Int J Adv Life Sci Res. Volume 9(4) 001-018
https://doi.org/10.31632/ijalsr.2026.v09i04.001

International Journal of Advancement in Life Sciences Research

Online ISSN: 2581-4877

Journal homepage http://ijalsr.org



Review Article

Natural Product Nanomedicine for Enhanced Bioavailability and Targeted Drug Delivery: Translational and Personalized Therapeutic Perspectives

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Abstract

Natural products and their derivatives from plant, microbial, and marine sources have long served as important drug leads because of their structural diversity and broad biological activities. However, poor aqueous solubility, low chemical stability, rapid metabolism, limited membrane permeability and restricted bioavailability continue to limit their clinical translation. Nanotechnology-based delivery systems provide a practical strategy to improve solubilization, pharmacokinetics, tissue targeting, controlled release and safety. Polymeric nanoparticles, liposomes, dendrimers, micelles, solid lipid nanoparticles and mesoporous silica carriers have been explored to enhance the delivery of curcumin, ginsenosides, baicalin, resveratrol, gambogic acid and paclitaxel. Advanced strategies such as receptor-mediated uptake, blood-brain barrier penetration, pH- and redox-responsive release, microfluidic manufacturing, artificial intelligence-supported optimization, and personalized nanomedicine further improve therapeutic precision. Extraction yield varied significantly with solvent polarity, with methanol extract exhibiting the highest yield (38%), indicating efficient recovery of polar bioactive constituents. Physicochemical parameters confirmed the stability and quality of the extracts. Qualitative phytochemical analysis revealed the presence of alkaloids, flavonoids, phenols, tannins, saponins, steroids, glycosides, and proteins in different solvent extracts. Quantitative analysis demonstrated that CNBP is a rich source of carbohydrates, proteins, amino acids, dietary fiber, vitamins, lipids, cardiac glycosides, and essential minerals. Aqueous extracts exhibited higher protein (159.65 ± 0.41 mg BSA/g) and flavonoid contents (366.6 ± 0.57 mg QE/g), whereas methanolic extracts showed elevated phenols and alkaloids. Hydroethanolic extracts demonstrated higher amino acid concentrations, suggesting improved extraction efficiency for mixed-polarity biomolecules. Nevertheless, scalability, long-term stability, immunogenicity, cost, reproducibility, regulatory evaluation and clinical validation remain major barriers. Overall, nanotechnology-based natural product delivery represents a promising approach for targeted therapy in oncology, neuroprotection and inflammatory diseases, provided that translational and regulatory challenges are addressed systematically.

Keywords: *Dendrimers; Liposomes; Nano-Drug Delivery; Nanotechnology; Natural Products; Paclitaxel; Personalized Nanomedicine; Polymeric Nanoparticles;Targeted Delivery*

Received on :30th January 2026; Revised version received on :8th July 2026; Accepted:3rd August 2026

Introduction

Natural products synthesized by bacteria, plants, animals and fungi exhibit diverse chemical structures and notable bioactivities. Research in this field includes extraction, purification, structural elucidation by spectroscopic and chromatographic methods, and biological evaluation (Najmi *et al*., 2022). Historically, natural products have served as essential sources of medicines and drug templates by providing molecular scaffolds that are difficult to obtain through synthetic chemistry alone (Singh *et al*., 2025). Recent developments in separation science, high-throughput screening and analytical techniques, including gas chromatography-mass spectrometry (GC-MS), liquid chromatography-mass spectrometry (LC-MS), liquid chromatography-nuclear magnetic resonance (LC-NMR) and metabolomics, have accelerated discovery (Ekiert & Szopa, 2020; Newman & Cragg, 2020; Huang *et al*., 2024). Important examples include paclitaxel from the Pacific yew tree for oncology, penicillin as a foundational antibiotic, artemisinin for malaria and curcumin for antioxidant and anti-inflammatory applications. Marine-derived compounds have also gained importance in antiviral, antibacterial and anticancer research, with several candidates under clinical evaluation. (Ahmad *et al*., 2025; Banday *et al*., 2024) Despite this promise, the clinical development of natural products remains limited by formulation and pharmacokinetic barriers, making advanced delivery technologies essential for modern natural product drug development (Lv *et al*., 2023).

Challenges in Natural Product Translation

The translation of natural products into marketable drugs is frequently hindered by low aqueous solubility, chemical instability, enzymatic degradation, rapid first-pass metabolism, limited permeability, efflux transporter activity and variable composition arising from source, season, extraction method and processing conditions. These limitations may produce inconsistent exposure, short duration of action, high dose requirements and dose-related toxicity. In addition, laboratory-scale nanoformulations may fail during scale-up because of batch-to-batch variability, difficulty maintaining particle size distribution, excipient-related safety concerns, sterilisation challenges and the need for robust quality control. Recent reviews therefore emphasise that nano-drug delivery systems should not be presented only as solubility enhancers; they must also address stability, reproducibility, manufacturability, safety, regulatory documentation and clinically meaningful therapeutic benefit (Liu *et al*., 2024; Huang *et al*., 2024; Lv *et al*., 2024).

Fundamentals of Nanotechnology in Drug Design

Nanotechnology involves the design and application of materials within the 1-100 nm scale, utilizing distinct physical, chemical and biological properties for drug delivery, diagnostics and cancer therapy. Nanoparticles can improve absorption, targeted delivery and controlled release because of their small size, large surface area and modifiable surface chemistry. Deoxyribonucleic acid (DNA) nanotechnology and engineered nanostructures also support precision targeting and early disease detection, contributing to personalized treatment with reduced systemic toxicity. Nanocarriers address conventional drug delivery barriers by improving solubility, stability, biodistribution and targeting, while minimizing off-target exposure (Ezike *et al*., 2023; Iravani & Varma, 2022; Wróblewska *et al*., 2021; Li *et al*., 2024). The enhanced permeability and retention (EPR) effect can support tumor accumulation, although its clinical variability must be acknowledged rather than assumed to be universal. Material selection-polymers, lipids, inorganic materials or proteins-should be guided by drug properties, route of administration, biodegradability, toxicity and manufacturability. Thapa and Kim (2023), Halwani (2022), and Hussain *et al*. (2026) explained that targeted nanocarriers improve therapeutic action by using passive targeting through the enhanced permeability and retention effect and active targeting through ligand-mediated recognition, thereby increasing drug localization and reducing systemic toxicity.

Categories of Nanoformulations

Polymeric nanoparticles (PNPs) improve bioavailability, protect drugs and facilitate targeted delivery through surface functionalization (Begines *et al*., 2020). In cancer therapy, they enhance both imaging and treatment, for example through poly (lactic-co-glycolic acid) (PLGA) carriers for sustained terpenoid

delivery in hepatocellular carcinoma. Andrographolide (AG), derived from *Andrographis paniculata*, exhibits anti-inflammatory, anticancer and antiviral properties. It has been formulated into injectable PLGA microspheres for prolonged release using emulsion-solvent evaporation, optimized through response surface methodology (RSM) (Kulsirirat *et al*., 2021). Liposomes and solid lipid nanoparticles (SLNs) also enhance the solubility and bioavailability of hydrophobic drugs. SLNs, composed of physiological lipids and Generally Recognized as Safe (GRAS) surfactants, are classified into homogeneous matrix, drug-enriched shell and drug-enriched core models, each offering distinct release profiles. Viegas *et al*. (2023) and Khan *et al.* (2026) discussed nanoplatforms for the targeted delivery of phytochemicals such as curcumin, resveratrol, quercetin, and berberine as a strategy to enhance anticancer efficacy while minimizing toxicity. Bhajan *et al. (2026)* further reviewed nanoparticle-mediated delivery of bioactive natural products in cancer therapy and highlighted that liposomes, polymeric nanoparticles, metallic nanoparticles, and biopolymer-based carriers can improve solubility, pharmacokinetics, tumor accumulation, and controlled release. Gao *et al. (2025)* described nano-drug delivery systems as useful platforms for improving the stability, bioavailability, and disease-targeted applications of natural products, while also noting the need for stronger clinical translation evidence.

Enhanced Solubility of Gambogic Acid and Baicalin for Cancer Therapy

Gambogic acid (GA), a xanthone derived from *Garcinia hanburyi*, demonstrates anticancer properties. However, its clinical use is limited by poor solubility, short half-life, systemic toxicity and formulation instability (Liu *et al*., 2020). GA-mPEG2000 micelles, synthesized through direct dissolution and ultrasonication, improved solubility and suppressed tumor growth in murine models (Chen *et al*., 2012). Baicalin, a flavone glycoside derived from *Scutellaria baicalensis*, exhibits antioxidant and anticancer properties. However, its oral bioavailability is very low because of poor solubility, limited permeability and extensive metabolism (Wei *et al*., 2016). Baicalin-loaded nanoemulsions (Figure 1), optimized with excipients such as soy lecithin, Tween 80, PEG 400 and isopropyl myristate, can improve solubilization and absorption, thereby supporting their potential application in liver cancer therapy (Singh *et al*., 2021; Wang *et al*., 2022).

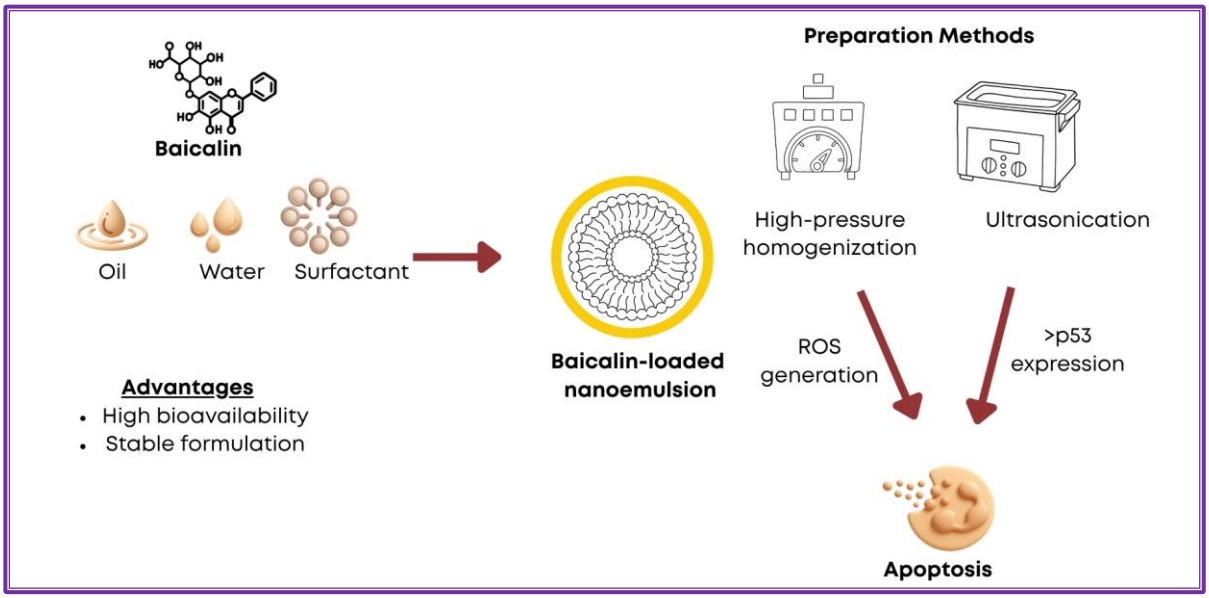


Figure 1:*Baicalin-Loaded Nanoemulsion System for Cancer Therapy. The Figure Illustrates Formulation Components, Nanosized Droplet Formation, Solubility Enhancement and Proposed Apoptosis-Related Anticancer Mechanisms*

Dendrimers as Nanocarriers for the Delivery of Drugs Obtained from Natural Products

Dendrimers, also known as dendritic polymers, are nanoscale drug delivery systems (1–100 nm) that enhance bioavailability by improving drug solubility. Alkaloids such as quinoline, quinolizidine, and indole exhibit antitumor, anti-inflammatory, and immunosuppressive properties. However, they are

characterized by low stability, solubility, and bioavailability (Madaan *et al*., 2014; An *et al*., 2023; Giuliani *et al*., 2018; Wang *et al*., 2017; Chen *et al*., 2011). For example, berberine (BBR) demonstrates an oral bioavailability of only 0.68%. PEGylated dendrimer conjugates, created through biotinylation cross-linking, improve circulation, optimize tumor targeting, and enable controlled release while reducing side effects (Yadav *et al*., 2023; Kyriakoud *et al*., 2021). Polyphenols—including phenolic acids, flavonoids, tannins, stilbenes, and lignans also face challenges of poor solubility and stability (Blanco *et al*., 2015 & Liu *et al*., 2023). Quercetin, despite its strong anticancer properties, has extremely low aqueous solubility (0.000171 mg/mL), a limitation addressed by PAMAM dendrimers through amine-group interactions and encapsulation (Figure 2). Targeted systems such as margetuximab-PEG-PAMAM dendrimers and folic acid-modified Fe_3O_4 nanoparticles enhance selective cancer cell uptake, induce apoptosis via Bax and caspase-9 activation, and improve anticancer efficacy (An *et al*., 2023 & Wang *et al*., 2022). Mesoporous silica nanoparticles (MSNs), exemplified by MCM-41 with 5.4 nm pores, offer a high surface area and tunable surface chemistry for drug loading and targeted delivery. Hollow silica nanoparticles (HSNs), produced via templating or sol–gel methods, further enhance pore volume (Giuliani *et al*., 2018; Wang *et al*., 2017; Chen *et al*., 2011). Nanocarrier design faces several challenges: (i) drug–polymer compatibility, exemplified by curcumin (CUR) from *Curcuma longa*, where phosphocholine-based liposomal encapsulation improves stability and delivery; (ii) scalability, hindered by synthesis variability but improved through techniques such as membrane extrusion, SC-CO_2 methods, continuous flow, microfluidics, and spinning-disc processing; and (iii) stability, threatened by lipid oxidation or hydrolysis but mitigated by using saturated lipids and optimized formulations (Kyriakoud *et al*., 2021).

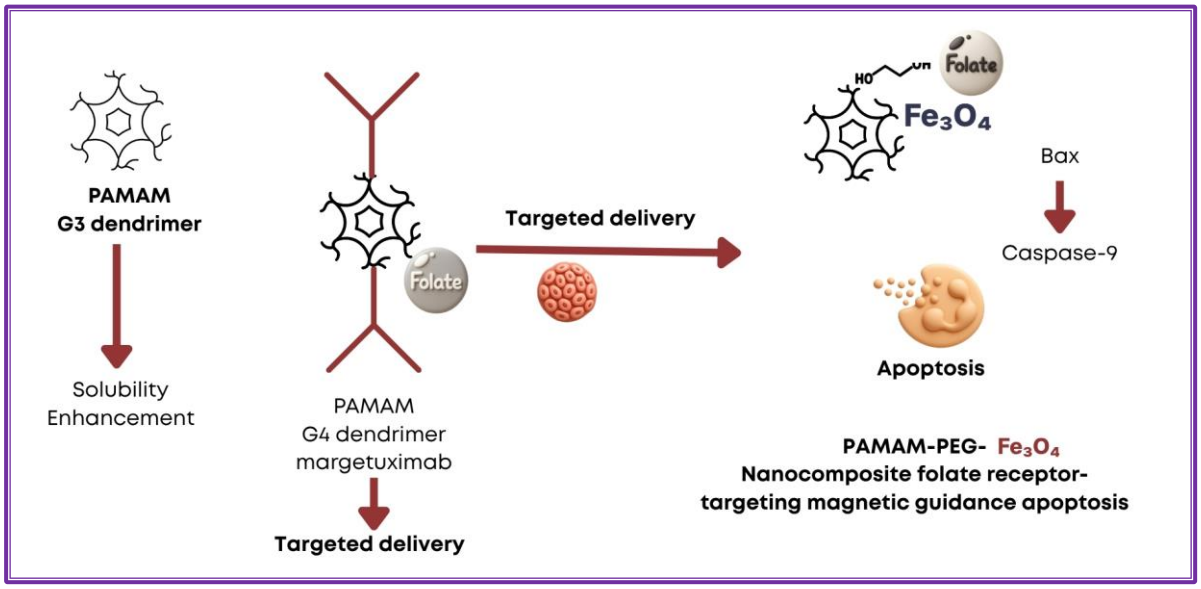


Figure 2. *Dendrimer Nanocarriers for Quercetin Delivery in Cancer Therapy. The Figure Shows Solubility Enhancement, Ligand-Mediated Targeting, Magnetic Guidance and Apoptosis-Associated Mechanisms*

Systematic approaches such as Quality by Design (QbD) can statistically optimize nanoprecipitation parameters, including polymer concentration, solvent-to-antisolvent ratio, mixing rate, surfactant concentration and temperature (Thomas-Moore *et al*., 2022; Naziris *et al*., 2023). In nanoprecipitation, polymer or lipid solutions in water-miscible organic solvents such as ethanol, acetone or tetrahydrofuran (THF) are introduced into aqueous non-solvents, forming nanoparticles through solvent displacement and the "Ouzo effect"; however, aggregation and particle growth remain important risks (Beck-Broichsitter, 2021; Lepeltier *et al*., 2014). Computational modelling and molecular dynamics simulations can further predict drug-carrier interactions and support rational design of stable nanocarriers before scale-up (Boggula *et al*., 2022; & Stipa *et al*., 2021).

Applications for Nanotechnology in Natural Product Delivery

Ginsenoside Compound K: A54 Peptide-Modified Micelles for Liver Cancer Models

Ginseng (*Panax ginseng*) is a medicinal herb with distinctive therapeutic and health-promoting properties. Compound K (CK) is an active metabolite generated through the conversion of major ginsenosides and shows improved bioavailability and solubility compared to its parent ginsenosides. The primary pharmacologically active constituents of ginseng are triterpene glycosides, commonly referred to as saponins, and specifically named ginsenosides or panaxosides (Sharma & Lee, 2020). The A54 peptide, when modified and PEGylated to form APCssA (A54-PEG-CSO-ss-SA), functions as a reduction-cleavable glucolipid conjugate capable of delivering doxorubicin into cells. The APCssA/DOX system achieved tumor growth inhibition comparable to commercial doxorubicin hydrochloride but without side effects. Results indicated that APCssA/DOX holds strong potential for more effective tumor therapy through tumor-specific targeting, selective intracellular drug release, synergistic enhancement of antitumor activity via the EPR effect, and reduced toxicity to normal tissues. (Liu *et al*., 2016) One study demonstrated CK's role in liver cancer by evaluating its effects on HepG2 and SMMC-7721 cells, as well as xenografts of human hepatocellular carcinoma (HCC) mice. CK was shown to inhibit the DNA-binding activity of STAT3 in these cells. Furthermore, inhibition of STAT3 via CRISPR/Cas9 technology led to a compensatory increase in CK-induced endoplasmic reticulum stress and cell death. In human liver cancer cells, CK exerts an apoptosis-inducing effect through the inhibition of p-STAT3. Another study revealed that CK counteracts nuclear factor-kappa B (NF-κB) by primarily targeting Annexin A2, ultimately producing cytotoxic effects via proliferation arrest [57]. Previous research also found that CK suppresses cell proliferation and induces apoptosis in the MHCC97-H hepatocellular carcinoma cell line through Fas- and mitochondria-mediated caspase-dependent pathways. This was accompanied by inhibition of Akt phosphorylation, downregulation of pro-caspase-3 and -9, and upregulation of Fas, FasL, and the Bax/Bcl-2 ratio. A separate report established a synthetic route to a mono-octyl ester of CK (CK-O) to evaluate its anticancer activity. *In vitro*, CK-O exhibited cytotoxic and apoptosis-inducing properties in murine H22 cells, and *in vivo* effects were dose-dependent. More recently, studies have focused on CK's role in suppressing the proliferation of human liver cancer cells via regulation of the HIF-1α–glycolysis pathway. CK was shown to downregulate Bcl-2-associated transcription factor 1 in hypoxia-exposed liver cancer cells, as well as inhibit the HIF-1α–mediated glycolysis pathway that otherwise promotes tumor proliferation (Zhou *et al*., 2022).

Curcumin: Hyaluronic Acid-Coated Ethosomes for Psoriatic Skin Delivery

Curcumin, a natural compound found in the rhizomes of *Curcuma longa*, modulates gene expression, regulates cellular signaling pathways, and interacts with receptors, enzymes, and co-factors. It inhibits the expression of key inflammatory mediators, including interleukins, tumor necrosis factor, and nuclear factor κB, which regulate genes associated with skin inflammation (Waghule*et al*., 2020). Psoriasis is a chronic immune-mediated skin disease that is difficult to treat and prone to recurrence. Patients face both physical and psychological challenges, as keratinocyte hyperplasia produces scaly, plaque-like lesions that lead to severe itching and discomfort (Ding *et al*., 2022). Curcumin nanoparticles can be engineered to manipulate release profiles and enhance chemical stability (Rahiman *et al*., 2022). For HA-ES preparation, Hyaluronic Acid (HA) was covalently conjugated to propylene glycol-based ethosomes and used as a carrier for topical curcumin therapy. Plant-derived ethosomes served as control formulations for comparison in an imiquimod-induced animal model. The HA-ES system, supported by the HA gel network, reduced curcumin leakage and significantly improved its transdermal delivery compared to ES. After 8 hours, cumulative transdermal penetration and skin retention were 1.6- and 1.4-fold higher, respectively, than with ES, and 3.1- and 3.3-fold higher than with the curcumin Propylene Glycol Solution (PGS). *In vivo*, curcumin retention in psoriatic skin was 2.3- and 4.0-fold greater with HA-ES than with ES or PGS. Psoriasis-like skin induced by imiquimod expressed CD44 at 2.7-fold higher levels than normal skin. The specific binding of HA-ES to CD44 increased drug accumulation, as confirmed by immunostaining. Topical HA-ES treatment in mice alleviated inflammatory symptoms and reduced expression of TNF-α, IL-17a, IL-17f, IL-22, IL-1β (mRNA), and

CCR6 (protein), compared with ES and PGS groups. HA-ES effectively targeted highly expressed CD44 in psoriatic tissue, enhancing curcumin uptake in inflamed regions. This innovative approach shows promise for developing topical drug delivery systems for inflamed and aggravated skin. Zhang *et al*. (2019) and Lu *et al. (2025)* reviewed nanotechnology-based transdermal treatment of allergic skin diseases with natural drugs and reported that polymeric nanoparticles, lipid-based nanocarriers, inorganic nanostructures, microneedles, and hydrogel systems can enhance solubility, skin permeation, lesion targeting, and sustained release.

Targeted Delivery Mechanisms

Receptor-Mediated Uptake: Galactosylated Chitosan Nanoparticles for ASGPR-Targeted Triptolide Delivery

The cross-linking technique using tripolyphosphate was employed to prepare galactosylated chitosan–triptolide nanoparticles (GC-TP-NPs), which demonstrated high drug-loading capacity for targeted delivery to hepatocellular carcinoma (HCC) (Figure 3). GC-TP-NPs exhibited a sustained-release profile, favorable in vitro asialoglycoprotein receptor binding and cellular uptake, high hepatic tumor accumulation *in vivo*, and reduced systemic and male reproductive toxicities compared with free triptolide (TP) (Zhang *et al*., 2018).

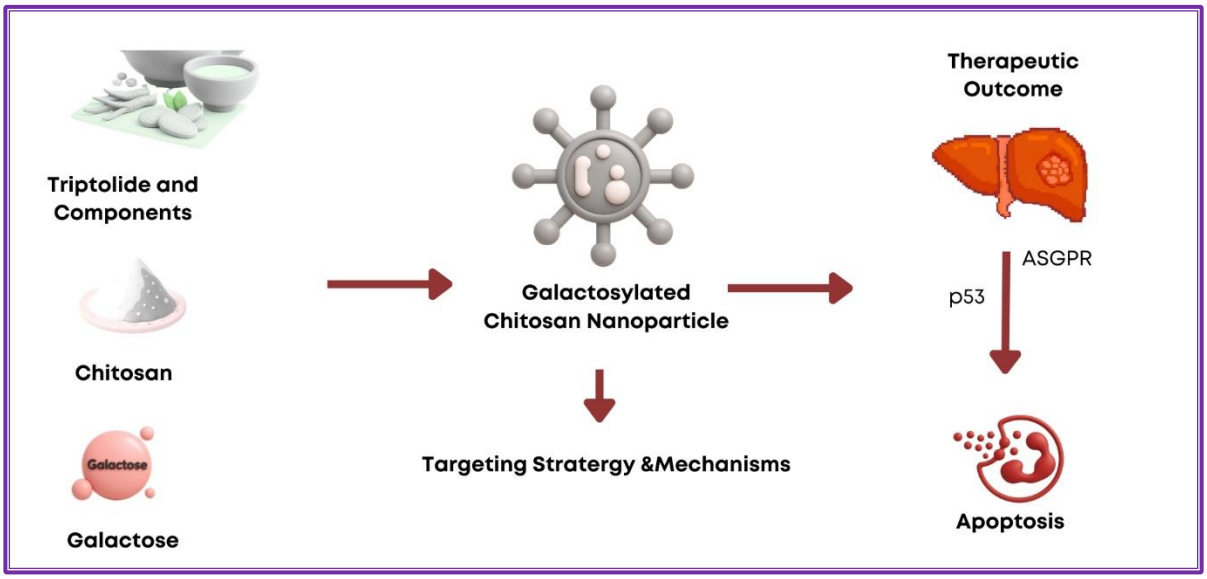


Figure 3: *Galactosylated Chitosan Nanoparticles for Targeted Triptolide Delivery to Liver Cancer. The Figure Summarises ASGPR-Mediated Targeting and Apoptosis-Related Therapeutic Outcomes*

The asialoglycoprotein receptor is a carbohydrate-specific, calcium-dependent type C lectin that is predominantly expressed on the hepatic plasma membrane of hepatocytes (Das *et al*., 2019). Although TP shows strong potency against various cancers, including HCC, its clinical application is limited by severe toxicity, poor solubility, and uncertain targeting mechanisms. To overcome these limitations, GC-TP-NPs were designed as receptor-targeted nanocarriers with improved drug-loading efficiency (Slowing *et al*., 2007; Fatima *et al*., 2025). GC-TP-NPs preserved the anticancer activity of free TP, maintaining its pro-apoptotic and anti-proliferative effects in HCC cells *in vitro* while providing additional benefits of enhanced tumor reduction *in vivo*. Further studies revealed that GC-TP-NPs induce apoptosis in cancer cells through inhibition of the TNF/NF-κB/BCL2 signalling pathway. Zhang *et al*. (2019) and Muteeb *et al*. (2025) reviewed advanced delivery systems for natural products in hepatocellular carcinoma and emphasized that nanocarriers can improve drug stability, targeted delivery to liver cancer cells, controlled release, and reduction of non-specific toxicity. Kumar *et al. (2026)* discussed nanotechnology-based targeted drug delivery systems for breast cancer and highlighted the promise of liposomes, polymeric nanoparticles, and quantum dots in improving tumor-specific delivery through active and passive targeting approaches.

Blood-Brain Barrier (BBB) Penetration: RVG29 Peptide-Modified Nanoparticles for Baicalin Neuroprotection

Considerable attention has been directed toward neuroprotection in cerebral ischaemia. Effective delivery of therapeutic agents to the brain remains a major challenge due to the complexity of the brain environment. Nose-to-brain delivery has emerged as a promising approach. In this study, a neuroprotective nanocarrier system was optimized for intranasal administration by formulating RVG29 peptide-bearing polyethylene glycol/polylactic acid-co-glycolic acid nanoparticles (PEG/PLGA RNPs) (Stipa *et al*., 2021). These nanoparticles were designed to provide controlled and sustained drug release, thereby improving the bioavailability of neuroprotective agents. Specifically, RVG29-decorated PEG/PLGA nanoparticles were used to deliver Baicalin (BA) for targeted brain therapy. Their brain delivery characteristics were evaluated *in vivo* by monitoring the uptake of DiR-labelled formulations in rats. The therapeutic efficacy of BA-loaded nanoparticles was further tested in a rat model of cerebral ischemia induced by Middle Cerebral Artery Occlusion (MCAO). Results demonstrated improved brain delivery and therapeutic performance compared with conventional preparations. This research highlights a potential strategy for enhancing the clinical use of BA and provides a basis for the development of new natural medicines for ischemic brain injury. An NP preparation process was also established based on NBDD, serving as a platform for processing natural medicines into effective neuroprotective formulations (Li *et al*., 2022).

Stimuli-Responsive Delivery Systems

pH-Responsive Carriers: Metal-Polyphenol Networks for Shikonin Release in Tumour Microenvironments

Antitumor drugs can be delivered using pH-responsive polymer nanoparticles, which release their therapeutic payload within tumor tissues after penetrating the tumor microenvironment. pH-sensitive nanomaterials are broadly classified into three groups: organic (e.g., liposomes, polymer micelles, polymer capsules, nanogels, dendrimers), inorganic (e.g., carbon, silica, gold nanoparticles), and composite systems (e.g., metal–organic frameworks and metal–phenolic networks). These nanomaterials exhibit diverse architectures, including linear (e.g., homopolymers, diblock and multiblock copolymers, organic–inorganic hybrids), branched (branched or hyperbranched polymers), and network (grid-like) structures. Among these, amphiphilic block copolymers and linear homopolymers are most widely utilized, with the latter often forming dendritic macromolecules, vesicles, nanogels, and micelles. Because pharmaceutical compounds differ greatly in physicochemical properties, the choice of nanomaterial must be tailored to the specific drug. Antitumor agents can be incorporated into pH-responsive polymer systems through three primary loading strategies: (i) physical encapsulation, (ii) intermolecular interactions, and (iii) covalent chemical bonding between the drug and the polymer matrix (Tang *et al*., 2018).

Mechanism of pH-Responsive Carriers in Tumour Therapy

pH-responsive polymer nanoparticles loaded with antitumor drugs can selectively release their payload in tumor tissues by exploiting the acidic microenvironment. These systems employ mechanisms such as polymers that alter charge characteristics under pH shifts or chemical linkages that hydrolyse in acidic conditions. By responding to environmental pH fluctuations, the nanocarriers undergo structural changes that trigger drug release, remove protective barriers, and promote carrier disassembly at tumor sites. This enhances targeted drug delivery and improves therapeutic efficacy (Chu *et al*., 2022).

Metal-Polyphenol Networks

In recent years, metal–phenolic networks (MPNs) have attracted considerable attention in bionics, materials science, and biomedicine. The pyrogallol functional group within polyphenols confers several valuable biological properties, including strong adhesion, versatile drug-loading capacity, stimuli-responsive dissociation, controlled drug release, photothermal conversion, and Fenton reaction activity. Many polyphenolic compounds such as tannins, epigallocatechin gallate, ellagic acid, and gallic acid share this functional group, enabling MPNs to serve as multifunctional platforms for diagnosis and

therapy (Chang *et al*., 2023). While MPNs are primarily studied as nanocarriers for the transport and release of metal ions, their intrinsic polyphenol bioactivities are often overlooked. Notably, MPNs have not previously been reported to induce ferroptosis and necroptosis in tumor cells while simultaneously enhancing immunogenicity to boost immunogenic cell death (ICD)-mediated anticancer immunity. To address these issues, we developed Fe^{3+}–Shikonin MPNs (FeShik) as multifunctional nanomedicines and immunoadjuvants for tumor vaccination. FeShik nanomedicines overcome the major drawbacks of shikonin, including high toxicity to healthy tissues and poor bioavailability, by combining its therapeutic activity with the biological functions of Fe ions. They also prolong blood circulation, enhancing antigen accumulation in tumor tissues. Following phagocytosis by tumor cells, FeShik nanomedicines disintegrate in the tumor microenvironment, releasing Fe^{2+} and Shikonin. This triggers ferroptosis and necroptosis while also promoting macrophage repolarization, cytotoxic T lymphocyte infiltration, dendritic cell maturation, and antigen cross-presentation. These processes, together with ICD-induced tumor cell lysates and pro-inflammatory cytokine release, activate robust adaptive immune responses against solid tumors. FeShik nanomedicines harness the complementary activities of Shikonin and Fe^{3+}/Fe^{2+} ions through supramolecular interactions to provide multiple therapeutic benefits, including tumor accumulation, direct tumor eradication, modulation of the immunosuppressive microenvironment, and safe biodegradation after therapy. Furthermore, tumor-fragment-loaded FeShiknanovaccines (TF@FeShik) demonstrated long-term immune memory against metastasis and recurrence, a strong abscopal effect to suppress distant tumor growth, and effective eradication of primary tumors (Feng *et al*., 2023).

Redox-Sensitive Nanoparticles: Disulphide Bonds for Intracellular Gambogic Acid Release

Redox potential differs significantly between extracellular and intracellular environments, as well as between healthy and malignant tissues. Glutathione (GSH; γ-glutamyl-cysteinyl-glycine) concentrations are markedly higher in cancer cells compared with normal cells. Within the cytosol and subcellular compartments such as lysosomes and endosomes, GSH levels reach 2–10 mM, which is 100–1000 times greater than extracellular concentrations (2–10 μM). Exploiting this physiological gradient, researchers have developed redox-sensitive nanocarriers that remain stable during circulation but rapidly degrade within tumor cells, thereby triggering controlled drug release (Han *et al*., 2017). One such agent is gambogic acid (GA; $C_{38}H_{44}O_8$), a bioactive xanthone isolated from the brownish-orange resin of the *Garcinia hanburyi* tree. Owing to the wide distribution of G. hanburyi in East Asia and India, along with the simplicity of its extraction, GA is readily available for pharmacological applications. GA was first reported in peer-reviewed scientific research in 1966 (Hatami *et al*., 2020).

Gambogic Acid-Based Redox-Responsive Co-Delivery Systems

Stimuli-responsive co-delivery systems can be engineered by introducing functional groups that enable controlled release, targeted distribution, and regulated drug delivery. These devices exploit endogenous stimuli such as redox potential, pH, temperature, and enzymatic activity, as well as exogenous stimuli including heat and light, to achieve site-specific therapeutic action. Among these, redox sensitivity driven by the intracellular-to-extracellular redox potential gradient is particularly important. The elevated reducing capacity of tumor cells compared with normal cells enables rapid payload release in redox-triggered drug delivery while maintaining stability in extracellular environments. Redox-sensitive nanocarriers often employ disulphide linkages in the main chain, side chain, or crosslinkers, which undergo thiol–disulphide exchange reactions with intracellular reducing agents such as glutathione (GSH). This mechanism induces swelling and disintegration of the nanocarrier, thereby promoting drug release. Poly (amido amines) (PAAs) containing disulphide bonds have shown enhanced binding affinity for siRNA, good buffering capacity, and low cytotoxicity, making them attractive cationic polymers for gene delivery. Reducing enzymes can cleave disulphide bonds in degradable PAAs, enabling siRNA or shRNA release into the cytoplasm and nucleus while maintaining stability in the extracellular medium. Furthermore, reducible branched PAAs have been modified with various functional side groups, which significantly increase transfection efficiency compared with the standard reference polymer polyethyleneimine (PEI, 25 kDa). Although relatively few studies have been conducted, these systems show promise as co-delivery carriers for combining chemotherapy and gene

therapy. Gambogic acid (GA), the principal component of gamboge resin, exhibits potent antitumor activity against cancers such as leukemia, breast cancer, and melanoma. In one study, GA was conjugated to PAAs via amide bonds, producing a novel co-delivery system for small-molecule drugs and plasmid shRNA. The resulting GA-conjugated PAAs (PAG), an amphiphilic block copolymer, self-assembled into micelles in aqueous solution, with PAAs forming the hydrophilic shell and GA acting as the hydrophobic core. This dual-function system provides both intrinsic anticancer activity from GA and carrier capability for gene and drug co-delivery. Unlike conventional amphiphilic copolymer micelles, PAG micelles exhibit inherent anticancer properties, while their disulphide linkages enable rapid, reductant-triggered release of cargo in the cytoplasm (Jiao *et al*., 2016).

Translational Case Studies

Paclitaxel: Albumin-Bound Nanoparticles and Recent Paclitaxel Nanomedicine Developments

Paclitaxel (PTX) was first isolated from *Taxus brevifolia* in 1966, purified in 1969 and structurally elucidated in 1971 (Chen *et al*., 2022). Although PTX is one of the most effective anticancer agents, conventional formulations are limited by poor water solubility, excipient-related hypersensitivity reactions, nonlinear pharmacokinetics and dose-limiting neurotoxicity. Albumin is an attractive nanocarrier because of its biocompatibility, drug-binding capacity and involvement in endogenous transport pathways. Nanoparticle albumin-bound paclitaxel (nab-paclitaxel; Abraxane) remains an important clinically translated benchmark because it delivers PTX without Cremophor EL and supports improved dosing convenience and tumor exposure. The clinical relevance of nab-paclitaxel should be presented as a translated benchmark rather than as a recent discovery. According to current drug information, paclitaxel albumin-stabilized nanoparticle formulation is FDA-approved for metastatic breast cancer after prior chemotherapy, metastatic non-small cell lung cancer in combination with carboplatin for patients unsuitable for curative surgery or radiation, and metastatic pancreatic cancer in combination with gemcitabine as first-line therapy. (National Cancer Institute, 2024) Recent work has shifted toward improving PTX delivery further through polymeric nanoparticles, pH-responsive micelles, redox-responsive micelles, ligand-functionalized carriers, nanobubbles, biomimetic systems, and combination nanotherapies designed to enhance tumor accumulation, overcome multidrug resistance and reduce systemic toxicity (Raza *et al*., 2022). Recent pharmacovigilance analysis of Abraxane-related adverse events also highlights the need for continuous post-marketing surveillance, particularly for hematological, hepatobiliary, infectious, gastrointestinal and neuropathy-related events (Zhao *et al*., 2024). Therefore, future paclitaxel nanomedicine development should balance improved targeting and efficacy with long-term safety, reproducible manufacturing and regulatory comparability.

Resveratrol: Transferrin-Conjugated Liposomes Inducing Glioblastoma Apoptosis through Caspase-3/7 Activation

Glioblastoma (GBM) is the most common primary malignant brain tumor, accounting for a substantial proportion of primary central nervous system (CNS) neoplasms. Genetically, GBMs are heterogeneous: primary GBMs with isocitrate dehydrogenase 1 (IDH1) mutations are relatively uncommon, tend to occur in younger patients and share features with secondary GBMs, which are often characterized by TP53 mutations but lack epidermal growth factor receptor (EGFR) amplification. This biological heterogeneity makes targeted delivery particularly relevant for improving drug accumulation in tumor tissue while limiting off-target toxicity. Resveratrol (RES) encapsulated in transferrin-conjugated liposomes (Tf-RES-L) has been investigated for its potential to induce apoptosis in U-87 MG GBM cells. Using the Apo-ONE® assay, Tf-RES-L at 50 μM produced significantly greater caspase-3/7 activation compared with free RES or standard RES-loaded liposomes (RES-L), indicating enhanced pro-apoptotic efficacy through targeted delivery. At 200 μM, caspase activation was similar across all formulations, although Tf-RES-L showed slightly higher activity, confirming its role in promoting GBM cell apoptosis via caspase-3/7 activation (Jhaveri *et al*., 2018).

Safety, Regulatory and Manufacturing Challenges

Inorganic Nanoparticles: Potential Oxidative Stress Induced by Silver or Gold Nanoparticles

Gold nanoparticles (GNPs) range in size from 2 to 100 nm, with optimal cellular uptake typically observed at 20–50 nm. Particles in the 40–50 nm range show efficient tumor penetration but may also exhibit size-dependent toxicity, while larger particles (80–100 nm) tend to localize near blood vessels (Herdiana *et al*., 2022). The size of GNPs can be tuned during synthesis and functionalization, which is influenced by the thiol-to-gold ratio; higher thiol concentrations promote the formation of larger, non-nanoscale particles (Wei *et al*., 2025; Hennebelle *et al*., 2024). GNPs are valued for their biocompatibility, selective distribution via blood flow, and low cytotoxicity to normal cells. They can be synthesised through physical, chemical, or biological methods, although physical methods yield low quantities, chemical approaches rely on hazardous reagents, and biological (green) synthesis offers an environmentally sustainable alternative. GNPs exist in diverse morphologies, including nanorods, shells, cages, and spheres (Vivero-Escoto & Huang, 2011). Silver nanoparticles (AgNPs), once regarded only as bulk metallic silver, now display nanoscale-specific properties that support wide biomedical applications, especially in cancer therapy. AgNP-based biosensors exhibit optical activity, alongside antibacterial, antifungal, antiviral, anti-inflammatory, and osteoinductive effects. In oncology, both GNPs and AgNPs accumulate in tumour cells via passive diffusion, active targeting, or ligand–receptor interactions. AgNPs release silver ions (Ag^+), which generate intracellular free radicals that disrupt mitochondrial function, modulate p53, and activate caspase-3, ultimately triggering apoptosis. After endocytosis, AgNPs degrade in lysosomes, releasing ions that react with thiol groups in enzymes. At low doses, AgNPs may induce DNA damage and chromosomal alterations without causing systemic toxicity. Additionally, green-synthesised gold and silver nanoparticles derived from *Cornus mas*, a plant rich in flavonoids and phenolics, demonstrated significant antiproliferative activity against DLD-1 colorectal cancer cells. These nanoparticles were characterized using transmission electron microscopy (TEM), zeta potential analysis, hydrodynamic diameter measurement, ultraviolet-visible spectroscopy (UV-Vis), energy-dispersive X-ray spectroscopy (EDX) and X-ray diffraction (XRD) (Bidian *et al*., 2023).

Immune Recognition: Opsonisation of PEGylated Carriers and Its Impact on Circulation Time

Polyethylene glycol (PEG) is widely employed in pharmaceuticals, cosmetics, and drug delivery systems. PEGylation—the process of attaching PEG chains to nanoparticles—enhances drug stability, reduces toxicity, and prolongs systemic circulation. However, PEGylated nanocarriers can also induce immunogenic responses, potentially limiting their long-term or repeated clinical use (Schneider *et al*., 2020). By reducing phagocytosis and opsonization, PEGylation significantly extends nanoparticle half-life. A notable example is Doxil® (FDA-approved in 1995), the first PEGylated liposomal formulation of doxorubicin. Doxil® made doxorubicin about three times more available in the body. Its plasma half-life was about 72 hours, and its circulation half-life was about 36 hours. Furthermore, the density of PEG on nanoparticle surfaces plays a critical role in modulating delivery efficiency, with demonstrated advantages in systemic, mucosal, and ocular drug delivery applications (Suk *et al*., 2016).

Regulatory Hurdles

Approved nanomedicines demonstrate enhanced efficacy, bioavailability, targeting or safety by leveraging nanoparticle properties such as high surface-area-to-volume ratio, tuneable composition and modifiable surfaces. However, regulatory and translational hurdles persist, including physicochemical complexity, limited market scale, ethical and environmental concerns, risk of market failure, high development costs and difficulty demonstrating sameness for follow-on nanomedicines. Current development therefore requires rigorous characterization of particle size distribution, surface charge, morphology, drug loading, release profile, sterility, stability, biodistribution, immunogenicity and batch reproducibility. Overcoming these barriers will require robust regulatory frameworks, sustainable investment and strengthened public trust to support translation from laboratory innovation to mainstream healthcare (Musazzie *et al*., 2023; Farjadian *et al*., 2019; Abdel-Mageed *et al*., 2021). Recent reviews consistently indicate that clinical translation remains limited by large-scale

manufacturing, reproducibility, regulatory approval, long-term safety, and cost-related barriers; therefore, natural product nanomedicines require rigorous quality control and clinically meaningful efficacy data before routine therapeutic use (Bhajan *et al*., 2026; Gao *et al*., 2025).

Future Perspectives and Personalized Nanomedicine

Predictive Modelling and High-Throughput Screening in Nanomedicine

Machine learning (ML) is increasingly applied to optimize nanoparticle parameters such as size, charge, shape, and drug-release profiles, thereby enhancing targeted delivery and reducing side effects. Both organic and inorganic nanoparticles, as well as hybrid systems, undergo *in vitro* and *in vivo* release evaluations, where drug release is influenced by factors including protein binding, enzymatic degradation, and formulation properties. *In silico* approaches employing artificial intelligence (AI) have been used to design nanoparticles for cancer therapy by analyzing biological datasets and predicting optimal configurations, thus improving therapeutic index and minimizing toxicity. High-throughput screening (HTS), combined with AI-based algorithms, enables the rapid identification of synergies between natural products and nanocarriers, while also mapping molecular targets, drug–drug interactions, and mechanistic pathways.

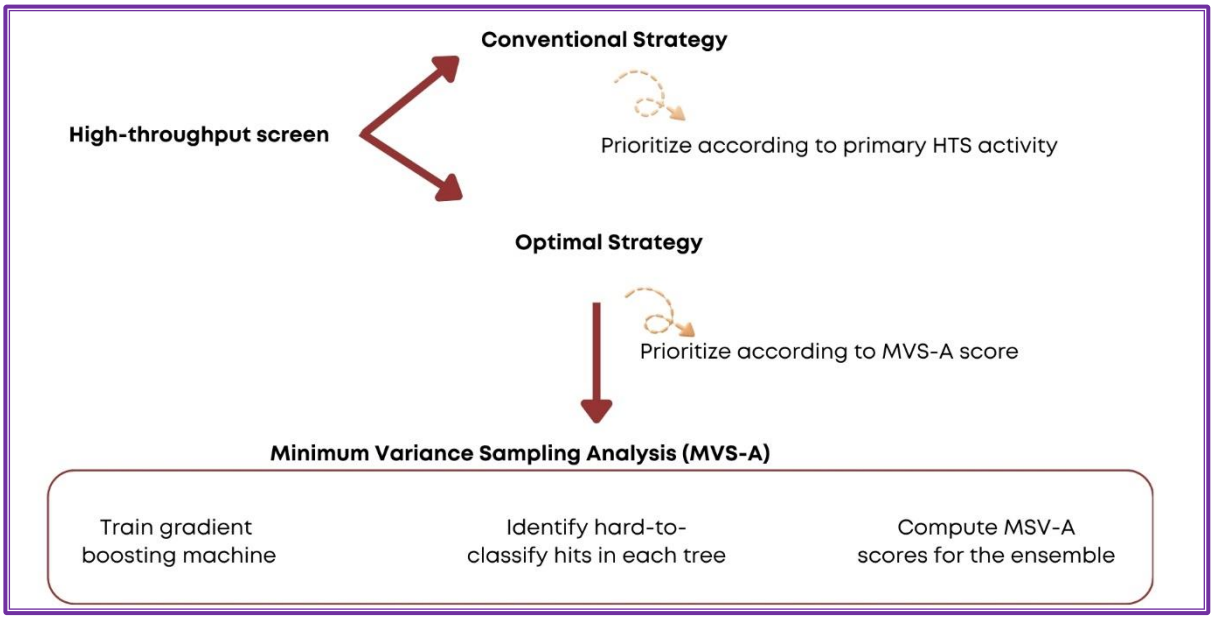


Figure 4: *Predictive Modelling and High-Throughput Screening in Nanomedicine. The Figure Shows How Minimum Variance Sampling Analysis Can Support Prioritisation of Formulation Candidates*

The integration of artificial intelligence (AI), high-throughput screening and nanotechnology holds transformative potential but faces challenges related to limited high-quality datasets, poor model interpretability, cross-disciplinary knowledge gaps, data privacy, algorithmic bias and equitable access. (Mao *et al*., 2024) These constraints should be addressed through transparent reporting, external validation, experimentally verified predictions and ethical governance before AI-driven nanomedicine can be reliably translated (Figure 4).

Continuous Manufacturing

The continuous manufacturing of poly (lactic-co-glycolic acid) (PLGA) nanoparticles using ovalbumin as a model protein offers a scalable and efficient production method. Spray drying, when combined with double emulsification, enables rapid solvent removal, transforming nanoparticle suspensions into dry powders commonly referred to as “Trojan particles” or nanoparticles-in-microparticles (Shur *et al*., 2012; Pasero *et al*., 2024; Kállai-Szabó *et al*., 2024). In this approach, nanoparticle size is determined by feed atomization rather than dispersed-phase droplet size. PLGA/PVA double emulsions produced by spray drying yield nanoparticles comparable in size to those obtained through direct solvent displacement

(Paczkowska-Walendowska *et al*., 2021). Although excipient type does not markedly influence particle size, the surfactant P-407 reduces hydrodynamic diameter, suggesting it could replace PVA at the liquid–liquid interface. PVA remains the most effective stabilizer for double emulsions, particularly when combined with trehalose and leucine, resulting in high yields and uniform particle distributions. To achieve fully continuous and commercially viable nanoparticle production, emulsification processes must be further optimized or replaced with innovative methods such as microfluidics.

Microfluidic Systems

Microfluidics enables the on-demand synthesis of Lipid Nanoparticles (LNPs) for personalized dosing, offering advantages over conventional liposome production methods, which are solvent-intensive, costly, and limited in scalability (Piunti & Cimetta, 2023; Liu *et al*., 2022; Wang *et al*., 2024). Liposomes are biocompatible vesicles composed of cholesterol and phospholipids (Butreddy *et al*., 2021). They share structural similarities with extracellular vesicles but differ in molecular composition and complexity. Microfluidic platforms allow the one-step generation of monodisperse liposomes (20–100 nm) with tunable size and surface properties by adjusting flow rates, device geometries, solvent polarities, and lipid precursor compositions (Kias & Bodmeier, 2024). Techniques such as hydrodynamic flow focusing (HFF) and micromixer-based methods provide precise control over liposome characteristics, making microfluidics a powerful approach for the development of drug delivery systems (DDS).

Personalized Nanomedicine

Personalized nanomedicine aims to match nanocarrier design, drug selection, dose and treatment schedule with patient-level biological information, tumor phenotype, disease stage, organ function and treatment response. Rather than designing a completely unique product for every individual, a more practical approach is to develop nanomedicine strategies for molecularly defined patient subgroups and then refine treatment using imaging, biomarkers and therapeutic monitoring. Recent precision nanomedicine discussions emphasize targeted drug delivery, tumor biomarker detection, *in vivo* imaging and treatment monitoring as the most realistic near-term applications (Mao *et al*., 2024). In this context, nanomedicine can support personalized therapy by improving drug accumulation in selected tissues, enabling co-delivery of synergistic agents, incorporating stimuli-responsive release mechanisms and integrating diagnostic or imaging functions. However, clinical implementation requires evidence that the nanocarrier improves outcomes beyond standard therapy, identifies the patients most likely to benefit and maintains acceptable safety, cost and manufacturability.

Challenges in Personalized Nanomedicine

Personalized nanomedicine encompasses prediction, treatment and prevention at the individual or subgroup level. The growth of pharmacogenomics, proteomics, metabolomics, single-cell analysis and imaging has expanded the information available for patient stratification. However, the presence of biological data alone does not guarantee therapeutic success; the nanocarrier must still cross biological barriers, avoid rapid immune clearance, release the payload at the intended site and produce a clinically meaningful effect. Despite these advances, only a limited number of nanomedicine products currently support truly personalized use. Many approved systems remain first-generation products that depend mainly on passive accumulation, while active targeting and stimuli-responsive platforms often show strong preclinical performance but limited clinical validation. Major barriers include tumor heterogeneity, variable EPR effect, protein corona formation, immune recognition, uncertain long-term toxicity, lack of predictive animal models and incomplete correlation between *in vitro* release and *in vivo* behavior (Mao *et al*., 2024). Economic and operational barriers also remain important. Fully patient-specific nanomedicines are difficult to manufacture, validate and regulate at scale. A more feasible strategy is to identify patient subgroups with shared molecular or pharmacokinetic characteristics, use scalable platforms such as microfluidics and continuous manufacturing, and apply adaptive clinical designs to evaluate benefit in defined populations. This approach may support precision therapy without making production and regulatory review impractical.

Future Scope

Future research should focus on clinically translatable natural product nanoformulations with reproducible quality, scalable manufacturing, long-term safety, and validated therapeutic efficacy. To confirm whether improved delivery produces meaningful patient-level benefits, we need more pharmacokinetic studies, disease-relevant animal models, and well-designed clinical trials.

Limitations

Despite strong preclinical promise, many natural product nanocarriers remain limited by batch-to-batch variability, incomplete toxicity data, regulatory complexity, and insufficient clinical evidence. Additional concerns include immunogenicity, nanoparticle accumulation, cost, and uncertain performance in heterogeneous patient populations.

Conclusion

Natural products hold significant therapeutic potential but are frequently limited by poor solubility, low stability, rapid metabolism, limited permeability and low bioavailability. Nanotechnology offers effective strategies to address these barriers through polymeric nanoparticles, liposomes, dendrimers, micelles, solid lipid nanoparticles, nanoemulsions and mesoporous silica systems. These carriers enable sustained release, improved targeting and enhanced efficacy for bioactive compounds such as paclitaxel, curcumin, resveratrol, baicalin, gambogic acid and ginsenosides. Clinically translated examples such as nab-paclitaxel demonstrate the feasibility of nanocarrier-based therapy, while recent developments in natural product nano-delivery, paclitaxel nanomedicine, AI-guided optimisation, microfluidics and continuous manufacturing show that the field is moving toward more precise and scalable platforms. Nevertheless, translation requires careful attention to reproducibility, stability, immunogenicity, toxicity, cost, regulatory expectations and clinically meaningful benefit. Future progress will depend on integrating rational nanocarrier design, robust quality control, recent evidence, transparent safety evaluation and patient subgroup-based precision approaches.

List of Abbreviations

NP: nanoparticle; PNP: polymeric nanoparticle; PLGA: poly(lactic-co-glycolic acid); SLN: solid lipid nanoparticle; MSN: mesoporous silica nanoparticle; BBR: berberine; CUR: curcumin; GA: gambogic acid; CK: ginsenoside compound K; RES: resveratrol; PTX: paclitaxel; HCC: hepatocellular carcinoma; GBM: glioblastoma; CNS: central nervous system; BBB: blood-brain barrier; EPR: enhanced permeability and retention; PEG: polyethylene glycol; AI: artificial intelligence; ML: machine learning; HTS: high-throughput screening; QbD: Quality by Design; GSH: glutathione; TEM: transmission electron microscopy; UV-Vis: ultraviolet-visible spectroscopy; EDX: energy-dispersive X-ray spectroscopy; XRD: X-ray diffraction; ASGPR: asialoglycoprotein receptor.

Conflict of Interest

The authors declare no conflicts of interest in this work.

Acknowledgement

The authors sincerely acknowledge the support and encouragement provided by affiliated institutions, friends and family members. The authors further acknowledge the researchers whose published work has been cited in this review, as their contributions formed the foundation for this compilation.

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