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Expatiating the pivotal role of Dendrimers as emerging nanocarrier for management of Liver Disorders

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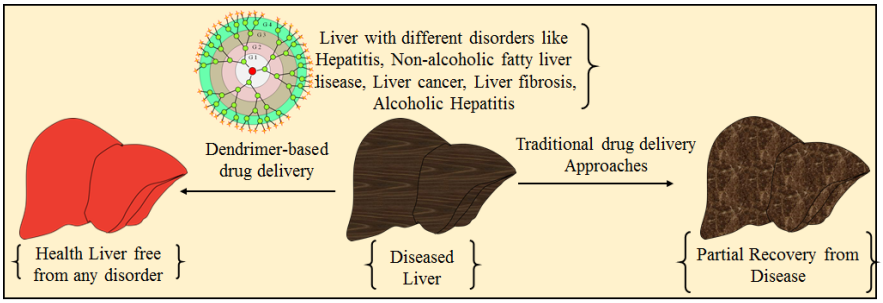
ABSTRACT



Despite advancements in medical science, liver disorders remain to be significant global health challenge, and drug toxicity frequently makes pharmacological therapy difficult. Dendrimers are polymeric three-dimensional structures with a central core, branches, and functional groups at their ends which have distinguished characteristics like high aqueous solubility, well-defined structure, biocompatibility and high encapsulating efficiency for numerous drugs. These have high ratio of terminal groups to molecule volume and therefore acts as potential drug delivery vehicle. Dendrimers have considerable potential to improve biological and physicochemical properties of drugs like enhanced solubility, bioavailability and drug targeting via transporting drugs to their targets at lower dosages, considerable potential for increasing drug safety and minimizing drug-related toxicity. In recent decades, significant improvement has been achieved in utilization of dendrimers in therapeutic, preventive and diagnostic purposes for management of liver diseases. This review highlights about structure and chemistry of dendrimers, dendrimer synthetic approaches *i.e.* divergent approach, convergent approach, orthogonal coupling and double exponential approach, brief summary of different liver disorders, drugs used for treatment of liver disorders, advantages of dendrimer based drug delivery over conventional systems and applications of dendrimers as nanocarriers for therapeutics of liver disorders. Patent literature status related to application of dendrimers in liver disorders has been updated in this review.

Keywords: Liver Disorders, Dendrimers, Drug Delivery, Divergent Approach, Convergent Approach, Orthogonal Coupling

INTRODUCTION

Numerous medicinal compounds have several obstacles in drug delivery application because of poor solubility, toxicity and stability issues, which prevent them from being used in clinical studies despite their high potency.[1] Consequently, this is essential to explore vaious drug delivery techniques which have capablity to provide effective drug administeration. Various polymers have been acknowledged as potential drug carrier system in the past, however, have key issues like poorly defined chemical structures. Scientists are attempting to resolve these challenges.[2] Scientists have investigated the use of nanotechnology as a way to address these difficulties and augment the biological and physicochemical characteristics of chemical entities, leading to improved solubility, bioavailability and drug targeting.[3–5] Numerous nanoparticle-based medicinal products are commercially available, while several are undergoing clinical and pre-clinical testing.[6] Nanotechnology has been proved to commence substantial potential in increasing drug targeting and minimizing drug-related toxicity.[7–11] Furthermore, scientists' keen interest in developing a single system suitable for delivering diagnostic, targeted and therapeutic chemicals has led to development of new category of multifunctional nanoparticles. Dendritic nanostructures have captured the concern of researchers

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owing to their unique physicochemical and structural features among other nanomaterials.[12–14] Dendrimers are nanoscale three-dimensional structures with tree-like branches that are well-defined.[15] The dendrimers have attracted numerous interest in drug delivery application, particularly in development of personalized medicine systems.[16] In the field of nanotechnology, dendrimers are regarded to be the most recent nano-tools for nanoencapsulating and delivering a broad variety of biologically active substances.[17] Dendrimers has been defined as macromolecules that form a tree-like structure to facilitate proficient encapsulation and distribution of bioactive substances to their targets. These nanoparticles are monodisperse and have a nanoscale dimension (1-100 nm) as globular form. [18–21] Dendrimer's physical characteristics such as their spatial configuration, the presence of terminal groups on their surfaces and their dimension are regulated by manufacturing process.[22,23] The dendrimers have three distinct main components *i.e.* core, branches and terminal groups as depicted in Figure 1.

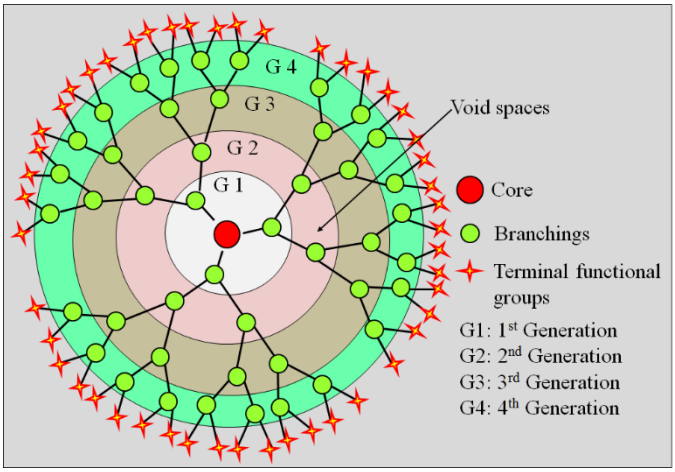

Figure 1. Structure of dendrimer

The terminal groups which are also known as surface groups or functional groups mediate the interactions between dendrimers and other groups or molecules. Therefore, dendrimers' physical and chemical characteristics are influenced by both the branching units and the functional groups on their surfaces. Dendrimers have emerged as an essential research tool in the field of nanomaterials due to their capacity to regulate the physical and chemical features of these structures throughout the production process by regulating the core groups, the amount of branching, and the kind and/or quantity of functional groups on the surface.[6,24,25] The dendritic polymer configuration forms internal voids into which the medication may be deposited, therefore enhancing its stability and solubility.[26] These synthetic macromolecules contains repeating monomer units which are represented by extremely uniform branching units grouped in layers has been termed as 'generations'.[27] The surface characteristics of dendrimers could potentially influence its regulation of biodistribution and clearance throughout the human body.[28–32] Since, their dimensions, form and geometry, surface functionality and flexibility can be adjusted at molecular scale and therefore, dendrimers have potential for exploration as fundamental structural units and nanocarrier which can proficiently and precisely manipulates molecular weight and chemical composition.[33,34] The variety of biological applications are being investigated for possible use of these unique synthetic, extensively branched, nano-spherical macromolecules due to their distinct characteristics in comparison to conventional linear, cross-linked and branched polymers.[35] This review summarizes the structure and chemistry of dendrimers, dendrimer synthetic approaches and their potential application in management of liver disorders. In order to achieve these objective, comprehensive search of available literature was executed using PubMed, Google Scholar and ScienceDirect databases. A literature review was carried out from publications published in peer reviewed journals from year 2000 to 2022. This review has also briefly summarized recent patents literature related to application of dendrimers in liver disorders.

STRUCTURE AND CHEMISTRY

Dendrimers have unique properties due to their well-ordered production and hyper-branched structure.[36] Dendrimer molecules have centre atom or collection of atoms known as the core, which serves as skeleton of the molecule. During a sequence of chemical reactions, carbon and other elements are repeatedly supplemented to the central core of dendrimers, resulting in a spherical dendritic structure. Certain dendrimers such as polyamidoamine (PAMAM) do not have appropriate spherical shape due to series of chemical reactions which must be repeated with the purpose to get required spherical dendritic structure.[37,38] The significant branching surrounding the central core leads to production of several internal layers contains repeating units. The void spaces are generated inside the gaps of dendrimer building blocks which allows better encapsulation of guest molecules. The "generation number" refers to total count of branching points between the central core and the surface.[39] For example, a dendrimer is said to be of the "fifth generation" when it has five branching points, and this kind of dendrimer is denoted by notation "G5-dendrimer." The dendrimer's core section is commonly referred to as "zero generation (G0)" since it lacks branching points in the structure and the dendrimer's "shell" is area between focal (branching) points.[40,41] The surface of dendrimer is third and outermost part which contains numerous functional groups which can be tailored to interact with external molecules or groups. The physical and chemical characteristics of dendrimers depends upon the number of functional groups on the surface and branching units of the molecule.[42,43] Surface functional groups are sometimes termed "surface groups" or "terminal groups". For instance, a dendrimer with amine functional groups on the surface is referred to as an amino-terminated dendrimer. During the process of dendrimer production, the molecular mass of the dendritic structure increases by factor of two with each generation.[44–46] The physicochemical characteristics of dendrimers are greatly influenced by presence of various functional groups on their surfaces, which also perform an important function in their biological interactions.[47] As a result, chemical modification of surface groups may be employed to modulate cellular interactions and dendrimer distributions in a biological system. The dendrons are dendritic structures that do not have a core and dendrimers of

various types may be made by linking two or more dendrons together.[48]

CLASSIFICATION OF DENDRIMERS

Since, the dendrimers have varying composition and structures; therefore, have been classified into several categories on the basis of their composing moiety (Figure 2) and structural differences (Figure 3).[49–52]

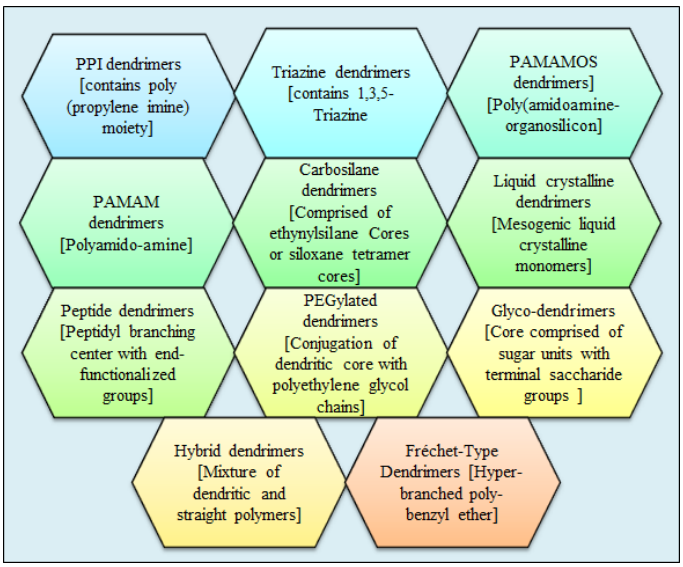

Figure 2. Types of dendrimers based upon the composition.

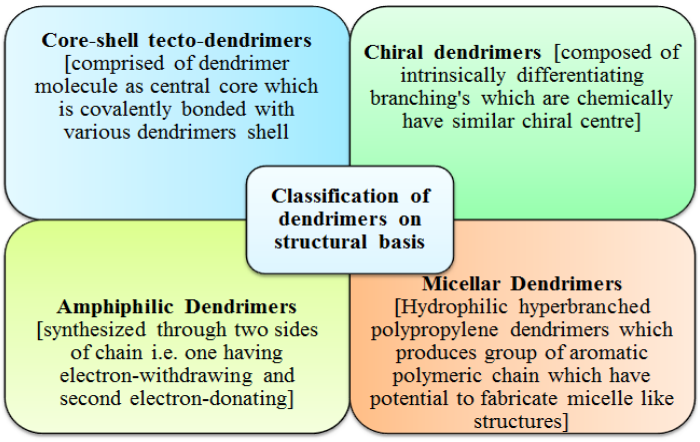

Figure 3. Classification of dendrimers on the basis of structural design.

SYNTHETIC APPROACHES FOR DENDRIMERS

The production of dendrimers is closely connected to polymer and molecular chemistry. They are associated with the world of molecular chemistry due to regulated step-by-step production, and are associated with the world of polymers because of usage of monomers. These are created through series of reactive stages which progresses from 1st generation (G1) to the 2nd generation (G2) and continues likewise.[53,54]

Dendrimers are often manufactured using techniques that offer full structural control throughout the manufacturing process at every step. The various techniques which can be employed for synthesis of dendrimers are depicted in Figure 4. Divergent and convergent dendritic structures are the two common strategies used to produce dendritic structures.[55,56]

Divergent and Convergent approach

The divergent synthesis starts at the dendrimer's core and progresses to adds an additional layer of branching units which causes dendrimer's structure to grow by one generation number as illustrated in Figure 5.[57–59] It is possible to create a variety of dendritic structures using a divergent technique, including poly (amidoamine) dendrimers, phosphorus-based dendrimers, and poly (propylene imine) dendrimers. The divergent technique of dendrimer has few issues as mentioned in Figure 6.[60] However, despite these disadvantages, the divergent method has been demonstrated to be effective in the synthesis of a broad range of dendrimers.[61–63]

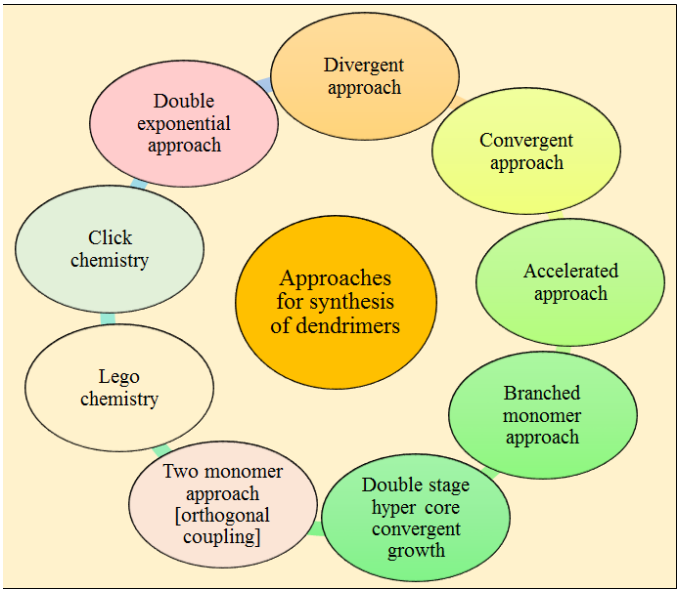

Figure 4. Various approaches employed for synthesis of dendrimers.

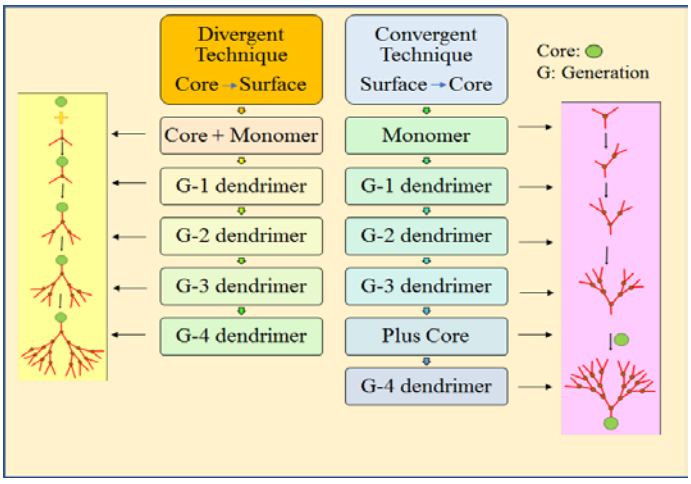

Figure 5. Schematic depiction of (a) divergent growth approach and (b) convergent growth approach for dendrimer synthesis.

Disadvantages of Divergent Approach

- The percentage of reaction sites increases rapidly throughout production process which causes considerable increase in molecular weights.
- Divergent technique exhibits slow reaction kinetic and encounters challenge during development of higher generation dendritic networks.
- Numerous deletions take place during dendrimer formation which leads to development of different faults in resulting dendrimer products.
- Significant molecular similarity between intended and by-products which makes separation process quite difficult.

Figure 6. Disadvantages of divergent growth approach for synthesis of dendrimer.

Convergent approach

The convergent approach aims to address the shortcomings of divergent technique.[64,65] In convergent growth strategy, the dendritic segment is mainly formed by coupling two surface groups to a monomer (dendron generation zero). The convergent synthesis process concludes in the core when two or multiple dendrons are fused together to produce dendrimer as illustrated in Figure 5.[66–69] The convergent approach confers several advantages as mentioned in Figure 7.[70–73]

Advantages of Convergent Approach

- Possibility of regulation of structure of dendritic products with more precision in comparison to the divergent approach since this involves fewer coupling reactions at each growth stage and therefore, increase the probability of synthesis of dendritic products having higher purity.
- This technique have prospective to be applied in synthesis of asymmetric dendrimers, such as Janus dendrimers composed of distinct portions which are joined collectively to generate dendrimers with diverse morphologies.
- Capable of incorporating many active sites into single dendrimer to form a multifunctional excipient

Figure 7. Disadvantages of divergent growth approach for synthesis of dendrimer.

Accelerated approach

Traditional tehniques of dendrimer synthesis involve enormous reaction steps which increases the wastage of starting chemical materials but also raise the possibility of incorporating structural faults in dendritic structure. Consequently, the manufacturing of dendrimers becomes more expensive and time-consuming. The most significant challenge that should be resolved during production of high-generation dendrimers is to ensure complete replacement of all reactive groups in an attempt to prevent structural deficiency. Therefore, several accelerated methods comes into sight which facilitate reduction in reaction time, number of reaction steps, usage of starting materials and the production-related expenses.[74,75]

Branched monomer approach

This method employs hyper branched fragment monomers in the production of dendrimers of a higher generation. This results in two or three dendritic layers being anchored in a single phase.[76]

Double stage hyper core convergent growth

This permits the formation of monodispersed high-generation dendrimers in a short period of time. Small dendritic wedges are attached to a hyper branching dendritic core or hyper core that has a high number of reactive functional groups and may be generated by convergent synthesis is an important part of the process. In general, the core's surface functionality that has the least amount of steric influence is used. This is due to the reactive functional groups being separated from the branching units. Thus, it provides enough space between the reactive groups at the ends of each chain, which is necessary for efficient anchoring.[77–79]

Two monomer approach [orthogonal coupling]

Frechet proposed this approach in which two different monomers react precisely and preferentially react with a set of orthogonal functionalities such that only chosen reactive functional groups conduct the reaction, resulting in anchoring, while the other functionalities remain unaffected. This approach has the advantage of eliminating protecting and de-protecting reactions while simultaneously promoting the production of multilayer block dendrimers.[80,81]

Lego chemistry

This process is based on the highly branched monomers and highly functionalized cores often used in the production of phosphorus dendrimers. This method facilitates the laborious and costly synthetic manufacture of dendrimers with complicated structures and a greater number of surface functional groups using fewer solvents. The main benefits of this strategy are the ease with which desired products and environmentally friendly by-products like as nitrogen and water may be purified.[82,83]

Click chemistry

According to this theory, a chain of reactions leads to the development of a stable, multifunctional, high-yielding product with little or no by-products.[84,85] The purification of the products is possible by utilizing non-chromatographic procedures. The production of dendrimers is both fast and efficient since it involves the joining of small branching units or wedges to build suitable dendritic structures under simple reaction parameters with a minimal quantity of solvents. Cu(I)-synthesized G2 and G3 triazole dendrimers result in dendrimers that can be isolated into pure solids.[86,87]

Double exponential approach

This method, which is analogous to a fast growth process for linear polymers, permits the production of monomers from a distinct preliminary substances via divergent as well as convergent technique. The two products that arise as a result of the reaction are then used in a subsequent reaction to form an orthogonally protected trimer that may be used in further runs of the growth process. The benefit of the double exponential technique is its quick synthesis and adaptability to either divergent or convergent methods.[88–90]

LIVER DISORDERS

The incidence of hepatic disorder is actually increasing in some nations, despite the fact that hepatic disorder has been foremost causes of disease and mortality across the world and is mostly as a result of the combined effects of alcohol-related liver disease, nonalcoholic fatty liver disease and viral hepatitis. The liver disease remains asymptomatic until it has progressed to severe stage; therefore, contribute to serious hepatic problems which makes the burden of hepatic disorder highly distressing.[91] Liver disorders are conditions that influence both the health of the liver and its ability to function normally.

Hepatitis

Hepatitis is a condition in which the liver becomes inflamed. Although, viral infectivity is the main prevalent cause of hepatitis, however, there are a number of additional factors that could also play significant role in its development. These conditions include autoimmune hepatitis as well as hepatitis that develops as a result of using drugs, taking medications, or being exposed to toxins. Autoimmune hepatitis is a type of the disease that expresses itself when the body produces antibodies that are directed against the liver tissue.[92]

Hepatitis viruses are classified into hepatitis type A, B, C, D and E. Particularly, types B and C are the most common cause of chronic disease, which includes liver cirrhosis and cancer, and are responsible for the condition in hundreds of millions of people.[93] Type A and type E hepatitis are commonly transmitted through the consumption of contaminated water or food. Hepatitis B, C, and D are generally transmitted through parenteral contact with contaminated body fluids. The most common ways for these viruses to spread are through the usage of infected blood or blood products, invasive medical procedures that make use of contaminated equipment, and, in the case of hepatitis B, through sexual contact, mother-to-child transmission at birth, and transmission from family member to child.[94–96]

Non-alcoholic fatty liver disease (NAFDL)

NAFLD condition primarily affects adults in their middle to late years. NAFLD may have an effect on people of any age, and it has been described in people of virtually every racial group. Although the actual frequency of NAFLD is unknown, it is estimated that 10 to 24 % of the general population in a variety of nations are affected by the condition. Patients with obesity, type 2 diabetes mellitus and hyperlipidemia are highly prone to NAFLD.[97–101]

Liver cancer

Liver cancer is a potentially fatal disease that is among the fastest growing cancer types in the United States. Primary and secondary liver carcinoma are the two primary types of this disease. Primary cancer begins in the liver. Secondary cancer spreads from another part of the body to the liver.[102] Hepatocellular carcinoma, hepatoblastoma, cholangiocarcinoma, and angiosarcoma are subtypes of PLC.[103,104] Cholangiocarcinom is responsible for 10-15 % of all malignancies that occur in the liver.[105] The prevalence of primary liver cancer varies greatly across different regions of the world; in fact, approximately 80 % of PLC cases are reported in developing nations, most notably in south east Asian and sub-Saharan African nations.[104] Malignant cancers are another name for secondary liver cancer. Secondary liver cancer occurs when a malignancy that originated in another organ has progressed to the liver. The origin of a malignancy is known as the primary cancer. Because it originates in another part of the body and then spreads to the liver, this type of cancer is very hazardous. It can begin in the stomach, colon, oesophagus, pancreas, lung, or breast and then travel to the liver.[106] The process by which cancer spreads to liver is known as metastasis. In the event that some cancer cells separate from the primary cancer, they may spread throughout the body via the bloodstream or lymphatic systems. They spread to a different body place, where they can create a new cancer also known as a secondary cancer which are referred as metastases. The secondary cancer is composed of identical cell types to the primary cancer. It can happen at the time of initial diagnosis or after the primary tumour has been removed. To plan successful therapy, it is necessary to first determine extent of the disease. Early diagnosis and treatment can improve patient survival while lowering treatment costs.[107]

Alcoholic Hepatitis

The main reason of alcohol-related deaths worldwide is alcoholic liver disease. Consuming alcohol is associated with an increased risk of developing hepatocellular carcinoma and also promotes to the progression of liver disorders caused by various etiologies. Consuming an excessive amount of alcohol can result in injuries to liver, ranging from those that are barely noticeable to those that are more severe, such as fatty infiltration or cirrhosis, which can develop over the period of many years.[108,109] Alcohol steatohepatitis, also referred to as alcoholic hepatitis, is a more severe form of liver disease that can develop as a result of drinking large amounts of alcohol for an extended period of time. This type of liver disease can be fatal. Depending on the severity of the inflammation and damage, these conditions can eventually result in fibrosis, which can then progress to cirrhosis and liver failure. Alcoholic hepatitis is liver damage caused by drinking an excessive amount of alcohol.[110,111] When someone has alcoholic hepatitis, initial phase of liver damage is usually reversible if they stop drinking, but resuming drinking raises the probability of damage progressing to cirrhosis and fibrosis, which are more severe forms of the disease. The fat accumulation in hepatocytes causes disruption of beta-oxidation of fatty acids in mitochondria, which results in deposition of lipotoxic metabolites and the generation of reactive oxygen species, both of these leads to cell death and inflammation of the liver.[112–114] Hepatic steatosis (the first stage of alcoholic liver injury) and necroinflammation are hallmarks of alcoholic hepatitis. Abstinence from alcohol can cure alcoholic hepatitis, but the chances of death will depend on extent of the liver damage and drinking habits.[115]

Liver fibrosis

Liver fibrosis is an inflammatory chronic liver damage conditions which can be caused by use of alcohol, non-alcoholic steatohepatitis, autoimmune hepatitis, viral hepatitis, NAFLD, and cholestatic liver diseases. The formation of chronic inflammatory response that results in an inadequate wound healing response is the common effect of all of these variables on the liver. A variety of cell types and mediators are involved in the process of encapsulating an injury. The activation of a fibrotic response in the

liver is responsible for the buildup of extracellular matrix (ECM) components, which ultimately results in the development of a fibrous scar.[116,117] The liver fibrosis process can be reversed prior to its progression to cirrhosis.[118] As long as the liver has not reached an advanced state of cirrhosis, the elimination of the fibrotic response-causing substance promotes regression of fibrosis.[119–121]

DRUGS USED FOR THE MANAGEMENT OF LIVER DISORDERS

Drugs used for treatment of several liver disorders like hepatitis C, chronic hepatitis B virus infections, hepatic encephalopathy, cirrhosis, alcoholic hepatitis, hepatocellular carcinoma and non-alcoholic fatty liver disease has been listed in Table 1.

Table 1. Commonly used drugs for treatment of liver disorders

Liver disease	Drugs with therapeutic efficacy
Hepatitis C[122]	Telaprevir
	Simeprevir
	Boceprevir
	Sofosbuvir
Chronic Hepatitis B Virus (HBV) Infections[123]	Interferon-alpha, Pegylated interferon-alpha
	Lamivudine, Entecavir, Telbivudine
	Adefovir dipivoxil, Tenofovir disoproxil fumarate
	Emtricitabine and Clevudine
Hepatic encephalopathy[124–126]	Rifaximin
	Lactulose (beta-galactosidofructose) and lactitol (beta-galactosidosorbitol)
	Neomycin
	Metronidazole
	Nitazoxanide
	Ornithine-aspartate
	L-ornithine phenylacetate
	Sodium benzoate and sodium phenylacetate
	L-Carnitine
	Flumazenil
	Probiotics
Cirrhosis[127–131]	Spironolactone, Potassium Canrenoate
	Furosemide
	Tolvaptan
	Propranolol, Nadolol, Timolol. Carvedilol
	Cefotaxime, Amoxicillin-clavulanate, Ciprofloxacin, Norfloxacin, Trimethoprim, sulfamethoxazole, Tigecycline
	Interferon, Lamivudine, Tenofovir disoproxil fumarate
	Celecoxib, Aspirin, Etanercept, Simvastatin, Emricasan, Lanifibranor
Alcoholic Hepatitis[115,132]	Pentoxifylline, Etanercept, Infliximab, N-acetylcysteine, Corticosteroids, Acamprosate, Naltrexone, S-adenosylmethionine, Propylthiouracil, Polyenylphosphatidylcholine,
Hepatocellular carcinoma[133,134]	Sorafenib, Doxorubicin
Non-alcoholic fatty liver disease[135–137]	Nifedipine, Resveratrol, Rapamycin
Antitumor effect on human liver cancer[138,139]	Cisplatin, Paclitaxel

ADVANTAGES OF DENDRIMER BASED DRUG DELIVERY OVER CONVENTIONAL SYSTEMS

The majority of therapeutic agents have several drawbacks such as poor aqueous solubility, less permeability and short half-lives on conventional drug delivery. Therefore, this has been essential to develop novel drug delivery system for achieving effective drug delivery. The dendrimer-based drug delivery have immense prospective for modifying drug's characteristics to overcome such limitations. Several dendrimer-based therapeutic products have recently been introduced into market, and others are undergoing clinical and preclinical evaluations[140]. The dendrimers have achieved explicit attention in pharmaceutical and biological applications which is attributable to their high aqueous solubility, biocompatibility, polyvalency, precise molecular weight and drug targeting capabilities[26,141,142]. Sorafenib tosylate has poor bioavalaibility of approximately 38% due to poor aqueous solubility. Recently, Sandhya et al synthesized Sorafenib tosylate encapsulated G4-PAMAM dendrimers which caused 36-fold increase in aqeuous solubility. In another research, PAMAM fluorescein dendrimers were synthesized for encapsulation of sorafenib which cause increased drug stability and exhibited sustained drug release[133,143,144]. Table 2 illustrates that several drugs used in management of liver disorders belongs to BCS class II or IV which therefore necessitate synthesis of their dendrimer based drug delivery for solubility enhancement.

Table 2. Depiction of BCS class of drugs used in therapeutics of liver disorders.

Drug	Liver disorder	BCS Class
Sorafenib[133]	Hepatocellular carcinoma	II*
Doxorubicin[134]	Hepatocellular carcinoma	III**
Ursodeoxycholic acid[145]	Cirrhosis, Primary sclerosing cholangitis, Hepatitis C	II*
Nifedipine[135]	Non-alcoholic fatty liver disease	II*
Resveratrol[136]	Non-alcoholic fatty liver disease	II*
Rapamycin[137]	Hepatic steatosis, Liver injury in non-alcoholic fatty liver disease	II*
Entecavir[146]	Hepatitis B viral infections	III**
Paclitaxel[138]	Liver tumors	IV***
Cisplatin[139]	Liver tumors	IV***
Pentoxifylline[147]	Fibrosis, Cirrhosis	II*

*Low aqueous solubility; **Low permeability; ***Low solubility and permeability

APPLICATION OF DENDRIMERS IN THE MANAGEMENT OF LIVER DISORDERS

Dendrimers are advanced drug delivery system attributable to their characteristic physical and chemical qualities, like their uniform dimensions, a significant amount of branching, water-solubility, polyvalency, and biocompatibility. Although, extensive amount of scientific literature addressing dendrimer uses, there is currently a lack of comprehensive information about their function in liver disorders. The liver is an essential organ and the biggest gland in the body. It is the "engine-room" of the body's metabolic processes. Since the liver is responsible for the metabolism and detoxification of medicines, foods, and water components, it is often subjected to a variety of diseases that may cause variety of clinical syndromes. There are several types of substances, foods, medicines, and infections (bacterial, viral, parasitic, or fungal) that may cause a range of liver illnesses. The examples of liver diseases include hepatitis, cirrhosis, jaundice, and liver cancer. A physician is seldom capable to give particular therapy due to the wide range of liver dysfunctions and the challenges in making an accurate diagnosis. Supportive and symptomatic therapies are offered at most, but the variety of disturbed functions makes therapy more difficult.[148,149] Furthermore, modern (allopathic) medications have considerable toxicity, necessitating the research for alternative pharmaceuticals carrier with maximal therapeutic benefit and no or little toxicity. The liver is an important organ that performs a vital role in the control and regulation of several physiological functions. The metabolic process as well as the release and storage of substances are both affected by its presence, and it plays a crucial part in both of these processes. The liver is responsible for production of bile which plays many vital roles in the digestive process. Liver disorders are one of the most dangerous medical conditions. The majority of liver disorders are caused by ingestion of excessive amounts of alcohol, toxic substances, infections, and autoimmune disorders. This was widely believed that there was no effective therapy for liver disorders. Although, development of dendrimers as revolutionary nanocarrier have changed scenario significantly, and various researchers suggests that dendrimers have significant effect in drug delivery for treatment of liver problems.[150,151] Table 3 discloses various applications of dendrimers as drug carrier for several molecules explored in recent years for therapy of liver disorders.

Zhou et al. developed a small RNA dendrimer delivery system that integrates degradability into dendrimers and diversifies cores, peripheries, and generations to avoid various delivery challenges, achieving an optimal balance between low toxicity and high effectiveness. A significant challenge in treatment of aggressive liver cancer may be solved by employing dendrimers as drug carriers which have great potency in tumours without harming normal tissues[152]. Sepúlveda-Crespo et al. utilized polyanionic carbosilane dendrimers for identification of compounds having antiviral actions against hepatitis C virus infections and to demonstrate that these compounds decrease the effective virus adsorption of primary HCV genotypes[153]. Zhang et al. developed G4.5-COOH PAMAM dendrimer which can prevent TNF- from damaging hepatocytes and alleviate cholestatic liver injury. Moreover, protective role of G4.5-COOH PAMAM dendrimer can be inter-realted to suppression of P-Akt PmTOR production through partial up-regulated PPAR-γ-expression mechanism[154]. Sharma et al. developed galactose dendrimer which produced targeted effect over asialoglycoprotein receptor-1 expressed on hepatocytes and exhibited considerable deposition in hepatic cells within 1 hr after systemic administration[155]. Huang et al. used G5-triethanolamine core based PAMAM dendrimers for delivery of small activating RNA specific for upregulating hepatocyte nuclear factor 4-alpha. This has been evident that i.v. administration of synthesized dendrimers caused considerable decrease in liver triglyceride, rise in ratio of high density lipoprotein to low-density lipoprotein and reduction in ratio of white adipose tissue to body weight[156]. Motoyama et al. demonstrated potential of siRNA loaded thioalkylated mannose-based-G3-dendrimer conjugated with alpha-cyclodextrin for treatment of lipopolysacharide/d-galactosamine induced fulminant hepatitis in mouse model[157]. Chen et al. developed arginine-glycine-aspartic acid-polyethylene glycol-PAMAM dendrimer conjugate which promoted hepatic cell proliferation and affected gene expression and enhanced ammonia metabolism of hepatic cells[158]. Gupta et al. prepared and evaluated sulfasalazine loaded fucosylated PPI dendrimer which revealed their decreased toxicity, exhibited sustained drug release, reduced synthesis of IL-12-p40 in lipopolysaccharides-induced macrophages and also prevented NF-kB activation.[159] Melgar-Lesmes et al. investigated graphene nanostars based PAMAM-G5 dendrimer which exhibited targeted delivery of plasmids with potential to express collagenase metalloproteinase-9 over inflammatory macrophages in livers of cirrhotic mice[160]. Shafie et al. evaluated role of PAMAM-dendrimer loaded with sorafenib in development of liver ascites, collagen deposition and blood flow through liver. These dendrimers at 30 mg/kg and 60 mg/kg doses leads to reduction in development of liver ascites, decreased collagen deposition within liver, increased liver blood flow and overcome hematological adverse effects of sorafenib[161]. Iacobazzi et al. developed lactobionic acid conjugated-fluorescein labelled-sorafenib loaded G4-PAMAM dendrimers for targeting the liver cancer cells. The results indicated that synthesized dendrimers were stable, exhibited sustained release and produced prolonged effect in contrast to free sorafenib at equimolar doses[143]. Sharma et al. prepared PAMAN dendrimer conjugated podophyllotoxin which significantly enhanced its stability, demonstrated sustained drug release for prolonged period, reduced concentrations of IL-6 and NF-κB in serum and tissues and caused significant decrease in histopathological transformations in liver tissue.[162]

Table 3. Perspectives of applications of dendrimers as drug delivery nanocarrier for the treatment of liver disorders.

Type of dendrimer; (disease)	Outcome and Reference
Lead dendrimers; (Liver cancer)	Lead dendrimer (5A2-SC) served as suitable carrier for let-7G microRNA delivery and provided exceptional effectiveness in tumors without harming normal tissues and efficiently inhibited development of aggressive liver cancers.[152]
Polyanionic carbosilane dendrimers; (Hepatitis C virus infection)	G2-S24P, a polyanionic carbosilane dendrimer (PCDs) were chosen to find antiviral agents that limited the virus

	adsorption of main HCV genotypes or enhance virus eradication. In conjunction with sofosbuvir or telaprevir, this compound has an additive effect.[153]
Polyamide-amine [PAMAM] dendrimer; (Cholestatic liver disease)	PAMAM dendrimers (G4.5-COOH) inhibited TNF-α from damaging hepatocytes and reduced cholestatic liver damage and G4.5-COOH might protect by inhibiting P-Akt P-mTOR expression via a mechanism based on PPAR-γ up regulation.[154]
Galactose Dendrimer; (Hepatic necrosis, Nonalcoholic steatohepatitis)	Hepatocyte targeting glycodendrimer (GAL-24) was intended to naturally target hepatocytes' asialoglycoprotein receptor 1 and accumulates in the liver within 1 hour after systemic delivery (20% of injected dose) and the GAL-24 concentrated predominantly in the liver following systemic treatment in healthy mice, with a 20% injected dose at 1 hour and a 2% injected dose 48 hour later, clearing rapidly from the entire body.[155]
PAMAM dendrimers; (Non-alcoholic fatty liver disease)	5-(G5)-triethanolamine-core PAMAM dendrimers were used as a carrier for small activating RNA (saRNA) oligonucleotide. On intravenous delivery, liver expression of HNF4A increased which lead to reduction in triglyceride and increase in HDL/LDL and reduction in white adipose tissue/body weight.[156]
Thioalkylated Mannose-modified Dendrimer (G3); (Fulminant Hepatitis)	Decreased NF-κB p65 mRNA and nitric oxide production from LPS-stimulated NR8383 cells and i.v. injection of complex produced in-vivo RNAi response by suppressing inflammatory cytokines and NF-κB p65 mRNA expression in the liver of mice having fulminant hepatitis induced through LPS/D-galactosamine.[157]
Arginine-glycine-aspartic acid PEG-PAMAM dendrimer; (Liver-function failure)	These dendrimers stimulated hepatic cells to cluster collectively and increased the metabolism of ammonia in hepatic cells by stimulating the AKT-MAPK system.[158]
Sulfasalazine loaded fucosylated poly (propylene imine) dendrimer; (Cytokine-induced liver damage)	Suppressed IL-12 p40 secretion in LPS-activated macrophages and activated NF-kB.[159]
Graphene-(PAMAM) dendrimer nanostars; (Hepatic fibrosis)	Dendrimer-graphene nanostars transported metalloproteinase 9-encoded plasmid into macrophages enabling the production and release of the enzyme to degrade collagen fibers. This targeted gene treatment decreased collagen fibers in cirrhotic mice's fibrotic tracts and enhanced liver repair after 10 days.[160]
Sorafenib-loaded PAMAM dendrimer; (Hepatic fibrosis)	Decreased ascites development, collagen accumulation and adverse hematological effects induced by the drug as well as in contrast to Sorafenib received groups, these dendrimers decreased bile duct ligation-induced liver damage and lowered VEGF in serum and liver tissue.[161]
Acetylation Lactobionic acid G (4)-PAMAM fluorescein (Ac-La-G-(4)-PAMAM-FITC) dendrimer loaded with sorafenib; (Hepatocellular carcinoma)	Sorafenib incorporated in the dendrimer exhibited sustained release, maintained its efficacy and produced a longer-lasting impact than free sorafenib.[143]
PAMAM dendrimer-conjugated podophyllotoxin; (Hepatocellular carcinoma)	Podophyllotoxin-conjugated-PAMAM dendrimer therapy decreased the amounts of inflammatory markers NF-κB and IL-6 in tissue and serum and also decreased fibrous tissue deposition in the liver.[162]

HDL: high density lipoprotein; i.v.: intravenous; LDL: low density lipoprotein; LPS: lipopolysacharide; PAMAM: polyamidoamine VEGF: vascular endothelial growth factor

PATENT LITERATURE STATUS RELATED TO APPLICATION OF DENDRIMERS IN LIVER DISORDERS: CURRENT STATE OF ART

The patent and associated investigations were conducted through patent website i.e. 'World Intellectual Property Organization' to review and systematize the recent applications of dendrimers in liver disorders and has been summarized inTable 4.

Table 4. Patents published about applications of dendrimers for management of liver disease conditions.

Patent name	Patent number (Publication date)	Applicant & Reference
Galactosylated dendrimers for targeted intracellular delivery to hepatocytes.	WO2022055950 (17.03.2022)	The Johns Hopkins University [US]/[US][163]
Dendrimer-Resveratrol complex.	CN113350324 (07.09.2021)	Concordia University[164]
Compositions comprising a Dendrimer-Resveratrol complex and methods for making and using the same.	US20210267910 (02.09.2021)	Concordia University[165]
Triantennary N-Acetylgalactosamine modified Hydroxyl Polyamidoamine dendrimers and methods of use thereof.	WO2021113657 (10.06.2021)	Ashvattha Therapeutics, Inc. [US]/ [US][166]
Polydopamine nanoparticles modified with PAMAM dendrimers, method of their production and their use in anticancer therapy, in particular in the treatment of liver cancer.	PL430511 (11.01.2021)	Uniwersytet IM. Adama Mickiewicza W Poznaniu[167]
Nano gene medicine for liver-related diseases as well as preparation method and application thereof.	CN110721320 (24.01.2020)	Fudan University[168]
Preparation method of shellfish high F value oligopeptides.	CN110144377 (20.08.2019)	Ludong University[169]
Preparation method and application of multi-stage liver-targeted intelligent nano drug delivery system.	CN106389384 (15.02.2017)	Sichuan University[170]

CONCLUSION

The goal of this review was to emphasize the great promise of dendrimers as a therapy for liver disorders. Dendrimers are becoming more essential as tools for the development of new drugs due to the simplicity with which their surfaces may be modified and their capacity to interact with charged functional groups. In recent years, a comprehensive analysis has been carried out, and a significant amount of progress has been achieved in the area of dendrimers and their use in liver disorders. The ability to construct dendrimers with distinctive characteristics and functions has prompted scientists to consider their use as promising delivery systems for the treatment of liver disorders.

FUTURE PERSPECTIVE

Dendrimer-based delivery systems are becoming more interesting as a means of transporting a wide variety of bioactive substances to targeted sites. In the 21st century, dendrimers have emerged as a promising macromolecule in the field of nanotechnology, and they might have potential uses in fields of medicine, pharmaceuticals, and biopharmaceuticals. The discovery of dendrimers have presented oppurtunities to scientists with exciting new possibility to construct macromolecular structures with function that is exclusively suited to their needs. Dendrimers have significant benefits over other macromolecular structures because of their potential to fabricate extremely monodisperse systems with exceptional control over their ultimate size and surface functionality. These molecules are perfect carriers in field of drug delivery because of their carefully regulated architecture, which enables alteration of dendrimers to be made in accordance with their needs. Dendrimers are efficient carriers of drugs, and they may be precisely designed for biomolecules delivery to specific cells. This makes it possible to utilize reduced doses of the drugs, which in turn results in fewer adverse effects. Additional benefits of this nanocarrier includes their safety, compatibility and efficacy via numerous routes of administration. As a consequence of this, it enables us to broaden the spectrum of medications that have therapeutic potential but are not currently used by drug companies due to their poor aqueous solubility. Moreover, the irritating action of polycationic dendrimers towards biomembranes causes transitory nanoholes, which give an additional alternative in the process of exchanging payload across the biomembrane. It has been demonstrated that dendrimers might be promising potential as novel generation drug delivery carrier which ia attributable to their highly customizable surfaces which faciliates the possibility control of their features in ways that are not feasible with other forms of nanocarriers.

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CONFLICTS OF INTEREST

The authors do not have any conflicts of interest.

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