



PHYTOSOMAL DRUG DELIVERY SYSTEMS FOR THE MANAGEMENT OF HYPERLIPIDEMIA: A COMPREHENSIVE REVIEW

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ABSTRACT

Hyperlipidemia is a serious metabolic illness marked by high levels of circulating lipids notably low-density lipoprotein cholesterol and triglycerides and is a significant risk factor for cardiovascular disease. Although standard lipid-lowering medicines are beneficial long-term usage may result in side effects unpredictable therapeutic responses poor adherence and residual cardiovascular risk. There has been a growing interest in naturally produced phytoconstituents with antihyperlipidemic antioxidant and anti-inflammatory properties. Their therapeutic use is typically restricted due to poor water solubility instability low gastrointestinal absorption extensive metabolism and low systemic bioavailability. Phytosomes are sophisticated phospholipid-based delivery systems intended to increase the therapeutic efficacy and bioavailability of phytoconstituents that are poorly absorbed. Bioactive plant components interact with phospholipids in phytosomes to create molecular complexes that improve membrane permeability and lipid affinity. An overview of hyperlipidemia its pathogenesis risk factors and current pharmacological care is given in this review. The limits of traditional lipid-lowering medication are then discussed. Important phytoconstituents with antihyperlipidemic potential such as curcumin quercetin kaempferol resveratrol berberine and phytosterols are also summarized. The idea principles process of production preparation techniques and characterisation of phytosomal formulations are then covered in the review. The possible ways that phytosomal systems may improve lipid metabolism increase bioavailability lessen oxidative stress and inflammation and ultimately aid in the management of hyperlipidemia are given special attention. Additionally included are the benefits drawbacks current developments new trends and available preclinical and in vivo data. Lastly prospects for formulation improvement scalable production pharmacokinetic analysis safety evaluation clinical validation and targeted administration are discussed. All things considered phytosomal drug delivery is a viable method for boosting the therapeutic potential of bioactive phytoconstituents and might be a useful supplementary strategy for the treatment of hyperlipidemia and related cardiovascular issues.

KEYWORD: Hyperlipidemia Dyslipidemia Curcumin Phytosome Phosphatidylcholine Phytoconstituents Lipid-lowering activity Flavonoids Bioavailability Novel drug delivery system.

INTRODUCTION

Hyperlipidemia: An Overview

An abnormal increase in one or more lipid components in the blood such as total cholesterol (TC) low-density lipoprotein cholesterol (LDL-C) very-low-density lipoprotein (VLDL) and triglycerides (TG) or a change in the concentration of high-density lipoprotein cholesterol (HDL-C) are the hallmarks of hyperlipidemia a common metabolic disorder. Essential biological molecules lipids are involved in hormone manufacturing cellular membrane integrity energy storage and other

physiological activities. On the other hand endothelial dysfunction inflammation the development of atherosclerotic plaque and an elevated risk of cardiovascular problems might arise from the accumulation of circulating lipids inside the artery wall.^[1]

Primary and secondary hyperlipidemia are two general categories for hyperlipidemia. Genetic disorders affecting lipid production transport metabolism or clearance are the main cause of primary hyperlipidemia.

One significant example is familial hypercholesterolemia which is frequently caused by abnormalities in the LDL receptor apolipoprotein B or other proteins involved in LDL processing. Secondary hyperlipidemia on the other hand results from underlying illnesses lifestyle choices or drug usage. Abnormal lipid levels can be caused by a number of conditions including diabetes mellitus obesity hypothyroidism chronic renal disease liver illness excessive alcohol use physical inactivity and diets high in saturated fats. Lipid metabolism may potentially be negatively impacted by some drugs.^[2]

LDL is one of the circulating lipoproteins that has a particularly significant role in the development of atherosclerotic cardiovascular disease. LDL carries cholesterol from the liver to peripheral tissues however high LDL particle concentrations make it more likely that the particles will enter and stay in the artery intima. LDL that has been altered or oxidized can activate macrophages and endothelial cells encouraging the production of foam cells and the release of inflammatory mediators. Fatty streak formation and the subsequent development of atherosclerotic plaques are facilitated by the progressive buildup of lipid-rich foam cells. The development and instability of plaque may eventually lead to arterial constriction or rupture raising the risk of ischemic stroke myocardial infarction and thrombosis.^[3]

Another lipid measure that is clinically significant is triglycerides. Triglyceride-rich lipoproteins such chylomicrons and VLDL are the main means of transportation. Obesity insulin resistance metabolic syndrome and type 2 diabetes mellitus are often linked to hypertriglyceridemia. Acute pancreatitis might also be more likely in cases with severe elevated triglycerides. On the HDL takes part in reverse cholesterol transport which moves extra cholesterol from peripheral tissues to the liver for further processing and removal. The main goal of modern cardiovascular risk management is to lower atherogenic lipoproteins especially LDL-C even if HDL-C is a crucial aspect of lipid evaluation. Hyperlipidemia frequently presents clinically as asymptomatic especially in the early stages. As result many people do not realize they have abnormal lipid levels unless they get regular biochemical testing or experience cardiovascular issues. Physical symptoms such tendon xanthomas xanthelasma or ocular arcus may appear in severe hereditary forms. Triglycerides LDL-C HDL-C and total cholesterol are typically measured in laboratory evaluations. Other metrics such apolipoprotein B and non-HDL cholesterol may offer further details on the load of atherogenic lipoproteins in certain people.^[4]

Genetic nutritional metabolic and environmental variables all have a role in the development of hyperlipidemia. Lipid metabolism and cardiovascular risk can be negatively impacted by diets heavy in trans and saturated fats excessive caloric consumption sedentary lifestyles obesity and smoking. Insulin

resistance may cause the liver to produce more VLDL and raise triglyceride levels. An individual's reaction to environmental and nutritional variables can be further altered by genetic predisposition. Reducing atherogenic lipid concentrations and preventing cardiovascular events are the main goals of managing hyperlipidemia. The cornerstone of management is lifestyle modification which includes eating a balanced diet high in fruits vegetables whole grains legumes and dietary fiber limiting trans and saturated fats engaging in regular exercise maintaining a healthy weight; and avoiding tobacco exposure. Pharmacological intervention may be necessary for people who are at higher risk of cardiovascular disease or who cannot reduce their cholesterol with lifestyle changes alone.^[5]

Because they inhibit 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase a crucial enzyme involved in hepatic cholesterol formation statins are frequently employed as first-line lipid-lowering medications. Hepatic cholesterol reduction increases the expression of LDL receptors and improves the removal of circulating LDL particles. Additional treatment options include bile acid sequestrants fibrates for some patients with severe hypertriglyceridemia cholesterol-absorption inhibitors like ezetimibe and more recent drugs like PCSK9 inhibitors. The patient's lipid profile cardiovascular risk comorbidities medication response and tolerance all influence the choice of therapy. Even if traditional lipid-lowering medications are clinically beneficial problems such side effects drug interactions poor adherence expense and inconsistent therapeutic response still motivate research into complementary and alternative therapies. Due to the hypolipidemic antioxidant anti-inflammatory and cardioprotective qualities of a number of plant-derived chemicals natural phytoconstituents have garnered significant interest. The potential of substances including flavonoids polyphenols terpenoids and other bioactive compounds to control cholesterol production promote lipid clearance prevent lipid oxidation and boost overall lipid metabolism has been studied.^[6]

A number of phytoconstituents have drawbacks such as limited systemic bioavailability fast metabolism low gastrointestinal absorption chemical instability and poor water solubility. Despite their encouraging pharmacological action these variables may limit their therapeutic efficacy. The sophisticated drug delivery systems have become a crucial tactic for enhancing the distribution of bioactive phytoconstituents. Phytosomes are one of these systems that has attracted a lot of attention for increasing the bioavailability of substances obtained from plants. Standardized plant extracts or specific phytoconstituents combine with phospholipids most frequently phosphatidylcholine to create molecular complexes known as phytosomes. Complexation has the ability to increase the gastrointestinal absorption and systemic exposure of poorly absorbed phytoconstituents by improving their physicochemical and biological

properties. A viable method for converting the pharmacological potential of natural substances into more powerful therapeutic treatments for hyperlipidemia is phytosomal administration.^[7]

All the considered hyperlipidemia is a major and avoidable cause of cardiovascular morbidity and death. Controlling high cholesterol levels and lowering long-term cardiovascular risk requires early identification proper risk assessment lifestyle adjustment and efficient pharmaceutical therapy. Simultaneously further research into phytoconstituents and novel delivery methods like phytosomes may offer further chances to create safe efficient and bioavailable treatment approaches for the control of hyperlipidemia.^[8]

1. Pathophysiology and Risk Factors of Hyperlipidemia

Dysregulation of lipid production absorption transport metabolism or elimination leads to hyperlipidemia which is characterized by elevated levels of cholesterol triglycerides LDL-C or other atherogenic lipoproteins in the blood. Lipoproteins such as chylomicrons VLDL LDL and HDL carry dietary and endogenous fats through the blood under normal physiological circumstances. By producing cholesterol and triglycerides packing lipids into lipoproteins and eliminating circulating lipoproteins via receptor-mediated mechanisms the liver plays a crucial part in preserving lipid homeostasis. Persistent increases in circulating lipids can result from disruptions in these mechanisms.^[9]

Increased LDL particle synthesis or decreased LDL particle clearance is a primary factor causing hypercholesterolemia. LDL carries cholesterol to peripheral tissues from the liver. Hepatic LDL receptors normally identify and eliminate LDL from the blood. LDL builds up in plasma when there is a decrease in LDL-receptor activation an increase in hepatic cholesterol synthesis or an increase in circulating LDL generation. Severe primary hypercholesterolemia can result from genetic abnormalities affecting the LDL receptor apolipoprotein B or PCSK9-mediated control. Lipid metabolism might be further hampered by secondary variables such as obesity diabetes hypothyroidism and certain eating habits. Increased hepatic production of VLDL excessive transport of free fatty acids to the liver or poor peripheral clearance of triglyceride-rich lipoproteins can all lead to hypertriglyceridemia. Insulin resistance stimulates hepatic triglyceride production and VLDL secretion by increasing the supply of free fatty acids to the liver and promoting adipose tissue lipolysis. Plasma triglyceride concentrations may rise higher if lipoprotein lipase an enzyme that hydrolyzes triglycerides in circulating chylomicrons and VLDL is less active.^[10]

Atherogenesis and the pathophysiological relevance of hyperlipidemia are intimately related. Excess LDL particles in circulation have the ability to pass through

the artery's endothelium and stay inside the arterial intima. Endothelial activation and inflammatory reactions may result from these particles undergoing oxidation or other changes. After migrating into the artery wall monocytes develop into macrophages which use scavenger receptors to absorb changed LDL. Fatty streaks and lipid-laden foam cells are created when macrophages gradually accumulate cholesterol. Atherosclerotic plaque formation is facilitated by persistent inflammation migration of smooth muscle cells extracellular matrix deposition and lipid buildup. Advanced plaques may become unstable and burst forming thrombus and possibly leading to an ischemic stroke or myocardial infarction.^[11]

Risk Factors of Hyperlipidemia

Hyperlipidemia risk factors can be broadly classified as either modifiable or non-modifiable. Genetic predisposition aging and some hereditary lipid metabolism problems are examples of non-modifiable variables. An inherited vulnerability to aberrant lipid metabolism may be indicated by a family history of severe hypercholesterolemia or early cardiovascular disease. Lipid concentrations can be considerably raised by genetic disorders that impact apolipoprotein metabolism LDL-receptor function or lipid-processing enzymes. Unhealthy eating habits are one of the most significant controllable variables. Lipid profiles can be negatively impacted by consuming too many calories processed carbohydrates cholesterol-rich meals trans fats and saturated fats. Sedentary lifestyles and physical inactivity can lead to decreased HDL-C increased triglycerides weight gain and insulin resistance. An unfavorable lipid profile and metabolic syndrome are closely linked to obesity especially increased visceral adiposity.^[12]

Two significant metabolic risk factors are insulin resistance and diabetes mellitus. Increased hepatic VLDL synthesis decreased triglyceride clearance and increased release of free fatty acids from adipose tissue are all facilitated by insulin resistance. Because decreased thyroid hormone activity reduces hepatic LDL-receptor expression and hinders LDL clearance hypothyroidism can also increase LDL-C. Lipid metabolism can be disrupted by both chronic renal disease and certain liver illnesses.^[13]

Excessive alcohol intake smoking psychological stress and the usage of certain drugs are other contributing factors. While smoking increases oxidative stress endothelial dysfunction and cardiovascular risk generally alcohol may significantly raise triglyceride levels in those who are vulnerable. Some individuals lipid levels may be negatively impacted by medications such as beta-blockers retinoids thiazide diuretics some corticosteroids and antiviral drugs. The genetic vulnerability metabolic abnormalities dietary variables lifestyle and underlying disorders all combine to cause hyperlipidemia a complex ailment. Early detection appropriate risk assessment

prevention of atherosclerotic cardiovascular disease and the development of successful therapeutic approaches—such as traditional lipid-lowering medications and novel phytoconstituent-based delivery systems—all depend on an understanding of its pathophysiological mechanisms and related risk factors.^[14]

2. Current Pharmacological Management of Hyperlipidemia

Reducing circulating atherogenic lipoproteins especially low-density lipoprotein cholesterol (LDL-C) and preventing the onset or progression of atherosclerotic cardiovascular disease (ASCVD) are the main goals of pharmaceutical therapy of hyperlipidemia. The degree and kind of dyslipidemia the patient total cardiovascular risk related comorbidities age treatment response and tolerance all influence the choice of medication. When lipid objectives are not sufficiently met pharmaceutical therapy is typically paired with lifestyle adjustment which is still a crucial part of treatment.^[15]

Statins

The mainstay and most popular pharmaceutical treatment for high LDL-C is statins. The enzyme that limits the rate of hepatic cholesterol production 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase is inhibited by them. Reduced hepatic cholesterol increases the clearance of circulating LDL particles from the circulation by stimulating hepatocytes' upregulation of LDL receptors. Atorvastatin rosuvastatin simvastatin pravastatin and fluvastatin are statins that are often used. Statins have been shown to reduce cardiovascular events and significantly lower LDL-C. Some patients may have negative side effects such as symptoms connected to their muscles or abnormalities in their liver enzymes and intolerance may restrict therapy for certain people.

Ezetimibe

Another significant lipid-lowering medication is ezetimibe which targets the Niemann-Pick C1-like 1 (NPC1L1) transporter to specifically prevent intestinal cholesterol absorption. It increases hepatic LDL-receptor activation and decreases the amount of cholesterol delivered to the liver which further lowers circulating LDL-C. When more LDL-C reduction is needed or when high-intensity statin medication is not well tolerated ezetimibe can be administered as monotherapy in some individuals or more frequently in conjunction with a statin.^[16]

PCSK9 targeting therapies

Treatments that target PCSK9 offer a powerful way to reduce LDL-C. In order to decrease the availability of hepatic LDL receptors for LDL clearance PCSK9 typically encourages their destruction. PCSK9 inhibition protects LDL receptors and improves the elimination of LDL from the bloodstream. Patients with very high cardiovascular risk familial hypercholesterolemia or insufficient response to traditional medication might benefit greatly from monoclonal antibodies like

vedolizumab and alirocumab which can significantly lower LDL-C. Another strategy is incising a small interfering RNA-based treatment that targets PCSK9 production and offers long-term PCSK9 suppression with occasional doses.^[17]

Bempedoic acid

ATP-citrate lyase an enzyme involved in hepatic cholesterol production upstream of HMG-CoA reductase is inhibited by the oral lipid-lowering medication bempedoic acid. It can lower LDL-C and could be especially helpful for people who can't handle high statin dosages. Depending on the patient's clinical needs it may also be used in conjunction with ezetimibe or other lipid-lowering treatments.

Bile acid sequestrants

Cholestyramine colestipol and Colestipol are examples of bile acid sequestrants that decrease intestinal reabsorption of bile acids. Increased hepatic cholesterol conversion to bile acids increases the expression of the hepatic LDL receptor and improves the removal of LDL from plasma. Despite their effectiveness some drugs may interfere with the absorption of other medicines and have gastrointestinal side effects. Their usage is usually restricted to certain patients.^[18]

Fibrates

The main purpose of fibrates like fenofibrate and gemfibrozil is to control high triglyceride levels. higher fatty acid oxidation higher lipoprotein lipase activity and better clearance of triglyceride-rich lipoproteins are the outcomes of their activation of peroxisome proliferator-activated receptor-alpha (PPAR-α). Fibrates may be taken into consideration when the risk of pancreatitis is elevated and are especially helpful in people with severe hypertriglyceridemia.

Omega 3 fatty acid preparation

Elevated triglycerides can also be managed using omega-3 fatty acid formulations. Eicosapentaenoic acid (EPA) prescription formulations either with or without docosahexaenoic acid (DHA) can lower circulating triglyceride levels and decrease hepatic VLDL-triglyceride synthesis. The degree of hypertriglyceridemia and the patient's cardiovascular risk profile determine their clinical role.^[19]

Niacin (nicotinic acid)

By lowering hepatic VLDL production and release niacin (nicotinic acid) can lower LDL-C and triglycerides while raising HDL-C. Despite niacin's positive effects on a number of lipid parameters its routine use has decreased due to side effects such as flushing gastrointestinal problems hyperglycemia and hepatotoxicity as well as the fact that the additional cardiovascular benefit when combined with modern statin therapy has not typically outweighed the tolerability burden.^[20]

When a single medication is insufficient to control cholesterol or when a patient's cardiovascular risk is extremely high combination treatment may be necessary in clinical practice. Statins with ezetimibe statins and PCSK9-targeting therapies or other customized regimens are common combos. In addition to addressing secondary causes of dyslipidaemia treatment should include dietary changes weight control exercise and care of related metabolic illnesses.

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Even while well-established pharmaceutical treatments are successful their drawbacks-such as side effects inconsistent patient response drug intolerance expense long-term adherence and the requirement for combination treatment-continue to spur research into alternative therapeutic modalities. In this regard scientists are becoming more interested in natural phytoconstituents that have anti-inflammatory antioxidant and hypolipidemic qualities. Their limited intestinal absorption low systemic bioavailability instability and poor water solubility may limit their therapeutic use. To enhance the bioavailability and therapeutic efficacy of promising plant-derived drugs for the control of hyperlipidemia advanced delivery methods such phytosomes liposomes nanoemulsions and lipid-based nanoparticles are being studied.^[22]

3. Limitations of Conventional Lipid-Lowering Therapy

Conventional lipid-lowering medications have greatly enhanced cardiovascular disease prevention and treatment but there are a number of drawbacks to their clinical application. The main pharmacological treatments for lowering LDL-C are statins which are quite efficient. Some individuals have raised liver enzymes statin-associated muscular complaints or other side effects. Treatment effectiveness may be lowered if tolerability issues result in dosage decrease drug withdrawal or poor medication adherence. Variable treatment response is another significant drawback. Individual variations in medication metabolism adherence drug interactions genetics and illness condition all affect how much lipid is reduced. The certain high-risk individuals may need combination therapy if statin monotherapy is unable to produce the required LDL-C concentration. Treatment complexity drug burden and total expense can all rise when many lipid-lowering medications are used.^[23]

Bile acid sequestrants fibrates niacin and other traditional treatments have drawbacks as well. Fibrates play a relatively limited function in lowering LDL-C and are mainly helpful for hypertriglyceridemia. Niacin's routine clinical usage is restricted due to its potential for hepatotoxicity flushing gastrointestinal distress and glycemic abnormalities. Bile acid sequestrants can impede the absorption of certain medications and cause constipation bloating and other gastrointestinal side effects. The Long-term adherence may be impacted by tolerability. Because hyperlipidemia is often asymptomatic long-term therapy necessitates ongoing patient compliance which can be difficult. When they do not see an instant improvement patients may stop therapy especially if there are side effects. Polypharmacy can make adherence even more difficult and raise the risk of drug-drug interactions in older people and patients with several chronic diseases.^[24]

The complex character of cardiovascular illness presents additional challenges for conventional treatment. While lowering LDL-C is essential for lowering cardiovascular risk oxidative stress inflammation endothelial dysfunction insulin resistance and other metabolic abnormalities may still contribute to the advancement of the illness. Even after attaining a significant decrease in LDL-C some individuals still have a significant residual cardiovascular risk. From a pharmacological standpoint the pharmacokinetic and therapeutic characteristics of some medicinal drugs may be affected by their low water solubility restricted bioavailability significant first-pass metabolism or formulation-related constraints. The creation of innovative drug-delivery strategies aimed at enhancing drug solubility stability absorption targeting and bioavailability has been prompted by these difficulties.^[25]

Interest in natural bioactive substances and cutting-edge delivery methods has increased as a result of the shortcomings of traditional treatment. Although a number of phytoconstituents have potential hypolipidemic antioxidant and anti-inflammatory properties their poor solubility chemical instability fast metabolism and low bioavailability frequently limit their clinical use. By complexing phytoconstituents with phospholipids to enhance their absorption and systemic availability phytosomal systems present a viable approach. The creation of phytosome-based formulations may offer a chance to improve the therapeutic potential of naturally occurring substances that are poorly bioavailable while advancing the more general objective of efficient and patient-friendly hyperlipidemia therapy.^[26]

4. Phytoconstituents with Antihyperlipidemic Potential

Naturally occurring bioactive substances derived from medicinal plants phytoconstituents have garnered significant interest as possible therapeutic agents for the treatment of hyperlipidemia. Many substances produced

from plants have hypolipidemic antioxidant anti-inflammatory and cardioprotective properties. They may also affect various lipid metabolic pathways. Inhibition of intestinal cholesterol absorption suppression of hepatic cholesterol synthesis enhancement of LDL-receptor activity modulation of lipid-metabolizing enzymes stimulation of fatty-acid oxidation and reduction of oxidative stress and vascular inflammation are some of their possible mechanisms. However low oral bioavailability fast metabolism instability and poor water solubility restrict the therapeutic use of several phytoconstituents.^[27]

One significant class of phytoconstituents being studied for its potential to prevent hyperlipidemia is flavonoids. Hesperidin rutin kaempferol quercetin and catechins have all shown promise in improving lipid profiles and preventing oxidative damage related to lipids. While kaempferol may regulate fat buildup and strengthen antioxidant defenses quercetin has been shown to affect inflammatory pathways oxidative stress and cholesterol metabolism. The effects of catechins especially green tea's epigallocatechin gallate (EGCG) on lipid metabolism and cardiovascular health have also been well studied.^[28]

Because of their anti-inflammatory and antioxidant qualities polyphenolic substances like resveratrol curcumin and chlorogenic acid have drawn a lot of attention from researchers. Curcuma longa contains curcumin which may affect oxidative stress inflammatory signaling cholesterol homeostasis and hepatic lipid metabolism. The effects of resveratrol which is mostly linked to grapes and Polygonum cuspidatum on lipid metabolism mitochondrial function and vascular protection have been studied. Numerous fruits vegetables and coffee contain chlorogenic acid which has also shown promise as an antioxidant and lipid modulator. Another significant family of plant components that may have antihyperlipidemic properties are saponins. By interacting with bile acids and cholesterol plant-derived saponins may lower intestinal cholesterol absorption and affect hepatic lipid metabolism. The potential of several saponin-rich medicinal herbs to lower blood triglyceride and cholesterol levels has been studied.^[29]

Lipid-lowering effects may also be attributed to terpenoids and related substances. It has been observed that several diterpenes triterpenes and other terpenoid constituents affect inflammatory pathways fatty acid oxidation and cholesterol production. Because they are structurally similar to cholesterol and can compete with dietary and biliary cholesterol for intestinal absorption phytosterols-such as β -sitosterol campesterol and stigmasterol -are especially important. The possible effects of alkaloids and other nitrogen-containing phytochemicals on lipid metabolism have also been studied. Certain plant alkaloids may have antioxidant or anti-inflammatory properties in addition to controlling

enzymes involved in the metabolism of fatty acids and cholesterol. The overall antihyperlipidemic efficacy of medicinal plant extracts may be influenced by polyphenolic acids tannins lignans and other secondary metabolites.^[30]

The capacity of phytoconstituents to operate at several biological sites summarizes their potential antihyperlipidemic actions. HMG-CoA reductase inhibition peroxisome proliferator-activated receptor (PPAR) modulation LDL-receptor-mediated cholesterol clearance enhancement intestinal cholesterol absorption inhibition sterol regulatory element-binding protein (SREBP) regulation fatty acid oxidation promotion and reduction of oxidative stress and inflammatory mediators are some of these. Because of their multitarget action phytoconstituents are appealing options for additional lipid control strategies. Many phytoconstituents have limited bioavailability which might restrict their therapeutic effectiveness after oral treatment despite encouraging pharmacological findings. Low concentrations at the site of action may be caused by poor water solubility insufficient membrane permeability gastrointestinal tract degradation significant first-pass metabolism and quick systemic clearance. Merely raising the dosage may not be sufficient to get over these biologic restrictions and may raise the possibility of unfavorable side effects.^[31]

These restrictions can be overcome with the use of cutting-edge medication delivery technology. Because they create molecular complexes between phytoconstituents and phospholipids that can enhance lipid compatibility gastrointestinal absorption and systemic bioavailability phytosomes stand out among the others. Other methods for improving the transport of poorly accessible phytoconstituents have also been studied including nanoemulsions liposomes solid lipid nanoparticles polymeric nanoparticles and nanostructured lipid carriers. Because of their varied biological activities and capacity to influence many pathways linked to lipid metabolism and cardiovascular protection phytoconstituents generally provide a promising source of antihyperlipidemic medicines. To prove their effectiveness and safety further pharmacokinetic mechanistic toxicological and carefully monitored clinical research is needed. Promising phytoconstituents may be able to overcome bioavailability constraints and improve their therapeutic potential in hyperlipidemia by being included into appropriate advanced delivery methods especially phytosomal formulations.^[32]

5. Phytosomes: Concept and Fundamentals

Phytosomes are sophisticated lipid-based drug delivery systems designed to enhance the therapeutic efficacy bioavailability and absorption of physiologically active phytoconstituents. The words "phyto" which means plant and "some" which means cell-like body combine to form the word phytosome. Phytosomes entail the creation of a

molecular complex between a standardized plant extract or purified phytoconstituent and phospholipids most frequently phosphatidylcholine in contrast to traditional herbal extracts where phytoconstituents may show limited absorption due to poor solubility or membrane permeability. The phytoconstituent's interaction with biological membranes is enhanced by this complexation which also makes absorption easier.^[33]

In contrast to liposomes which are vesicular structures in which active substances are typically trapped within an aqueous or lipid compartment phytosomes represent a molecular interaction or complex between the phytoconstituent and phospholipid. Instead of only being physically encapsulated the phytoconstituent in phytosomes is often incorporated into the phospholipid complex. This distinction could enhance the stability absorption and bioavailability of a number of substances originating from plants. Because phosphatidylcholine is biocompatible biodegradable and found naturally in biological membranes it is frequently used in the creation of phytosomes. It may enhance the partitioning of poorly absorbed phytoconstituents into biological lipid environments and promote interaction between the phytosomal complex and cellular membranes. Depending on the necessary formulation qualities and the physicochemical parameters of the chosen phytoconstituent other phospholipids may also be studied.^[34]

Phytosome development can enhance a number of significant biopharmaceutical characteristics of phytoconstituents. While compounds with low gastrointestinal permeability may show increased absorption poorly water-soluble compounds may show improved dispersibility and membrane contact. Phytosomal complexation may improve the bioactive compound's residency within biological membranes and offer protection against gastrointestinal or environmental breakdown. Improved pharmacological action at relatively lower dosages may therefore be possible with increased systemic exposure. In order to create phytosomes the phytoconstituent and phospholipids must interact in a suitable solvent solution under carefully monitored circumstances. Solvent evaporation anti-solvent precipitation rotary evaporation thin-film hydration and mechanical or ultrasonic processes are examples of common approaches. The physicochemical properties of the phytoconstituent phospholipid type solvent system drug-to-phospholipid ratio temperature and processing circumstances all influence the choice of production technique. To create a stable and repeatable phytosomal formulation these factors must be optimized.^[35]

Particle size polydispersity index zeta potential shape entrapment or complexation efficiency drug content and in vitro release behavior are some of the metrics used to assess the physicochemical properties of phytosomes. Molecular interactions complex formation crystallinity

and thermal behavior can be studied using spectroscopic and thermal methods such as Fourier-transform infrared spectroscopy (FTIR) differential scanning calorimetry (DSC) nuclear magnetic resonance (NMR) and X-ray diffraction (XRD). The development and stability of the phytosomal complex are established by these characterisation investigations. Many bioactive substances such as flavonoids polyphenols terpenoids saponins and other components originating from plants have been studied for delivery via phytosomes. They have demonstrated potential uses in the treatment of neurological disorders liver diseases metabolic disorders cardiovascular problems inflammation and other chronic illnesses. Phytosomes may be especially helpful for enhancing the delivery of poorly bioavailable phytoconstituents with hypolipidemic antioxidant and anti-inflammatory qualities in the setting of hyperlipidemia.^[36]

The capacity of phytosomal technology to combine enhanced biopharmaceutical performance with the pharmacological advantages of natural bioactive substances is its primary advantage. Phytosomes can get around some of the main drawbacks of traditional phytoconstituent delivery by boosting membrane affinity and perhaps improving absorption and systemic bioavailability. Their effective pharmaceutical development formulation optimization long-term stability scalability safety assessment pharmacokinetic characterization and clinical validation continue to be crucial factors.^[37]

6. Mechanism of Phytosome Formation

A stable phytosome complex with enhanced physicochemical and biological characteristics is formed by the molecular interaction of a phytoconstituent and a phospholipid. Phytoconstituents with low membrane permeability quick degradation poor water solubility or restricted oral bioavailability benefit greatly from this approach. Phosphatidylcholine (PC) is the most widely utilized phospholipid due to its amphiphilic nature biocompatibility and capacity to interact with both hydrophilic and lipophilic molecules. The selection and preparation of the phytoconstituent is the initial stage in the creation of phytosomes. A pure bioactive molecule or standardized plant extract with appropriate functional groups-especially hydroxyl carbonyl or other polar groups-is chosen. Phospholipids may form complexes with flavonoids polyphenols tannins terpenoids and other substances produced from plants. Next under carefully regulated formulation circumstances the phytoconstituent is mixed with a suitable quantity of phospholipid.^[38]

The basic process is an intermolecular contact between the polar head group of phosphatidylcholines and the polar functional groups of the phytoconstituent. Two hydrophobic fatty acid chains and a hydrophilic phosphocholine head make up phosphatidylcholine. Through van der Waals forces hydrogen bonds and electrostatic interactions the polar areas of the

phytoconstituent engage with the phosphate and other polar groups of the phospholipid. Instead of only physical mixing these interactions lead to the creation of a phytoconstituent-phospholipid complex. The phospholipid ratio and the phytoconstituent's chemical structure determine the kind and strength of these interactions. The phytoconstituent associates with the polar area of the phospholipid during complex formation while the lipophilic fatty-acid chains of the phospholipid stay oriented toward the surrounding lipid environment. This configuration results in complicated amphiphilic properties. The phytosomal complex can interact with biological membranes more successfully due to the improved lipid compatibility. The phytoconstituent could show better partitioning into cellular and intestinal membranes which would make absorption easier.^[39]

The production procedure is carried out in an appropriate organic solvent solution that can dissolve the phospholipid and phytoconstituent. Depending on the physicochemical characteristics of the component solvents like ethanol methanol acetone or other appropriate medicinal solvents may be chosen. To encourage molecular interaction the mixture is kept at a regulated temperature and stirred. The phytosomal complex is then formed once the solvent is eliminated usually by rotary evaporation or similar solvent-removal method. To achieve the required formulation further drying precipitation or size-reduction techniques may be used. Complex formation and formulation performance are significantly influenced by the phytoconstituent-to-phospholipid ratio. A suitable ratio prevents needless surplus phospholipid while providing enough phospholipid molecules for efficient interaction with the phytoconstituent. Temperature reaction duration concentration agitation drying conditions and solvent composition are further important factors. To achieve consistent complexation efficiency particle size stability and drug-loading properties these parameters must be optimized.^[40]

Several physicochemical characterisation methods are used to validate phytosome production after preparation. Changes in distinctive functional-group vibrations can be detected by FTIR spectroscopy which also offers proof of intermolecular interactions. While XRD can show changes in the phytoconstituent's crystalline structure DSC can show variations in thermal behavior. Further proof of molecular interaction might come from NMR spectroscopy. The quality and stability of the produced phytosomes are further assessed using particle size polydispersity index zeta potential shape drug content and complexation efficiency. When compared to the free phytoconstituent the resultant phytosomal complex may show improved solubility membrane affinity gastrointestinal absorption and systemic bioavailability. Phytosome production is a logical way to get around significant biopharmaceutical restrictions on chemicals originating from plants. This strategy may improve the administration of poorly bioavailable phytoconstituents

with hypolipidemic antioxidant and anti-inflammatory qualities in the treatment of hyperlipidemia potentially increasing their therapeutic efficacy.^[41]

7. Preparation Methods of Phytosomes

A phytoconstituent or standardized plant extract and an appropriate phospholipid-most frequently phosphatidylcholine-form a molecular combination to create phytosomes. Complexation efficiency particle size shape stability drug loading and finally the phytoconstituent's bioavailability are all influenced by the production technique. The physicochemical properties of the phytoconstituent phospholipid type solvent system drug-to-phospholipid ratio and planned route of administration all influence the choice of an acceptable method. Numerous methods such as solvent evaporation anti-solvent precipitation thin-film hydration reflux process mechanical dispersion and ultrasonic-assisted procedures have been described for phytosome production.^[42]

A. Solvent Evaporation Method

One of the most popular methods for creating phytosomal complexes is the solvent evaporation method which involves dissolving or dispersing the chosen phytoconstituent and phospholipid in a suitable organic solvent or solvent mixture (ethanol methanol acetone or other suitable solvents may be used depending on the solubility of the formulation components). The mixture is then continuously stirred at a controlled temperature to facilitate interaction between the phytoconstituent and phospholipid and the solvent is removed under reduced pressure using a rotary evaporator. This process creates a dry or semisolid phytosomal complex which can be further dried ground sieved and stored under suitable conditions.^[43]

B. Anti Solvent Precipitation Method

The phytoconstituent and phospholipid are first dissolved in an appropriate organic solvent in the anti-solvent precipitation procedure. After that the resultant solution is gradually added to a suitable anti-solvent while being continuously stirred. The phytosomal complex separates from the solution due to the components' decreased solubility in the anti-solvent. Filtration or centrifugation are used to separate the precipitated material which is then dried. Compounds that show appropriate solubility differences between the chosen solvent and anti-solvent may benefit from this quite easy technique.

C. Thin Film Hydration Method

The phytoconstituent and phospholipid are dissolved in a volatile organic solvent as part of the thin-film hydration process. A thin homogeneous coating is created on the flask surface by removing the solvent under low pressure usually with a rotary evaporator. After that the resultant film is hydrated with a suitable aqueous medium while being stirred and kept at a regulated temperature. The phospholipid material reorganizes and forms phytosomal structures when it is hydrated. To achieve a more

consistent particle-size distribution further size reduction techniques like homogenization or sonication may be used.^[44]

D. Reflux Method

In the reflux approach the phytoconstituent and phospholipid are combined in an appropriate solvent and heated under reflux for a predefined amount of time. Reflux settings minimize solvent loss while promoting molecular interaction between the phytoconstituent and phospholipid. The solvent is eliminated and the resultant complex is dried once the reaction is finished. Although the process is rather simple it necessitates careful temperature control since too much heat can degrade thermolabile phytoconstituents.

E. Mechanical and Ultrasonic Assisted Methods

Ultrasonic-assisted methods and mechanical dispersion can be used separately or as additional processing stages. The components of the formulation can be uniformly dispersed using mechanical stirring homogenization or high-shear mixing. Acoustic energy produced by ultrasonication can enhance dispersion decrease particle size and promote phytoconstituent-phospholipid interaction. To avoid overheating or deterioration processing parameters including temperature amplitude and sonication duration must be properly regulated.^[45]

F. Preparation by Film Formulation and Solvent Removal

Another method is creating a homogenous phytoconstituent-phospholipid solution and then carefully removing the solvent. The concentrated complex can then be dried using methods like spray drying or vacuum drying. An appropriate powder can be obtained by milling and sieving the dry product. When a dry phytosomal product with better storage stability is sought these methods could be helpful.

8. Characterization of Phytosomal Formulations

Determining the physicochemical characteristics quality stability molecular interactions and possible biopharmaceutical performance of phytosomal formulations requires characterization. In addition to providing details on particle size surface properties drug loading release behavior and stability proper characterization verifies the formation of the phytosome complex. For thorough assessment a mix of analytical microscopic and performance-based methods is often used.^[46]

A. Particle size and polydispersity Index

Because it affects surface area dispersion stability dissolution cellular contact and biological absorption particle size is a crucial factor. The polydispersity index (PDI) and mean particle size of phytosomal formulations are frequently measured using dynamic light scattering (DLS). More heterogeneity is suggested by a higher PDI whereas a more uniform particle-size distribution is often indicated by a lower PDI. Phospholipid content

phytoconstituent-to-phospholipid ratio solvent composition preparation technique and processing conditions all have a significant impact on particle size and PDI.

B. Zeta Potential

The electrical potential at the sliding plane of dispersed particles is represented by the zeta potential which is frequently used to gage the electrostatic stability of phytosomal compositions. Particle aggregation can be decreased and electrostatic repulsion can be encouraged by a sufficiently strong positive or negative zeta potential. Zeta potential should be read in conjunction with other stability measures because the stability of phytosomes may also depend on steric stabilization and the kind of phospholipid.^[47]

C. Morphological Characterization

Microscopic methods including atomic force microscopy (AFM) transmission electron microscopy (TEM) and scanning electron microscopy (SEM) can be used to study the morphology and surface properties of phytosomes. Particle shape surface texture aggregation and structural features are all revealed by these methods. While TEM may offer comprehensive information on nanoscale particle structure SEM is especially helpful for analyzing the surface appearance of dried phytosomal powders.

D. Entrapment or Complexation Efficiency

The percentage of phytoconstituent linked to the phospholipid complex is determined by complexation efficiency. The amount of free and complexed phytoconstituent in a known quantity of the formulation is determined using a suitable analytical technique such as high-performance liquid chromatography (HPLC) or UV-visible spectrophotometry. High complexation efficiency is a crucial measure of formulation efficacy since it shows that the phytoconstituent and phospholipid are effectively associated.^[48]

E. Drug Content

To evaluate the consistency and precision of the formulation the drug or phytoconstituent content is ascertained. An appropriate solvent is used to dissolve or extract a precisely weighed amount of phytosomal formulation and then a validated analytical method is used for quantitative analysis. The % medication content helps guaranty dosage homogeneity and provide information about formulation consistency.

F. Fourier Transform Infrared Spectroscopy

Phytoconstituent-phospholipid interactions are frequently studied using Fourier-transform infrared (FTIR) spectroscopy. A comparison is made between the characteristic absorption bands of the physical mixture phospholipid pure phytoconstituent and phytosomal complex. Peak position intensity broadening or disappearance changes can assist the establishment of the

phytosomal complex and reveal intermolecular interactions especially hydrogen bonding.^[49]

G. Differential Scanning Calorimetry

The thermal behavior of the phytoconstituent phospholipid physical combination and phytosomal formulation is assessed by differential scanning calorimetry (DSC). Evidence of molecular interaction or complex building can be seen in changes in distinctive melting transitions. Changes in the phytoconstituent's molecular environment or physical condition may be indicated by a shift widening or disappearance of the initial thermal peak.

H. X-Ray Diffraction Analysis

The crystalline or amorphous state of phytosomal preparations is examined using X-ray diffraction (XRD). A shift toward a less crystalline or amorphous state may be indicated by a decrease or elimination of the phytoconstituent's distinctive crystalline peaks after complex formation. Improved solubility and possibly increased bioavailability may result from such structural alterations.^[50]

I. Nuclear Magnetic Resonance Analysis

To learn more about molecular interactions and the structural environment of the phytoconstituent and phospholipid nuclear magnetic resonance (NMR) spectroscopy may be used. Changes in chemical shifts can assist determine the type of interactions within the phytosomal complex and offer proof of molecular connection.

J. In Vitro Drug Release

To ascertain the phytoconstituent's release pattern from the phytosomal formulation in vitro release tests are carried out. Depending on the features of the formulation diffusion cells dialysis membrane technologies or other appropriate procedures may be employed. To comprehend the underlying release mechanism release data can be fitted to kinetic models including zero-order first-order Higuchi and Korsmeyer-Peppas models.^[51]

K. Solubility and Dissolution Studies

It is possible to assess how phytosomal complexation affects poorly soluble phytoconstituents' water solubility and dissolution behavior. Improvements in apparent solubility dissolving rate and dispersion characteristics can be shown by comparing studies between the phytosomal formulation and the pure phytoconstituent.

L. Stability Studies

Determining the physical and chemical integrity of phytosomal compositions during storage requires stability study. In accordance with applicable stability-testing criteria formulations are kept at specific temperatures and humidity levels. Particle size PDI zeta potential drug content appearance and release behavior are all tracked at predetermined intervals.^[52]

9. Phytosomal Drug Delivery for Hyperlipidemia Management

Elevated levels of cholesterol low-density lipoprotein cholesterol (LDL-C) triglycerides or other atherogenic lipoproteins in the blood are indicative of hyperlipidemia a serious metabolic condition. Despite the effectiveness of traditional lipid-lowering medications including statins ezetimibe fibrates and PCSK9-targeting therapies long-term usage of these medications may be linked to side effects treatment intolerance drug interactions expense and poor adherence in certain individuals. These restrictions have increased interest in bioactive substances derived from plants that have antihyperlipidemic anti-inflammatory antioxidant and cardioprotective qualities. However poor aqueous solubility chemical instability low gastrointestinal permeability significant first-pass metabolism and limited systemic bioavailability limit the medicinal use of several phytoconstituents. One possible method for getting over these biopharmaceutical restrictions is phytosomal drug delivery.^[53]

Phytoconstituents and phospholipids especially phosphatidylcholine combine to create molecular complexes known as phytosomes. A complex with improved lipid compatibility is created when the polar head group of the phospholipid interacts with the polar functional groups of the phytoconstituent. This enhanced amphiphilic nature may improve gastrointestinal absorption and make it easier to interact with biological membranes. Phytosomal administration may enhance the pharmacological efficacy of low accessible phytoconstituents and raise systemic exposure. Numerous phytoconstituent classes have shown promise in the treatment of hyperlipidemia. Quercetin kaempferol rutin and catechins are examples of flavonoids that may affect oxidative stress inflammation cholesterol metabolism and lipid buildup. The potential of polyphenols like curcumin and resveratrol to control lipid metabolism and offer antioxidant and vascular protective properties has been studied. By competing with cholesterol for integration into mixed micelles phytosterols such as stigmasterol and β -sitosterol may lower intestinal cholesterol absorption. Other phytoconstituents such as phenolic acids terpenoids and saponins may affect inflammatory pathways lipoprotein metabolism fatty acid oxidation and cholesterol production.^[54]

Phytosomal formulations may have an antihyperlipidemic effect through a number of complimentary mechanisms. Enhanced absorption may make bioactive substances more systemically available enabling them to influence inflammatory signaling fatty acid metabolism hepatic cholesterol production LDL-receptor activation and lipid oxidation. Some phytoconstituents may improve fat consumption control PPAR and SREBP pathways inhibit HMG-CoA reductase or lessen LDL oxidative modification. Their anti-inflammatory and antioxidant qualities may help

prevent endothelial dysfunction and the advancement of atherosclerosis. Compared to traditional administration of free phytoconstituents phytosomal technology may offer a number of benefits. While molecular complexation may enhance dispersion and shield delicate molecules from deterioration increased membrane affinity may enhance absorption. Increased bioavailability might make it possible to achieve therapeutic effects at lower or more manageable dosages. Phytosomal administration in conjunction with adequate lipid-lowering medication may provide a supplementary approach for treating aberrant lipid levels as well as related oxidative or inflammatory processes; nevertheless such combinations necessitate sufficient pharmacological and clinical evaluation.^[55]

Preformulation studies phytoconstituent and phospholipid selection phytoconstituent-to-phospholipid ratio optimization complex preparation physicochemical characterization in vitro evaluation stability testing and in vivo pharmacological assessment are typically involved in the development of phytosomal formulations for hyperlipidemia. To determine formulation quality and performance parameters such particle size PDI zeta potential complexation efficiency drug content morphology FTIR DSC XRD in vitro release and pharmacokinetic behavior can be examined. Phytosomal systems have a lot of potential but they also need more research on large-scale production batch-to-batch repeatability long-term stability pharmacokinetic variability safety and clinical efficacy. Because differences in phytochemical content might affect formulation performance and therapeutic effects standardization of plant extracts is especially crucial.^[56]

10. Antihyperlipidemic Phytoconstituents and Their Phytosomal Formulations

Through regulation of cholesterol production lipid absorption fatty acid metabolism oxidative stress and inflammatory pathways a number of phytoconstituents produced from plants have shown encouraging antihyperlipidemic potential. Curcumin a significant polyphenolic component of *Curcuma longa* has been studied for its anti-inflammatory antioxidant and lipid-lowering qualities. A flavonoid found in many fruits and medicinal plants quercetin may affect lipid metabolism and lessen oxidative modification linked to atherosclerosis. Kaempferol has demonstrated the ability to enhance antioxidant defense and control lipid buildup. Resveratrol silymarin berberine rutin epigallocatechin gallate (EGCG) and phytosterols like β -sitosterol are other significant phytoconstituents whose effects on the metabolism of triglycerides and cholesterol have been investigated.^[57]

Many of these chemicals have poor aqueous solubility limited gastrointestinal absorption chemical instability extensive metabolism or quick elimination despite their promising biological activity. These restrictions may significantly lower their therapeutic efficacy and oral

bioavailability. The phytosomal formulations have become a desirable method for enhancing the delivery of these substances. A phytoconstituent and phospholipids most frequently phosphatidylcholine produce phytosomes through molecular interaction. In addition to improving lipid compatibility this interaction may improve systemic bioavailability gastrointestinal absorption and membrane penetration.^[58]

Curcumin silymarin quercetin resveratrol and other polyphenolic chemicals have all been studied in phytosomal formulations to enhance their pharmacological and biopharmaceutical qualities. By affecting hepatic cholesterol production LDL-receptor function lipid oxidation and inflammatory signaling increased bioavailability may enable these substances to more effectively produce their antihyperlipidemic effects. Phytosomal technology offers a viable platform for transforming naturally occurring chemicals with low bioavailability into lipid-management formulations that are more effective. However more research is needed to determine uniform formulations long-term stability safety pharmacokinetic profiles and therapeutic efficacy in hyperlipidemic individuals.^[59]

11. Mechanisms of Action of Phytosomal Systems in Hyperlipidemia

Antihyperlipidemic phytoconstituents' solubility membrane affinity gastrointestinal absorption and systemic bioavailability are the main ways that phytosomal systems increase their therapeutic potential. Phytoconstituents and phospholipids especially phosphatidylcholine molecularly bind to form phytosomes. This interaction helps poorly absorbed chemicals connect with biological membranes and increases their lipid compatibility. A larger percentage of the bioactive substance may enter the bloodstream and start to have pharmacological effects.^[60]

The biological characteristics of the integrated phytoconstituent have a major role in the antihyperlipidemic effect of phytosomal systems. By affecting enzymes involved in cholesterol biosynthesis such as HMG-CoA reductase a variety of flavonoids and polyphenols can regulate hepatic cholesterol metabolism. Increased expression of hepatic LDL receptors and improved removal of circulating LDL particles may result from suppression of hepatic cholesterol production. Several phytoconstituents may affect sterol regulatory element-binding proteins (SREBPS) which control genes related to the synthesis of fatty acids and cholesterol. Phytosomal formulations may enhance the administration of substances that control the metabolism of fatty acids and triglycerides. Some phytoconstituents can increase fatty acid oxidation decrease hepatic triglyceride production and activate peroxisome proliferator-activated receptors (PPARs). These effects might lead to better plasma triglyceride levels and less VLDL formation.^[61]

Antioxidant and anti-inflammatory action is another crucial mechanism. Increased cholesterol can lead to vascular inflammation endothelial dysfunction lipid peroxidation and oxidative stress. Reactive oxygen species can be scavenged and inflammatory pathways can be modulated by phytoconstituents such as curcumin quercetin resveratrol and related polyphenols. These preventive effects may be strengthened by increased bioavailability via phytosomal transport which may also lessen oxidative alteration of LDL and the inflammatory development of atherosclerotic plaques. Phytosomes may enhance the intestinal transport of substances that lower the absorption of cholesterol. By interfering with intestinal cholesterol uptake or bile acid-mediated cholesterol absorption phytosterols and certain saponins can lower the amount of cholesterol that enters the systemic circulation.^[62]

The integrated phytoconstituent determines the unique antihyperlipidemic actions whereas phytosomal systems function mainly as bioavailability-enhancing carriers. Phytosomes are a promising platform for the development of phytoconstituent-based interventions for hyperlipidemia because they may improve modulation of cholesterol synthesis LDL clearance triglyceride metabolism oxidative stress inflammation and intestinal lipid absorption through improved absorption and delivery.^[63]

12. Preclinical and In Vivo Evidence

The potential of phytoconstituents and phytosomal delivery methods in the treatment of hyperlipidemia has been encouragingly demonstrated by preclinical and in vivo studies. Numerous plant-derived chemicals have been shown in experiments employing animal models and cell-based systems to control lipid metabolism lower oxidative stress and dampen inflammatory processes linked to dyslipidemia and atherosclerosis. The phytoconstituent dosage formulation experimental model and length of therapy all affect how strong these effects are. Phytoconstituents like curcumin quercetin resveratrol silymarin berberine catechins and phytosterols have been shown in animal experiments to lower serum total cholesterol LDL-C triglycerides and VLDL while in certain cases raising HDL-C levels. These effects have been linked to intestinal lipid absorption fatty acid oxidation hepatic cholesterol production and antioxidant defense systems. Several substances have shown decreases in inflammatory indicators and hepatic fat buildup indicating possible protection against vascular and metabolic problems.^[64]

To address the low bioavailability frequently seen with a number of natural substances phytosomal formulations have been studied. When compared to the administration of the appropriate free phytoconstituent phytosomal delivery has often been linked to better absorption and systemic exposure in preclinical trials. Increased biological activity at same or lower dosages may be the consequence of improved pharmacokinetic performance.

For instance in animal settings phytosomal preparations of low accessible polyphenols have shown better plasma exposure and improved pharmacological effects.

It is possible to assess the potential antihyperlipidemic benefits of phytosomal systems using well-established animal models such as dyslipidemia caused by chemicals or genetics high-fat diet-induced hyperlipidemia and cholesterol-enriched diet models. Serum total cholesterol triglycerides LDL-C HDL-C hepatic lipid content oxidative stress indicators inflammatory mediators and histological alterations in the liver and vascular tissues are examples of common outcomes. Preclinical evidence cannot prove clinical efficacy directly but it does offer a scientific foundation for future research. The translational value of results may be impacted by variations in animal metabolism formulation composition dosage and experimental settings. To ascertain the long-term safety and therapeutic efficacy of phytosomal systems in human hyperlipidemia standardized formulations thorough pharmacokinetic research toxicity studies and carefully monitored clinical trials are required.^[65]

13. Advantages of Phytosomal Drug Delivery

Phytosomal drug delivery has a number of benefits for enhancing the therapeutic efficacy of phytoconstituents that are poorly bioavailable. Improved bioavailability is the main benefit. A phytoconstituent's lipid compatibility is enhanced and its interaction with biological membranes is facilitated when it is complexed with phospholipids especially phosphatidylcholine. When compared to administering the free phytoconstituent this can improve gastrointestinal absorption and systemic availability. Phytosomes can enhance the solubility and dissolving characteristics of substances produced from plants that are weakly soluble in water. Improved pharmacological activity and absorption may be facilitated by increased dispersion and interaction with bodily fluids. This is especially crucial for flavonoids polyphenols and other natural substances whose restricted aqueous solubility limits their medicinal use.^[66]

Enhanced membrane permeability is a significant additional benefit. The phytosomal complex can effectively interact with intestinal and cellular membranes because the phospholipid component of phytosomes shares structural similarities with biological membranes. This could enhance the related phytoconstituent's exposure at the site of action and facilitate its movement across biological barriers. Phytosomal systems may also offer defense against deterioration. Sensitive phytoconstituents can be shielded from oxidation hydrolysis and enzymatic degradation by complexing with phospholipids. Increased therapeutic consistency could be a result of improved stability. By boosting the portion of the injected phytoconstituent that becomes systemically accessible phytosomes may also allow for dose reduction and enhanced therapeutic efficacy. Although dosage optimization needs to be

determined experimentally increased bioavailability may be able to lower the quantity of active ingredient needed to provide a particular pharmacological effect. Additional benefits include the use of biocompatible and biodegradable phospholipids comparatively easy production possible increases in patient compliance and compatibility with a range of plant-derived substances. Phytosomal formulations can be added to a variety of pharmaceutical dosage forms such as tablets capsules powders solutions and topical treatments.^[67]

These benefits should enable more efficient distribution of phytoconstituents with hypolipidemic antioxidant and anti-inflammatory qualities in hyperlipidemia. All things considered phytosomal technology offers a viable method for improving the potential therapeutic value of natural substances while overcoming significant biopharmaceutical constraints. The prior to widespread therapeutic application formulation optimization stability assessment safety evaluation and clinical validation are still required.^[68]

14. LIMITATIONS AND CHALLENGES

Despite their potential phytosomal drug-delivery systems have a number of drawbacks that could impede their clinical translation and pharmaceutical development. Because phytosome production depends on the physicochemical properties of the phytoconstituent phospholipid type phytoconstituent-to-phospholipid ratio solvent system temperature and processing conditions formulation optimization is sometimes difficult. Because the chemical makeup of plant extracts can vary depending on the plant source growing conditions extraction technique and storage these variations can also have an impact on complex formation. Some phytoconstituents may bind weakly or insufficiently with phospholipids which would lead to inefficient complexation. Obtaining repeatable formulations requires standardized raw ingredients and meticulously optimized manufacturing conditions.^[69]

Stability and storage are another significant challenge. While several phytoconstituents are susceptible to light oxygen moisture and temperature phospholipids may experience oxidation or hydrolysis during storage. Particle size zeta potential complexation efficiency and therapeutic effectiveness could all be affected by this deterioration. It can also be challenging to maintain physical stability and avoid aggregation especially in liquid or nanoscale formulations. Additionally specialized machinery and stringent process parameter control may be necessary for large-scale manufacture. Batch-to-batch consistency and product quality can be impacted by differences between laboratory-scale and industrial-scale production. These elements could raise the cost and complexity of manufacturing.^[70]

There is still relatively little clinical evidence linking phytosomal systems to hyperlipidemia. Direct comparison is challenging due to variations in

experimental model dosages formulations and outcome measurements despite the fact that several phytoconstituents have shown encouraging antihyperlipidemic benefits in laboratory and animal research. Long-term safety and pharmacokinetic behavior also need more research. Better clinical results are not always ensured by a phytosomal formulation's increased bioavailability. Determine the therapeutic efficacy ideal dosage safety stability and possible interactions with traditional lipid-lowering medications well-designed clinical trials are necessary. Another significant obstacle to the broader clinical implementation of complicated phytosomal preparations is regulatory standardization.^[71]

15. Recent Advances and Emerging Trends

Enhancing the bioavailability stability targeting and therapeutic efficacy of poorly absorbed phytoconstituents has been the focus of recent developments in phytosomal drug delivery. To achieve reduced particle sizes better dispersion and increased membrane contact nanophytosomes and tailored phospholipid complexes are being investigated more and more. High-shear homogenization ultrasonication solvent evaporation and controlled precipitation are examples of advanced preparation processes that have increased formulation reproducibility. To find crucial formulation factors and maximize product performance design-of-experiment and Quality by Design (QbD) techniques are also being used. Phytoconstituent combinations with complementary pharmacological properties are being studied for their potential to produce synergistic lipid-lowering anti-inflammatory and antioxidant effects.^[72]

The creation of tailored multifunctional phytosomal systems that can simultaneously address several disease processes is an emerging concept. For metabolic and cardiovascular conditions researchers are looking into phytosomes that contain terpenoids flavonoids polyphenols and other bioactive substances. Controlled distribution and tissue exposure may be further enhanced by hybrid systems that combine phytosomes with nanoparticles nanoemulsions hydrogels or other lipid-based carriers. Formulations that improve the delivery of poorly bioavailable chemicals while concurrently addressing oxidative stress inflammation and aberrant lipid metabolism are receiving special attention in hyperlipidemia. Compared to the traditional administration of free phytoconstituents such methods might have advantages.^[73]

The growing focus on clinical validation and translational research is another significant development. Phytosome structure molecular interactions pharmacokinetics and biological distribution are being better understood with the application of contemporary analytical and imaging tools. To guaranty repeatable treatment results better standardization of botanical extracts and identification of active markers are also crucial. Scalable production long-term stability

regulatory acceptability tailored treatment and carefully monitored clinical trials are anticipated areas of future research. The development of more potent and bioavailable phytoconstituent-based treatments for hyperlipidemia and associated cardiovascular conditions may eventually be aided by the integration of phytosomal technology with nanomedicine and sophisticated formulation optimization.^[74]

16. FUTURE PERSPECTIVES

Because phytosomal drug delivery has the potential to overcome the poor solubility instability restricted absorption and low bioavailability of various naturally occurring antihyperlipidemic substances it seems to have a bright future for managing hyperlipidemia. Future studies should concentrate on creating standardized and optimal phytosomal formulations with well-characterized phytoconstituents like terpenoids flavonoids polyphenols and phytosterols. The use of advanced analytical tools computational modeling design-of-experiment methodologies and Quality by Design (QbD) may enhance formulation reproducibility and assist in identifying crucial material and process factors. Transforming laboratory-scale phytosomal formulations into commercially viable pharmaceutical medicines will also require the development of scalable manufacturing techniques.^[75]

Future studies should focus further on toxicity pharmacokinetics pharmacodynamics and clinical assessment. Evidence from carefully monitored human clinical trials is still required despite the fact that several phytosomal formulations have shown enhanced bioavailability and encouraging antihyperlipidemic benefits in preclinical research. The best dosage frequency of administration long-term safety drug-drug interactions and comparative efficacy with well-established lipid-lowering treatments should all be investigated. Established biomarkers including cardiovascular risk indicators oxidative stress markers lipid profiles and inflammatory mediators may aid in more accurately determining therapy results. To reduce variance in phytochemical content and guaranty consistent therapeutic results botanical extracts must be better standardized.^[76]

The development of multifunctional and tailored phytosomal systems that may concurrently address insulin resistance oxidative stress inflammation hyperlipidemia and endothelial dysfunction is a significant future goal. Multiple bioactive substances may be delivered in a regulated or site-specific manner using hybrid nanocarriers and combination phytosomal systems. Therapeutic effects may be further improved by tailored techniques based on individual lipid profiles metabolic state genetic traits and treatment response. Product development might be accelerated by combining phytosomal technology with sophisticated manufacturing artificial intelligence-assisted formulation optimization and contemporary nanomedicine. In order for

phytosomal systems to become useful supplementary or alternative methods for managing hyperlipidemia successful translation will ultimately depend on the establishment of reliable production regulatory requirements long-term stability clinical efficacy and cost-effectiveness.^[77]

17. CONCLUSION

One significant metabolic condition and a significant modifiable risk factor for atherosclerotic cardiovascular disease is hyperlipidemia. Endothelial dysfunction oxidative stress inflammation and the development of atherosclerotic plaque can all be facilitated by long-term increases in LDL-C triglycerides and other atherogenic lipoproteins. The major strategy for managing aberrant cholesterol levels and lowering cardiovascular risk is still conventional lipid-lowering medications especially statins. The need for alternative therapy approaches is highlighted by constraints related to side effects inconsistent therapeutic response drug resistance long-term adherence and residual cardiovascular risk. In this regard there has been a great deal of scholarly interest in naturally occurring phytoconstituents having antihyperlipidemic antioxidant and anti-inflammatory qualities.

Numerous pathways involved in lipid metabolism have been shown to be modulated by phytoconstituents such as curcumin quercetin kaempferol resveratrol catechins silymarin berberine and phytosterols. Inhibition of cholesterol production improvement of LDL clearance control of triglyceride metabolism decrease of intestinal cholesterol absorption and suppression of oxidative and inflammatory processes are some of their possible mechanisms. However poor water solubility chemical instability limited gastrointestinal absorption extensive metabolism and low systemic bioavailability limit the therapeutic use of several phytoconstituents. By molecularly complexing phytoconstituents with phospholipids especially phosphatidylcholine phytosomal drug delivery offers a viable answer to these problems. Membrane affinity absorption stability and systemic exposure can all be enhanced by this method.

All things considered phytosomal technology is a promising cutting-edge delivery method for boosting the antihyperlipidemic phytoconstituents' therapeutic potential. Enhanced bioavailability might boost their pharmacological efficacy and offer chances to create safer and more effective plant-based treatments. Although preclinical research has shown promising results there are still significant obstacles to overcome in the areas of formulation optimization botanical material uniformity long-term stability scalable production pharmacokinetic variability safety and regulatory approval. Therefore methodical formulation creation mechanistic studies carefully planned animal studies pharmacokinetic and toxicity evaluations and well-powered clinical trials should be the focus of future research. If these systems are successfully translated

phytosomal formulations may become useful supplements to traditional lipid-lowering treatments and help control hyperlipidemia and the cardiovascular problems it causes.

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