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Review

Nanocarrier-Based Herbal Drug Delivery System for the Management of Liver Diseases

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Abstract: Liver disease poses potential therapeutic challenges, as ongoing hepatic injury is correlated with oxidative stress, inflammation, mitochondrial dysfunction, fibrosis, and impaired hepatocellular function. There are many medicinal plants and their bioactive ingredients with hepatoprotective, antioxidant, and anti-inflammatory properties, but their effectiveness is restricted by problems with water solubility, bioavailability, instability, rapid metabolism, and hepatic delivery. To address this issue, the use of nanocarriers for the delivery of herbal bioactives has become a promising approach to enhance their therapeutic potential. This review focuses on a targeted introduction of the herbal nanocarrier-based treatment approach for liver diseases and the correlation between the various properties of the nanocarrier and the enhancement effect of the plant-derived compounds' delivery in the liver. Important nanocarrier-based systems such as liposomes, phytosomes, niosomes, solid lipid nanoparticles, nanostructured lipid carriers, polymeric nanoparticles, dendrimers, and other emerging systems are mentioned in relation to their structural features, drug-loading capacity, stability, controlled-release features, bioavailability, and hepatic targeting possibilities. It also highlights some of the herbal bioactives that have been attached to nanocarriers and their uses in hepatotoxicity, fatty liver syndrome, fibrosis, inflammation, and liver cancer. Mainly the nanocarriers help increase the solubility of bioactive molecules, prevent their degradation, extend systemic action, improve their accumulation in the liver, and increase their efficacy in treatment relative to classical herbal formulations. Finally, current state-of-the-art limitations, formulation challenges, safety and standardization aspects, and future possibilities for clinical translation in the context of herbal nanocarrier systems are presented.

Keywords: fatty liver; nanostructured lipid carriers; fibrosis; niosomes; phytosomes

1. Introduction

The liver, a powerhouse within the human body, orchestrates an array of vital functions, encompassing synthesis and detoxification. Its pivotal role hinges on a complex interplay of enzymes and transporters, rendering it more susceptible to inherent metabolic anomalies than any other organ [1]. This vulnerability manifests in staggering global statistics, with approximately 2 million annual deaths attributable to liver-related ailments. Among these, cirrhosis and the trinity of viral hepatitis, hepatocellular carcinoma, and complications thereof claim a devastating toll of 1 million lives each. Presently, cirrhosis stands as a prevalent global nemesis, eclipsing other causes of mortality. Concurrently, liver cancer holds its position as the 16th leading cause of death worldwide, amplifying the urgency of understanding and addressing hepatic concerns. The widespread consumption of alcohol, engaging approximately 2 billion individuals globally, poses a dire threat. A staggering 75 million are diagnosed with alcohol use disorders, perpetually exposed to the looming specter of alcohol-associated liver diseases [2]. Shifting focus to India, a poignant landscape of hepatic disorders unfolds. As of the latest available data in 2023, the nation grapples with a substantial burden of liver maladies. A 2022 study estimates the prevalence of chronic liver disease to loom at a staggering 10–12%, with viral hepatitis (B&C), alcohol abuse, and alcoholic fatty liver disease emerging as primary culprits. Within this mosaic, hepatocellular carcinoma emerges as a formidable adversary, ranking as the 11th most common cancer in India as of 2020. An alarming 100,000 new cases annually underscore the urgency of addressing this insidious threat [3]. Interestingly, the prevalence of hepatocellular carcinoma disproportionately burdens the northeastern states of Manipur & Mizoram, dwarfing

incidence rates elsewhere in the country by 10–20 fold. This regional disparity amplifies the urgency for targeted interventions and heightened vigilance within these areas, signifying the need for region-specific strategies and resources to combat this alarming trend [4]. Since ancient times, humanity has relied on the therapeutic potential of natural products and compounds, woven into the fabric of herbal remedies. These plant-derived secondary metabolites, known as phytochemicals and natural products, encompass a vast array of biological activities within the human body, including their capacity to shield the liver from harm. Notably, many of today's best-selling pharmaceuticals trace their origins to these natural compounds or their derivatives. The spectrum of phytochemicals spans diverse molecular sizes, chemotypes, and structural features, encapsulated within extracts, fractions, or refined bioactive compounds obtained through meticulous purification processes. Amid these compounds lie the bioactive phytocompounds, coveted for their therapeutic promise. While numerous studies have showcased the potential of various plant-derived extracts and fractions, a prevailing consensus underscores the need to identify and isolate these bioactive phytocompounds based on their specific biological actions [5]. This precision is pivotal in unlocking the full potential of phytochemicals as safe and efficacious phytomedicines, ensuring their reliability in promoting human health and well-being. Researchers have developed several innovative delivery systems for hepatoprotective properties, such as liposomes, phytosomes, solid lipid nanoparticles, nanostructured lipid carriers, dendrimers, and polymeric nanoparticles, by implementing nanotechnology processes that improve the pharmacokinetics and pharmacodynamics of phytochemicals and natural compounds [6]. The realm of nanotechnology-driven drug delivery has unveiled promising avenues for safeguarding the liver. These innovative systems not only refine drug delivery pathways but also mitigate adverse side effects while amplifying therapeutic effectiveness. Diverse nanocarriers, spanning from nanoparticles to phospholipid nanoconstructs, have been meticulously engineered to serve as vehicles for hepatoprotective drug delivery. Remarkably, Precision Nanoconstructs (PNCs) crafted through microemulsification techniques have showcased a mastery of controlled drug release, ushering in heightened bioavailability and fortified hepatoprotective effects [7]. In the arena of liver cancer treatment, nanoparticles have emerged as formidable allies, wielding hepatoprotective effects. A striking example lies in dual drug-loaded nanosystems meticulously designed for precision-targeted delivery to liver cancer cells. This pioneering approach has yielded profound results, stymying tumor growth significantly while concurrently curtailing toxic side effects, a groundbreaking stride toward safer and more effective treatments [8]. Moreover, the realm of nanocarrier-based drug delivery systems extends its reach toward the management of a spectrum of hepatic disorders, encompassing conditions like liver fibrosis and metabolic-associated fatty liver disease. These systems offer a repertoire of advantages, boasting high drug-loading efficiency, pinpoint accuracy in drug delivery and a commendable track record of minimal side effects. In the grand tapestry of medical innovation, nanotechnology-based drug delivery systems stand tall as beacons of hope for fortifying the liver's defense mechanisms across various liver diseases. Their potential heralds a future where precision and efficacy converge to offer safer and more impactful treatments for these intricate and critical ailments [9].

2. Mechanisms Underlying Hepatotoxicity and Liver Injury

Liver damage, also termed hepatotoxicity, arises from an array of causes, encompassing medications, viral infections, and alcohol consumption. The intricate mechanisms triggering liver damage are diverse and contingent upon the specific cause. Within the liver's processing of certain substances, the production of deleterious byproducts can ensue, wreaking havoc on liver cells. These byproducts disrupt cellular functions, affix to proteins, or impair genetic material, culminating in cellular injury or demise [10]. Occasionally, the body's immune defences erroneously target the liver, spurred by diverse factors like viral onslaughts, exaggerated immune responses, or adverse drug reactions. These immune attacks often precipitate inflammation, scarring, and potentially, liver failure. Mitochondria, the cellular powerhouses generating ATP, crucial for cellular operations, fall prey to damage, disrupting ATP synthesis and ultimately causing cellular demise. Mitochondrial dysfunction is intricately linked to a spectrum of liver ailments, encompassing alcoholic and non-alcoholic fatty liver diseases [11]. Certain substances wield direct harm upon liver cells upon contact; high doses of specific drugs, alcohol, industrial chemicals, or environmental pollutants directly inflict damage. Other substances impede the normal flow of bile from the liver, culminating in cholestasis, where accumulated bile acids and substances instigate harm to liver cells and bile ducts, exacerbating liver injury [12]. Genetic variances hold sway over an individual's susceptibility to liver damage from specific substances; certain genetic disparities in enzymes responsible for drug metabolism or detoxification render some individuals more susceptible to hepatotoxic agents. The spectrum of liver damage spans from mild to life-threatening. In some instances, the liver exhibits remarkable regenerative capabilities, capable of self-healing from injury. Nevertheless, in other scenarios, the inflicted damage may well prove irreversible, leading to lasting liver impairment [13].

3. Different Nanocarriers for Herbal Hepatoprotective Drug Delivery

When it comes to medicine distribution, nanocarriers stand out as a groundbreaking approach that significantly enhances both the precision and efficacy of drug delivery. These minuscule vehicles, ranging from 1 to 100 nm in size, are intricately designed to encapsulate therapeutic substances such as medications or genes. The primary objective is to optimize the targeted delivery of these agents to specific regions within the body. Compared to conventional drug administration methods, nanocarriers offer a plethora of advantages, including heightened bioavailability, prolonged circulation times, and reduced side effects. Their composition, derived from materials like lipids, polymers, and inorganic nanoparticles, can be tailored to specific applications. Surface modifications, incorporating ligands that bind to receptors on particular cells, further facilitate precise and targeted distribution [14]. The ongoing research on nanocarriers holds immense potential to revolutionize disease treatment, presenting more tailored and customized therapeutic approaches with minimized systemic toxicity. Recent discoveries in the field have extended to plant-based nanocarriers and their hepatoprotective properties. These carriers exhibit expertise in encapsulating bioactive substances sourced from medicinal plants, such as soft coral extracts and curcumin derivatives, thereby enhancing their therapeutic efficacy [15]. The utilization of nanoparticle-based drug delivery systems, particularly those employing plant-based nanocarriers, offers significant benefits, enhancing bioavailability and effectiveness. An illustrative example involves chitosan nanoparticles loaded with soft coral extract, demonstrating hepatoprotective effects in experimental models. This approach not only restored normal liver enzyme levels but also augmented antioxidant capacity. Beyond hepatoprotective applications, plant-based nanomaterials show promise in microbiology, spanning antibacterial applications and advancements in wound dressing techniques. These collective findings underscore the tremendous promise of plant-based nanocarriers, not only in hepatoprotection but also in broader applications within microbiology and medicine. The study of plant-based nanocarriers represents a notable advancement in medical research, showcasing their potential for hepatoprotective purposes and their broader impact on novel therapeutics. Their ability to encapsulate biologically active compounds from medicinal plants, such as soft coral extracts and curcumin derivatives, enhances their therapeutic efficacy, particularly in the liver [16]. The application of nanoparticle-based drug delivery systems, especially those utilizing plant-based nanocarriers, significantly improves the bioavailability and effectiveness of bioactive compounds. For instance, chitosan nanoparticles loaded with soft coral extract have demonstrated hepatoprotective properties in experimental mice, highlighting their potential to reduce liver damage and promote overall hepatic health. Moreover, the versatility of plant-derived nanomaterials extends beyond hepatoprotective applications, showing promise in microbiology for wound dressings and antibacterial therapies shown in Figure 1. Their adaptability and biocompatibility make them desirable for a range of therapeutic procedures, emphasizing their multifaceted contributions to the advancement of medical science. In summary, the exploration of plant-based nanocarriers is not only promising for hepatoprotection but also indicative of their broader influence on medical research and novel therapeutic approaches shown in Table 1.

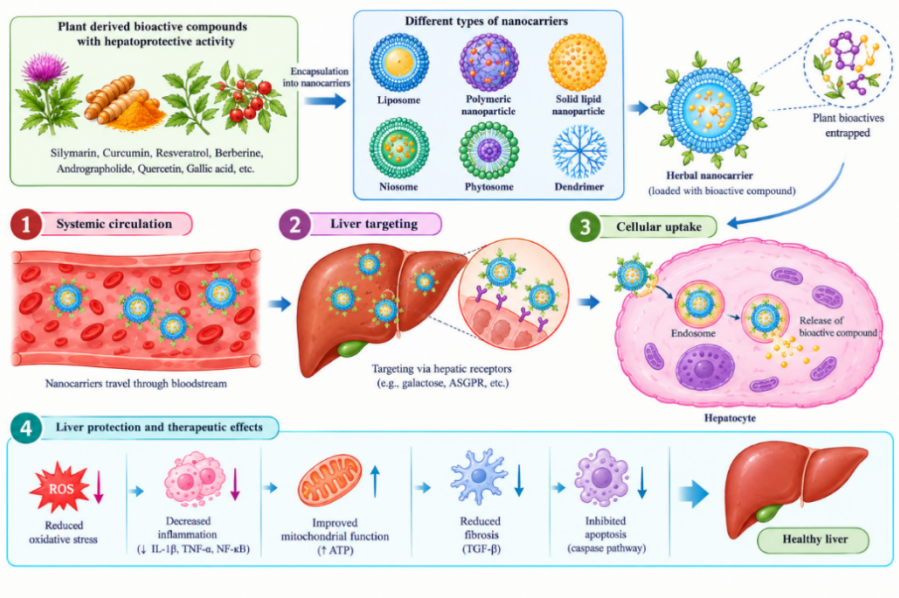

Figure 1. Schematic illustration of nanoformulations encapsulating plant-based hepatoprotective agents for liver protection and targeted delivery.

3.1. Liposome

Liposomes, spherical sacs of phospholipid molecules enclosing water droplets, were initially described by Alec D. Bangham and colleagues at the University of Cambridge in the 1960s. These artificial structures have gained recognition for their versatile applications, serving as pharmaceutical delivery vehicles, chemical microreactors, and model biomembrane systems [17]. Comprising concentric layers of phospholipids, liposomes can be tailored in composition, charge, size, and lamellarity. With diameters ranging from 50 to 1000 nm, these lipid bilayers encapsulate aqueous compartments that carry various therapeutic substances, such as peptides, proteins, hormones, enzymes, antibiotics, antifungal, and anticancer agents. The hydrophilic part of phospholipids contains phosphoric acid bound to water-soluble molecules, while the hydrophobic part consists of two fatty acid chains. In an aqueous environment, these phospholipids self-orient to form a bilayer, providing a protective barrier for encapsulated substances. Liposomes, primarily composed of phospholipids and cholesterol, have demonstrated hepatoprotective effects in various studies [18]. Liposomal formulations of antioxidants, like γ-oryzanol and ferulic acid, exhibit potent scavenging efficacy against reactive oxygen species, preventing liver damage induced by oxidative stress. Galactosylated chitosan-modified liposomes enable targeted drug delivery to hepatocytes, enhancing the anti-tumor efficacy of compounds like oleanolic acid in hepatocellular carcinoma. Quercetin (QC), a flavonoid abundant in nature, shows therapeutic potential against diverse diseases. Administering QC in galactosylated liposomes may contribute to reducing oxidative damage induced by $NaAsO_2$ and provide a protective mechanism against liver fibrosis. Liposome-encapsulated astaxanthin has demonstrated improved hepatoprotective effects in acute hepatotoxicity models. In studies, liposomes co-encapsulating astaxanthin and capsaicin exhibited higher protective effects on acute liver injury compared to liposomes encapsulating either compound alone. Liposomal silymarin, investigated for hepatoprotective effects, has shown promise in various hepatotoxicity models. Silymarin-encapsulated liposome nanoparticles decreased liver enzymes and improved spatial memory in rats with copper toxicity-induced liver dysfunction. Liposomal oxymatrine formulations have enhanced bioavailability, liver target distribution, and hepatoprotective activity. These formulations, such as RGD peptide-labeled liposomes, demonstrated improved targeting efficiency for hepatic stellate cells, suggesting potential therapeutic efficacy in hepatic fibrosis. In conclusion, liposomes, with their tunable characteristics, have emerged as versatile carriers for delivering various therapeutic agents, showing promise in hepatoprotective applications and liver-related conditions [19].

3.2. Polymeric Nanoparticles

Polymeric nanoparticles (PNPs) have garnered significant attention due to their unique properties arising from their small size range of 1 to 1000 nm. These versatile nanoparticles can encapsulate active compounds within their polymeric core or have them surface-adsorbed onto the nanoparticle. Recognized for their potential in diagnostics and drug delivery, PNPs offer advantages such as controlled release, theranostic capabilities (combining therapy and imaging), drug protection, specific targeting, and improvements in the therapeutic index [20]. Nanocapsules and nanospheres, constituting the term "nanoparticle," differ in morphology, with nanocapsules having an oily core and nanospheres based on a continuous polymeric network. The regulation of drug release from PNPs traditionally involves controlling polymer biodegradation rates and drug diffusion. Recently, stimuli-triggered release methods selective to specific disease microenvironments have gained attention. The success of polymeric drug delivery relies on polymer biodegradability and biocompatibility. Biodegradable polymers, eliminated through natural metabolic pathways, offer advantages over synthetic counterparts. While natural polymers are biocompatible, batch variations limit their use, and synthetic polymers offer controlled composition [21]. Various polymers, including proteins, sugars, biodegradable, and non-biodegradable types, have been employed to create PNPs using diverse preparation techniques. Despite differences, all methods involve a common step—polymer precipitation. The resulting PNPs are often produced in aqueous suspension, posing stability challenges. Freeze-drying has been widely adopted to enhance stability, albeit stressing the nanoparticles. Cryoprotectants during freezing and drying help mitigate damage. In the realm of hepatoprotection, PNPs have demonstrated efficacy through enhanced bioavailability, cellular uptake, and controlled release kinetics. For instance, liquid crystalline nanoparticles of hispolon (HP-LCNPs) show improved bioavailability and antioxidant activity in hepatocellular carcinoma treatment [22]. Redox-responsive polymeric nanoparticles designed to target cancer cells have undergone in vitro assessment for hepatotoxicity, revealing sub-lethal toxicity. These findings underscore the potential of PNPs in hepatoprotection and the treatment of hepatic diseases. Furthermore, polymeric nanoparticles have demonstrated significant promise for hepatoprotective uses. For example, when β-Sitosterol (BSS) was prepared into lipid-polymer hybrid nanoparticles (LPHNPs), its hepatoprotective impact was amplified. Both chitosan and chitosan nanoparticles are antioxidants and can prevent liver damage brought on by ethanol.

Additionally, in hepatocellular carcinoma (HCC) models, poly(ethylene glycol)-b-poly(lactic acid) (PEG-b-PLA) nanoparticles loaded with sorafenib demonstrated enhanced treatment efficacy [23]. Numerous studies have shown the hepatoprotective efficacy of polymeric nanoparticles loaded with sesamol. These nanoparticles shielded rat hepatocytes against aluminum oxide nanoparticle-induced hepatorenal damage and improved defense against doxorubicin-induced oxidative stress. Furthermore, compared to sesamol or selenium nanoparticles alone, sesamol-PEG-selenium nanoparticles significantly suppressed HepG2 cancer cells, exhibiting increased apoptosis. In multiple models of liver injury, curcumin nanoparticles have demonstrated hepatoprotective properties, effectively mitigating liver damage caused by cyclophosphamide, cypermethrin, paracetamol, and carbon tetrachloride (CCl4). These nanoparticles may be able to lessen the liver damage induced by CCl4, as they enhance liver function, decrease oxidative stress, and lower levels of inflammatory cytokines. Ursodeoxycholic acid (UDCA) and silybin in polymeric form have shown promising modes of action in the treatment of liver disease. Polymeric nanoparticles coated with silybin decrease liver inflammation, prevent NF-κB translocation into the nucleus, and restore CYP3A production and activity. Polymeric nanoparticles loaded with UDCA demonstrate a range of hepatoprotective and anticholestatic characteristics, including altering the constituents of the bile acid pool, inducing hepatobiliary secretion, providing cytoprotective effects, preventing cholangiocytes from absorbing bile acid, and exhibiting immunomodulatory activity. In vitro research on silybin and UDCA polymeric forms have demonstrated greater hepatoprotective activity than their free forms, indicating improved therapeutic efficacy in the treatment of liver disease [24].

3.3. Solid Lipid Nanoparticles

Solid lipid nanoparticles (SLNs) are a novel class of drug delivery vehicles with great potential for use in the pharmaceutical industry. These nanoparticles, which are usually between 10 and 1000 nm in size, are made of lipids that are solid at body temperature as well as room temperature. Made up of common lipids including triglycerides, fatty acids, and waxes, the solid lipid matrix shields the payload from degradation while offering a stable and biocompatible environment for effective drug encapsulation [25]. The manufacture of solid lipid nanoparticles (SLNs) involves the use of techniques such as high-pressure homogenization, solvent emulsification-evaporation, and microemulsion procedures, which provide precise control over particle size and drug-loading capacity. Since the lipids solubilize hydrophobic molecules, an inherent benefit of SLNs is their capacity to increase the bioavailability of medications that are poorly soluble in water. Stability against drug leakage is guaranteed by the solid lipid matrix, which also makes regulated release over time easier. Additionally, due to the biocompatibility and non-toxic nature of lipid components, SLNs have the unique potential to protect sensitive medications from environmental influences and enzymatic degradation, which enhances their safety profile [26]. The ability of SLNs to encapsulate a wide range of therapeutic agents, from tiny molecules to peptides and nucleic acids, highlights their adaptability in drug delivery applications. Furthermore, targeted drug delivery is made possible by surface modifications using polymers or ligands, which improve SLN accumulation in particular tissues or cells. This reduces off-target effects and maximizes total therapeutic efficacy. Solid lipid nanoparticles (SLNs) have shown great promise in the pharmaceutical field for treating various diseases, including cancer, infectious diseases, and neurological disorders. Because of their unique combination of biocompatibility, stability, and versatility, SLNs can effectively cross biological barriers and deliver drugs to precise target sites, which makes them particularly attractive for personalized medicine and precision therapies [27]. As our understanding of SLNs continues to develop, ongoing research is focused on improving their formulation, increasing drug-loading efficiencies, and investigating novel applications in diagnostics and theranostics. The hepatoprotective effects of bixin are amplified when it is loaded into solid lipid nanoparticles. A new Nrf2 activator called bixin has cytoprotective effects on inflammation and oxidative stress in the liver. When compared to the bixin solution, the accumulation of bixin in the liver was better when it was put into solid lipid nanoparticles (SLNs). As demonstrated by decreased serum aminotransferase release, retained glutathione reductase activity, and decreased lipid peroxidation and histopathological damage, the SLNs effectively protected the liver against carbon tetrachloride (CCl4)-induced damage. The preventive effect of bixin against CCl4-induced hepatotoxicity is attributed to its antioxidant activity [28]. Bixin's hepatoprotective activity is therefore improved by loading it onto solid lipid nanoparticles, which also improves its accumulation in the liver. Hepatoprotective activity has been demonstrated by ganoderic acid-loaded solid lipid nanoparticles (GA-SLNs) in the treatment of hepatocellular carcinoma (HCC). Studies conducted both in vitro and in vivo have shown the effectiveness of GA-SLNs in reducing the size of hepatic nodules, inhibiting tumor growth, and reducing oxidative stress levels. GA-SLNs were found to be more cytotoxic against HCC cells when compared to free GA solution. The optimized GA-SLNs formulation displayed stable properties over a 12-week storage period. All things considered, GA-SLNs have demonstrated superior

therapeutic action and have the potential to be an effective treatment for HCC [29]. Resveratrol (RSV)-loaded cationic solid lipid nanoparticles (SLNs) have demonstrated therapeutic potential for hepatocellular carcinoma (HCC). These SLNs can increase RSV's bioavailability and tumor-targeting capacities, which will boost the virus' therapeutic efficacy. RSV can be delivered to hepatoma cells more effectively when cationic SLNs are used, which raises drug concentrations around the tumor. RSV's cytotoxic effect on HCC cells is amplified by its encapsulation in SLNs, which improves its anticancer effectiveness. Furthermore, ligands such as glycyrrhetinic acid (GA) and folate (FA) added to the surface of SLNs improve their ability to target tumors. These results imply that cationic SLNs loaded with RSV may prove to be a useful therapeutic tool in the management of HCC [30]. Solid lipid nanoparticles based on the alpha-lipoic acid–stearylamine combination (ALA-SA SLNs) have been demonstrated to modify the hepatotoxicity of tamoxifen (TMX). When compared to TMX suspension, the ALA-SA SLNs increased the relative bioavailability of TMX by 1.59 times by improving its oral bioavailability. Furthermore, the hepatotoxicity of TMX was shown to be reduced when ALA-SA SLNs were used to administer it, according to a histological analysis of liver tissues. Additionally, it was discovered that the SLNs have a great deal of potential for improving the oral bioavailability of poorly soluble medications like TMX, which would make them appropriate for long-term anticancer therapy with negligible side effects. All things considered, ALA-SA SLNs are a potential drug delivery technology for TMX since they can lower hepatotoxicity and enhance the pharmacokinetics of the medication [31]. The therapeutic potential of Ficus benjamina solid lipid nanoparticles (FBSLNP) against alcohol abuse/antabuse-induced hepatotoxicity was assessed during their preparation. Effective antioxidant, anti-inflammatory, and detoxifying qualities were shown by the FBSLNP formulation, providing notable defense against hepatic and cardio-renal damage brought on by long-term alcoholism and alcoholism associated with disulfiram. Solid lipid nanoparticles (SLNs) have several benefits, including focused therapeutic action, controlled release, and improved bioavailability, making them a promising drug delivery technology [32]. Lipid-based nanoparticles (SLNs), such as FBSLNP, have demonstrated promise as biocompatible drug delivery vehicles. The potential of lipid nanoparticles in treating hepatotoxicity is suggested by the considerable increase in medication uptake in the liver seen following surface modification of Embelin-loaded GA-PEG-PLGA nanoparticles. To enhance the liver targeting effect and bioavailability of syrigopicroside, a traditional Chinese medicine that is effective against the hepatitis B virus, syrigopicroside solid lipid nanoparticle formulation was produced. These solid lipid nanoparticles showed decreased toxicity and adverse effects, extended action period, and stability [33].

3.4. Phytosomes

The term "phyto" signifies plant, and "some" refers to cell-like structures. Herbosomes, sometimes referred to as phytosomes, are a type of vesicular drug delivery system used to increase the bioavailability and absorption of low-soluble medications. These complexes are made up of phospholipids and naturally occurring active phytochemicals that are created when phosphatidylcholine (or any other hydrophilic polar head group) reacts with plant extracts in an aprotic solvent. Phytosomes have better pharmacological and pharmacokinetic characteristics than common preparations. Enhanced absorption and transport across biological membranes are made possible by phytosomes' capacity to mimic the body's natural phospholipid bilayer structure. This is one of their main advantages [34]. Higher bioavailability and better pharmacokinetic characteristics of bioactive plant components result from this capacity. Many phytoconstituents, including flavonoids, polyphenols, and alkaloids, have been delivered via phytosomes with a wide range of therapeutic uses, including liver support, cardiovascular health, anti-inflammatory, and antioxidant benefits. Phytosomes have been especially well-received by herbal medicine, which has redesigned conventional plant medicines to optimize the therapeutic effects of their active ingredients [35]. Phytosomal formulations of silymarin from milk thistle, which protects the liver, and curcumin, which has anti-inflammatory and antioxidant qualities, are two noteworthy examples. To sum up, phytosomes provide a novel strategy in herbal medicine and natural product treatments, offering a solution to the problem of low bioavailability linked to specific chemicals produced by plants. Because of their skill at improving solubility, absorption, and general efficacy, phytosomes are seen as crucial instruments for developing phytotherapeutic formulations that produce better therapeutic results.When it comes to increasing the oral bioavailability of phytoconstituents with limited water solubility—including those with hepatoprotective activity, phospholipid-based delivery systems, or phytosomes, have shown to be an effective method. The phytosomes that create these vesicles enhance the bioavailability and absorption of polyphenolic chemicals present in herbal extracts, transporting them to the intended location without causing any changes to their metabolic processes [36]. Research validates the hepatoprotective effectiveness of phytosomes by reestablishing normal levels of antioxidant enzymes and reducing hepatotoxic-induced cellular abnormalities. Moreover, phytosomes and substances like soy lecithin have been

shown to have synergistic antioxidant action. Because of their excellent pharmacokinetic and pharmacodynamic qualities, phytosomes are used as nutrition transporters, antioxidants, and hepatoprotective agents in the pharmaceutical sector. Studies have demonstrated the hepatoprotective and antioxidant properties of ginkgo biloba. When paired with other plant extracts, it enhances antioxidant qualities and scavenges free radicals. It has been discovered that ginkgo biloba leaf extract (GbE) has a hepatoprotective action against liver injury caused by substances like CCl4. While enhancing antioxidant markers, GbE therapy decreased the levels of liver enzymes and oxidative stress markers. It has been demonstrated that GbE mitigates methotrexate-induced liver damage by lowering inflammation and oxidative stress. GbE has also been demonstrated to have beneficial benefits on oxidative stress-related illnesses, including liver damage, brain damage, and neurodegenerative diseases. Furthermore, GbE has been demonstrated to influence important oncogenic pathways and reduce the tumorigenic potential of hepatoma cells [37]. In numerous investigations, phytosomes comprising a blend of Piper longum and Abutilon indicum have demonstrated a strong hepatoprotective effect. When compared to the medication extract in its crude form alone, these phytosomes are safer and more efficacious. Piper longum and Abutilon indicum together have long been used to treat liver disease symptoms, and the phytosomal formulation increases the extract's absorption. The phytosomes have been found to protect against liver damage generated by substances such as carbon tetrachloride and thioacetamide. Furthermore, curcumin, a primary component of Curcuma longa, has shown high hepatoprotective activity in the phytosome formulation. These results imply that curcumin, Piper longum, and Abutilon indicum-containing phytosomes may be useful hepatoprotective drugs [38]. The hepatoprotective properties of phytosomes containing Bombax ceiba leaf ethanolic extract have been investigated. Huh7 cells were exposed to the Bombax ceiba flower ethanolic extract, which caused DNA fragmentation and showed cytotoxicity. Furthermore, a high concentration of phenol compounds was found in the leaf extract of Bombax ceiba. These compounds have the potential to significantly lower insulin, insulin resistance, fasting blood sugar, lipid profiles, and IL-6 levels while raising serum levels of LDL, ITLN1, p38 MAP kinase, and PPAR-α. Additionally, rats fed a high-carbohydrate, high-fat diet showed improvements in glucose, HOMA-IR, cholesterol, triglycerides, AST, ALT, IL-6, RBP-4, and salicin-β levels, suggesting that Bombax ceiba extract has potential hypoglycemic, hypolipidemic, and hepatoprotective effects. These results imply that phytosomes containing Bombax ceiba leaf ethanolic extract may have hepatoprotective properties [39]. Numerous studies have demonstrated the hepatoprotective effects of gallic acid. It has been discovered to guard against CCl4-induced liver and kidney damage in rats; at varying dosages, gallic acid phytosomes (GAP) exhibit protective properties. Additionally, gallic acid has been tested for its ability to prevent acute liver injury and decrease oxidative stress in response to multiorgan injury caused by LPS and D-GalN. Furthermore, research has been conducted on the potential of gallic acid in preventing and treating liver illnesses, such as hepatocellular carcinoma (HCC) and hepatitis C virus (HCV) infection. Additionally, it has been demonstrated that gallic acid shields mice from dimethylnitrosamine-induced acute liver damage, potentially by activating Nrf2 and upregulating phase I enzymes. These investigations indicate that gallic acid, even in the form of phytosomes, has a hepatoprotective impact and might be helpful in the management and avoidance of liver disorders [40].

Table 1. Nanoformulations for the plant-based hepatoprotective agent.

Type of Nanocarrier	Formulation (Ratio)	Active Compound	Model	Remarks	Ref.
Liposome	PE, cholesterol, DCP, and QC in molar ratio 7:1:1:1	Quercetin	Arsenite-Induced Liver Fibrosis in Swiss albino rats	Nontoxic herb-origin polyphenolic compound QC selectively to the liver might be useful in therapeutic applications to prevent $NaAsO_2$-induced liver fibrogenesis.	[41]
	L-phosphatidylcholine (LPC), Cholesterol, chloroform/methanol, Astaxanthin	Astaxanthin	Lipopolysaccharide-induced acute Hepatotoxicity in Sprague-Dawley rats	Liposome-encapsulated AST can exhibit highly stable circulation in the blood and efficient uptake by the liver, enhancing intrahepatic cellular antioxidant enzyme activities, leading to a more effective antioxidative effect	[42]
	Silymarin, phosphatidylcholine, cholesterol and methanol-chloroform mixture	Silymarin	Alcohol-induced hepatotoxicity in Wistar rats	Liposomal formulations of silymarin are a suitable candidate and can be used as a liver protectant.	[43]
	Phospholipids of PS (Phosphatidylserine) and PC (Phosphatidylcholine) dissolved in anhydrous ethanol	Phosphatidyl serine	Carbon tetrachloride-induced hepatotoxicity in Wistar rats	PS has protective effects on CCl4-induced hepatotoxicity through the reduction of serum levels of liver aminotransferase and the improvement of the oxidative state	[44]

Table 1. *Cont.*

Type of Nanocarrier	Formulation (Ratio)	Active Compound	Model	Remarks	Ref.
Liposome	Hydrogenated Soy Phosphatidylcholine, cholesterol, DSPE-PEG2000, glycyrrhizic acid ammonium salt & ethanol	glycyrrhizin	Alcohol-induced liver injury in Harlan-Wistar rats	The liposomal glycyrrhizin treatment tempered the effects of ethanol, so it can be a potent medicine with numerous anti-alcoholic, long-term effects and may play a role as an active substance as well as a targeting agent in the therapies of the liver	[45]
Polymeric Nanoparticles	PLGA, Curcumin, Acetone, Polyvinyl Alcohol (PVA)	Curcumin	CCl_4-Induced Subacute Hepatotoxicity in Wistar Rats	Oral administration of ηCur (Curcumin Nanoparticles) attenuates CCl_4-induced subacute liver injury	[46]
	Poly (D-L-lactide-co-glycolic acid), andrographolide, chloroform, heparin & pluronic F-127	Andrographolide	Paracetamol induced Hepatotoxicity in Swiss albino mice	AG was evaluated for the first time as an efficient therapeutic against APAP-induced progressive hepatotoxicity.	[47]
	Sesamol, PLGA, acetone, polyvinyl alcohol, distilled water	Sesamol	CCl_4-Induced Subacute Hepatotoxicity in Wistar Rats	Shows hepatoprotective activity	[48]
Solid-Lipid Nanoparticles	polysorbate 80, soy lecithin, sesamol, and water	Sesamol	CCl_4-Induced Subacute Hepatotoxicity in Wistar Rats	Shows well-established hepatoprotective effect	[49]
	Dynasan and lecithin (5:5, 6:4, 7:3, 8:2 and 9:1)	Ganoderic acid	ameliorate D-galactosamine induced hepatotoxicity in Wistar rats	GA-SLN presented a substantial increase in the hepatoprotective activity of GA when encapsulated in SLN, as depicted by the normalization of hepatic injury markers and a noteworthy increase in the enzymatic and non-enzymatic antioxidant levels in hepatotoxicity	[50]
	Trimyris and glycerol monostearate	Bixin	Paracetamol-induced hepatotoxicity in Wistar rats	Enhances hepatic protection	[51]
	glycerol tripalmitate and soybean phospholipid (1:1)	Berberine	Ameliorate hepatosteatosis in db/db mice	Shows hepatoprotective activity	[52]
Phytosomes	Silymarin, methanol, petroleum ether	Silymarin	CCl4-induced hepatotoxicity in albino rats	Efficient hepatoprotection	[53]
	-	Curcumin	aluminum-induced hepatotoxicity in albino rats	curcumin phytosome (CP) is a promising formula for the treatment of AlCl3 hepatotoxicity.	[54]
	Soya lecithin, Chloroform, Butea monosperma extract, methanol	Butea monosperma flower extract	-	Shows liver protecting activity	[55]
	Phospholipids: Cholesterol and T. chebula in the ratio of 0.5:0.4:1, 1:0.8:1, 1.5:1.2:1, 2:1.6:1	T. chebula leaf extract	-	Shows hepatoprotective activity	[56]
	curcumin and phosphatidylcholine at different molar ratios: 1:1; 1:2; 1:4	Curcumin	paracetamol-induced liver toxicity in Swiss mice	Shows hepatoprotective effect	[57]

4. Utility of Nanocarrier in Liver-Specific Herbal Drug Delivery

Growing attention has been paid in recent years to developing medication delivery methods by investigating nanoparticles with dimensions between 1 and 1000 nm. The many benefits that nanoparticles offer over conventional drug delivery techniques, such as increased stability, target specificity, and the capacity to transfer both hydrophilic and hydrophobic drug molecules, are driving this change [58]. The distinct physical and chemical characteristics of nanomaterials, such as their size, shape, molecular weight, purity, stability, and solubility, are crucial in determining how they behave physiologically. It is essential to thoroughly characterize nanomaterials to guarantee their quality, safety, and the informed development of nanomedicines. Transmission electron microscopy (TEM), which enables imaging at the nanoscale resolution and offers insights into the morphology and size distribution of nanoparticles, is one of the main methods used for this characterization. Scanning electron microscopy (SEM) also provides important details on surface characteristics. The hydrodynamic size and size distribution of nanoparticles in solution can be measured using dynamic light scattering (DLS), which provides insight into the colloidal stability of the particles. For figuring out the crystal structure and phase purity of nanoparticles, X-ray diffraction (XRD) is essential. The electrical and chemical characteristics of nanoparticles can be better understood with the use of spectroscopic techniques such as Fourier-transform infrared (FTIR)

spectroscopy and UV-Vis spectroscopy. Atomic force microscopy (AFM) provides topographical information and mechanical characteristics, and zeta potential studies help comprehend the stability and surface charge of colloidal systems [59]. Pharmaceutical nanocarriers are a type of tailored drug delivery technology that is intended to reduce cytotoxic side effects on normal cells and premature drug breakdown. By improving medication accumulation at the targeted site of action, these nanocarriers increase bioavailability. Optimizing medication delivery and targeting requires customizing nanocarriers with precise architectures, compositions, and characteristics, along with domains that are assigned for drug loading. To accomplish these objectives, surface functionalization becomes crucial. The characterization of nanoparticles about hepatoprotective action includes size, surface charge, composition, structure, stability, and release kinetics. This multimodal strategy is essential for the careful engineering of nanoparticles, guaranteeing the efficient delivery of hepatoprotective drugs to the liver. This approach has great potential to treat hepatic problems since it can maximize therapeutic benefits and minimize side effects [60].

5. Future Perspectives

In the fields of drug delivery and nanomedicine technology, nanocarriers have grown in importance and are now receiving more attention from the medical world. Precision medicine, which allows for the personalization of therapeutic techniques, is a key area of advancement for nanocarrier technology. It is possible to create extremely accurate and efficient medication delivery systems by customizing nanocarriers to each patient's specific traits, such as their genetic makeup and illness features. This customized approach may increase treatment effectiveness while reducing unwanted side effects because drugs are administered to target body tissues or cells exactly [61]. The creation of nanocarriers that react to particular signals in the body to allow for the targeted delivery of medications at specified times and locations is an exciting field of study. These smart nanocarriers can be engineered to react only to changes in temperature, pH, or the presence of specific biomolecules. This accurate regulation of drug release could maximize therapeutic effects and reduce unwanted side effects, which would be a breakthrough in the field of precision drug delivery. Furthermore, it is expected that nanocarriers will be essential for overcoming obstacles associated with crossing biological barriers, like the blood-brain barrier. Creative formulations can be designed to make it easier for therapeutic substances to pass through these obstacles, opening up new possibilities for the treatment of illnesses affecting organs that have historically been difficult to target. The idea of co-delivery, the combination of several medicinal substances in one nanocarrier is becoming more and more popular [62]. The combined action of several medications is made possible by this tactic, which may help overcome drug resistance and improve treatment outcomes all around. Furthermore, it exhibits promise in managing complex illnesses with diverse pathogenic pathways. Ensuring patient compliance becomes crucial for reaching therapeutic goals in the management of hepatic diseases, when ongoing and prolonged treatment may be required. Through a variety of delivery routes, masking disagreeable tastes, optimizing controlled drug release, strengthening the stability of active drugs, and improving target specificity, nanocarriers have been shown to improve patient adherence and therapeutic success. To summarise, the potential for tailored hepatoprotective therapy is presented by the utilization of nanocarrier-based drug delivery systems. This includes treating liver diseases including hepatocellular carcinoma and acute liver injury, and there has been a noticeable surge in the study of nanocarriers as hepatoprotective agents recently [63].

6. Conclusions

Presently, numerous plants have undergone clinical validation for their hepatoprotective attributes, gaining recognition as viable alternatives to allopathic medications. The spotlight has gradually shifted toward these plant-based remedies, prompting extensive research into nanocarrier formulations for bioactive compounds and plant extracts with hepatoprotective properties. Traditional medication delivery systems' drawbacks are successfully addressed by hepatoprotective formulations that use plant-based nanocarriers. These nanocarriers improve medication stability and bioavailability by offering regulated release characteristics. These nanocarriers' unique physicochemical characteristics which are molded by the substance and arrangement of components obtained from plants have a major role in how well they can carry therapeutic medicines to the liver tissues. As such, herbal hepatoprotective medication-based nanocarriers have great promise as complementary therapies for a range of hepatic conditions. However, more investigation is needed to pinpoint particular nanocarriers that have a high therapeutic efficacy in treating a range of hepatic disorders. Continued research in this area is crucial to improving our knowledge of and ability to treat hepatic diseases using nanocarrier-based therapies.

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Abbreviations

ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
CAT	Catalase
CYP	Cytochrome P450
DNA	Deoxyribonucleic Acid
GGT	Gamma-Glutamyl Transferase
GPx	Glutathione Peroxidase
GSH	Reduced Glutathione
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IL	Interleukin
LDH	Lactate Dehydrogenase
LPO	Lipid Peroxidation
MDA	Malondialdehyde
mRNA	Messenger Ribonucleic Acid
NF-κB	Nuclear Factor Kappa B
Nrf2	Nuclear Factor Erythroid 2–Related Factor 2
P450	Cytochrome P450 Enzyme
RNA	Ribonucleic Acid
ROS	Reactive Oxygen Species
SOD	Superoxide Dismutase
TGF-β	Transforming Growth Factor Beta
TNF-α	Tumor Necrosis Factor Alpha

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