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•Review•

Approved natural products-derived nanomedicines for disease treatment

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[ABSTRACT] In recent years, there has been an increasing emphasis on exploring innovative drug delivery approaches due to the limitations of conventional therapeutic strategies, such as inadequate drug targeting, insufficient therapeutic efficacy, and significant adverse effects. Nanomedicines have emerged as a promising solution with notable advantages, including extended drug circulation, targeted delivery, and improved bioavailability, potentially enhancing the clinical treatment of various diseases. Natural products/materials-derived nanomedicines, characterized by their natural therapeutic efficacy, superior biocompatibility, and safety profile, play a crucial role in nanomedicine-based treatments. This review provides a comprehensive overview of currently approved natural products-derived nanomedicines, emphasizing the essential properties of natural products-derived drug carriers, their applications in clinical diagnosis and treatment, and the current therapeutic potential and challenges. The aim is to offer guidance for the application and further development of these innovative therapeutic approaches.

[KEY WORDS] Nanomedicine; Drug carriers; Natural properties; Diagnosis; Disease treatment; Safety
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Introduction

Several challenges impede the clinical application of traditional pharmaceuticals, including poor water solubility, instability, toxicity, adverse side effects, and lack of drug specificity. Recent advancements in nanotechnology have introduced novel opportunities for treating numerous significant diseases through the development of nanomedicines. In comparison with conventional therapeutics, nanomedicines demonstrate substantial potential in enhancing solubility, extending drug circulation time, overcoming biological barriers, improving bioavailability, increasing drug retention in focal diseases, and mitigating drug resistance and adverse side effects [1]. Notably, nanomedicines can facilitate targeted drug delivery, controlled release, and maintenance of therapeutic concentrations over extended periods [2-4]. Upon reaching the targeted site, the nanocarrier can release the drug in a controlled manner *via* mechanisms such as diffusion, degradation, or external triggers [5, 6].

Drug delivery technology emerged in 1952. The introduction of Lupron Depot® in 1989 represented a significant advancement, achieving sustained drug release through slow-release technology [7, 8]. In 2000, the US government initiated the National Nanotechnology Initiative, fostering the rapid development of nanodrugs, a strategy subsequently adopted by countries worldwide [9]. Over the past seven decades, nanotechnology has become increasingly integrated into medical treatments. The development of coronavirus disease in 2019 (COVID-19) vaccines exemplifies ongoing progress in nanomedicines [10]. According to data from the US Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER), over 350 products have revealed a rise in the submission of drugs containing nanomaterials from 1973 to 2024. Of these submissions, 65% are research-based new drugs, 17% are new drug applications, and 18% are abbreviated new drug applications. Liposome formulations for cancer treatment constitute the largest category of these products [11]. Moreover, this nanomedicine research spans various fields, including drug delivery, vaccine development, antibacterial treatment, diagnostic and imaging tools, wearable

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devices, implants, and high-throughput screening platforms (Fig. 1). A comprehensive analysis of these nanomedicines reveals the utilization of biological, abiotic, bionic, or hybrid materials, with many of these innovations now transitioning into viable clinical products [12].

Natural products-derived nanomaterials, including liposomes, polysaccharides, proteins, cells and their derivatives, bacteria, and viruses, have emerged as crucial components of nanoparticle delivery systems, attracting considerable research interest [13-17]. Over recent decades, these natural materials have demonstrated exceptional biological safety and therapeutic efficacy, playing pivotal roles in clinical diagnostics, antitumor and anti-inflammatory treatments, and vaccine development [18-21]. This review comprehensively examines emerging natural products-derived nanomedicines and their unique properties, with a particular focus on lipid and protein-based natural products-derived nanomedicines, their current clinical applications, and future prospects. Notably, we analyze the clinical therapeutic potential and challenges associated with natural products-derived nanomedicines, aiming to stimulate reflection and provide guidance for the further development of nanomedicines.

Emerging Natural Products-Derived Carriers of Nanomedicines

The characteristics of nanomedicines are typically associated with the properties of their nanocarriers. As research into natural products-derived materials progresses, an increasing number of naturally-derived carriers are being discovered, facilitating the clinical application of safer and more effective nanomedicines. The development of nanomedicines typically encompasses five stages, spanning from fundamental research on nanomaterial properties to market-ready drugs. While few nanomedicines have advanced to clinical research and commercial availability, the majority remain in developmental phases. To elucidate and evaluate the prospects of nanomedicines, we identified the advantages and distinctive features of these natural products-derived carriers (Fig. 2). This analysis aimed to provide insights into their potential and the future landscape of nanomedicine applications.

Lipid carriers

The discovery of phospholipids' unique ability to form stable, closed bilayer structures in aqueous systems has propelled lipid carriers, particularly liposomes and lipid nano-

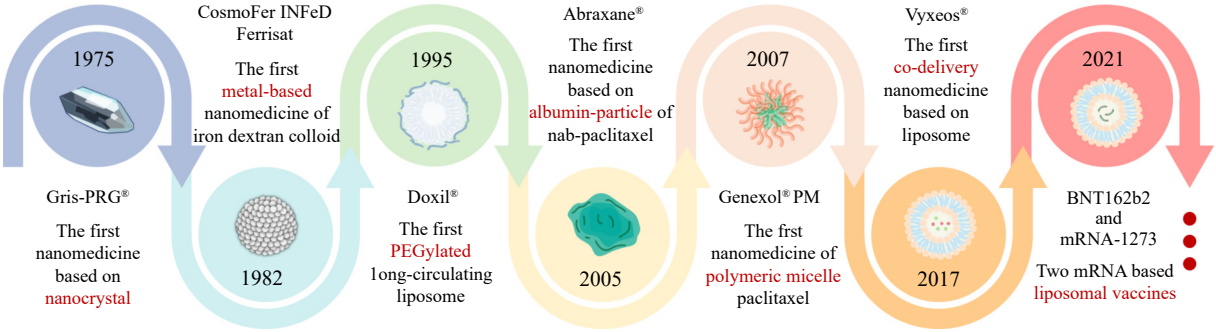

Fig. 1 Timeline of approved nanomedicines during the past decades.

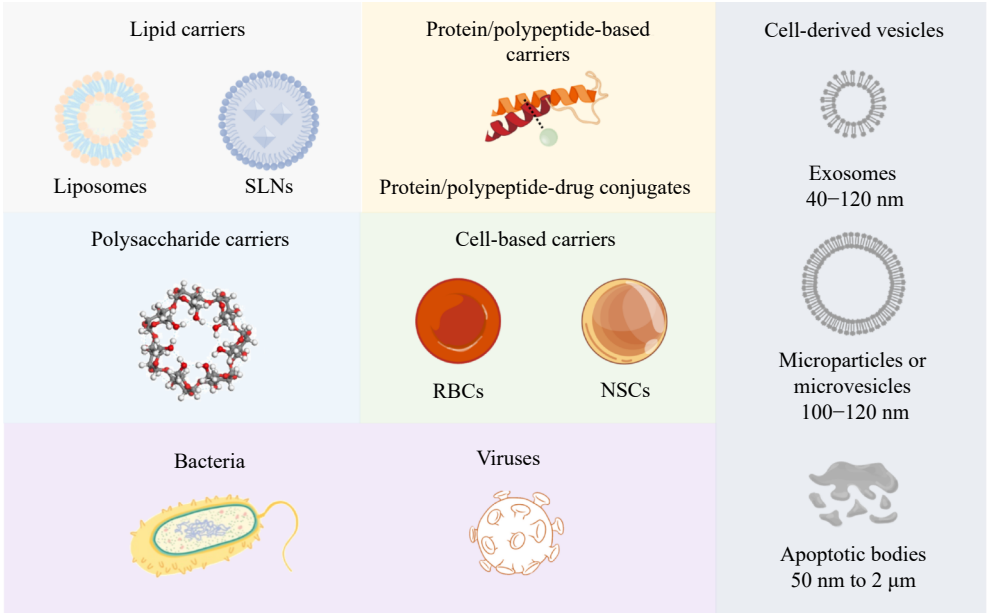

Fig. 2 Emerging natural products-derived carriers of nanomedicines on the market or in the clinical stage.

particles (LNPs), to the forefront of nanomedicine development [22]. In addressing associated challenges, researchers have engineered numerous LNPs with advanced functionalities. These enhanced carriers demonstrate improved drug delivery and accumulation within disease microenvironments, effectively mitigating issues such as premature drug release and leakage [23].

Liposomes, primarily composed of lecithin, cholesterol, and polyethylene glycol, possess a spherical structure resembling cell membranes. This structure enables the encapsulation of drugs with varying lipophilicity through the formation of hydrophilic and hydrophobic phospholipid bilayers [24]. Typically, highly lipophilic drugs are predominantly encapsulated within the lipid bilayer, while strongly hydrophilic drugs are almost entirely located in the aqueous cavity. Drugs with intermediate lipophilicity are distributed between the lipid and water phases. Through diverse formulations and preparation methods, liposomes can be engineered to exhibit enhanced *in vivo* activity, active targeting capabilities, improved stealth properties, and controlled drug release characteristics [25-27].

Since the initiation of clinical trials for the first liposome medicine in 1985, more than 20 liposomes and LNP nanomedicines have gained market approval (Supporting Information Table S1) [36-72]. Liposome-based nanomedicines, such as AmBisome® and Doxil®, have demonstrated substantial clinical benefits, achieving notable market sales. Amikacin liposomes, formulated with dipalmitoylphosphatidylcholine (DPPC) and cholesterol, have exhibited the capacity to extend the retention time of drug-loaded liposomes in the lungs of healthy volunteers [28]. Furthermore, long-acting liposomal formulations of local anesthetics have shown the ability to prolong analgesic effects and reduce peak drug concentrations in the bloodstream. This allows for safer administration of larger anesthetic doses and extended analgesia duration. Bupivacaine polycystic liposomes, for instance, demonstrated a five-fold increase in analgesic effect compared with bupivacaine alone [29]. In another example, intravenous administration of cefuroxime sodium liposomes maintains effective blood concentrations for a longer period than cefuroxime sodium alone [30]. This enhanced efficacy and prolonged duration make it more effective and convenient for treating bovine mastitis, necessitating long-term maintenance therapy.

Liposomes, however, are susceptible to capture by the liver's reticuloendothelial system, thereby reducing drug efficacy [31]. In response, researchers have endeavored to design long-circulating liposomes to act as "stealth" agents in systemic circulation, avoiding accumulation in non-target tissues. PEGylated liposomes are widely recognized for achieving extended circulation to some degree. However, the accelerated blood clearance (ABC) phenomenon induced by PEGylation significantly constrains the clinical application of conventional stealth liposomes [32]. XIA et al. incorporated natural phytosterol into phospholipid membranes to formulate ginsenoside Rg3 liposomes (Rg3-Lips) [33]. Their findings indicate that the fundamental properties of Rg3-Lips align with those of several control groups and exhibit good stability. Pharmacokinetic data demonstrate that incorporating Rg3 could increase the system's $t_{1/2}$ by a factor of 1.33, while additional PEGylation did not significantly extend circulation further. Moreover, in repeated injection experiments, the circulation time of the second injection of PEGylated cholesterol-containing liposomes (Chol-PEG-lips) was markedly reduced, with greatly increased liver accumulation. Conversely, following the second injection of Rg3-lips, the system predominantly remained in systemic blood circulation, evading liver capture. In conclusion, the natural phytosterol Rg3 can function as a liposome membrane regulator, providing stabilization similar to cholesterol. Notably, compared with traditional Chol-PEG-lips, Rg3-lips possess a simpler structure without TI-2 subunits, enabling prolonged circulation while averting B cell activation and immunoglobulin M (IgM) secretion, thus mitigating complement activation and the subsequent ABC phenomenon.

Solid lipid nanoparticles (SLNs) represent an emerging alternative to colloidal systems for controlled and targeted drug delivery, exhibiting excellent biocompatibility and efficient drug delivery properties [34]. SLNs loaded with diclofenac sodium, utilizing glutamic acid lipid as the primary lipid component, demonstrate favorable physical properties and acceptable stability [35]. Furthermore, these nanoparticles exhibit advantageous drug release and penetration characteristics. Additionally, a drug delivery system incorporating SLNs loaded with oxyconazole nitrate in a local gel formulation enhances the efficacy of oxyconazole nitrate in treating tinea infections while significantly reducing associated side effects.

Protein/polypeptide-based carriers

Amino acids undergo "dehydration condensation" to form bonds and create peptides, which subsequently fold and coil to shape complex biological macromolecules known as proteins. These proteins possess a three-dimensional configuration that offers controllable drug loading efficiency, surface functional modification capabilities, and inherent biocompatibility. These attributes facilitate their transformation into specific molecules or nanoparticles, generating considerable interest in their application for biosensor construction and the development of effective diagnostic and therapeutic systems [36-38].

The US FDA has approved more than 60 polypeptide protein drugs for listing [39-41]. Proteins possess various functional groups, including carboxyl, sulfhydryl, and hydroxyl, enabling them to bind with a diverse array of substances. These substances range from water molecules to metal ions, small molecules, and macromolecular compounds. This inherent versatility renders proteins particularly valuable for applications in disease diagnosis, targeted drug delivery, and drug loading systems.

Daunomycin, an anthracycline drug or its conjugate, represents a promising approach for tumor treatment. Despite its

high efficacy, the administration of daunomycin may lead to numerous side effects, including vomiting, hair loss, and nausea. Strategies involving protein binding modifications, such as coupling daunomycin with cationic, amphoteric, or anionic branched-chain polypeptides, can significantly enhance the drug's antitumor activity while reducing its toxicity and side effects [42, 43]. Cyclosporine A (CSA), a potent macrolide immunosuppressant used to treat various autoimmune diseases, faces limitations in clinical application due to its poor solubility, bioavailability, and potential severe adverse reactions. To address these issues, researchers fused the homologous human receptor cyclophilin A (CyPA) with a 73 kDa elastin-like peptide (ELP) named A192. In an autoimmune dacryocystitis model of Sjögren syndrome (SS), male non-obese diabetic (NOD) mice received subcutaneous injections of the fusion protein for two weeks. The Ca192-CSA conjugate significantly increased tear production compared with Ca192 alone. Additionally, the delivery of CSA *via* Ca192 significantly reduced the indications of CSA nephrotoxicity compared with free CSA [44].

Polysaccharide carriers

Natural macromolecular polysaccharides are primarily composed of monosaccharides such as glucose, fructose, and galactose. These monosaccharides can form repeating units individually or link alternately with various sugars. The structure of polysaccharides ranges from simple linear homopolymers to complex branched heteropolymers. In different biological systems, they serve as energy-storage molecules or structural materials [45, 46]. These natural macromolecular polysaccharides can be extracted from diverse sources, including plants (e.g., cellulose and pectin), animals (e.g., chitosan and chondroitin), microorganisms (e.g., xanthan gum, pullulan polysaccharide, dextran), and algae (such as alginate). Additionally, researchers are continuously developing various polysaccharides, including those derived from tea, oranges [47], and angelica [48], for potential medical applications.

Polysaccharides present multiple advantages, including abundant availability, cost-effective production, and scalability, leading to their widespread application in agriculture, food science, chemical engineering, biomedicine, and related fields. In the biomedical domain, natural polymer polysaccharides have attracted considerable interest due to their unique biological activities, encompassing exceptional biocompatibility, biodegradability, distinctive biological properties, and accessibility [49-51].

Curcumin, a bioactive polyphenol molecule extracted from the traditional medicinal plant *Curcuma longa*, demonstrates a variety of pharmacological effects, including anti-inflammatory, antiviral, antibacterial, antioxidant, and anticancer properties [52, 53]. Nevertheless, its therapeutic potential is constrained by poor solubility, bioavailability, and pharmacokinetics. Leveraging natural polysaccharides' solubility and encapsulation capabilities, curcumin encapsulated in polysaccharide nanocarriers has shown enhanced stability and bioavailability [54]. Furthermore, polysaccharide FP, derived from the lateral root of oxidized *Aconitum*, has been utilized as a polymer carrier in an intra-articular drug delivery system containing methotrexate. By developing an improved in situ gel delivery system, a polysaccharide-based carrier may reduce the systemic toxicity and irritation associated with oral methotrexate while enabling long-term controlled drug release [55]. Moreover, magnolol nanoparticles (HNK NPs) have been developed using a novel biodegradable polysaccharide polymer as the carrier, markedly enhancing the solubility of magnolol [56]. Polysaccharides can also function as nanocarriers to improve the bioavailability of orally administered proteins and peptides [57].

Moreover, polysaccharides possess a variety of functional groups, including hydroxyl (-OH), amino (-NH_2), sulfate, aldehyde, and carboxyl groups. These groups can participate in reactions such as azo reduction and glycosidic bond hydrolysis [58]. Such reactions enable the alteration of polysaccharide properties. Through chemical modification and the introduction of additional functional groups, polysaccharides can be transformed into sophisticated and highly functional drug delivery vehicles.

Cell-based carriers

In 1973, researchers initially demonstrated the potential of red blood cells as enzyme carriers for disease treatment [59]. Recent years have witnessed continued progress in utilizing various cell types, including platelets, macrophages, lymphocytes, mesenchymal stem cells, and red blood cells, as carriers for drug delivery systems (DDS). The construction of cell-based DDS employs several strategies: (i) Direct intracellular drug uptake [60, 61]; (ii) Surface attachment of antibody-bound nanoparticles through antigen-antibody interactions [62]; (iii) Intracellular introduction of biomacromolecules and nanoparticles coupled with cell-penetrating peptides [63, 64]; (iv) Cellular entry of drug-loaded carriers *via* membrane fusion [65].

Red blood cells have emerged as one of the most extensively researched cell-based carriers. Numerous methods have been successfully employed to enhance their *in vitro* storage capacity without significantly altering cellular biology or drug delivery efficacy [66]. Incorporating drugs into red blood cells has demonstrated a marked alteration in the pharmacokinetic profiles of these drugs in both animal models and human subjects. This approach enhances drug uptake by the liver and spleen, facilitating targeted delivery to the reticuloendothelial system (RES). The judicious selection of cell-based carriers tailored to specific conditions can substantially improve the *in vivo* fate of encapsulated drugs. Notably, alterations based on cell properties can significantly enhance the targeted delivery efficiency of therapeutic agents, improve bioavailability, and mitigate systemic toxicities.

Cell-based drug carriers are currently the most extensively researched in clinical tumor treatment. A study on cell-based virus delivery outlined the characteristics of an ideal cell vector: susceptibility to virus infection, facilitation of vir-

us infection, retention of immunosuppressive properties to protect the loaded virus from host immune responses, and, crucially, inherent tumor-homing abilities for effective virus transport to the target tumor site, as exemplified by stem cells [67]. During transmission, the virus antigen remains concealed, thereby mitigating the potentially severe adverse effects associated with systemic virus dissemination [68]. Moreover, the limited ability of existing viral vectors to effectively target micrometastatic tumor burdens has significantly impeded the potential application of oncolytic adenovirus in anticancer treatment. Neural stem cells (NSCs), with their inherent tumor migration capabilities, emerge as suitable candidates for targeted delivery of oncolytic adenovirus. NSC-based vectors protect therapeutic viruses from host immune responses and selectively enhance therapeutic payload accumulation at tumor sites. This approach shows promise for improving the clinical efficacy of anti-glioma viral therapy [69].

Cell-derived vesicles

Cell-derived vesicles represent another category of naturally derived carriers in nanomedicine development. Extracellular vesicles can be classified based on their biosynthesis process and molecular size into three main types: exosomes, microvesicles (or microparticles), and apoptotic bodies (ABs). Exosomes have a diameter ranging from 40 to 120 nm. Microvesicles, which are released directly from the plasma membrane, typically range from 100 nm to 1 μm in diameter. ABs have a diameter spanning from approximately 50 nm to 2 μm [70]. Among these cell-derived vesicles, exosomes have been the most extensively studied for developing drug delivery carriers.

Exosomes originate from the late endocytic pathway and are secreted by most hematopoietic and epithelial cells *in vitro*. These extracellular vesicles carry diverse biological molecules, including nucleic acids, proteins, and lipids, facilitating material and information exchange between cells [71]. For example, exosomes mediate cross-communication between immune and epithelial cells in individuals with asthma and allergies, promoting site-specific inflammation through the production of proinflammatory mediators such as leukotrienes [72]. Moreover, specific signals expressed by exosomes can indicate the presence of tumors. Most microvesicles released by malignant cells are termed tumor-derived (TD) exosomes [73]. TD-exosomes reflect the molecular characteristics of TD lesions. Research has shown that TD-exosomes found in the blood of patients with glioblastoma multiforme and advanced gliomas contain neural markers (e.g., LiNCAM), while exosomes from melanoma express molecules associated with melanin synthesis and other melanoma markers (e.g., Melan-A) [74].

Exosomes possess advantageous physical properties, including stability, biocompatibility, permeability, low toxicity, and low immunogenicity, enabling their widespread application in immunotherapy, gene therapy, protein therapy, and other treatments. For example, exosomes derived from breast cancer (MDA-MB-231) cells (231 exo) demonstrate the ability to recognize A549 cells in the bloodstream and effectively evade immune surveillance *in vitro*. When loaded with microRNA molecules, specifically miRNA-126 (miRNA-231-exo), these exosomes inhibit the proliferation and migration of A549 lung cancer cells. Intravenous administration of miRNA-126-carrying exosomes in mice exhibits an effective lung-homing effect. In a lung metastasis model, miRNA-231-exo significantly inhibits the formation of lung metastases *in vivo* [75]. Exosomes delivering STING agonist cyclic GMP-AMP (iExo (STINGa)) exhibit more potent tumor inhibition and cell uptake efficiency than STINGa alone. This approach circumvents the limitations associated with the adverse pharmacological properties and low targeting efficiency of STING agonists (STINGa) as cancer therapeutic agents [76]. Despite their numerous advantages, exosomes' targeting ability alone is insufficient to overcome the low cumulative efficiency at the target site resulting from non-specific distribution. Consequently, recent research has focused on loading proteins, nucleic acids, and other chemicals into exosomes to enhance their functionality [77, 78]. For instance, Temozolomide (TMZ) was encapsulated *via* electroporation into folate (FA) modified exosomes. The results indicated that TMZ@Astro-exo-FA exhibited enhanced anti-glioma effects compared to TMZ alone [79]. Furthermore, numerous studies have explored the application of exosomes in anti-inflammatory treatments, spinal cord injury prevention, and trauma repair [80].

Microvesicles, akin to exosomes, are vesicles that emanate from the plasma membrane and are often collectively referred to as small extracellular vesicles (sEVs) [81]. However, microvesicles can exceed exosomes in size by more than tenfold, enabling them to carry a broader range of proteins [82]. Furthermore, microvesicles exhibit greater similarity to the protein types of their parental cells compared to exosomes. Primarily, microvesicles serve as delivery vehicles for immunotherapy, particularly in cancer treatment. RAZA et al. developed a tumor microvesicles (TMVs) system for liver cancer therapy, incorporating the traditional Chinese medicine arsenic trioxide (ATO) to enhance anticancer effects [83]. They modified the microvesicles with SP94 peptides, facilitating active targeting of liver cancer cells and accumulation at tumor sites, subsequently triggering immune responses due to associated antigens. Various formulations demonstrated particle sizes of approximately 600 nm and achieved substantial drug loading capacity. *In vitro* cellular experiments revealed that this functionalized microvesicle exhibited the highest tumor cell toxicity among the control groups. Utilizing H22-bearing tumor mice as an *in vivo* research model, the system achieved a tumor inhibition rate of 53.23%, approximately double that of other control groups. In terms of immunotherapy, these TMVs enhanced the infiltration and proportion of $CD8^+$ T cells in tumors, effectively activating the immune response against tumors *in vivo*.

Apoptosis, a fundamental physiological process, encom-

passes distinct phases of cellular demise. Initially, nuclear chromatin undergoes condensation, followed by membrane blebbing, culminating in the fragmentation of cellular contents into various membrane-enclosed vesicles, forming ABs [84]. ABs generated by different cell types exhibit unique properties. For instance, stellate cells have been observed to engulf ABs originating from hepatocytes, triggering kinase signaling pathways that lead to fibrotic reactions [85]. Conversely, ABs derived from bone marrow mesenchymal stem cells have been found to suppress fibrosis in endometrial interstitial cells through modulation of the Wnt/*β*-catenin signaling pathway [86]. Additionally, ABs play a role in information transmission [87]. Certain cell-derived ABs possess distinctive anti-inflammatory capabilities and immune regulatory functions [88, 89]. For example, in response to tissue injury, endothelial cell-derived ABs induce the synthesis of chemokine CXCL12, thereby attracting progenitor cells to the injury site [90]. In 2011, BERDA Haddad et al. proposed that ABs originating from non-phagocytic endothelial cells are inflammatory and function as carriers for IL-1*α* [91]. Furthermore, research utilizing a mouse model of acute lung injury (ALI) has demonstrated that ABs released by transplanted human umbilical cord mesenchymal stem cells (UC MSCs) induce a shift in macrophages from a proinflammatory state to an anti-inflammatory state [92].

Bacteria and viruses

Numerous clinical conditions, particularly tumors, generate an optimal hypoxic environment that facilitates the growth of anaerobic bacteria. Several anaerobic bacterial species have shown the ability to surmount physiological barriers that typically hinder conventional chemotherapy, proliferating selectively within tumor tissues [93, 94]. This distinctive characteristic offers a promising approach for precise tumor localization. However, therapeutic efficacy is often limited by the elimination of bacteria before they colonize specific targets, necessitating the mitigation of systemic toxicity through chemical and genetic modifications of the bacteria [95]. Multiple bacterial strains, including *Salmonella* and *Salmonella typhimurium*, have been attenuated *via* the deletion of critical virulence factor genes [41, 96].

Bacteria currently show promise as drug carriers for tumor therapy, demonstrating the ability to overcome physical barriers, target and accumulate in tumor tissues, and elicit antitumor immune responses. Through genetic and chemical modifications, these bacteria can produce and deliver anticancer drugs to tumor tissues, thereby enhancing the safety and efficacy of cancer treatment [94, 97]. Uirich *et al.* reported a method where the bacterial wall of *E. coli* is decorated with azide groups, while alkyne strain groups are attached to the surface of adriamycin. These functional groups form stable triazole bonds *via* a click-type reaction, allowing nanoparticles to be covalently grafted onto living bacteria. The researchers assessed the motility and penetrability of these modified bacteria in a 3D tumor matrix model consisting of a dense collagen extracellular matrix containing human fibrosarcoma cells. Their findings confirmed the bacteria's ability to transport nanoparticles through the thick collagen layer, resulting in the destruction of nearly 80% of tumor cells beneath it [98].

Viruses are acellular entities consisting of nucleic acid molecules and proteins [99]. They depend on host cell infection for replication and assembly. Various viruses exhibit distinct core regions. For example, the central immune-dominant c/e1 epitope region of the hepatitis B virus core antigen (HBcAg) contains an exogenous sequence of either 50 or 100 amino acids, making the c/e1 region a promising insertion site [100]. Recombinant hepatitis B virus core (HBc) functions as a key non-infectious vector for exogenous immune epitopes, enabling the display of dominant immune epitopes from hepatitis B, hepatitis C, hepatitis E, and other viruses, as well as specific bacterial and protozoan protein epitopes [100].

Numerous studies have extensively explored the potential of viruses as drug-delivery vehicles. The unique attenuated gene of the Dengue virus [101] and the tightly wrapped nucleoprotein of the rabies virus [102] present attractive vectors for developing live attenuated vaccines. Viruses, composed of nucleic acid molecules and proteins, lack cellular structure and rely on host cell infection for replication and assembly. Each virus possesses distinctive core regions. For instance, the central c/e1 epitope region of the HBcAg features an exogenous sequence of 50 or 100 amino acids, making it an appealing insertion site. Recombinant HBc serves as a fundamental non-infectious vector for exogenous immune epitopes, facilitating the presentation of dominant immune epitopes from hepatitis B, C, E, and other viruses, as well as specific bacterial and protozoan protein epitopes [103, 104]. Other viruses function as vaccine carriers or nanoparticles for drug delivery. Virus-excited nanoparticles can serve as multifunctional antibacterial carriers against gram-negative and gram-positive bacteria [105]. Inactivated tick-borne encephalitis virus can be utilized as a carrier to combine with antigens, generating high antibody titers against very low doses of tetanus toxoid (TT) [106]. Novel virus-like particles (VLPs) extracted from Drosophila X virus (DxV) can act as nanocarriers to deliver dsRNA to insects [107] and enhance the oral delivery of insect-specific neurotoxic peptides [108]. Furthermore, VLPs, functioning as carriers for antigens/allergens, can significantly enhance antigen immunogenicity and may be particularly suitable for allergy prevention [109].

Current Clinical Applications of Natural Products-derived Nanomedicines

Natural products-derived nanomedicines have garnered increasing attention, with a rapid rise in the number of related products undergoing clinical investigations. Over 100 nanomedicine applications and products have received approval for commercial distribution [110]. Notably, 25% of significant pharmaceutical compounds and their derivatives originate from natural resources [111, 112]. This section focuses on compiling and analyzing natural products-derived nanom-

edicines that are either commercially available or under investigation for their therapeutic potential across various diseases and indications (Fig. 3).

Cancer

According to statistics published by the American Cancer Society, in 2024, cancer affected over 2 million individuals, with a new diagnosis occurring approximately every 15 seconds, continuing to significantly impact lives globally [113, 114]. Cancer treatment modalities include chemotherapy, radiotherapy, phototherapy, and chemo-kinetic therapy, among others. However, conventional chemotherapy drugs face considerable challenges, such as low response rates, high drug resistance, severe side effects, limited bioavailability, and unpredictable distribution patterns. In contrast, natural products-derived nanomedicines offer a potential solution to the selectivity issues associated with traditional drugs. Notably, nature-derived nanomedicines demonstrate advantageous characteristics including excellent biocompatibility, low immunogenicity, and targeted drug delivery, thereby enhancing drug safety, tolerability, and efficacy [115, 116].

Doxorubicin inhibits RNA and DNA synthesis, effectively inactivating tumor cells across various growth cycles [117]. However, its administration is associated with significant toxic effects, including alopecia and cardiotoxicity [58]. To mitigate these adverse effects and enhance drug delivery specificity to tumors while minimizing exposure to cardiac and gastrointestinal tissues, researchers initiated clinical trials as early as 1993 utilizing doxorubicin liposomes (TLC-D99) [118]. Subsequently, doxorubicin liposomes, Doxil®, received approval for clinical application in 1995. Compared with traditional doxorubicin formulations, Doxil® offers an extended half-life and reduced distribution of free drugs in tissues [119]. In 2006, as part of increasing efforts to develop natural products-derived nanomedicines, Hauck *et al.* encapsulated doxorubicin with low-temperature sensitive liposomes (LTSLs) [120]. Furthermore, in 2018, Lyon *et al.* investigated the feasibility of utilizing thermosensitive liposome doxorubicin in combination with noninvasive focused ultrasound hyperthermia to treat solid tumors. This approach, examined in clinical trials (NCT02181075), demonstrated the potential to enhance drug delivery within tumors [121]. In 2019, Gray and MD *et al.* introduced a novel approach to release doxorubicin from thermosensitive liposomes using a clinically approved focused ultrasound system (NCT02181075). This method safely achieved targeted and noninvasive drug delivery to liver tumors, presenting a promising avenue for improving drug delivery in solid tumors [122].

Vincristine sulfate liposome injection (VSLI) is a liposomal formulation that encapsulates vincristine within a lipid bilayer composed of sphingomyelin and cholesterol. This formulation demonstrates significant therapeutic potential in disease treatment. Clinical trials have evaluated VSLI for meta-

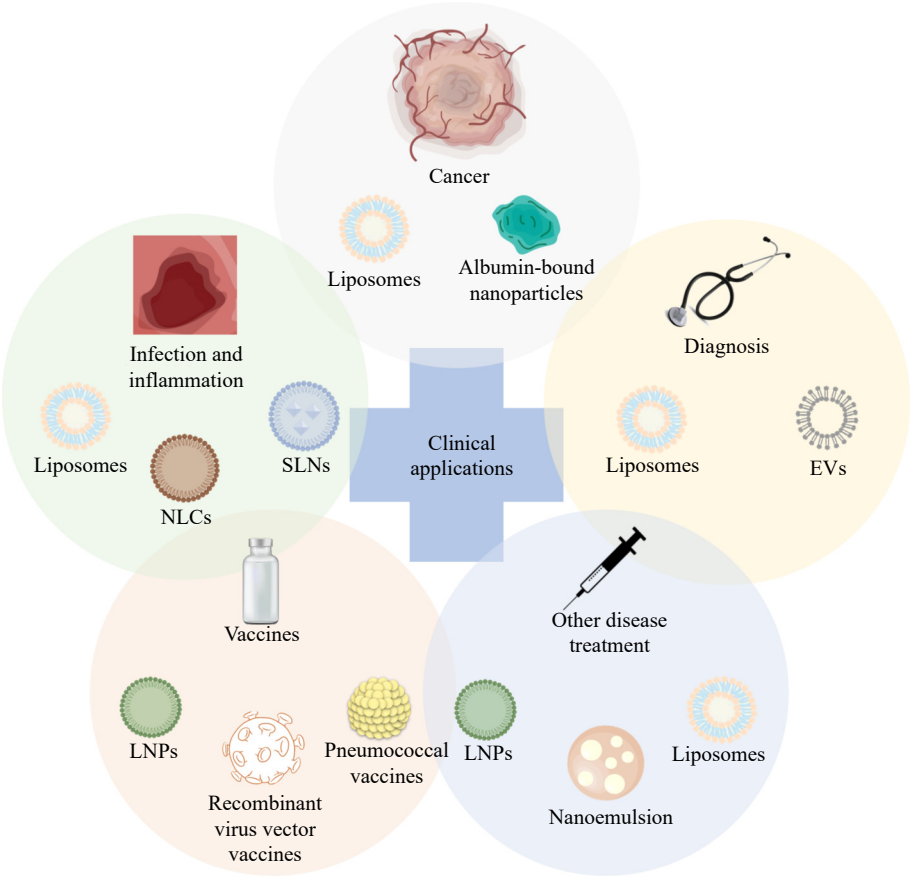

Fig. 3 Current clinical applications of natural products-derived nanomedicines.

static melanoma, invasive non-Hodgkin's lymphoma, and acute lymphoblastic leukemia [123, 124]. These studies reveal that VSLI exhibits an extended drug half-life. Marqibo® (vincristine sulfate injection), a commercially available formulation, has undergone clinical assessment for its pharmacokinetics and safety profile in patients with melanoma and cancer, including those with compromised liver function. The clinical trials indicated that the drug was generally well-tolerated [125]. Marqibo® is primarily used in pediatric patients with acute lymphoblastic leukemia. The 2.25 mg·mL^{-1} dose has been observed to have no significant neurotoxic effects in children [126]. Additionally, cationic liposomes have been investigated for the treatment of head and neck squamous cell carcinoma (HNSCC) [127, 128], while ursolic acid liposome (UAL) has been studied [129, 130]. Furthermore, PEGylated liposomes have been extensively explored for clinical applications [131].

Paclitaxel, a cornerstone treatment for metastatic breast cancer, is an efficacious antitumor agent with the potential for severe toxicity [132]. Albumin's ability to reversibly bind paclitaxel enhances its transfer to vascular endothelium and improves drug concentration within tumor lesions. The FDA has sanctioned a solvent-free paclitaxel formulation for metastatic breast cancer treatment. This formulation utilizes the 130-nanometer albumin binding (NAB™) technology, marketed as Abraxane®, comprising albumin-bound paclitaxel nanoparticles [133, 134]. This approach effectively mitigates drug toxicity while enhancing tissue distribution and tumor penetration, thus improving efficacy and safety [135]. The NAB™ technology shows promise in cancer treatment, with ongoing clinical trials exploring its potential. Additionally, this technology is being applied to formulate other insoluble anticancer drugs, including docetaxel and rapamycin [136].

Infection and inflammation

Infections and inflammatory diseases have consistently posed significant challenges to human health. Traditional medicines often demonstrate limited therapeutic efficacy and are susceptible to drug resistance and adverse side effects. As early as 1997, researchers employed liposome-based nanomedicine in combination with antibiotics and antifungal agents to treat 120 cases of suppurative inflammatory diseases affecting the respiratory and digestive systems [137]. The development of natural products-derived nanomedicines has substantially addressed the limitations of conventional therapeutics, including poor water solubility, drug resistance, and undesirable side effects.

Historically, Amphotericin B has been the preferred treatment due to its broad spectrum of antifungal activity and minimal development of drug resistance. However, its administration is associated with adverse effects, including nausea, vomiting, and renal toxicity. To address these issues, researchers encapsulated amphotericin B within liposomes, resulting in the formulation known as AmBisome® [138]. Additionally, poly (lactic-co-glycolic acid) (PLGA) nanoparticles (AMB NPs) loaded with amphotericin (AMB) ignificantly enhance the solubility of the drug [139]. Moreover, these AMB NPs exhibit strong potential for sustained-release treatment of leishmaniasis.

Acne is characterized as a chronic inflammatory condition affecting the pilosebaceous unit [140]. It results from increased androgen-induced sebum production, altered keratinization patterns, inflammation, and Propionibacterium acnes colonization. Primarily localized to the face, neck, chest, and back, acne represents a complex interplay of physiological processes within the skin's structure [141]. Spironolactone (SP), an antiandrogen medication, is known for its efficacy in reducing sebum secretion [142]. However, its oral administration presents challenges due to poor gastrointestinal absorption. Researchers have investigated SP encapsulation within LNPs to mitigate potential systemic side effects while enhancing its therapeutic benefits. Their findings demonstrate the effectiveness of SP-loaded nanostructured lipid carrier formulations (SP NLCs) in reducing lesion counts, thereby contributing to acne vulgaris management and promoting dermatological health [143].

In the treatment of pityriasis versicolor (PV), incorporating the antifungal drug fluconazole (FLZ) into SLNs within a topical gel formulation has shown improved efficacy. Comparative analysis against the commercial product Candistan® (1% cream) revealed significantly higher clinical and mycological cure rates, indicating the superior therapeutic outcomes achieved with FLZ-loaded SLNs topical gel [144]. Additionally, the application of solid LNP gel containing podophyllotoxin and clobetasol propionate has demonstrated effectiveness in treating condyloma acuminatum, resulting in reduced recurrence rates [145, 146]. Importantly, the adverse reactions observed with this treatment approach are generally mild and well-tolerated.

Diagnosis

Timely and precise diagnosis of severe ailments is crucial. However, limitations in conventional diagnostic methods often result in late-stage diagnoses of diseases like cancer, significantly complicating effective disease management [147]. The emergence of nanomaterials has markedly improved the precision of disease diagnosis and detection. These materials function in multiple capacities, serving as contrast agents for both anatomical and functional imaging [148, 149]. By facilitating visualization of internal body structures, nanomaterials assist in differentiating between healthy and diseased tissues. Furthermore, they can act as disease markers, enabling detection in various bodily fluids, such as blood and urine, as well as other tissues [150].

Natural products-derived nanomedicines have been developed for various diagnostic applications in medicine. For example, Triombrast, a liposome-encapsulated water-soluble X-ray contrast agent, was administered to 23 patients with Hodgkin's disease, 9 with liver cirrhosis, and 6 with malignant tumors in different locations. Following intravenous injection, clear liver and spleen images were observed after approximately 2−2.5 h [151]. In 2000, imaging using 99mTc peg

liposomes was utilized to non-invasively assess the extent of Crohn's colitis [152]. However, severe adverse reactions occurred during clinical trials after the administration of 99mTc peg liposomes. In 2012, a modified version of 99mTc peg liposome re-entered clinical trials. This formulation showed no adverse reactions, demonstrating potential safety and utility in detecting infections, inflammation, and tumors in equines. This development marked a significant improvement following the earlier severe adverse reactions encountered during clinical trials [153]. Lipimage815, a contrast agent composed of LNPs, showed promise in canine oncological surgery, assisting in the evaluation of intraoperative fluorescence imaging (IOFI) to effectively differentiate malignant tumor tissues from healthy sites [154].

The presence or alteration of certain natural drug carriers in blood and urine can serve as indicators of disease onset or progression. For example, EV subsets derived from prostate cancer (PCA) cells contain double-stranded genomic DNA (gDNA) fragments. These fragments may carry specific mutations, rendering EVs a promising biomarker for cancer diagnosis and prognosis [155, 156]. Hepatocellular carcinoma (HCC), a common transformation of HCC, exhibits high incidence and mortality rates worldwide [60]. HCC, particularly in the context of chronic liver cirrhosis, poses significant challenges. Researchers have investigated the potential of SeVs isolated from serum samples of individuals with liver cancer, liver cirrhosis, and healthy controls, as well as from culture media of hepatocellular carcinoma cells (HepG2) and normal hepatocytes (LO2). These SeVs were characterized *via* size distribution analysis, morphological analysis, and surface biomarker testing, providing insights into disease progression [157].

Vaccines

The emergence of COVID-19 significantly altered global lifestyles. While research continued on preventive and therapeutic drugs for major diseases, considerable focus shifted toward developing vaccines for self-protection. Various vaccine types have been developed, including whole virus vaccines, protein-based vaccines, and nucleic acid vaccines [158-160]. RNA vaccines, in particular, have garnered widespread interest. These vaccines encode the SARS-CoV-2 spike antigen and are delivered *via* LNPs [161]. In 2020, Maruggl *et al.* evaluated an RNA vaccine prior to clinical trials (NCT04758962). The SARS-CoV-2 Spike Antigen mRNA (LNP) candidate vaccine demonstrated favorable safety profiles and elicited a robust protective immune response against various SARS-CoV-2 variants [162]. Subsequently, Sahin *et al.* reported that BNT162b2, administered as an mRNA LNP vaccine, could neutralize 22 viruses carrying different SARS-CoV-2 variants. The majority of participants exhibited a strong response characterized by IFN-$\gamma^{(+)}$ or IL-$2^{(+)}$ $CD8^{(+)}$ and $CD4^{(+)}$ T helper 1 cells, detectable throughout the 9-week post-vaccination observation period [163]. Notably, BNT162b2 and mRNA-1273 LNP vaccines have received clinical approval for COVID-19 prevention [164]. Additionally, several bivalent and multivalent vaccines are currently undergoing clinical research [165].

Pneumococcal diseases have been a global concern, with drug resistance presenting an urgent worldwide challenge. Vaccines play a crucial role in controlling these diseases, extending the clinical efficacy of antibiotics by reducing both the frequency of antibiotic use and pneumococcal infections. The FDA approved the marketing of a 14-valent pneumococcal polysaccharide vaccine as early as 1978 [166]. Subsequently, in 1985, the first capsular polysaccharide vaccine for Haemophilus influenzae type B was licensed [167]. In 2000, Wyeth developed the world's first PCV7 (4, 6B, 9V, 14, 18C, 19F, and 23F), which was approved for infants under 5 years old [168]. Later clinical trials (NCT00861380 and NCT00839254) demonstrated high efficacy of the 10-valent pneumococcal conjugate vaccine in preventing invasive pneumococcal diseases when administered nationwide [169]. Notably, Mexican infants generally exhibited higher antibody responses to pneumococcal serotypes and protein D compared to the antibody response observed in Europe (NCT00489554) [170]. Vaccination during pregnancy with pertussis, TT, diphtheria toxoid (DT) vaccine, and pneumococcal vaccine containing DT mutants like CRM197 as a carrier protein can significantly influence the infant's response to DT. This may also interfere with the infant's response to combined pneumococcal vaccines containing DT mutants as carrier proteins [171].

Recombinant virus vector vaccines present a promising alternative to conventional inactivated vaccines. These vaccines employ viruses to express influenza antigens in a natural manner, potentially enhancing immunogenicity within the vector environment [172]. Adenovirus, a non-enveloped virus with a double-stranded DNA genome, can serve as a vaccine vector to elicit various immune responses for HIV and Ebola [173]. Among these vectors, the one based on human adenovirus 5 (Ad5) is the most commonly utilized [174]. Notably, Ad5 Ebola vaccines have received approval for clinical trials and have demonstrated sustained prevention of Ebola virus disease (Clinical trial registrations: NCT02326194 and NCT02533791) [175].

Other diseases treatment

Natural products-derived nanomedicines present a promising approach for diagnosing and treating various diseases beyond tumors and inflammation. Transthyretin amyloidosis is a hereditary and life-threatening condition characterized by abnormal transthyretin protein deposition [176]. Patisiran, an RNA interference therapeutic drug, demonstrates potential in inhibiting transthyretin protein synthesis. Encapsulated within second-generation LNPs to form ALN-TTR02, clinical trials have shown that patisiran is generally well-tolerated and results in significant dose-dependent down-regulation of transthyretin protein (NCT01148953 and NCT01559077) [177]. The 0.3 $mg \cdot kg^{-1}$ dosing regimen of patisiran appears to be effective across the spectrum of patients with hereditary transthyretin amyloidosis (NCT01617967). These findings sug-

gest that this dosage may provide a standardized and practical treatment approach for individuals affected by this condition [178, 179].

The exploration of sirolimus for treating posterior segment ophthalmopathy (PSED) has garnered considerable attention due to its potential benefits. However, the challenges associated with its physical and chemical properties have hindered its clinical application. To address this limitation, researchers have investigated polyol-modified lipids, which can efficiently traverse the blood-retinal barrier and deliver sirolimus to the posterior segment of the eye. This approach shows promise as a viable strategy for managing PSED, offering new possibilities for enhancing treatment outcomes in affected individuals [180, 181]. Dry eye disease (DED) is a complex disorder characterized by tear film instability and ocular discomfort [182]. CSA can alleviate related symptoms, but its hydrophobic nature significantly restricts drug delivery. Restasis® is a cyclosporine nanoemulsion formulated to address the solubility challenges associated with cyclosporine. By incorporating cyclosporine into a nanoemulsion, Restasis® enhances its solubility and prolongs its retention time on the ocular surface. This innovative formulation improves efficacy and extends therapeutic effects, making it a valuable option for managing ocular conditions such as dry eye syndrome [183].

Cystic fibrosis, a multisystem disorder resulting from a single gene mutation, once posed a significant threat to human life. Traditionally, it was treated *via* vitamin supplementation [184, 185]. Early research indicated that tocophersolan (TPGS), a water-soluble form of vitamin E, showed potential in modifying vitamin status, but its efficacy was limited in addressing persistent cases of vitamin deficiency [186]. In response, scientists developed a liposome-based formulation for a clinical trial (DRKS00014295), which demonstrated a marked improvement in vitamin bioavailability, potentially addressing this deficiency [187]. Nevertheless, further investigation is necessary to address issues related to fat indigestion and malabsorption following the administration of vitamin liposomes.

Clinical Therapeutic Potential and Challenges of Natural Products-derived Nanomedicines

Nanotechnology has transformed drug delivery approaches and offered significant promise in clinical treatment. Natural products-derived nanomedicines are increasingly being investigated for treating conditions such as cancer, inflammation, and atherosclerosis, demonstrating remarkable targeted therapeutic efficacy and clinical safety. Nevertheless, several critical factors must be thoroughly considered when designing nanomedicines, including hemorheology and vascular fluid dynamics, tumor interstitial pressure and nanoparticle extravasation, multidrug resistance from drug efflux pumps, as well as cell membrane penetration and subsequent endosomal compartmentalization.

The translation of natural products-derived nanomedicines from fundamental research to clinical application remains a significant challenge (Fig. 4). A recent survey reveals a failure rate of 52% in phase II trials, escalating to 86% in phase III trials. These failures often result from nanomedicines' insufficient ability to overcome persistent physical barriers. Consequently, beyond developing additional carrier materials, there is a critical need to enhance our comprehension of the properties, mechanisms, and principles underlying the preparation process based on nanotechnologies and nanomaterials. Researchers have gained insight into the *in vivo* fate of some relatively established natural nanocarriers. Moreover, they have begun exploring the co-delivery of multiple drugs to achieve efficient and simultaneous delivery, accumulation, and penetration of various medications into target sites/tissues [188, 189]. Notably, certain natural

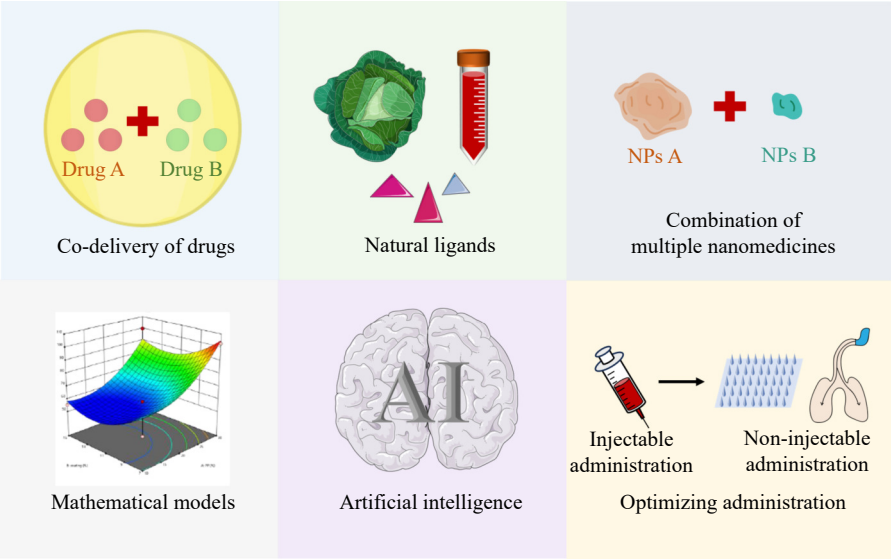

Fig. 4 Strategies for the clinical development of natural products-derived nanomedicines.

products have been utilized to modify nanoparticle surfaces, such as ligands, to achieve active targeting or other capabilities [190]. Furthermore, therapeutic approaches combining multiple nanomedicines or strategies integrating various drugs into a single nanomedicine offer increased potential for treating numerous diseases clinically. The release characteristics of different drugs following targeted delivery to the lesion are also crucial. More precise simulation and analysis are necessary for various lesion environments, such as integrating experimental and mathematical models [191]. Additionally, artificial intelligence may contribute to constructing models of natural products-derived nanomedicines and predicting or evaluating nanomedicine safety in the future.

Moreover, intravenous injection is still the most widely used administration method in clinical practice. However, this process is challenging to operate and has poor patient compliance. Combining the high permeability and sustained release characteristics of new natural nanomedicines can broaden the application prospects of other drug administration methods besides injection, such as transdermal and inhalation administration [192, 193]. Furthermore, natural nanomedicines can facilitate combined therapy approaches by integrating diverse treatment modalities. For instance, certain natural nanocarriers can simultaneously deliver drugs and photothermal agents, effectively combining chemotherapy with other treatments. For diseases that present diagnostic difficulties, natural nanocarriers can co-deliver diagnostic agents and therapeutic drugs, enabling real-time observation of pathological processes at the lesion site during treatment, thus achieving integrated diagnosis and therapy. These advancements in methods and tools hold promise for the progression of natural products-derived nanomedicines and the enhancement of disease treatment strategies.

Conclusion

Over the past several decades, nanomedicines have emerged as remarkable therapeutic agents for disease treatment, demonstrating significant improvements in therapeutic efficacy, *in vivo* pharmacokinetics, diagnosis, and safety. Notably, natural products-derived nanomedicines, as a crucial component of this field, have reached a significant milestone with numerous related products gaining market approval or entering clinical trials. While rapid advancements and innovations in nanocarriers (e.g., have yielded substantial progress and opportunities, natural products-derived nanomedicines continue to face considerable challenges in clinical translation, particularly in targeting efficiency, material toxicity, nanotoxicity, and other side effects. Consequently, more comprehensive studies are necessary to investigate nanomedicines, including their pharmacodynamic mechanisms, material and carrier properties, and *in vivo* fate. Moreover, expanding interdisciplinary research and collaborative efforts are urgently required to accelerate the development of natural products-derived nanomedicines.

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