International Journal of Biomedical Investigation

journal homepage: https://ijbi.edwiserinternational.com

Review Article

Phytoliposome-Based Targeted Drug Delivery in Tuberculosis Therapy: A Comprehensive Review

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ARTICLE INFO

Received 7 March 2026
Revised 10 April 2026
Available Online 15 April 2026

Keywords:
Nanocarriers
Tuberculosis
Phytoliposomes
Phytoconstituents
Targeted Drug Delivery

ABSTRACT

Tuberculosis remains a major global health burden, further complicated by prolonged treatment regimens, poor patient adherence and the emergence of multidrug-resistant strains. These challenges highlight the urgent need for advanced drug delivery approaches. The present review aims to evaluate the potential of phytoliposome based targeted drug delivery systems in improving TB therapy. A comprehensive narrative review methodology was adopted, analyzing literature published between 2010 to 2025 from scientific databases including PubMed, Scopus and Google Scholar. Phytoconstituents such as alkaloids, flavonoids and terpenoids exhibit significant antimycobacterial activity but suffer from poor bioavailability and pharmacokinetic limitations. Phytoliposomes, formed by complexation of phytochemicals with phospholipids, enhance solubility, stability and intracellular delivery, particularly to macrophages harbouring Mycobacterium tuberculosis. Key findings indicate a 2-5 fold improvement in drug efficacy, enhanced bioavailability, controlled release and reduced systemic toxicity. Targeted delivery strategies including ligand-mediated systems, further improve therapeutic outcomes and reduce drug resistance. In conclusion, phytoliposome based drug delivery systems represent a promising and innovative approach for TB management. Their ability to enhance drug performance and enable targeted therapy suggests strong potential for future clinical applications, particularly in addressing resistant and latent TB infections.

Introduction

Tuberculosis (TB) is a long-term infectious disease caused by Mycobacterium tuberculosis (Mtb) primarily affecting the lungs but also capable of involving extrapulmonary sites. As stated by the World Health Organization (WHO), TB is currently ranked among the leading causes of infectious death in 2022 in the world, cases were reported to be 10.6 million new cases. It is highly contagious and spreads through airborne transmission, particularly in densely populated areas.

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https://doi.org/10.31531/2581-4745.1000176

Since the 1950s, when chemotherapy was available TB control remains challenging as patients do not adhere to treatment and the treatment regimens are prolonged [1]. The development of drug-resistant strains has further complicated the process of eradicating TB in the world, making it necessary to find new approaches to treatment. TB remains a major burden to public health in the world and low and middle income countries are those especially affected. The estimates of WHO Global TB Report 2023 indicate that 1.3 million TB-related deaths are among Human Immunodeficiency Virus (HIV) negative and about 167,000 TB-related deaths are among HIV-positive patients. More than half of the worldwide TB incidence is in India, China, Indonesia and the Philippines. The rate of incidence decreased gradually between the year 2015 and 2020 but turned around during the COVID-19 pandemic because of interrupted healthcare facilities. Also MDR-TB covers almost 450,000 new infections every year which demonstrates the necessity to develop better methods of diagnosis and treatment [2].

TB pathophysiology entails the entry of Mtb bacilli into the lungs which get ingested by alveolar macrophages. Mtb does not get destroyed but survives in macrophages by inhibiting the fusion of phagosomes and lysosomes. This gives rise to the development of the granulomas which are synthesized immune structures to entrap the infection. The bacterial infection that remains dormant is known as latent TB infection and it afflicts about 25% of the world population. The reactivation may reoccur in the case of immunocompromised states, including HIV infection. The comprehensive interaction between host and pathogen and survival in the intracellular environment of Mtb plays a significant role in not allowing drugs to penetrate the host which leads to chronic infection and therapy failure [3]. Traditional TB treatment includes a mixture of first-line medications including isoniazid, rifampicin, pyrazinamide and ethambutol taken in 6-9 months. Nonetheless, increased duration of treatment usually causes low adherence levels of the patients, hence failure in treatment and development of resistance. Therapy is further complicated by adverse drug reactions or hepatotoxicity and neurotoxicity. Moreover, inadequate permeability of drugs to granulomatous tissues minimises therapeutic response. The development of MDR-TB and extensively drug-resistant TB (XDR-TB) has immensely lowered the efficiency of conventional regimens. These difficulties imply the weaknesses in traditional methods and the necessity of improved, targeted systems of drug delivery [4]. The drug delivery systems (DDS) represent the most advanced therapeutic to quell setbacks of traditional TB treatment. The systems increase the bioavailability of drugs, the effectiveness of targeted delivery to infected macrophages and decrease systemic toxicity. Liposomes, nanoparticles, Phytoliposomes and other nanocarriers have demonstrated better absorption within the intracellular area as a way of increasing the therapeutic outcomes. Until now, studies have reported a 2–5-fold enhancement of the efficacy of drugs based on nanocarrier-based systems. Also, the controlled release ensures a decrease in dosing rate, enhancing adherence to therapy. Thus, effective TB management is highly dependent on the development of the relevant DDS, especially in dealing with MDR-TB and latent infection [5].

Phytoconstituents in Tuberculosis Therapy

Classification of Phytoconstituents

Phytoconstituents are biologically active substances of plants that show a variety of pharmacological properties, such as anti-tubercular properties. All these compounds are categorized into primary and secondary metabolites according to their biosynthetic formation process. Primary metabolites include carbohydrates, proteins and lipids which are all crucial in the growth of plants but have minimal direct therapeutic value. Conversely, the secondary metabolites exhibit great biological activity against pathogens such as Mtb. The secondary phytoconstituents can also be further divided into major classes that include alkaloids, flavonoids, terpenoids, phenolics, glycosides and saponins [6]. Antimicrobial agents such as alkaloids such as berberine interfere with the microbial replication of DNA. Flavonoids such as quercetin are antioxidant and immunomodulatory factors. Terpenoids like artemisinin analogues have shown de-controlling activities in the synthesis of Mtb cell walls. The phenolic compounds help in the induction of oxidative stress in bacterial cells and increase bactericidal action. Recent discoveries show that more than one-third of screened plant-derived compounds exhibit measurable antimycobacterial activity with minimum inhibitory concentrations (MIC) ranging from 1–100 µg/mL. The classification will also allow the use to choose appropriate phytoconstituents to integrate in more advanced drug delivery systems Phyto-liposomes [7].

Anti-Tubercular Phytochemicals

Plant-based phytochemicals have drawn a lot of interest as possible anti-tubercular agents because of their multi-targeted mechanisms and wide range of chemical structures. In vitro and in vivo studies have shown several classes of compounds which include alkaloids, flavonoids, terpenoids and phenolics which are active against Mtb. Bacteriostatic effects of alkaloids (e.g., of berberine and piperine) by disrupting the production of

nucleic acids have been observed. Flavonoids such as quercetin and catechin can boost host immune response as well as prevent bacterial growth by regulating oxidative stress [8]. Terpenoids, such as ursolic acid and artemisinin derivatives, interfere with the integrity of the cell wall of mycobacteria which results in their greater permeability and death of the cells. Whereas phenolic compounds like curcumin have demonstrated minimum inhibitory concentrations of 2-50 µg/mL thus having a commendable potential against the mycobacterium. Also, saponins and glycosides lead to destabilization of membranes and enhancement of drug uptake. More recent reports (2018-2024) indicate that about 65-70% of phytochemicals tested have significant activity against Mtb, with some of them showing synergy with the effects of the first-line anti-TB drugs. Such results indicate that phytochemicals can be used as adjunct therapy in the management of TB [9].

Table 1: Anti-tubercular phytochemicals and activity profile [10-15].

Phytoconstituent	Class	Source Plant	Mechanism of Action	MIC Range (µg/mL)	Enhancement via Phytoliposomes	Remarks
Curcumin	Polyphenol	*Curcuma longa*	Inhibits cell wall synthesis, ROS generation	2-50	~3.5 fold increase in bioavailability	Poor solubility in free form
Berberine	Alkaloid	*Berberis vulgaris*	DNA gyrase inhibition	8-64	~2.8 fold intracellular uptake	Efflux pump inhibitor
Quercetin	Flavonoid	*Allium cepa*	Oxidative stress induction	10-80	~3 fold enhanced absorption	Immunomodulatory
Piperine	Alkaloid	*Piper nigrum*	Membrane disruption, bioenhancer	5-50	~2.5 fold permeability	Enhances drug bioavailability
Ursolic Acid	Terpenoid	*Ocimum sanctum*	Cell wall disruption	4-32	~3.2 fold delivery	Lipophilic nature
Catechin	Flavonoid	*Camellia sinensis*	Enzyme inhibition, ROS	10-100	~2.7 fold bioavailability	Antioxidant effect
Artemisinin	Terpenoid	*Artemisia annua*	Free radical generation	1-25	~3 fold targeting	Synergistic with drugs
Resveratrol	Polyphenol	*Vitis vinifera*	Inhibits signaling pathways	5-40	~2.9 fold stability	Anti-inflammatory
Andrographolide	Diterpenoid	*Andrographis paniculata*	Inhibits protein synthesis	6-45	~3.1 fold uptake	Immunostimulant
Allicin	Organosulfur	*Allium sativum*	Disrupts enzyme systems	3-20	~2.6 fold efficacy	Broad antimicrobial
Eugenol	Phenolic	*Syzygium aromaticum*	Membrane damage	5-60	~2.8 fold bioavailability	Volatile compound
Thymoquinone	Quinone	*Nigella sativa*	ROS-mediated killing	2-30	~3.3 fold delivery	Anti-inflammatory
Luteolin	Flavonoid	*Ocimum basilicum*	Enzyme inhibition	8-70	~2.9 fold absorption	Anti-inflammatory
Glycyrrhizin	Saponin	*Glycyrrhiza glabra*	Immune modulation	10-90	~2.7 fold uptake	Enhances host defense
Baicalin	Flavonoid	*Scutellaria baicalensis*	Inhibits bacterial enzymes	6-55	~3 fold stability	Anti-inflammatory

Mechanisms of Action

Phytochemicals act against tuberculosis by several pathways that are directed towards vital biological pathways of Mtb. Among the major mechanisms is that of suppressing cell wall biosynthesis, that is of mycolic acid and arabinogalactan layers required to support bacterial survival. The terpenoids and phenolic compounds disrupt the lipid-rich cell envelopes and make the cell membrane permeable which results in cell lysis. The other important mechanism encompasses the interference with the nucleic acid synthesis [16]. Alkaloids like berberine block the DNA gyrase and topoisomerase enzymes and in this way prevent bacterial multiplication. Also, various flavonoids cause oxidative stress by producing reactive oxygen species which cause destruction of proteins, lipids and DNA in Mtb cells. Phytochemicals also control host immune responses acting to stimulate macrophages and cytokines to increase intracellular killing of pathogens. Other compounds block efflux pump systems which cause resistance of drugs and this will restore the effect of traditional anti-TB medications. The articles published in the period 2016 to 2025 present experimental research where the combination of phytochemicals in treatment was able to enhance bacterial clearance rates up to 40% relative to monotherapy. These multi-targeted mechanisms make phytochemicals promising candidates in the fight against the stubborn and drug-persistent TB infections [17].

Limitations of Phytoconstituents

Although the phytoconstituents hold promise of being effective in anti-tubercular activities, they have a number of limitations that limit their use in clinics. One of such issues is low aqueous solubility that contributes to low bioavailability and prevents full systemic exposure. Several phytochemicals are fast metabolised and excreted thus having poor half-lives and insufficient concentrations in the site of infection to generate therapeutic effects. The other important limitation is low permeability in biological membranes especially in targeting intracellular pathogens such as Mtb which is harboured in the macrophages. Pharmacological activity is also not always consistent due to variability in sources of plants, methods of extraction and purity of compounds [18]. Furthermore, therapeutic doses are frequently high which puts the patients at risk of toxicity and adverse reactions due to involving large doses. Studies indicate that approximately two-thirds of potent phytoconstituents have not been advanced beyond preclinical trials because of pharmacokinetic limitations. All these factors require more sophisticated systems of delivery including Phytoliposomes to improve stability, bioavailability and targeted delivery of drugs.

Phyto-liposome

Phyto-liposome is a novel lipid-based drug delivery vehicles designed to optimize the bioavailability and therapeutic activity of the phytoconstituents. They are created by complexation of active compounds of plant origin with phospholipids, usually the phosphatidylcholine and the molecular complexation occurs rather than simple encapsulation. This special structure enhances solubility and membrane permeability of the poorly bioavailable phytochemicals [19, 20]. They are structurally composed of lipid bilayer where the phytoconstituent is in a stable association with the polar head of phospholipids by way of hydrogen bonding and hydrophobic interactions. This is unlike the traditional liposomes that simply encircle the drug on the aqueous core or lipid bilayer. Amphiphilic character of the complex allows the good integration into biological membranes which promotes intracellular delivery, especially to the macrophages infected with Mtb. It has been reported that Phytoliposomes are able to enhance bioavailability by 2-4 fold than when using free phytochemicals. Moreover, the particle size is usually 50-300 nm and this is ideal in cellular uptake and in passive targeting. This structural advantage makes phytoliposomes an efficient delivery system which makes it an efficient method of curing TBL [21].

Phytoliposome consist of phospholipids and phytoconstituents mainly making a stable lipid drug complex. Phosphatidylcholine is the phospholipid that is most frequently used because it is biocompatible and it has an amphiphilic property; it is derived out of soy or egg lecithin. Other constituents like cholesterol are also included to add stability to membranes so as to make them less permeable. The phytoconstituent connects with the polar head groups of phospholipids bonding to create, a complex in which the phytoconstituents are better soluble and absorbable. There are types of Phytoliposomes depending on their composition and structure properties. The traditional Phytoliposomes are made of a basic phospholipid-phytochemical complex. Functionalized Phytoliposomes have surface-functionalized systems used in targeted delivery and might involve ligands to achieve macrophage-specific endocytosis, e.g., mannose or antibodies. Also, the stealth Phytoliposomes are introduced by coating them with polyethylene glycol in order to extend systemic circulation and prevent early clearance by the reticuloendothelial system [22].

Phyto-liposome have a high potential as compared to traditional drug delivery system; especially in

promoting therapeutic value of phytoconstituents. They enhance bioavailability through enhancement of solubility and efficient membrane permeation. Research studies indicate that there is a 2-5 fold improvement on oral absorption over free compounds. Phytoliposomes can also deliver drugs to macrophages effectively with greater intracellular accumulation of drugs against Mtb. Also, they decrease systemic toxicity by minimizing off-target effects and can control drug release. Better pharmacokinetic and therapeutic characteristics are also facilitated by their biocompatibility and capacity to shield phytochemicals against degradation [23].

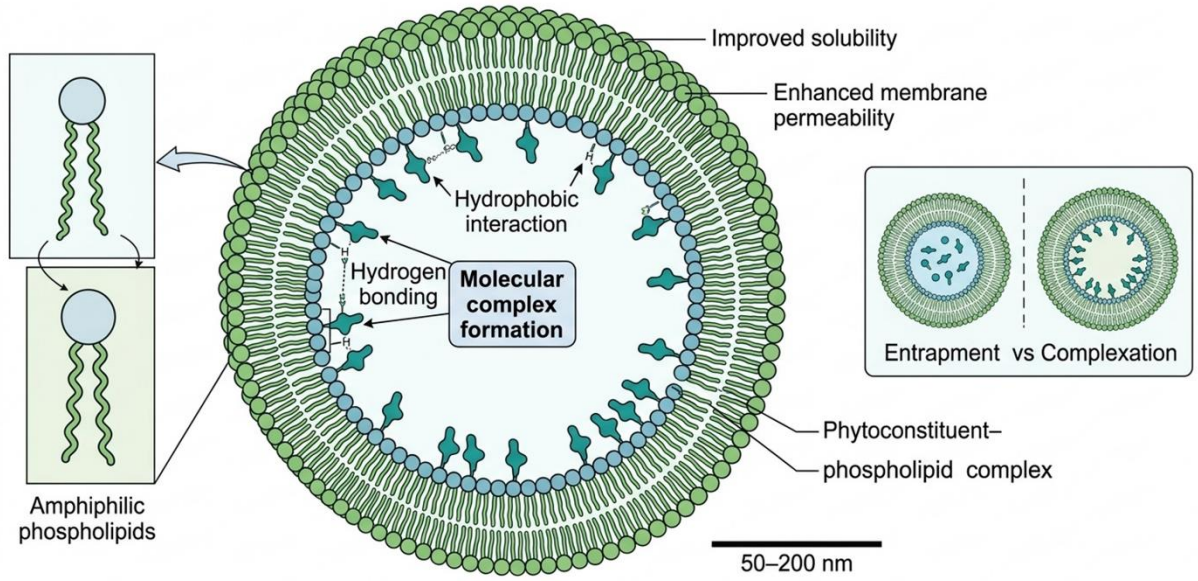

Figure 1: Structure and molecular complexation of Phytoliposomes.

Preparation And Characterization of Phytoliposomes

Preparation Methods

There are several formulation methods used to prepare Phytoliposomes and which guarantee effective complexation of phospholipids and phytoconstituents. The most commonly used of these is the solvent evaporation technique where there are relative simplicity and the ability to reproduce. This technique involves dissolution of phospholipids and phytoconstituents in an organic solvent like ethanol or chloroform and the solvent is then removed by applying reduced pressure using the rotary evaporator. This leads to the creation of a phospholipid film which then gets hydrated to form Phyto-liposomal vesicles. Another method that is widely available is the thin film hydration method in which controlled agitation and hydration event encourages the formation of uniform vesicles [24]. The parameters of hydration temperature, rotation speed and solvent composition have a strong impact on the particle size and entrapment efficiency. Anti-solvent precipitation is also applied especially in the case of poorly soluble phytochemicals. The lipid-drug solution is rapidly dispersed into a non-solvent resulting in self-assembled Phytoliposomes with a narrow size distribution, in this technique. Innovative methods have been tackled e.g. the use of supercritical fluid processing which has been considered to yield Phytoliposomes of high purity and low levels of solvent residues. This technique uses supercritical carbon dioxide to increase the solubility as well as to promote the growth of particles in a uniform manner. Research has shown that process parameters such as lipid-drug ratio, type of solvent and temperature play a paramount role in the processes of formulation. Entrapment efficiencies of over 80 % and particle sizes of less than 200 nm can be obtained using optimized preparation methods which is attractive to deliver the target to the Mtb-infected macrophages [25].

Particle Size and Zeta Potential

The size of particles is a key factor that determines the functionality of Phyto-liposome, especially in regard to cellular absorption, biodistribution and efficacy of phyto-liposome. Phytoliposomes are usually between 50 and 300 nm in size and this is regarded to be ideal in terms of passive targeting and increased permeability. The nanocarriers used in this size range can be effectively used to penetrate biological membranes and accumulate in the macrophages which are the major host cells of Mtb. A decrease in particle size correlates with a high surface area hence greater dissolution and absorption of phytoconstituents. Another physicochemical property that is crucial in the determination of stability in Phytoliposome

formulations is Zeta potential. It represents the charge of the particles on the surface and affects their aggregation process. Typically, a zeta potential of positive charge exceeding +30 mV or negative charge lower than -30 mV is a good sign of stability since the particles are electrostatically repelled. The Phytoliposomes tend to take the negative zeta potential as a result of the presence of phospholipid head groups which helps in colloidal stability. The research indicates that optimized formulations that contain particle sizes of less than 200 nm and zeta potential of about -35 mV manifest improved stability and increased circulation duration. The properties also enable easier interaction with cell membranes, leading to efficient intracellular delivery. So, the accurate regulation of particle diameter and zeta potential is a key to the effective and stable Phytoliposome based drug delivery system in TB therapy [26, 3].

Table 2: Physicochemical and functional characteristics of Phytoliposomes [27-31].

Parameter	Typical Range	Optimized Value	Impact on TB Therapy	Remarks
Particle Size (nm)	50-300	120-180	Enhances macrophage uptake	Ideal nanoscale
Zeta Potential (mV)	−20 to −40	~−35	Improves stability	Prevents aggregation
Entrapment Efficiency (%)	60-90	80-88	Sustained drug release	Lipid dependent
Drug Release (%)	60-95 (24-72 hr)	~85	Controlled delivery	Biphasic release
Bioavailability Enhancement	2-5 fold	~3.5 fold	Improves efficacy	Compared to free drug
Stability Duration	1-6 months	~3 months	Maintains integrity	Storage dependent
Lipid:Drug Ratio	1:1-3:1	2:1	Affects size & EE	Critical parameter
Targeting Efficiency (%)	50-85	~70	Improves intracellular delivery	Macrophage targeting
Polydispersity Index (PDI)	0.2-0.5	~0.25	Indicates uniformity	Lower is better
Surface Area (m^2/g)	10-80	~45	Enhances dissolution	Size dependent
Encapsulation Stability (%)	70-95	~85	Prevents drug leakage	Storage stability
Circulation Time (hr)	6-48	~24	Prolongs drug presence	Reduced clearance

Entrapment Efficiency

Efficiency of entrapment is a crucial parameter that will be used to calculate the percentage of phytoconstituent that has been incorporated successfully into the Phytoliposomes versus the amount of drug that was used in the formulation. It has a direct effect on drug loading capacity, therapy performance and the release performance. An increased entrapment efficiency guarantees extended trapping and high bioavailability. Average entrapment efficiency of Phytoliposomes is between 70% and 90 % and this depends on formulation factors like lipid-drug ratio, solvent regimen and preparation method. Hydrogen bonding of phospholipids and phytoconstituents increases the incorporation of drugs. Lipophilic compounds tend to have increased entrapment than hydrophilic molecules because of their enhanced affinity with the lipid bilayer. Entrapment efficiency is determined by common techniques of analysis like ultracentrifugation and dialysis. Engineered to high entrapment efficiency formulations are associated with minimized drug loss and delivery to a greater number of Macrophages infected with Mtb [32].

Morphology (TEM/SEM)

Phyto-liposome should be morphologically evaluated to evaluate their structural integrity, shape and surface properties. Detailed visualization is also used with transmission electron microscopy (TEM) and scanning electron microscopy (SEM). TEM will offer information about organization of the internal structure where the vesicles form and the lipid bilayer structure is found and SEM will be able to provide data about the surface structure and distribution of the particles. Phytoliposomes are normally spherical or nearly spherical in shape and bear smooth surfaces meaning they are uniform and stable. No aggregation or deformation will be a sure sign of appropriate formulation. Regular morphology facilitates efficiency in cellular internalization and is associated with optimal physicochemical characteristics that are essential to efficient delivery of drugs [33].

In Vitro Drug Release

In vitro drug release experiment is done to observe the behaviour of phytoconstituents of Phytoliposomes in analysis of release behaviour under controlled conditions. These experiments are typically carried out in the simulated physiological media with the dialysis membrane techniques. The typical characteristics of

Phytoliposomes are its biphasic release which is an initial burst release and a sustained release phase. The former is the release due to surface-associated drug and the latter is the release due to gradual diffusion of the drug out of the lipid matrix. Controlled release lasting up to 24-72 hours which can be done through optimized formulations that enhance therapeutic effects. This delayed delivery characteristic increases the availability of the drug at the site of action and decreases the need to take the drug [34].

Stability Studies

Stability studies determine the physical and chemical stability of Phytoliposomes when storing. Monitoring of parameters as particle size, zeta potential and entrapment efficiency takes place. Stable formulations are those in which there is a small change with time. Aggregation and degradation are avoided with proper storage at controlled temperatures which guarantees consistency in performance and lengthy shelf life [35].

Targeted Drug Delivery in Tuberculosis

Passive Targeting

Passive targeting involves the use of the physicochemical characteristics of the Phytoliposomes to cause an accumulation of the drug at an area of infection in the absence of particular ligands. The passive form of targeting used in TB therapy is mainly mediated by the enhanced permeability and retention effect whereby it aids in accumulation of nanosized carriers in tissues that are infected. Particles of less than 200 nm Phyto-liposomal size have been shown to efficiently circulate in the body and localize specifically to the macrophages which are the major host cells of Mtb. Their lipid composition improves their connection with the biological membranes, facilitating their cellular absorption via endocytosis. Also, the long residence time of Phytoliposomes provides long-term availability of the drug in the site of infection. This method is better in intracellular delivery of drug and improvement of therapy as well as reduction of systemic exposure and toxicity [36].

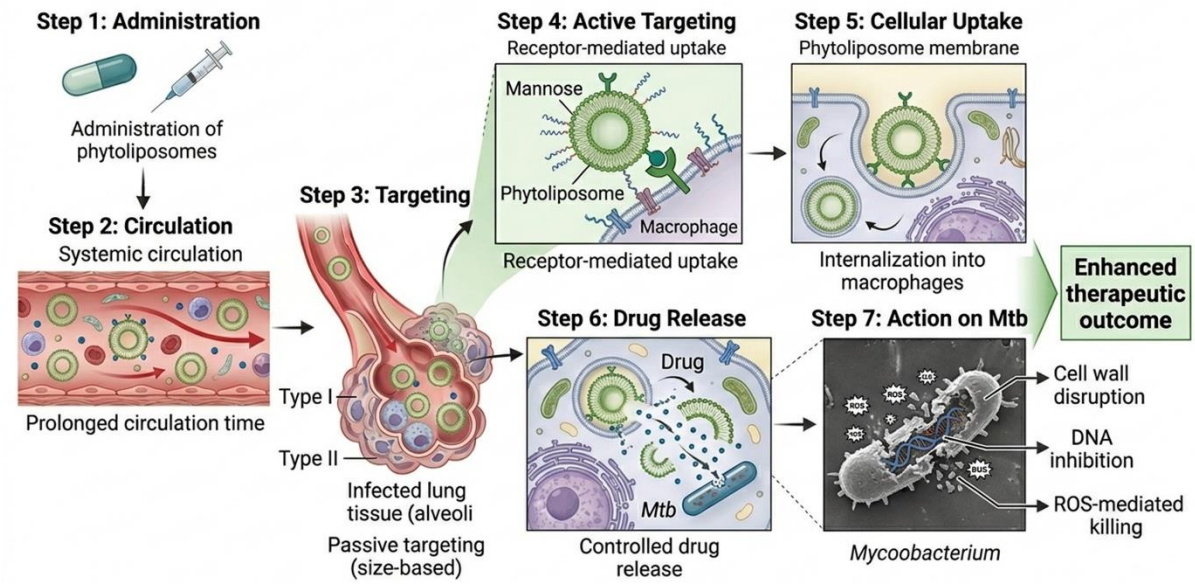

Figure 2: Mechanism of targeted phytoliposome delivery in tuberculosis therapy.

Active Targeting Strategies

Active targeting is the process that consists in the specific alteration of Phytoliposomes with certain ligands in order to deliver them selectively to infected cells. The method enhances the ability to target effectively through the receptor-mediated endocytosis, especially in macrophages that house Mtb. Phytoliposomes are typically functionalized with ligands like mannose, folate, peptides as well as antibodies. Mannose-receptors are mostly observed in macrophages and therefore mannose-functionalized Phytoliposomes can find application in the targeted delivery of drugs. In the same manner, folate receptors and other cell specific objects could be used to improve cellular uptake. Such ligand-receptor interactions facilitate endocytosis which directly leads to a high concentration of drug in the cell at the site of infection. Targeting is a vital therapeutic intervention as it has increased effectiveness with drugs by increasing levels in infected cells and decreasing extra curative distribution. This plan also helps reduce doses and lower the negative effects. Ligand-modified Phyto-

liposomes, therefore, are an excellent potential solution to enhancing the effectiveness of TB treatment [37].

Macrophage-Specific Targeting

Targeting macrophages is a key approach in the treatment of TB since Mtb is the main host residing in these cells. There is an optimization of the Phyto transfection process by the surface modification as well as the optimization of the size of the Phytoliposomes to improve selective uptake by the macrophages. The range of 100-200 nm is efficiently taken over through phagocytosis and endocytosis as nanocarriers. Functionalization of the surface with ligands like mannose enhances further recognition by macrophage receptors, making intracellular drug delivery greater. The targeted methodology guarantees increased drug concentration in the area of infection, leading to increased bacterial clearance. This means that macrophage-specific targeting can greatly enhance the therapeutic effects and also alleviate systemic toxicity and lower development of drug resistance [38].

Applications and Current Research Advances

Enhanced Bioavailability

Phytoconstituents also exhibit poor solubility and low permeability contributing to low bioavailability; Phytoliposomes to a great extent improve the solubility and consequently the bioavailability of phytoconstituents. Phytochemicals complexation with phospholipids enhances lipophilicity of phytochemicals, enabling the effective absorption of phytochemicals through cellular membranes. This increases systemic availability and concentrations of therapy in the target site. Phytoliposomes increase absorption through the gastrointestinal tract because of their ability to bind to lipid membranes and increase transcellular transport. Their nanoscale size also adds to their enhanced surface area which enhances the rate of dissolution and absorption [39]. Research indicates that Phytoliposomal preparations are capable of increasing the oral bioavailability of phytochemicals between 2-4 times that of the free phytochemicals. Phytoliposomes also ensure the survival of delicate phytoconstituents otherwise broken down by enzymes and other extreme conditions administered in the body. Such protective effect provides sustained availability of drugs and better pharmacokinetic profiles. High bioavailability eventually translates into high therapeutic efficacy, lower dosing rate and increased compliance by the patient causing the Phytoliposomes to be a potential candidate as a method of TB treatment [40].

Reduced Toxicity

Phyto-liposomes have a major role of alleviating toxicity of both the phytoconstituents and drugs used to treat TB. The active compounds driving into phospholipid structures or encapsulation lowers the immediate exposure of the active drug to the non-target tissues and thus reduces the number of systemic side effects. This is especially relevant to the TB treatment where prolonged treatment can result in hepatotoxicity and other adverse effects. The Phytoliposomes targeted to macrophages are effective in increasing the localization of drugs in the point of infection where lower doses of therapy help to achieve desired effects. Other factors that can lead to less toxicity and increased tolerance by patients include reduced dosing. Moreover, the phospholipids are biocompatible and biodegradable which guarantees the lowest immunogenicity and harmless metabolism in the body. Phytoliposomes also offer regulated and sustained release of drugs avoiding abrupt surges in drug concentration which are likely to cause drug toxicity. It has a controlled release profile which has enhanced safety and ensures that therapeutic levels are maintained throughout the course of time. In general, the system using Phytoliposomes is a safer substitute to an effective TB treatment [41].

Improved Therapeutic Efficacy

Phytoconstituents have effects such as enhancing drug delivery, stability and intracellular drug availability that increase the therapeutic efficacy of phytoconstituents using phyto-liposome. These combined with targetability to be delivered to macrophages they target give them high drug concentrations in the location of Mtb infection leading to an improved response to the bacteria. This is a targeted initiative that can rise above the weakness of low drug penetration in the conventional TB treatment. The constant therapeutic concentrations in the process induced by hydrogenized Phytoliposomes enable the sustained and microenvironmental controlled release of the drug over a long period resulting in reduced alterations of the drug concentration [42]. This helps in enhanced treatment results and a reduction in chances of development of resistance. Enhanced membrane permeability facilitates efficient intracellular delivery and interaction with intracellular pathogens. It has been argued that formulations of Phytoliposomes can increase the therapeutic response by 2-3 times that which are achieved using the free phytochemicals. It has also presented combinatorial effects which have enhanced efficacy because of the addition of the phytoconstituents of Phytoliposomes in combination with traditionally used anti-TB drugs. The mentioned advantages suggest that Phytoliposomes may be considered as a potentially

successful solution to make the treatment of TB even more effective [4, 6].

Recent Studies and Innovations

The latest developments in Phytoliposome technology have made a great contribution in the enhancement of TB treatment in terms of formulation and targeted delivery methods. Novel surface modifications like ligand conjugation and polymer coating have been achieved to improve the stability, cellular uptake and circulation time. To achieve an improved macrophage selective delivery system that results to enhanced accumulation of drug in cells, the moieties of the targeting formats, mannose and others are functionalized Phyto-liposomes. Plant-based liposomes coated with different nanocarrier systems and interacting with other nanocarriers have also taken place as alternative promising platforms [43]. These hybrid preparations have improved structural stability and release profiles and are able to release the drugs over time. Also, co-delivery of phytoconstituents in combination with anti-TB drugs have been found to synergize, increasing antimicrobial activity and self-efficacy of dosage-reduction. Alternative formulation techniques have been discovered like micro fluidization and supercritical fluid processing which helps in the creation of Phytoliposomes with homogenous small particles and with high entrapment. The techniques promote scalability and reproducibility which is a needed requirement in the industry. Secondly, the synthesis of nanotechnology and bioactive plant molecules have offered an avenue to personalized therapy of TB as well. Combined, all these innovations highlight the potential of incorporating Phytoliposomes into a high-tech and versatile drug delivery system to effectively control TB [44, 45].

Future Perspectives

TB Personalized medicines strategies are geared at attaining individualization of treatment based on individual aspects of a patient which include genetic recognition, immunological status as well as the extent of the disease. The Phytoliposomes otherwise offer a platform customisable to deliver specific phytoconstituent to a patient. This personalization can improve therapeutic results, maximizing the drug choice and dose. State-of-the-art diagnostic tools enable detecting patient-related variations and precisely attacking the Mtb infections. The Phyto-liposomal systems can be designed to incorporate the use of bioactive compounds along with conventional drugs enhancing the effectiveness of the treatment in a wide range of patients. Such strategies have the potential to reduce the adverse impact and increase the adherence of the patients through the reduction of unnecessary exposure to drug. The contact of Phytoliposomes and a personalized treatment strategy is one of the solutions to provide more successful and patient-friendly treatment of TB [46].

The usage of artificial intelligence (AI) and nanotechnology has been significantly integrated to enhance Phytoliposome based drug delivery system. The parameters of the formulation such as particle size, lipid composition and drug loading are optimized using the models that are made using AI based on predictions of system behaviour. This not only saves time on the experiment but it increases reproducibility. With nanotechnology, it is possible to effectively engineer Phytoliposomes and deliver them to specific locations and release them on demand. With nanotechnology as the combination of AI and nanotechnology, intelligent design of drug carriers is conveniently easier to be more efficient and stable. Such improvements aid the formulation of the optimal therapies to achieve better treatment of TB [47].

Phytoliposome have a tremendous potential in MDR-TB treatment as they improve intracellular delivery of drugs and surmount resistance. This provides them with abilities to enhance drug penetration in macrophages, thus making them target persistent Mtb. Besides, phytoconstituents can be used together with anti-TB drugs to block efflux pumps and to exhibit greater antimicrobial effects. This will lower the amount of drug needed and minimize the development of resistance. Phytoliposomes are, therefore, a prospective approach to enhance positive response to treatment in the TB cases that have become resistant [48, 49].

Conclusion

The use of Phytoliposome based drug delivery system is a potential solution to better TB therapy through the increases of bioavailability, target delivery and treatment. Their ability to overcome the limitations of traditional therapy and overcome drug resistance underscores their promise in the treatment of TB at an advanced stage. They can be further aided by continued research and optimization to assist their clinical application and enhance global TB control measures.

List of Abbreviations

AI: Artificial Intelligence; DDS: Drug Delivery System; DNA: Deoxyribonucleic Acid; HIV: Human Immunodeficiency Virus; MDR-TB: Multidrug-Resistant Tuberculosis; MIC: Minimum Inhibitory Concentration; Mtb: Mycobacterium tuberculosis; SEM: Scanning Electron Microscopy; TB: Tuberculosis; TEM: Transmission Electron Microscopy; WHO: World Health Organization; XDR-TB: Extensively Drug-Resistant Tuberculosis.

Author Contributions

Conceptualization, A.P; Methodology, G.K; Software, M.P; Validation, S.R; Formal analysis, A.P; Investigation, K.K.G; Resources, M.P; Data curation, S.R; Writing original draft preparation, A.P; Writing review and Editing, M.P; Visualization, G.P; Supervision, R.K.M.

Acknowledgement

All the authors would like to express the profound sense of gratitude and cordial thanks to our corresponding author for providing the necessary valuable guidance and support throughout the work.

Conflict of Interest

The authors declare no conflict of interest.

Funding

The authors did not receive any fundings from any private or government sources.

Ethical Approvals

This study does not involve experiments on animals or human subjects.

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