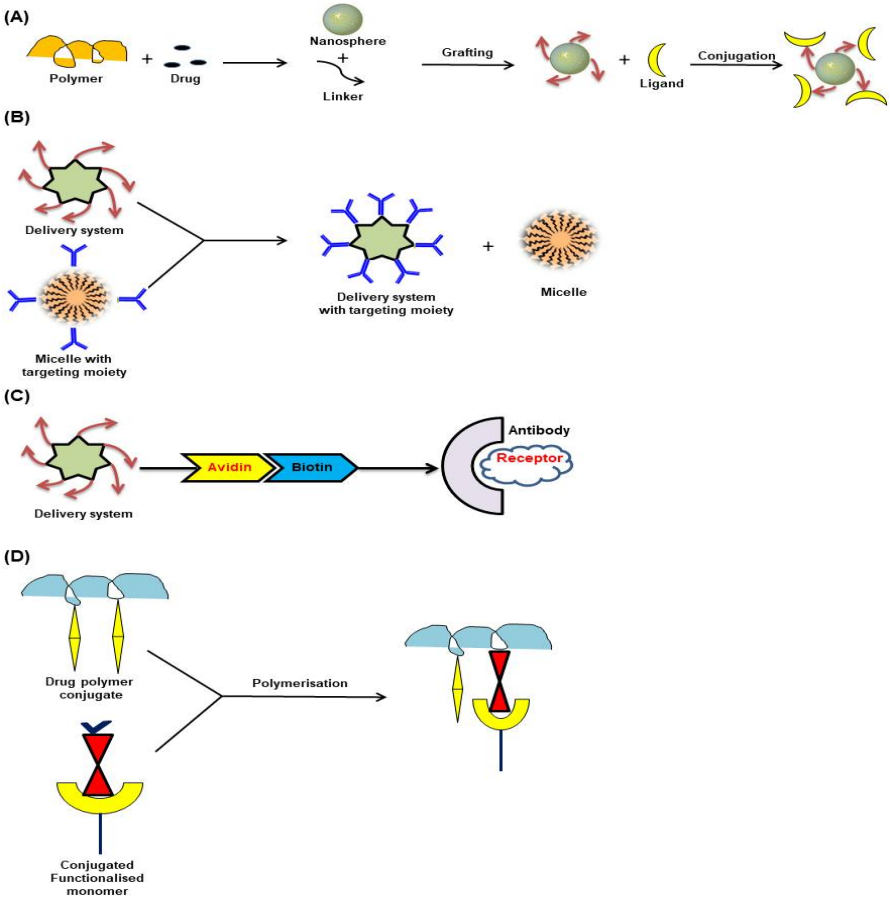

Figure3. Various strategies for attaching ligands molecules to drug delivery systems: (a) combining targeting moieties on premade nanocarriers. (b) The post-insertion approach of coupling targeted moieties. (c) Avidin/Biotin complexes that target moieties. (d) Targeting moieties are linked prior to the formation of nanocarriers.

CONCLUSION

Traditional approaches to the treatment of liver cancer have numerous limitations. A novel therapy or management approach for advanced liver cancer was needed in these situations. According to the study, there are some novel ways available to enhance therapy via hepatoprotective medications, such as the development and manufacturing of suitable polymeric materials to specifically target liver cells. Ingenious investigations in coupling and targeted moiety selection are necessary for them to be converted from bench to bedside. We talked about ligands selection and coupling to drugs/polymers that may possibly target parenchymal/non-parenchymal liver cells. The broad availability of non-invasive evaluations of liver fibrosis has changed the care of the world's 2 billion chronic liver disease patients. While liver biopsy examination is still useful in the diagnosis process, non-invasive tests such as transient elastography and serum biomarkers are very accurate in diagnosing advanced fibrosis and cirrhosis. This current review is based on the targeting aspects of liver fibrosis through the use of novel approaches such as non-invasive diagnosis and coupling mechanism by some specially designed novel therapeutic drug delivery system, which will provide a new direction in future experimentation and detailed study of hepatic fibrosis molecular and cellular biology.

ACKNOWLEDGMENT

All the authors involved in the preparation of this manuscript extend their sincere gratitude to the management of Centurion University of Technology and Management, Odisha and the faculties of School of Pharmacy and Life Sciences, CUTM and also the members of Centre for Drug Design because of their support and encouragement and providing necessary facilities to get this Manuscript as a great and fruitful product.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest in relation to this review work.

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CITATION OF THIS ARTICLE

G R Parida, G Pattnaik, A Behera, S Kanhar, S Sahoo. Novel Targeting Approaches in the Management of Hepatic Fibrosis: A Brief Review. Bull. Env.Pharmacol. Life Sci., Spl Issue [1] 2022 : 71-80