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Review

Harmonizing tradition and technology: Liposomal nanocarriers unlocking the power of natural herbs in Traditional Chinese Medicine

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ABSTRACT

Natural herbs demonstrate significant therapeutic potential in managing chronic and complex diseases; however, their clinical application faces limitations due to low bioavailability, instability, toxicity, and herb-drug interactions. Furthermore, insufficient standardized evidence and global acceptance impede their widespread adoption. Liposomes, nanocarriers consisting of a phospholipid bilayer enclosing an aqueous core, present a promising approach for enhancing the pharmacokinetics and therapeutic efficacy of herbal compounds. These adaptable systems can encapsulate both hydrophilic and hydrophobic agents, enabling targeted drug delivery and enhanced stability. Moreover, liposomes can be modified to carry diagnostic and imaging agents, enabling precise disease detection and monitoring. While liposomes offer potential as an innovative delivery technology for herbal remedies, their application in Traditional Chinese Medicine (TCM) remains relatively unexplored. TCM, with its holistic, energy-based approach to health and organ function, presents distinct challenges regarding formulation and delivery. This review examines the therapeutic potential of herbal medicines, emphasizing how liposomes address delivery challenges within the TCM framework. It also investigates the integration of TCM with Western medical practices, demonstrating how liposomal systems may bridge these approaches. The review analyzes key formulation techniques for TCM-loaded liposomes, particularly the microfluidic method, which demonstrates superior control over particle size and encapsulation efficiency compared to conventional methods. The analysis addresses barriers to integrating liposomal delivery systems with TCM, including physicochemical properties, scalability issues, and regulatory challenges. Finally, this review provides strategic recommendations for overcoming these obstacles and identifies future research directions to maximize the potential of liposomal technology in enhancing TCM therapies.

1. Introduction

Plants are essential to life on Earth, serving vital roles in ecological systems by providing sustenance, generating oxygen, and acting as primary sources for medicinal compounds. Throughout human history, diverse cultures have developed sophisticated systems of herbal medicine [1-3]. Traditional Chinese Medicine (TCM) represents a holistic medical system with extensive historical foundations, conceptualizing patients as microcosms of the natural universe based on holistic medicine principles. This framework establishes that the balance between two opposing forces, yin and yang, encompasses all aspects of life affecting health. TCM maintains that vital energy (Qi) flows through channels and meridians within the body, connecting organs, tissues, and cells. Optimal health persists when Qi flows smoothly and abundantly, while illness manifests when it becomes deficient or blocked. These principles have guided TCM disease treatment for centuries, maintaining relevance in modern medicine [4]. Substantial research demonstrates TCM's potential therapeutic benefits against various chronic and complex conditions, including infectious diseases, cancer, diabetes, cardiovascular disease, neurological disorders, and tissue regeneration [5-9] (Supplementary Table 1). However, herbal remedies in their unmodified form face considerable challenges, including low bioavailability, poor stability, high toxicity, herb-drug interactions, overdose risk, non-targeted delivery, insufficient evidence base, and limited global acceptance (Fig. 1). Consequently, enhanced delivery systems are essential to improve these remedies' efficacy and safety.

Liposomes, an innovative drug delivery technology, comprise spherical vesicles formed by lipid bilayers encompassing an aqueous core. Their structural similarity to cell membranes enables self-assembly through amphiphilic properties [10, 11]. Liposomal drug delivery has emerged as a significant advancement in modern medicine, evidenced by numerous Food and Drug Administration (FDA) approvals and research publications, particu-

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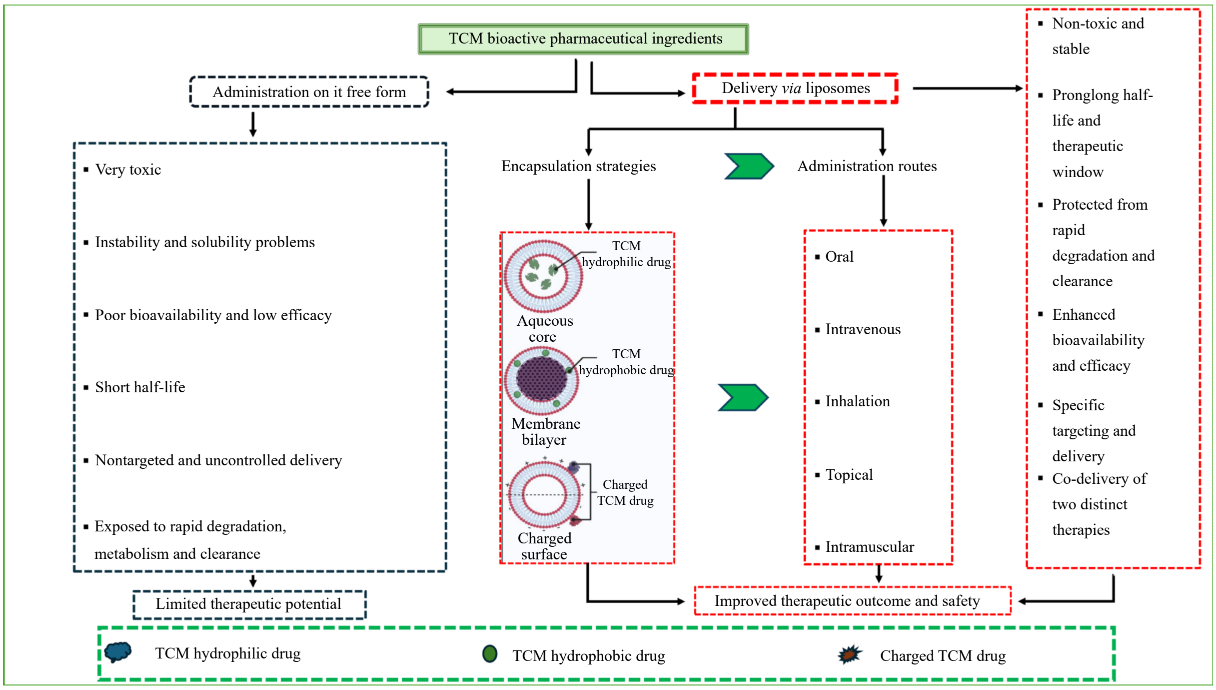

Fig. 1 Graphical abstract illustrating the therapeutic advantages of using liposomes for the delivery of TCM herbal remedies as compared to administering them in their free form.

larly regarding cancer treatment using doxorubicin (DOX) [12, 13]. As drug delivery systems, liposomes provide multiple advantages: enhanced drug solubility, improved bioavailability, sustained release, reduced toxicity, protection against degradation, rapid clearance, and immune attack, thus enabling effective disease targeting (Fig. 1). Furthermore, liposomes facilitate the co-delivery of Western medicine and TCM, serving as valuable tools for combination therapy. Consequently, liposomes have become the predominant nano-delivery system in Western medicine while showing considerable promise for herbal remedy delivery. Recent research indicates that liposomal delivery systems effectively enhance the efficacy and safety of TCM herbal remedies, supporting the hypothesis that liposomal delivery of natural herbs provides an effective solution to minimize systemic side effects and improve efficacy [14].

Contemporary research consistently supports the hypothesis that liposomal delivery of natural herbs presents an optimal solution for minimizing systemic side effects and enhancing efficacy. Accordingly, liposomal nano-delivery systems have demonstrated successful application in administering various TCM products, including triptolide [15], alkaloids [16], and bufalin [17]. Significant research findings have emerged in recent years, with Liang et al. examining aromatic resuscitation TCM drugs for brain penetration enhancement [18]. Lin et al. explored the efficacy of imperialine against non-small cell lung cancer [19]. Kang et al. examined the combined effects of TCM aromatic resuscitation and modern receptor-targeted technology utilizing liposomes to evaluate enhanced drug delivery to the brain for anti-glioma effect [20]. Zhao et al. engineered a TCM-loaded liposomal delivery system with low pH sensitivity for targeted drug delivery to tumor cells [21]. Wang et al. documented the safe delivery of berberine (BBR) [22]. Additionally, studies have demonstrated the application of liposomes in regenerative medicine, employing icariin (ICA) as a drug and biomedical-binding liposomes as delivery vessels targeting osteoporosis [23]. To extend liposome half-life, researchers have precoated them with artificial corona from human plasma proteins, preventing their capture by circulating leukocytes in the bloodstream [24].

Although liposomal drug delivery systems offer potential therapeutic benefits for TCM, multiple challenges and limitations hinder their development and application. These obstacles encompass the complex chemistry of natural products, lack of standardized quality control methods, instability issues, challenges in achieving controlled drug release, and uncertainties regarding the safety and efficacy of TCM-loaded liposomes in clinical trials, particularly when combined with Western medicine. Additionally, there remains a shortage of systematic and comprehensive reviews that synthesize and evaluate current research on liposomal nanocarriers for TCM. This review aims to examine liposomal technology as a novel delivery system for TCM, highlighting its advantages, challenges, and future research and development opportunities. It explores the history, evolution, and therapeutic potential of TCM, as well as the characteristics, classification, and properties of liposomal technology. Furthermore, it analyzes the preparation and characterization methods of TCM or TCM co-loaded with Western medicine, focusing on thin-film hydration and microfluidic techniques. This review also addresses the therapeutic applications and pharmacological mechanisms of TCM-loaded liposomes for various diseases and considerations for prospects and opportunistic directions of liposomal nanocarriers for TCM.

We hypothesized that liposomal nanocarriers could enhance the efficacy and safety of TCM by improving drug solubility, bioavailability, stability, targeting, quantification, and controlled release. To test this hypothesis, we conducted a comprehensive review and analysis of literature published over the past decade, comparing the performance of liposomal nanocarriers with conventional drug delivery systems. The analysis revealed substantial scientific evidence supporting TCM's effectiveness in treating various conditions, including cancer, inflammation, autoimmune diseases, malaria, reproductive system diseases, diabetes, and tissue regeneration [25-27]. However, significant challenges persist in TCM liposomal delivery, notably the complexity of developing liposomal formulation systems for TCM formulas due to the intricate chemistry of natural products [27]. Nevertheless, the straightforward preparation process and enhanced therapeutic efficacy establish liposomes as promising delivery vehicles for TCM therapies. The findings indicate that liposomes demonstrate significant potential for delivering TCM herbs and may soon become a versatile tool for TCM applications. To achieve this potential, TCM must embrace an evidence-based approach to developing new therapeutics, incorporating modern quality control methods, processing techniques, safer delivery options, and fostering international collaboration. As biomedical technology advances, TCM is evolving into an evidence-based medical system with the potential to significantly impact human healthcare, potentially challenging or surpassing Western medicine and establishing natural medicine as a promising research field for emerging researchers.

2. History, evolution, and therapeutic potential of TCM

TCM represents an ancient medical system developed over millennia. TCM research continues to draw inspiration from its extensive history, exemplified by the discovery of artemisinin for malaria treatment, derived from instructions in " *Ge Hong's Zhouhou Beiji Fang*" [28]. To establish a robust evidence base for TCM, it is essential to examine its historical context and contributions to modern medicine through case records. During the Zhou Dynasty, TCM achieved significant advancements in medical practice [29]. However, the Han Dynasty marked a pivotal turning point, with Cang Gong becoming the first physician to systematically document clinical cases and patient outcomes [30]. The Song Dynasty witnessed substantial progress in TCM, facilitated by advancements in printing technology and government support, leading to the establishment of specialized and reinforced medical practices. This period also marked the emergence of distinct TCM academic schools, each characterized by unique intellectual ideas, medical styles, and treatment techniques [31].

The Modern Era of TCM spans from 1912 to 1949. During this period, TCM practitioners incorporated Western medical knowledge into traditional TCM concepts and practices. Working alongside Western missionaries involved in the reform, they established TCM medical journals [32]. The early 20th century represented a pivotal transition for TCM in China, marked by modernization and standardization influenced by Western medicine's introduction. The government established regulatory measures for TCM, implementing a licensing and certification system for practitioners. TCM was strategically promoted to deliver accessible healthcare to the population, leading to the establishment of TCM hospitals and clinics throughout the nation. Currently, TCM maintains a crucial role in the Chinese healthcare system, with numerous herbs undergoing modernization and standardization to treat various diseases both domestically and internationally.

In the early 20th century, TCM experienced significant modernization and standardization while incorporating Western medicine elements. The Chinese government initiated TCM regulation and established a practitioner licensing and certification system. Authorities promoted TCM to provide widespread healthcare access, resulting in the establishment of TCM hospitals and clinics. Consequently, TCM has become fundamental to the Chinese healthcare system and maintains widespread usage. Many herbs have undergone modernization and standardization to treat various diseases within and beyond China. In recent years, TCM has gained significant recognition outside China, particularly in Western nations. There has been increasing interest in TCM's therapeutic potential as an alternative or complementary treatment for various conditions. While the scientific basis and efficacy of TCM remain debated, its significant impact on global healthcare merits acknowledgment and respect. TCM's recent advancement is evidenced by the exponential growth in research publications, the expanding TCM industry, and the development of new TCM-inspired drugs receiving FDA approval. Despite these achievements, TCM faces considerable challenges in its development, including the need for modern scientific evidence regarding safety, efficacy, quality, and mechanisms of action. To address these challenges, future TCM research must adopt scientific and evidence-based methodologies encompasses the following strategic priorities:

• Advancing the discovery and development of novel therapeutics that align with TCM principles.

• Implementing robust, standardized quality control systems for TCM products in accordance with international pharmaceutical and regulatory standards.

• Optimizing traditional processing techniques and developing advanced, biocompatible drug delivery platforms to enhance therapeutic efficacy and ensure patient safety.

• Promoting interdisciplinary integration and fostering international collaborations to expand the global footprint of TCM and facilitate comprehensive, cross-cultural evaluations of its clinical benefits.

Furthermore, prioritizing high-quality clinical trials is critical for securing regulatory approvals and enabling the global commercialization of TCM.

3. Differences between TCM and Western Medicine

TCM and Western Medicine represent distinct approaches to health and well-being, each possessing unique advantages and limitations. The selection between these approaches depends on multiple factors, including personal preferences, cultural background, and the specific nature of the health condition. Understanding these differences enables patients to make informed healthcare decisions and collaborate effectively with physicians to determine optimal treatment options. Both TCM and Western medicine provide substantial health benefits to patients globally [33].

TCM emphasizes harmony between the mind, body, and soul. Practitioners use acupuncture, dietary, and herbal remedies. In contrast, Western Medicine focuses on physical health through medication, surgery, and medical technology [34]. Another contrast lies in their diagnostic and treatment approaches [35]. TCM practitioners focus on symptoms and adopt a comprehensive understanding of a patient's health problems. Various factors, including emotional state, lifestyle, and physical symptoms, determine the root cause of an ailment. Acupuncture, herbal remedies, and dietary therapy are commonly used to treat symptoms because practitioners believe that these treatments work together to restore balance and promote healing [34, 36, 37]. In Western medicine, diagnosis is based on laboratory tests and imaging scans, while treatment relies on pharmaceuticals or medical procedures.

TCM practitioners emphasize the importance of patient participation in decision-making and active engagement in the recovery process. In contrast, Western medicine places greater emphasis on the physician's expertise and the administered treatment.

4. Liposomes as a drug delivery system

Liposomes are nanoscale vesicular systems extensively utilized in drug delivery, consisting of one or more concentric phospholipid bilayers surrounding an aqueous core [38, 39]. The bilayer structure enables liposomes to encapsulate both hydrophobic and hydrophilic compounds: hydrophobic molecules integrate within the lipid bilayer, while hydrophilic substances are contained in the aqueous core. The phosphate groups may be linked to other organic molecules, as shown in Fig. 2A [40]. The membrane bilayer consists of phospholipidseach, each containing a hydrophilic head and a hydrophobic tail. These amphiphilic lipids self-assemble in aqueous environments to form a bilayer structure (Fig. 2B). The resulting vesicles can encapsulate and transport hydrophobic herbal compounds within the bilayer. When arranged as liposomes, the lipids create an enclosed structure surrounded by the bilayer, termed an inner cavity or aqueous core, which can

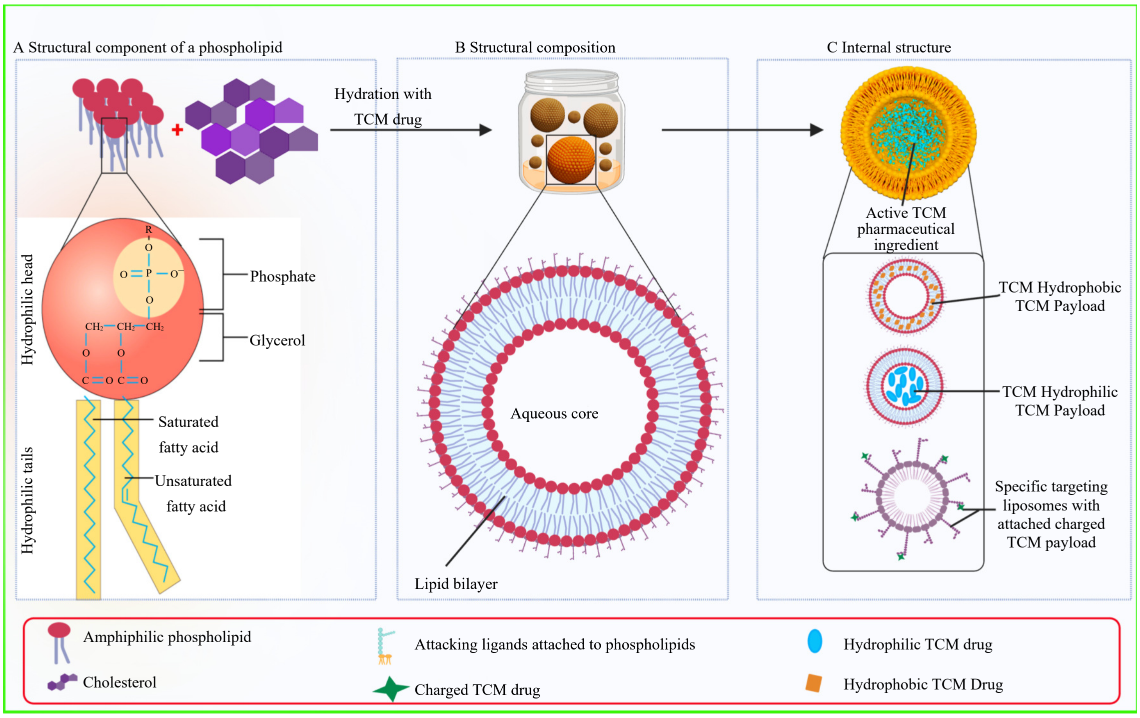

Fig. 2 Schematic illustration of the complex composition, general structure, and loading mechanisms of hydrophobic and hydrophilic TCM drugs within the lipid or aqueous components of liposomes.

encapsulate and transport hydrophilic herbal compounds, as shown in Fig. 2C [41, 42]. The phospholipid bilayer functions as a protective barrier for the encapsulated natural product, allowing the encapsulated active pharmaceutical ingredients (APIs) to avoid rapid clearance and degradation by physiological mechanisms.

Liposomes are classified according to multiple characteristics, including size, structure, composition, and applications. Size-based classifications include small unilamellar vesicles (SUVs), large unilamellar vesicles (LUVs), multilamellar vesicles (MLVs), giant unilamellar vesicles (GUVs), and multivesicular vesicles (MVVs), as depicted in Fig. 3. Additionally, liposomes are categorized by function into conventional, stealth, cationic, anionic, PEGylated, theranostic, and ligand-targeted varieties (Fig. 3). Compositional classifications include phospholipid, lipid-polymer hybrid, and lipid-protein hybrid liposomes.

Liposomes are additionally categorized into drug delivery, gene delivery, and diagnostic applications based on their intended purpose. Properties such as lipid composition, size, charge, and stability are fundamental for their effective application in drug delivery. These characteristics can be modified to address specific pharmaceutical requirements [38]. Liposomes approximately 200 nm in size demonstrate enhanced cellular uptake *in vitro*. This enhanced uptake results from smaller liposomes' superior ability to penetrate and enter cells. Additionally, biological cells typically possess negatively charged surfaces; therefore, positively charged (cationic) liposomes exhibit greater affinity for cellular membranes, enabling targeted drug delivery. Stability across varying pH conditions represents another crucial factor in liposomal drug delivery. The human body contains various anatomical compartments with distinct physiological pH environments. Maintaining liposome stability across this pH spectrum is essential to prevent premature drug release and ensure targeted delivery. This consideration is particularly significant for oral administration, given the acidic nature of gastric and gastrointestinal (GI) environments.

Studies have examined liposomal delivery systems for TCM herbs or herbs combined with western drugs targeting various conditions. Sun et al*.* developed bone-targeted ICA-loaded liposomes for osteoporosis treatment [43]. Gao et al*.* utilized surface-assisted rapid-release liposomes to enhance Bufalin's antitumor efficacy, with the delivery system significantly reducing the herb's cardiotoxicity [17]. Wang et al*.* investigated co-loaded ICA and tanshinone for Alzheimer's disease treatment [44]. These TCM liposomal formulations demonstrate distinctive properties that make them promising carriers for herbal medicines by potentially increasing drug solubility, improving bioavailability, enhancing cellular uptake through size reduction or surface modification, and improving stability in both *in vitro* and *in vivo* studies. Beyond targeted delivery, liposome systems can maintain adequate payload levels for extended periods, enhancing therapeutic efficacy. Regulatory authorities, including the FDA and European Medicines Agency (EMA), have approved liposomal drug products for clinical applications in treating pain, fungal infections, viral diseases, and cancer. Numerous additional products are undergoing clinical trials [45, 46]. Supplementary Tables 2 and 3 present TCM liposomal products in clinical trials worldwide.

4.1. Optimized liposomes for effective TCM delivery

TCM employs optimized or functionalized liposomes as carriers for drugs, nutritional supplements, and active herbal compounds. These liposomal formulations facilitate the treatment of various diseases, including cancer and inflammation, by improving drug delivery and offering protection against degradation. Additionally, liposomes can be modified to target specific diseased tissues or cells. Liposomal preparations of herbs, such as ginseng, are frequently employed to address fatigue, immune system deficiencies, and aging-related conditions. Multiple TCM-loaded liposomal products have demonstrated efficacy in clinical trials (Supplementary Table 3).

Liposomes possess unique physicochemical properties that distinguish them from other vesicular drug delivery systems. Composed of biocompatible lipid bilayers, they are especially well-suited for encapsulating and delivering bioactive constituents of Traditional Chinese Medicine (TCM). Their inherent non-toxic and biodegradable nature supports the safe and effective administration of various TCM formulations. To improve structural integrity, researchers have explored the incorporation of

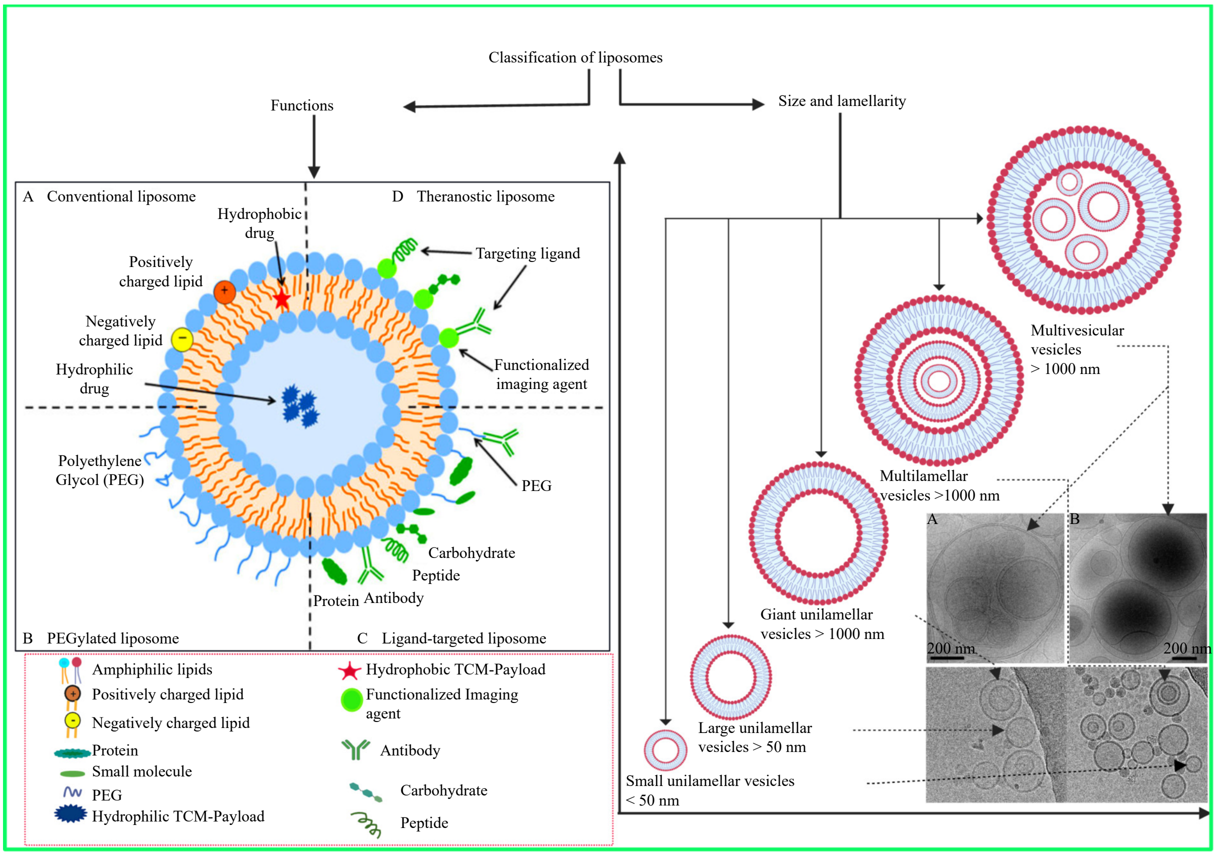

Fig. 3 Classifications of liposomes based on function, size, and lamellarity.

stabilizing agents that enhance liposomal stability. Moreover, liposomal designs have been optimized to promote efficient cellular uptake. *In vivo* studies have demonstrated that these delivery systems can enhance biodistribution of therapeutic compounds to target tissues while minimizing exposure to healthy cells, thereby potentially reducing systemic toxicity [45, 47].

Liposomes are characterized by distinct features such as lamellarity, surface charge, and vesicle size, which serve as key criteria for their classification. Based on these parameters, liposomes are typically categorized into unilamellar vesicles (ULVs), MLVs, GUVs, and MVVs, as shown in Fig. 3. This categorization makes them especially appropriate for encapsulating TCM compounds [48]. The composition and characteristics of different liposomes determine their applicability for specific uses, depending on the researcher's requirements and the properties of the TCM(s) intended for encapsulation and targeted delivery. Moreover, liposomes enhance both the delivery and efficacy of active ingredients while enabling the development of innovative treatments under various conditions.

4.2. Formulation of TCM-encapsulated liposomes

4.2.1. Conventional methods

Multiple methods exist for formulating TCM-loaded liposomes for therapeutic applications. The thin film hydration method represents one of the most straightforward and widely adopted techniques. Fig. 4 demonstrates the five basic steps involved in this process. Jiao Wang et al. utilized thin film hydration to co-load ICA and tanshinone IIA into Aniopep-2-modified liposomes [49]. Similarly, Wang et al. applied this method to load curcumin for glioma treatment [50]. Song et al. also formulated nano-liposomes co-loaded with curcumin and tetrandrine using thin film hydration [51]. Additional methods, including reverse-phase evaporation [52] and ethanol injection [53,54], have been employed to formulate liposomes for various therapeutic purposes.

4.2.2. Microfluidics methods

Microfluidic technology presents an innovative and promising approach for formulating TCM-loaded liposomes. This methodology employs a microfluidic chip with narrow channels, as shown in Fig. 5. The applications of microfluidics extend beyond formulation, with our previous research demonstrating its utility in disease diagnosis, including cancer detection [55]. The integration of microfluidics technology shows promise in multiple areas, including diagnostic applications, formulation, and delivery of TCM-loaded liposomes for targeted therapy. Additionally, microfluidic systems function as *in vitro* models for studying drug pharmacological effects. The microfluidic method enables precise control over liposomal size, shape, and composition, resulting in enhanced stability and therapeutic efficacy. A key advantage of microfluidics is its capacity to incorporate multiple TCM components into a single liposome, producing synergistic therapeutic effects by addressing various disease aspects. Through controlled component ratios within liposomes, microfluidics enhances therapeutic efficacy.

Microfluidic techniques utilize narrow channels and controlled fluid flow, presenting a more sophisticated process than conventional methods. The process begins with the fabrication of a specialized microfluidic chip with precise dimensions, including channel width, length, and depth. A buffer solution is then prepared by dissolving the lipid and herbal products in a solvent to create a homogeneous mixture. The microfluidic device facilitates the introduction of the mixture, and TCM-loaded liposomes form spontaneously through repeated mixing and shearing as the mixture traverses the channels under controlled flow rate, voltage, and pressure conditions. The liposomes are subsequently collected, purified, and characterized using nanoana-

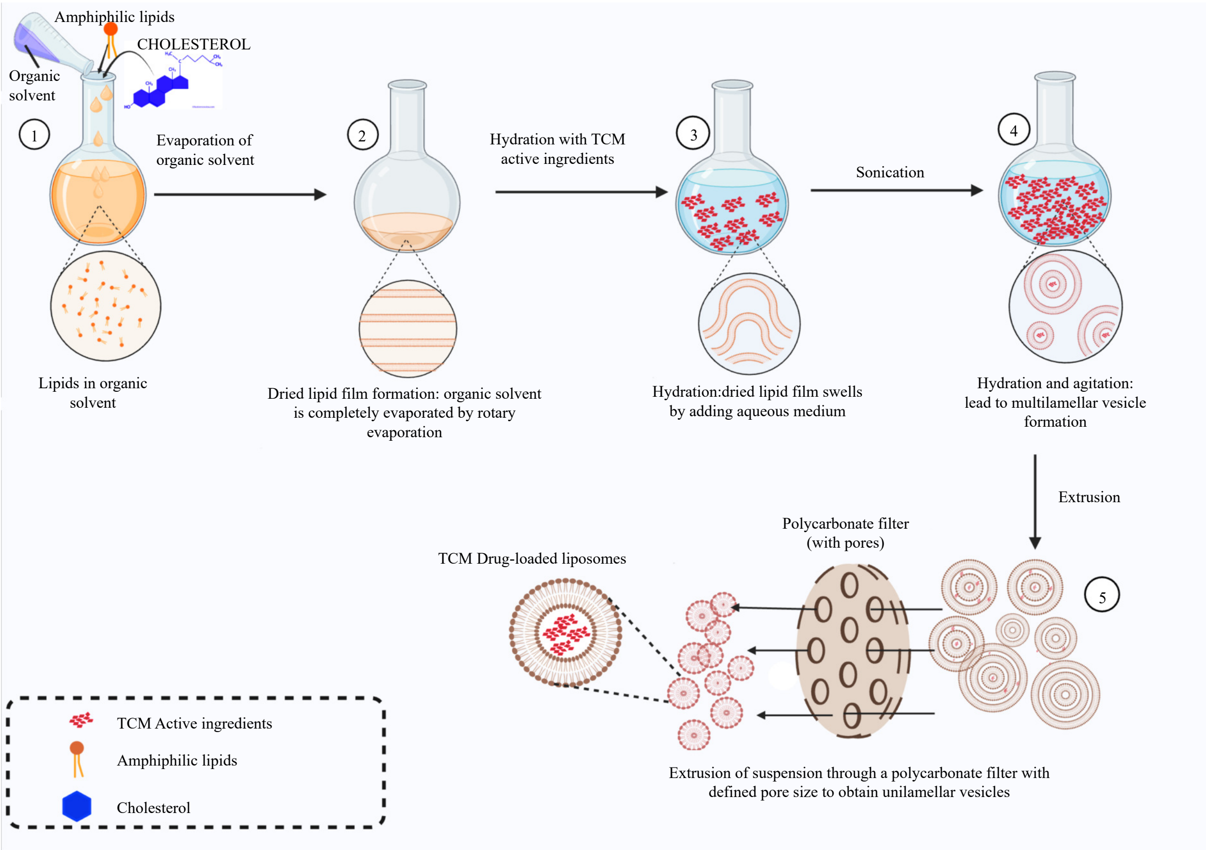

Fig. 4 A schematic illustration of the procedures of how TCM-loaded liposomes are formulated using thin film hydration: 1) Mix lipids and organic solvent. 2) A thin lipid film is formed after rotary evaporation. 3) The film is hydrated with the dissolved herbal product solution. 4) During the hydration and agitation step, the dissolved herb is loaded into the liposomes, protecting against degradation and enhancing its bioavailability. 5) Extrusion is carried out to obtain unilamellar herb-loaded liposomes with even size.

lysis devices such as dynamic light scattering (DLS) to assess their shape, size, polydispersity index (PDI), zeta potential, and drug loading capacity (Fig. 5). Differential scanning calorimetry (DSC) can enhance the encapsulation efficiency of liposomes post-formulation [56].

Microfluidics presents an innovative approach to TCM liposome preparation, with multiple microfluidic techniques applied in liposome formulation [57]. This review examines selected methods from this array. Microfluidic techniques address industrial-scale preparation repeatability through precise flow process control. The characteristics of the resulting liposomes are significantly influenced by factors including microfluidic channel pattern, reaction temperature, pH, osmotic pressure, and other environmental conditions.

4.2.2.1 Preparation of liposomes by flow-focused microfluidic technology

Flow focusing involves the flow of a multilayer fluid, where the outer fluid directs the middle layer to focus, producing a microjet that breaks into monodisperse droplets. In liposome preparation, an aqueous solution moves relative to the microfluidic channel wall, with the phospholipid solution in isopropanol or ethanol positioned in the middle. The aqueous solution flows on both sides relative to the movement; as microjets develop, the organic solvent concentration decreases gradually, and phospholipids hydrate to form liposomes. The organic-aqueous flow rate ratio determines liposome size. This method typically produces monodisperse liposomes with an average size of 50−150 nm.

4.2.2.2 Preparation of liposomes by droplet microfluidic method

The W/O/W complex emulsion droplet method produces liposomes. Initially, microchannels create an O/W colostrum. A three-phase microfluidic chip then enables the single-step W/O/W emulsification preparation. Microfluidic-prepared droplets facilitate rapid loading of hydrophilic drugs or biomacromolecules, achieving high encapsulation rates. However, this technique presents limitations, including potential biotoxicity from residual organic solvents and inherent liposome instability.

4.2.2.3 Preparation of liposomes by pulse jet

This method's preparation principle mirrors the process of blowing soap bubbles. The process begins with phospholipid film construction, followed by aqueous solution spraying into the film through a micro-nozzle, forming vesicles. This approach provides high encapsulation efficiency and enables biological macromolecule encapsulation. However, limitations include complex preparation conditions and significant solvent residue.

4.2.2.4 Coaxial electrospray microfluidics method

Coaxial electrospray microfluidics represents an innovative, rapid, real-time, and single-step method for preparing drug-loaded liposomes with nearly monodispersed PDI, controllable diameters, and adjustable surface properties. The process involves microfluidic device fabrication, followed by generating a coaxial flow of two immiscible fluids−one containing the drug and another containing lipids propelled by a syringe pump at controlled flow rates. An electric field from a high-voltage source subjects the fluids to form a Taylor cone, producing tiny charged droplets collected downstream. These droplets subsequently fuse to form liposomes loaded with active TCM herb, as shown in Fig. 5.

This liposomal formulation method offers distinct advantages over traditional techniques, including simplicity, enhanced control over size, lamellarity, and composition, compatibility with various lipid and solvent types, and scalability. The method has successfully created liposomes encapsulating diverse drugs, including curcumin, paclitaxel (PTX), and DOX, for targeted therapeutic applications [58, 59]. However, challenges include high

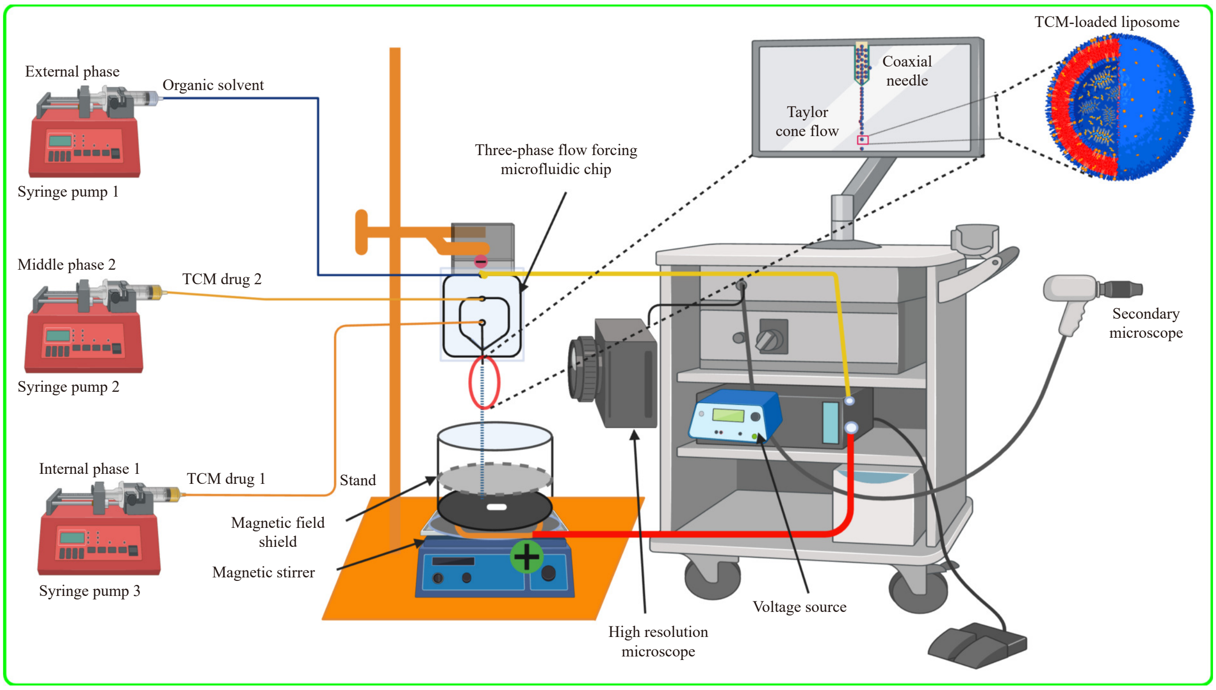

Fig. 5 A schematic illustration of a coaxial-electrostatic spraying platform based on microfluidic chips to prepare targeted liposomes. With a microfluidic chip, the platform generates a coaxial flow of lipids and active pharmaceutical ingredients. Separate inlets introduce the three solutions into the chip, then mix at precise flows and pressures. Electrostatically spraying the resulting coaxial flow through a needle creates uniform liposomes. This platform produces liposomes that contain an active pharmaceutical ingredient and a targeting ligand that binds to receptors on the surface of specific cells and enhances drug specificity and efficacy.

voltage requirements, careful flow rate optimization, precise microneedle geometry design, and additional post-processing steps for removing residual solvents and unencapsulated materials.

4.3. Benefits of microfluidic approach for TCM-loaded liposomes

The microfluidic method presents several advantages compared to conventional methods in formulating TCM-loaded liposomes. This approach demonstrates enhanced cost-effectiveness through minimal sample requirements during formulation. Furthermore, microfluidics-formulated liposomes demonstrate favorable characteristics, including low PDI, controlled size distribution, enhanced stability, superior drug loading, and high encapsulation efficiency [60, 61]. The liposome size can be precisely controlled by modifying the flow ratio and total flow rate of lipid and aqueous solutions in microfluidics [60, 62]. The technology also enables industrial-scale production of liposomes through precise control of lipid hydration and reduction of residual organic solvents [57]. Microfluidics allows real-time monitoring of liposome formation [61]. This approach facilitates the preparation of liposomes in a controlled and reproducible manner with high throughput. Microfluidics enables rapid production of liposomes with specific lipid concentrations and tailored sizes suitable for clinical translation [63]. While nanoparticles prepared through novel methods such as coaxial electrostatic spraying microfluidics have been extensively researched, this approach has limitations. The integration of microfluidics with coaxial electrostatic spray technology enables single-step preparation of complex nanoparticles through fluid manipulation in microchannels. Additionally, liposome yield can be enhanced using multiplex or array chips, advancing toward industrial-scale production.

4.4. Drawbacks of the microfluidic method in formulating TCM-loaded liposomes

While microfluidics represents an innovative approach to liposome production, it faces several challenges in both laboratory and industrial applications. The effectiveness of microfluidic techniques depends on multiple factors, including the properties of the encapsulated active compound, lipid formulation and concentration, residual solvent quantity, and production methodology, including microchannel design [57]. Significant initial investment is required for microfluidic device fabrication and equipment setup. Technical challenges include microchannel blockage, fluid leakage, sample contamination, and lipid degradation [57, 64].

The field encompasses numerous microfluidic methods for liposome production, including microfluidic hydrodynamic focusing (MHF), vertical flow focusing (VFF), mixer-assisted microfluidics, droplet-based microfluidics, pulse microfluidic jetting, transient membrane ejection method, electroformation, hydration, extrusion, pulsed jetting, double emulsion templating, ice droplet hydration, transient membrane ejection, droplet emulsion transfer, and MFH. This methodological diversity complicates the selection of optimal techniques for desired outcomes. Currently, no standardized approach exists for these techniques. Most methods represent miniaturized versions of conventional approaches and cannot be classified as true microfluidic methods, except for MHF. Despite MHF's microfluidic characteristics and potential for producing smaller lipid-based nanoscale liposomes beneficial for clinical studies, it has received limited recent attention.

Similar to other formulation methods, microfluidics involves multi-batch processes, limiting its broad application. Developing a cost-effective, robust, and scalable strategy for clinical translation may require significant time, affecting product value proposition. While most microfluidic methods can be optimized for large-scale production, scale-up challenges include stability issues, extensive organic solvent usage, limited loading capacity, poor reproducibility, and low bioactive molecule encapsulation efficiency. Research suggests microfluidics significantly affects lipid composition, bilayer fluidity, and elasticity. Additional research is necessary to address stability, scale-up production, and sterilization challenges in formulated liposomes.

4.5. Mechanisms of TCM-loaded liposomes in drug delivery

Liposomes demonstrate the ability to deliver APIs to diseased cells or tissues through multiple mechanisms. One mechanism involves the selective binding of liposomes to specific receptors expressed uniquely on diseased cell surfaces, enabling controlled payload release. Additionally, liposomes can stimulate the immune system, particularly monocytes or macrophages, which then recognize and target diseased cells.

Two primary targeting strategies enhance liposomes' versatility for TCM delivery. As shown in Figs. 6C and 6D, liposomes can target diseased cells through active targeting and passive targeting approaches. The targeting mechanism of liposomes remains a significant research focus. Research indicates that incorporating receptor-specific ligands on the liposome surface enables active tissue targeting through binding to cancer vasculature, while passive tissue targeting occurs *via* liposome accumulation in cancer vasculature [65]. Passive targeting strategies predominate in oncology research and treatment due to the unique pathophysiological characteristics of cancers and their microenvironments [66]. Active targeting, conversely, involves attaching functional targeting ligands to the liposome surface to enhance delivery specificity and efficiency. Various targeting ligands, including antibodies, nucleic acids, peptides, proteins, and small molecules such as vitamins, serve in active targeting to improve drug release and minimize toxicity [66, 67]. The attacking liposome's composition, size, charge, and surface modifications significantly influence the mechanisms through which liposomes target and combat diseases.

Liposomes deliver their payload to specific cells effectively through mechanisms including membrane fusion and endocytosis. As depicted in Fig. 6A, endocytosis involves the diseased cell's plasma membrane engulfing liposomal particles carrying cargo, forming endocytic vesicles within the cell. This process occurs through various mechanisms, including clathrin-dependent or caveolae-dependent endocytosis, micropinocytosis, or clathrin and caveolae-independent endocytosis. Successful liposomal endocytosis depends on liposome properties such as size, shape, charge, composition, surface modification, and the target cells' state and type.

Endocytosis enables TCM payload delivery to diseased cells, including cancerous or infected cells. However, endocytosis presents challenges, including potential liposome and payload degradation by lysosomal enzymes, liposome recycling or exocytosis to extracellular space, and risks of low specificity and efficiency in healthy cells. Developing enhanced strategies for liposomal endocytosis and facilitating their escape from endocytic vesicles remains crucial for improving therapeutic efficacy.

Liposomes containing APIs achieve site-specific payload release through stimuli-responsive release mechanisms. This method utilizes external or internal stimuli to trigger controlled and targeted release of the encapsulated APIs. External stimuli include light, heat, magnetic or electric fields, and ultrasound, while internal stimuli comprise pH, enzymes, and redox potentials. The stimuli-responsive release mechanism requires liposomes designed with specific properties that respond to these stimuli by modifying their physical structure, permeability, stability, or interactions with target cells, as shown in Fig. 6B. For example, pH-responsive liposomes incorporate poly (carboxylic acid) derivatives or amphiphiles that undergo conformational changes or hydrolysis in acidic environments, leading to membrane destabilization and drug release.

Thermosensitive liposomes, comprising phospholipids with high phase-transition temperatures or modified with thermosensitive polymers, exemplify advanced drug delivery systems. These liposomes demonstrate increased membrane fluidity and drug release at elevated temperatures due to changes in their hydration state or solubility. These characteristics provide multiple benefits, including controlled-release kinetics, enhanced specificity, improved bioavailability, and reduced toxicity. Nevertheless, challenges persist, including optimization of stimulus conditions and parameters, liposome stability and biocompatibility, complexity in synthesis and characterization processes, and potential interference from biological barriers or other stimuli [68].

4.6. TCM-loaded liposomes in regenerative medicine

Many organs in the body demonstrate dynamic, regenerative capabilities for minor injuries, with bone serving as a prime example. However, substantial defects with limited regenerative capacity can present significant clinical challenges for patients. While bone tissue engineering utilizing biologically active factors like bone morphogenetic protein-2 exists, it often proves costly and unstable. TCM has emerged as a viable alternative for promoting bone regeneration. Given the limitations of certain TCM

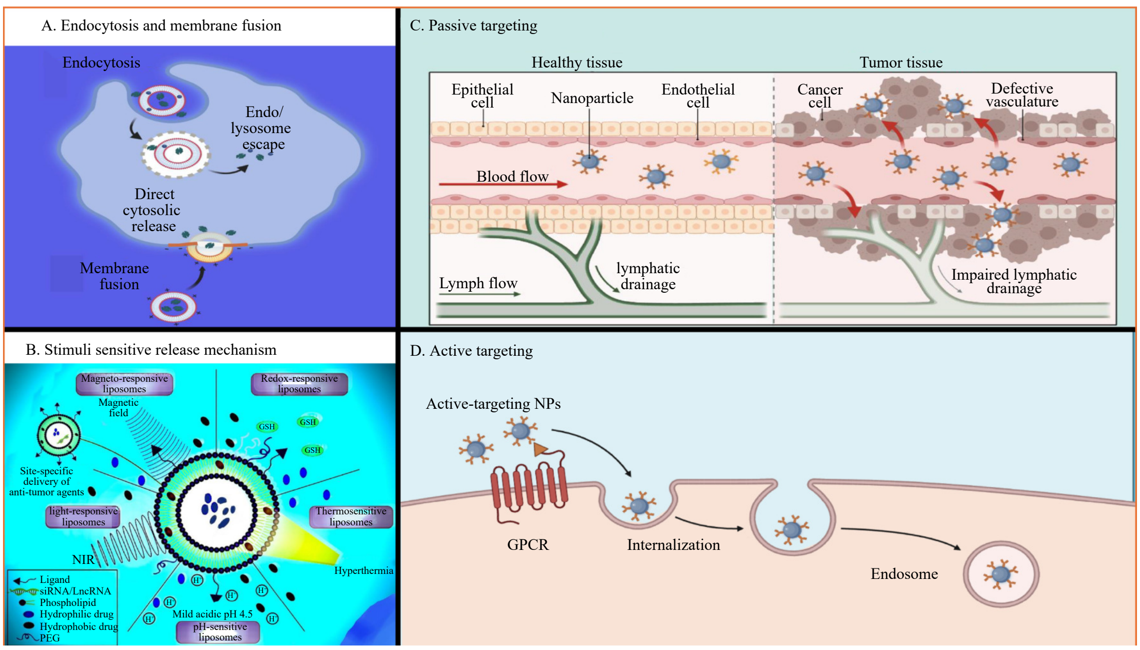

Fig. 6 The diagram illustrates the different mechanisms by which liposomes attack diseased cells and release the TCM active ingredient at the targeted site of the disease. A) Endocytosis and membrane fusion: B) Stimuli-sensitive: C) Passive targeting: D) Active targeting.

active compounds in therapeutic effects on organ or tissue regeneration, researchers have combined these compounds with materials such as liposomes to enhance both therapeutic efficacy and tissue regeneration [69]. The integration of TCM for regenerating musculoskeletal tissue has gained significance, offering promising treatment options for orthopedic conditions when combined with musculoskeletal tissue engineering (MTE) [70–73]. Researchers have identified, isolated, and purified various bioactive TCM compounds, including flavonoids, alkaloids, saponins, and terpenes [74]. These formulations effectively treat multifactorial orthopedic diseases by modulating multiple signaling pathways and targeting various cellular mechanisms [75]. The combination of materials with TCM compounds or their liposomal encapsulation has shown promising results in bone defect regeneration while improving release behavior, biocompatibility, mechanical properties, osteoconductivity, and osteoinductivity [69].

A study investigating the biomineral-binding icariin-loaded liposome (BBL) as a drug delivery system for enhanced osteoporosis bone-targeting treatment revealed significant regenerative potential. The BBL system enhanced liposome binding to bone tissue containing hydroxyapatite particles, resulting in markedly increased serum levels of alkaline phosphatase, indicating bone tissue regeneration, while reducing tartrate-resistant acid phosphatase 5b, a marker of bone tissue degeneration. Additionally, BBL enhanced bone remodeling and turnover in osteoporotic rats, improved midshaft mechanical strength, and preserved trabecular bone microarchitecture. These results indicate that the BBL TCM delivery system presents a promising regenerative medical approach for osteoporosis treatment [76]. Clinical trials have also shown that TCM intervention improved survival rates in patients with chronic hepatitis B-associated liver failure by enhancing kidney function to promote liver regeneration and repair through stem cell modulation and microenvironment optimization [43, 77]. Furthermore, Diwu Yanggan (DWYG), approved by the Hubei Food and Drug Administration, significantly increased survival rates and liver regeneration in 2-acetaminofluorene/partial hepatectomy (AAF/PH) rats. DWYG enhanced liver regeneration by modulating the hepatic microenvironment, gradually restoring levels of IL-1, GRO/KC, and VEGF [78]. Various TCM herbal products have demonstrated effectiveness against arthritis, while others have exhibited rapid and potent wound-healing properties [79, 80]

5. Liposomes as a strategy in co-delivering TCM and western medicine

Integrative medicine combines TCM and western medicine to deliver comprehensive patient care. This approach incorporates conventional pharmacotherapy interventions alongside complementary herbal alternatives, creating personalized therapeutic regimens that address both physical and psychological symptoms. The integration of TCM and western medicine within this framework optimizes treatment outcomes through synergistic effects. Evidence-based medicine and technological innovations remain essential for TCM's global development [81, 82]. However, considering modernized TCM as distinct from traditional TCM may impede its development and widen the gap between Western medicine and TCM. The modernization and integration of TCM into contemporary healthcare practices remains crucial. Artemisinin exemplifies this integration, being recognized both as a TCM and Western medicine component, utilized globally for patient benefit regardless of classification.

Combination therapy, regardless of classification, serves patients worldwide with critical needs.

Research has demonstrated combination therapy's potential to enhance understanding of syndrome molecular mechanisms [82] and improve treatment outcomes for severe acute respiratory syndrome (SARS) [83], COVID-19 [84], heart failure (HF) [85], asthma [86], and coronary heart disease, particularly when complicated by anxiety and depression [87].

Liposomes serve as a crucial delivery mechanism for integrating TCM and Western medicine; incorporating active compounds from both medical approaches into liposomes enhances treatment efficacy and improves patient outcomes. The combination of TCM botanical remedies with conventional Western drugs can alleviate symptoms and address underlying disease causes through liposome-mediated delivery. This combination therapy proves particularly valuable for multi-faceted approaches, such as cancer treatment, where chemotherapy agents and herbal remedies can work synergistically against malignancy. Additionally, liposomes enable the delivery of TCM remedies to previously inaccessible areas, such as the brain or joints, thus overcoming certain limitations associated with traditional TCM practices [88].

TCM and Western medicine are increasingly utilized in combination within research settings. The majority of these studies have advanced to clinical trials, with the aim of achieving complementary or synergistic therapeutic effects with the objective of achieving complementary or synergistic therapeutic effects [20]. However, concurrent administration of TCM and other medications may lead to adverse drug interactions. In specific cases, the integration of TCM and Western medicine demonstrates the potential for superior outcomes compared to either approach used independently. Despite these advantages, ensuring quality, standardizing TCM practices, and preserving traditional knowledge remain significant challenges. The study of herb-drug interactions continues to be a critical and dynamic field within pharmaceutical science [89].

TCM has been utilized by Asian practitioners for centuries to prevent and treat illnesses, though it has faced challenges in gaining widespread acceptance in Western countries. However, the World Health Organization (WHO) officially recognized TCM as a legitimate medical treatment in 2019, facilitating its international recognition and integration with Western medicine [90]. Furthermore, liposomal technology extends the shelf life of TCM remedies and nutritional compounds, enhancing their accessibility to target sites. Promoting the broader application of TCM in modern medicine and supporting the development of novel TCM-based interventions can facilitate its expanded utilization. The integration of TCM and Western medicine through liposomes provides practitioners with an effective tool for improving patient outcomes and addressing diverse health issues. Through leveraging the strengths of both medical systems, practitioners can deliver comprehensive and effective healthcare to patients.

5.1. Risks of combining TCM and Western medicine

The integration of TCM and Western medicine in a combined therapeutic approach presents potential pharmacological challenges, particularly regarding drug-herb or drug-drug interactions (Supplementary Table 1). The primary risk factors include the following:

5.1.1. Herb-Drug Interactions

Specific herbs utilized in TCM may interact with conventional pharmaceuticals, resulting in alterations in drug efficacy or adverse reactions [91]. For instance, ginseng has been demonstrated to influence blood glucose levels, requiring careful monitoring of patients who simultaneously take both ginseng and diabetes medication [92].

5.1.2. Dosage Variance

The differences in preparation and administration methods of TCM remedies and conventional drugs can lead to dosage inconsistencies, making it difficult to accurately predict therapeutic outcomes and increasing the risk of toxicity or overdose.

5.1.3. Lack of Standardization

TCM remedies are not regulated by the same stringent standards as conventional pharmaceuticals, potentially resulting in inconsistencies in quality and potency. These variations can complicate dosage determination and increase the risk of adverse reactions.

5.1.4. Inadequate Patient Monitoring

Patients receiving combined TCM and Western medicine therapy may experience less comprehensive monitoring compared to those under conventional treatment. This monitoring disparity increases the risk of adverse reactions and complicates treatment efficacy assessment. Healthcare providers must carefully evaluate these potential risks when implementing combined TCM and Western medicine therapy, ensuring thorough patient monitoring to maintain treatment safety and effectiveness. Patients should receive comprehensive information about the risks and benefits associated with this therapeutic approach and be encouraged to communicate openly with their healthcare providers. To minimize the risks of drug interactions during combination therapy with TCM and Western medicine, healthcare professionals can implement various preventive measures.

5.1.5. Patient Evaluation

Before initiating combination therapy, healthcare providers should conduct a thorough patient assessment to identify potential drug interactions or contraindications. This evaluation should encompass a comprehensive review of the patient's medical history, current medications, and ongoing treatments.

5.1.6. International Collaboration

To ensure optimal patient care and appropriate coordination of therapies, practitioners of TCM and Western medicine should collaborate to develop and prescribe comprehensive treatment plans.

5.1.7. TCM Remedy Standardization

Standardizing TCM remedies is crucial to ensure consistent and effective patient treatment. This goal can be achieved through developing comprehensive guidelines for the preparation, dosage, and labeling of TCM remedies, along with implementing rigorous quality control measures.

5.1.8. Monitoring and Record Keeping

Patients undergoing combination therapy require close monitoring for efficacy and potential adverse reactions. Healthcare providers should maintain detailed records of patient treatments to track progress and adjust therapeutic regimens as necessary.

5.1.9. Patient Education

To optimize patient care and minimize adverse drug interaction risks when combining TCM and western medicine, healthcare providers must emphasize patient education and transparent communication. Patients require comprehensive information regarding the potential benefits and risks of combination therapy, while practitioners should facilitate open dialogue regarding patient concerns and inquiries. This approach strengthens the patient-provider relationship, enhancing treatment engagement and compliance. Through these implemented strategies, healthcare professionals can effectively reduce drug interaction risks and deliver superior care to patients receiving combination therapy.

5.2. Overcoming TCM drug delivery challenges with liposomes

Since the US FDA approved the first nano-drug (PEGylated liposomal DOX; Doxil®) in 1995, liposomal drug delivery systems for natural products have gained increasing recognition in clinical settings [93, 94]. Liposomal formulations have received approval for treating various diseases in 19 clinical trials, with eight designated for cancer therapy [95]. The structural characteristics of liposomes facilitate the encapsulation, protection, and transport of TCM molecules with diverse physicochemical properties, establishing them as versatile colloidal carriers for delivering TCM-derived natural products. A key advantage of liposomal TCM drug delivery lies in the capacity to encapsulate two distinct ingredients from different sources and deliver them to a specific target site for simultaneous therapeutic action. This approach has been validated by multiple researchers, exemplified by the co-encapsulation of Curcumin and DOX within a single liposome for anticancer therapy [96].

Liposomes demonstrate remarkable versatility in TCM drug delivery, supporting oral, transdermal, and parenteral administration routes (Fig. 1). Targeted-release liposomes, a category of active liposomes, can deliver drugs to specific sites through affinity responses similar to antibody-antigen interactions. This targeted approach makes them particularly suitable for delivering bioactive alkaloids, including oxymatrine, berberine, vincristine (VCR), and other TCM active ingredients. The beneficial properties of liposomes offer promising solutions to various TCM-related challenges, as outlined below:

Coating liposomes with artificial coronas derived from human plasma enhances their circulation time in the bloodstream, mitigates the risk of leukocyte capture, and prolongs the half-life of the encapsulated TCM agent.

Recent research has revealed evidence supporting the potential of TCM-loaded liposomes as antitumor agents. These liposomes have demonstrated the ability to target tumors effectively while minimizing side effects. This discovery has catalyzed the development of innovative liposome variations, such as stimuli-sensitive and immuno-liposomes, which exhibit enhanced antitumor activity.

Encapsulating TCM compounds in liposomes can substantially enhance their therapeutic index by optimizing pharmacokinetic properties, altering biodistribution patterns, and reducing the toxicity of the encapsulated TCM agents.

The utilization of liposomes in TCM offers several advantages, including enhanced pharmaceutical solubility, improved stability of active ingredients, and reduced degradation rates for compounds that are typically unstable under normal physiological conditions.

Liposomes are considered to be effective in facilitating the delivery of TCM, which has the potential to stimulate the immune response of macrophages.

Liposomes exhibit versatility in their delivery, accommodating various routes of administration.

The development of liposomes as drug-delivery vesicles enables the combination of TCM and Western medicine while minimizing the potential for herb-drug interactions.

To develop TCM prodrugs with reduced toxicity compared to parent compounds, liposomes can be conjugated with specific drugs for targeted cellular delivery. Liposomes serve dual carrier functions: reducing drug toxicity in healthy cells and enhancing site- specificity in target cells. For therapeutic efficacy, drugs must be engineered to release in less toxic forms at action sites. Liposomal delivery systems enable the encapsulation of both hydrophilic and hydrophobic materials, enhancing therapeutic indices of encapsulated agents while increasing payload concentrations at disease sites. This enhanced drug concentration utilizes unique disease characteristics and affected areas, such as specific binding site expression and pH variations. This liposomal property facilitates API delivery to targeted sites, as expressed features often retain conventional liposomes, improving drug targeting and delivery. Liposomes demonstrate high biocompatibility, straightforward preparation methods, and chemical versatility. Their pharmacokinetic properties can be modulated through modifications to bilayer lipid composition.

6. Challenges of using liposomes in TCM drug delivery

Liposomes have demonstrated significant potential for the delivery of bioactive natural products derived from TCM and other natural sources [98]. The use of liposomes as a delivery system for bioactive TCM products enhances their pharmacokinetic properties, increases therapeutic efficacy, and mitigates adverse effects [16]. However, several challenges persist in the application of liposomes for the delivery of TCM-based drugs.

TCM active compounds comprise complex chemical mixtures, presenting challenges in standardizing their composition, purity, and potency. This complexity impedes the development and testing of TCM-loaded liposomal formulations, complicating the interpretation of their clinical effects. While liposomes can be engineered for specific tissue or cell targeting, which is essential for TCM compounds with narrow therapeutic windows or toxic side effects, targeted delivery necessitates a comprehensive understanding of disease biological characteristics and liposome-tissue interactions. Research on TCM-targeted agents continues, with numerous challenges remaining unresolved. The investigation of targeted delivery systems for TCM represents a significant challenge requiring dedicated attention. Moreover, the complexity of human biochemistry in relation to certain diseases presents treatment resistance issues for both TCM and Western medicine [99].

Certain active ingredients in TCM can exhibit significant toxicity when administered in their unbound form [100–102].

The encapsulation into liposomes is expected to substantially reduce toxicity and side effects. However, beyond TCM-related challenges, liposomes present additional unresolved issues, including leakage and self-induced toxicity or immunogenicity, particularly upon accumulation in the liver or spleen. These factors may limit TCM dosage or generate adverse effects that counteract therapeutic benefits. Liposomes frequently demonstrate instability in biological fluids, experiencing fusion, rapid degradation, and leakage, resulting in premature TCM compound release; this uncontrolled and non-targeted release potentially reduces efficacy and increases toxicity risks to healthy tissues. Physical and chemical instability represents a primary constraint in utilizing liposomes as TCM delivery systems. The life cycle and distribution of liposome-delivered drugs within the body significantly influence their therapeutic effects and safety. Liposome stability directly affects these characteristics. Stability remains the foremost limiting factor in liposome preparation, storage, and administration. Liposomes may experience instability due to physical, chemical, and environmental factors, including oxidation, hydrolysis, drug leakage, aggregate formation, or liposomal fusion [45].

TCM research advancement for cancer and other diseases faces substantial challenges due to the lack of standardized methods for production scale-up and ligand-functionalized liposome formulation characterization. Additionally, preclinical models evaluating liposome efficacy inadequately simulate *in vivo* diseased cells, such as tumors [97]. Significant obstacles persist in liposome production, evaluation, and clinical translation [103].

The complexity and diverse properties of TCM formula-extracted ingredients pose significant challenges in developing new drug delivery systems. A limited understanding of systemic treatment mechanisms with TCM formulas has hindered a clear grasp of their precise biological actions. Traditional liposomes for cancer treatment demonstrate limitations in capturing circulating tumor cells (CTCs) and regulating CTC-supportive metastatic niches. Despite liposome technology's promise, extensive scientific research in TCM therapy applications remains limited. Current conventional liposomes cannot capture sufficient capture CTCs for clinical benefit in cancer treatment, and their capacity to regulate CTC-supportive metastatic niches requires development. Despite multiple attempts, researchers have not achieved success in developing TCM formula nanocarriers. Insufficient research data has hindered the translation of these drug delivery approaches into regulatory approval for clinical application. Consequently, urgent development and utilization of liposomes in TCM applications is necessary.

TCM active compounds frequently demonstrate poor bioavailability due to rapid metabolism, limited solubility, and restricted cell membrane permeability. While liposomes can address these challenges through engineering, their efficacy depends on composition, stability, and size, which vary with specific TCM compound properties. TCM typically involves multiple herbs or compounds acting synergistically or antagonistically, and although liposomes can facilitate co-delivery, this process remains complex. Co-delivery of TCM and other active compounds requires careful optimization of liposomal composition, loading efficiency, and release kinetics. Biological fluid interactions present significant challenges, as liposomes may undergo opsonization, phagocytosis, or complement activation, potentially reducing circulation time, triggering immune responses, and causing adverse effects. Expert knowledge is crucial for understanding these mechanisms and associated therapeutic risks. Therefore, controlling or minimizing these interactions during TCM-loaded liposome formulation is essential for optimizing therapeutic efficacy and patient safety.

TCM-loaded liposome production presents significant challenges regarding costs, time investment, and requirements for advanced manufacturing techniques and specialized expertise. Maintaining consistent liposome size, high encapsulation efficiency, and physicochemical stability across large-scale production poses particular difficulties. The absence of scalable manufacturing processes limits TCM-loaded liposome production for clinical translation and widespread application. Furthermore, the requirement for high-throughput production technologies ensuring uniformity and reproducibility adds complexity to the process.

7. Conclusion and future directions

TCM has a rich historical legacy, and its significant advancements in recent decades have demonstrated its vital contribution to human health. While TCM's theoretical foundations and therapeutic approaches differ from Western medicine, it presents a viable alternative for treating various human conditions. Its expanding medical applications have shown promising therapeutic potential in addressing chronic and complex diseases. Liposomes have emerged as increasingly significant in TCM applications, proving essential in overcoming TCM limitations and facilitating the therapeutic integration of TCM and Western medicine. Liposomes have established themselves as among the most adaptable colloidal carriers in nano-delivery technology, offering unique capabilities in encapsulating, protecting, and transporting chemical and biological molecules with diverse physicochemical properties. Although widespread clinical implementation of liposomes in TCM practices may require additional time, these delivery systems are increasingly utilized to combat diseases and enhance patient safety. Future research priorities in TCM liposome development include examining liposome component compatibility with herbal extracts, developing novel liposome types, exploring alternative carrier materials and methods, investigating *in vivo* performance and toxicity, studying relevant pathways and mechanisms, and establishing new analytical methods and quality control standards to support TCM development and global adoption. TCM must embrace scientific, evidence-based methodologies to address its challenges, particularly in demonstrating safety, efficacy, quality, and mechanisms of action through modern scientific validation.

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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