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Phytochemical Nanocarriers: Translating Traditional Botanical Therapeutics into Modern Nanomedicine

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ABSTRACT

Natural products are a rich source of drug-like phytochemicals; however, the clinical success of promising candidates has been hampered by issues such as insolubility, instability, rapid metabolism, limited tissue distribution, and variation. Systems designed for drug delivery can tackle such problems by improving dispersion, protecting labile phytochemicals from degradation, customizing release kinetics, and changing membrane interactions. We review lipid carriers, liposomes, phytosomes, solid lipid nanoparticles, nanostructured lipid carriers, polymeric nanoparticles, nanoemulsions, micelles, nanocrystals, proteinaceous nanoparticles, and some hybrid systems for the delivery of phytopharmaceuticals. The original article searches PubMed/MEDLINE, ScienceDirect, Scopus-indexed articles, and Google Scholar. None of the search archives were exported for verification; thus, there is no documented date for the last search undertaken, no deduplication report, no documentation of screening by an independent reviewer, and the PRISMA diagram numbers cannot be verified. The unverified number of studies are not presented as systematic-review results in this updated article for these reasons. This review holds the most studied phytochemicals of curcumin, resveratrol, quercetin, berberine, epigallocatechin gallate, and silymarin, as the limitations to their delivery have been most clearly defined here. Many formulation studies show enhancement of properties such as perceived solubility, stability, release properties, or pharmacokinetic parameters; however, they are very dependent on formulation, dose, route, model, and comparison. Better delivery does not automatically demonstrate clinical effectiveness. There is insufficient pharmacokinetic profile data, incomplete quality attributes, scale-up issues or challenges, carrier toxicity, and fewer well-controlled clinical studies. Our product-by-product solution encompasses botanical verification, chemical fingerprinting, quality-by-design formulation, orthogonal characterization, case-specific safety evaluation, and controlled clinical testing when proper. Nanocarriers play a prominent role in the development of botanical

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medicines; however, they are NOT considered a basis for efficacy claims in and of themselves. Thus, the conclusions that may be drawn from the assessment of a drug delivery system should be equal with the level of quality and maturity of the data available.

1. INTRODUCTION

Medicinal plants have informed health practices in Ayurveda, Traditional Chinese Medicine, Unani, and Indigenous systems, and are an important source of pharmacologically active molecules. Contemporary phytopharmacology seeks to identify the active constituents, understand the mechanisms, and establish reproducible dosage forms. Botanical preparations are chemically complex; activity can arise from a single molecule, multiple constituents, metabolites, or interactions between constituents. This complexity is valuable but makes dose definition, quality control, and the interpretation of clinical outcomes challenging [1-8]. Many phytochemicals face delivery barriers. Hydrophobic compounds, such as curcumin, resveratrol, and quercetin, have limited aqueous solubility; some are unstable under light, oxygen, pH, or enzymatic exposure, and rapid conjugation or efflux may limit systemic exposure. Highly polar constituents may not cross lipid membranes. A conventional extract may vary with species identity, cultivar, geography, harvest, storage, extraction solvent, and processing [9-16].

Nanomedicine provides formulation approaches that can protect compounds, improve dispersion, alter release, and interact with barriers. The carrier itself does not confer pharmacological activity; it changes the exposure profile and may introduce new risks. The question is not whether a nanoformulation is smaller, but whether a defined formulation offers a meaningful, reproducible, and safe improvement on a suitable comparator [17-24]. This review connects traditional botanical medicines with modern carrier engineering. Carrier classes are evaluated, phytochemical examples are discussed, along with analytical and biological evidence, clinical translation, safety, and regulatory needs. Findings are described according to evidence level, and preclinical signals are not treated as human efficacy.

2. REVIEW OBJECTIVES AND QUESTIONS

This review aimed to respond to the following questions: (i) what carrier systems are used for phytochemicals; (ii) what formulation mechanisms can enhance stability, absorption, and targeting properties; (iii) which compounds and therapeutic areas are considered the most promising; (iv) what preclinical and clinical evidence can support the translation from in vitro and animal studies; and (v) what quality, safety, and regulatory issues need to be addressed before clinical applications.

3. MATERIALS AND METHODS

3.1 Review design

This article was designed as a **critical narrative review with a structured approach to literature identification and synthesis**. Its purpose was to examine phytochemical nanocarrier technologies, representative bioactive compounds, reported formulation outcomes, and barriers to clinical translation. The review does not claim to be a systematic review or meta-analysis because a complete reproducibility record was not available, including final database search histories, exported records, deduplication files, screening decisions, and study-level extraction sheets. Accordingly, the findings are presented as a structured critical synthesis rather than as a quantitative estimate of the literature. The review focuses on the strength and limitations of the available evidence and distinguishes physicochemical, in vitro, animal, and human findings. It does not treat improvements in formulation characteristics or preclinical outcomes as evidence of clinical effectiveness.

3.2 Information sources and search concepts

The initial literature search drew on PubMed/MEDLINE, ScienceDirect, Scopus-indexed publications, and Google Scholar. Reference-list screening and searches of authoritative regulatory or guidance documents were used to show added relevant material.

Search concepts combined terms for phytochemicals and botanical medicines with terms for nanocarrier-based delivery systems. Phytochemical and botanical terms included *phytochemicals*, *plant extract*, *herbal medicine*, *curcumin*, *resveratrol*, *quercetin*, *berberine*, *silymarin*, and *epigallocatechin gallate*. These terms were combined with delivery-related terms, including *nanocarriers*, *nanoparticles*, *liposomes*, *phytosomes*, *nanoemulsions*, *solid lipid nanoparticles*, *nanostructured lipid carriers*, *polymeric nanoparticles*, *micelles*, *nanocrystals*, *vesicles*, *targeting*, and *bioavailability*.

Because the exact database-specific search strings and final search dates from the first work were not kept, this review does not present the search process as fully reproducible or exhaustive. The literature was used to show recurring carrier strategies, representative phytochemicals, commonly reported outcomes, and major translational limitations.

3.3 Scope and eligibility of the literature considered

The synthesis considered peer-reviewed original research, review articles used for contextual background and citation tracking, human clinical studies, and official guidance relevant to nanomaterial-containing medicines. Priority was given to literature addressing plant-derived bioactives and nanocarrier systems in relation to formulation characteristics, stability, release, absorption, pharmacokinetics, biodistribution, biological activity, safety, manufacturing, or clinical translation. Studies focused exclusively on synthetic drugs or non-medicinal materials were not central to the review unless they provided directly relevant information on carrier design, characterization, safety assessment, or regulatory considerations applicable to phytochemical formulations. Review articles were used to contextualize the field and find relevant primary studies; they were not treated as independent experimental evidence.

3.4 Evidence organization and critical synthesis

The literature was organized according to carrier architecture, phytochemical class, therapeutic application, and stage of evidence. Evidence was categorized as physicochemical, in vitro, animal, human, or marketed-product evidence where applicable. The synthesis considered botanical or compound identity, carrier composition, particle size, and disparity when reported, encapsulation or loading, route of administration, comparator, biological outcome, safety information, and stated limitations. Given the marked diversity of carrier systems, active compounds, study models, routes of administration, doses, analytical methods, and outcome measures, a pooled quantitative analysis was not proper. Instead, the review critically examines whether reported formulation advantages are supported by suitable comparators and whether they provide a plausible basis for later translational development.

3.5 Interpretation of evidence and methodological limitations

The review applies an evidence-level framework to avoid equating laboratory or animal findings with clinical benefit. Improvements in particle size, encapsulation efficiency, stability, release behaviour, cellular uptake, or pharmacokinetic exposure are interpreted as formulation-related findings. Such outcomes may support further development but do not independently prove therapeutic superiority, safety, or clinical efficacy. The review has several limitations. A fully reproducible systematic-review process would require a dated search update, database-specific search strings, exported records, documented deduplication procedures, independent title-and-abstract and full-text screening, reasons for exclusion, and a PRISMA 2020 flow diagram based on an auditable screening record. Study-level risk-of-bias assessment would also be needed, using design-appropriate tools such as RoB 2 for randomized clinical trials and SYRCLE for animal studies.

Because these materials were not available for the present review, the findings should be interpreted as a critical narrative appraisal of the field rather than as a systematic estimate of the evidence base.

4. RESULTS

4.1 Overview of the evidence landscape

In the evidence configuration described many of the considered manuscripts are focused on formulations and preclinical findings. Indeed, the triple combination of curcumin, resveratrol and quercetin is mentioned several times due to its reported insufficient aqueous solubility, chemical instability, or rapid metabolic transformation. Berberine, epigallocatechin gallate, silymarin and other phytochemicals are also mentioned in the context of different carriers. In this regard, encapsulation is proposed to improve the content of the entrapped substance, decrease its degradation rate, change the release properties, or enhance the exposure of the target tissue. These are several aspects, and the cumulative evidence grade should not be confused by the presence of any single positive result. A higher encapsulation efficiency, reduced particle size, or increased in vitro efficacy message cannot be used as sufficient proof of a compound's superiority.

One of the key conclusions of this evidence synthesis is that the number of studies with potentially valuable formulations significantly exceeds the quantity of positive clinical findings. Preclinical and physicochemical data are represented by a substantial number of articles, while human evidence is mostly ranked as moderate or low due to the absence of consistent control groups. Animal studies are even more challenging to analyze due to the wide range of interventions and study designs used in different research groups. Therefore, comparative efficacy claims are mostly based on head-to-head trials, which directly compare the same test substance or combination. Indeed, comparing the same dose of the entrapped compound, the free drug formulation (if applicable) and carrier-alone is the optimal strategy to prove the value of a new delivery system. For pharmacokinetic claims, the use of validated and consistent analytical techniques is critical, while the inclusion of clinically relevant efficacy endpoints requires researchers to design a suitable control group. At the same time, the current state of the analyzed body of evidence does not allow for conducting large-scale quantitative analysis or producing a single grade for individual carriers. This is due to the lack of access to individual participant data and the completion of the risk of bias assessment by the original authors.

Table 1: Evidence domains used to compare phytochemical carrier studies.

Evidence domain	Common reported endpoint	Interpretive caution
Physicochemical	Particle size, PDI, zeta potential, loading, encapsulation efficiency	Values depend on method, medium, dilution, and storage; a single size value is insufficient.
In vitro delivery	Dissolution, release, cell uptake, cytotoxicity, antioxidant assays	Assay interference and non-physiological concentrations can exaggerate these effects.
Animal studies	AUC/Cmax, tissue distribution, disease scores, histology	Species, routes, model, and dose may not predict human benefit.
Human studies	Pharmacokinetics, tolerability, symptoms, biomarkers, clinical endpoints	Small sample sizes and surrogate outcomes may not show effectiveness.

The table summarizes commonly reported endpoints and the main cautions needed for interpretation; it is a framework for synthesis rather than a claim that every study reported every endpoint.

4.2 Major nanocarrier systems

4.2.1 Liposomes and related vesicles

Liposomes are phospholipid membranes that can encapsulate hydrophilic molecules in their aqueous cores and hydrophobic ones in the membrane itself. They can be made from various phospholipids, cholesterol, PEG, ligands, and other materials depending on the desired properties. Phytochemicals can be enclosed in liposomes to target certain tissues and provide therapeutic benefits. Their advantages include protection of the payload and altered biodistribution, while the challenges are leakage, lipid auto-oxidation or hydrolysis, stability, and cost [49–58].

Niosomes, transfersomes, and ethosomes are like liposomes but have several types of surfactants or can deform under pressure. Transfersomes and ethosomes are particularly interesting for the enhanced penetration of their contents into the skin layers. However, such data require other validation through permeation studies, as well as evaluation of irritation and systemic exposure if applicable [59–64].

4.2.2 Phytosomes and phospholipid complexes

Phytosomes can be described as association products of plant-derived material and phospholipids, not aqueous-core liposomes. The involvement of hydrogen bonding and other interactions may contribute to their enhanced partitioning and absorption of specific polyphenols such as curcumin, silybin or grape-seed polyphenols. Available phytosomal products on the market cannot prove their similarity in terms of the content of botanical ingredients or ratio of ligand/phospholipid, technological aspects, and clinical data [65–72].

4.2.3 Solid lipid nanoparticles and nanostructured lipid carriers

Solid lipid nanoparticles (SLNs) are formed from a solid lipid matrix, while nanostructured lipid carriers (NLCs) are composed of solid and liquid lipids, allowing the formation of a less ordered matrix having a higher amount of active compound and reducing its expulsion during storage. The use of SLNs and NLCs for the delivery of lipophilic phytochemicals can provide protection to the active compounds and can be developed in oral, topical or parenteral formulations. However, the potential limitations include drug expulsion due to crystal growth, polymorphic transformations, tolerability of surfactants used, lipid digestion and variable release rates in biological fluids [73–80].

4.2.4 Polymeric nanoparticles and nanocapsules

Polymeric carriers can be made from biodegradable polymers, such as poly (lactic-co-glycolic acid) (PLGA), polylactide, chitosan, alginate, gelatin, or other natural and synthetic polymers. Nanocapsules can generate a reservoir-type structure, while nanospheres have the active principle dispersed within the polymer matrix. Properties of surface chemistry, polymer molecular weight, degradation rate, and residual solvent should be considered. The fact that the polymer is biodegradable is not dispensable for the comprehensive evaluation of the product and its toxicity; thus, characterization of degradation products, immunological response and repeated-dose toxicity studies are needed [81-90].

4.2.5 Nanoemulsions, micelles and nanocrystals

Nanoemulsions are kinetically stable dispersions of oil in water stabilized by surfactants; they may enhance the plain solubilization and gastrointestinal dispersion of hydrophobic constituents. Micelles can solubilize hydrophobic molecules within hydrophobic domains and may be useful when the unperturbed compound precipitates out of aqueous media. Nanocrystals increase the surface area and thus the dissolution rate without requiring a large carrier mass. The technologies are not interchangeable: a nanoemulsion is not necessarily thermodynamically stable, and increased dissolution does not always lead to increased absorption [91–99].

4.2.6 Protein-based, polysaccharide and hybrid systems

Albumin, casein, zein, gelatin and other food-compatible proteins can interact with plant bioactives via hydrophobic interactions, hydrogen bonding, or electrostatic forces. Polysaccharides such as chitosan, alginate and pectin can provide mucoadhesion, pH sensitivity or protective matrices. Hybrid systems are combinations of materials to tailor loading, stability, or triggered release. Their performance is influenced by ionic strength, digestive enzymes, protein corona formation, presence of food components and batch-to-batch variations in materials [100–108].

4.2.7 Inorganic, metallic, and biomimetic systems

Gold, silver, silica, iron oxide, and other inorganic nanomaterials have been explored as carriers, imaging agents, or components of multifunctional systems. Their long persistence, surface reactivity and potential for accumulation make them different from many biodegradable organic carriers. Green synthesis using plant extracts may provide reducing or capping molecules, but plant-mediated synthesis is not guaranteed to produce reproducible, pure, or safe materials. Exosomes and cell-membrane-inspired systems are promising carriers, but require careful characterization of sources, scalable isolation methods, and control of the biological cargo [109–116].

Table 2: Comparison of major carrier platforms used for phytochemical delivery.

Carrier class	Potential advantage	Key limitations/tests
Liposomes/vesicles	Encapsulate polar and nonpolar compounds; modifiable surface	Leakage, oxidation, storage stability, sterilization and scale-up
Phytosomes	Phospholipid complex may improve partitioning and absorption	Must confirm complex formation, composition, and product-specific clinical evidence
SLN / NLC	Lipid compatibility; protect lipophilic actives	Polymorphism, drug expulsion, digestion, and surfactant effects
Polymeric nanoparticles	Tunable degradation and release; surface functionalization	Residual solvent, polymer impurities, degradation, and repeat-dose toxicity
Nanoemulsions/micelles	Improve dispersion and clear solubilization	Dilution/food effects, precipitation, surfactant burden, and stability
Protein/polysaccharide	Biocompatible matrices; mucoadhesion or pH response	Batch variability, digestion, allergenicity, and ionic sensitivity
Inorganic / hybrid	Imaging, external responsiveness, multifunctionality	Persistence, biodistribution, clearance, and long-term toxicology

Carrier selection should be guided by the compound's chemistry, route, target tissue, manufacturing constraints, and safety profile rather than particle size alone [17, 23, 49, 65, 73, 81, 91, 100, 109].

4.3 Representative phytochemicals and formulation rationale

4.3.1 Curcumin

Curcumin, an active part of Curcuma longa, has been subject to extensive investigation for its anti-inflammatory and antioxidant activity. However, the low aqueous solubility, chemical stability, and rapid metabolism limit the oral bioavailability. Various nanoparticle systems such as liposomes, polymeric nanoparticles, lipid-based carriers, micelles, nanocrystals, and phytosomes have been explored to improve the

delivery of curcumin. A systematic review of the literature focusing on the nanoparticle delivery of curcumin highlighted the need to differentiate between the enhancement of pharmacokinetic properties and antitumor efficacy and to compare the performance of different formulations [117–121]. In addition, curcumin-containing formulations require a chemical characterization of curcuminoids and their degradation products, and only formulations that have proven efficacy in a controlled clinical study of humans can make pharmacological claims.

4.3.2 Resveratrol

Resveratrol, a stilbenoid found in grapes and several other plant species, has poor aqueous solubility, undergoes photoisomerization, oxidation, and rapid metabolic conversion. Encapsulation in liposomes, polymeric nanoparticles, lipid nanocarriers, micelles, nanoemulsions, and protein carriers have been investigated. Recent reviews highlight the importance of optimizing formulations to improve pharmacokinetic parameters and underscore the need for further investigations of the therapeutic potential and safety of resveratrol in vivo [122–126].

4.3.3 Quercetin and other flavonoids

Quercetin is associated with low aqueous solubility and undergoes extensive metabolism. Thus, lipid-based formulations, polymeric systems, cyclodextrin complexes, micelles, and nanoemulsions have been explored for the delivery of this flavonoid. Similarly, other flavonoids including EGCG, naringenin, genistein, kaempferol, and fisetin have been studied; each exhibits different stability and metabolic profiles, and therefore, a flavonoid delivery platform cannot be extrapolated from one compound to another [127–132].

4.3.4 Berberine, silymarin and other botanical actives

Berberine is an isoquinoline alkaloid that is subject to limited oral bioavailability due to its poor absorption and extensive metabolism and/or excretion processes. Thus, nanocarriers reviewed by the authors of [129] are lipids, polymeric particles, and other systems designed to improve the pharmacokinetics and tissue distribution of the drug. At the same time, the study [129] notes that silymarin/silybin, artemisinin, celastrol, boswellic acids, andrographolide, and other phytochemicals have also been used to deliver various natural products. However, each of these compounds requires a detailed description of the chemical markers and a thorough assessment of interactions and safety data; thus, an isolated molecule of a drug is not identical to a complex of a natural product [133–138].

Table 3: Commonly investigated phytochemicals and their formulation rationale.

Phytochemical	**Botanical source (example)**	**Main formulation challenge**	**Platforms explored**
Curcumin	Curcuma longa	Poor aqueous solubility; rapid metabolism	Phytosomes, liposomes, polymeric and lipid nanoparticles
Resveratrol	Vitis vinifera and others	Solubility, photoisomerization, oxidation	Liposomes, micelles, lipid/polymeric particles
Quercetin	Many fruits and medicinal plants	Low solubility; extensive metabolism	Lipid carriers, polymeric systems, cyclodextrins
Berberine	Berberis spp., Coptis spp.	Low systemic exposure; transporter/metabolic effects	Polymeric and lipid-based nanocarriers
EGCG	Camellia sinensis	Chemical instability and limited exposure	Liposomes, polymeric and protein-based carriers
Silybin	Silybum marianum	Low solubility and variable absorption	Phytosomes, lipid carriers, nanoparticles

These examples reflect research directions and do not imply equivalent clinical evidence across products or indications [65–72, 117–138].

4.4 Mechanisms by which carriers may alter delivery

One of the basic characteristics of delivery carriers is the ability to prove activity through their action, regardless of the mechanism of action. The mechanism of action of the carrier can differ and include: (i) enhancement of wetting and dispersion; (ii) protection of the compound from hydrolysis, oxidation, photolysis or metabolic transformations; (iii) regulation of the dissolution profile; (iv) promotion of penetration through barriers (epithelial or cellular); (v) modulation of lymphatic absorption or the reticuloendothelial system; (vi) targeting of specific sites by virtue of a ligand, local administration, or response to a stimulus. In addition to the examples listed, the ability of a carrier to direct the drug to the site of action varies depending on the formulation and route of administration, and this must be considered when designing the system, not taken for granted [139–142]. Such factors as surface charge, particle size distribution, shape, rigidity, protein binding, and interaction with mucin also affect the properties of the carrier. One should be especially careful about the common assertion that nanoparticles are delivered to the tumour via the enhanced permeability and retention effect. Vascular permeability in humans is heterogeneous, and nanoparticle accumulation in tumour tissue in preclinical studies does not always translate into clinical success. Targeting using targeting ligands can increase cellular uptake but has slight effect on overall tissue distribution [20–24, 143–147].

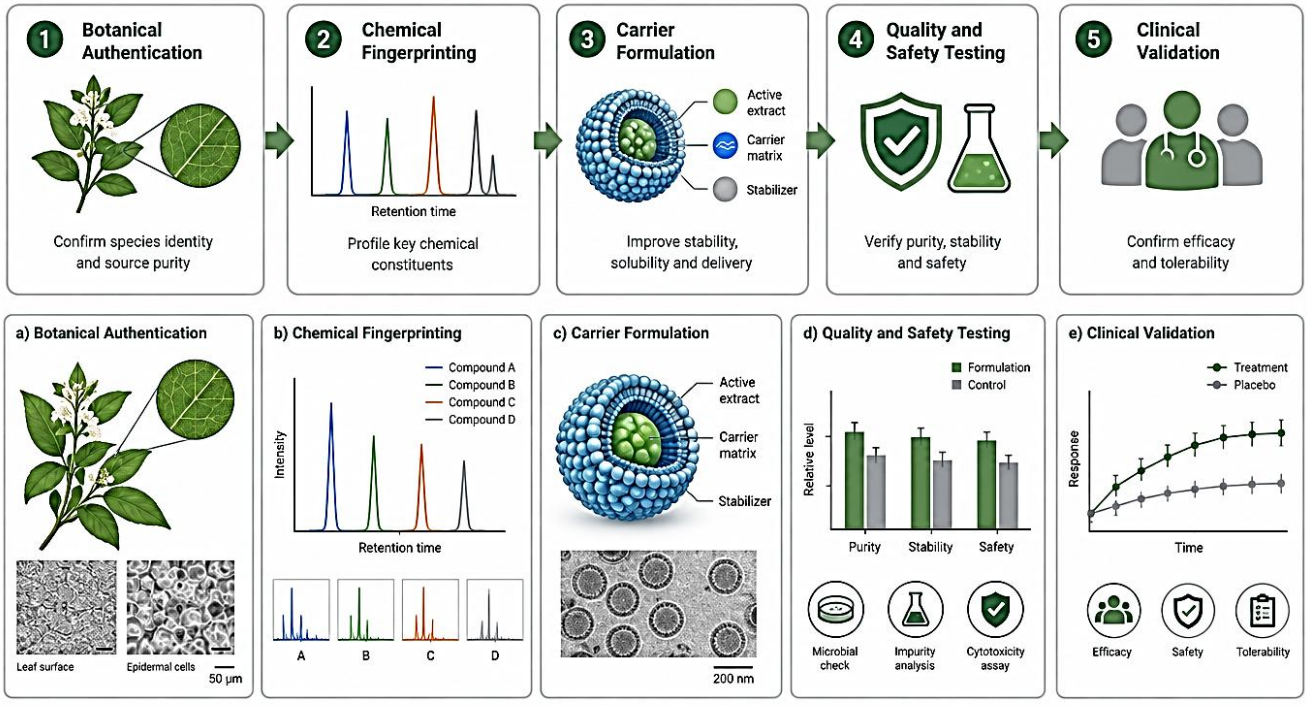


Figure 1: Product-specific development pathway for nano-phytomedicine

Figure 1 The pathway links botanical authentication and chemical fingerprinting with formulation, quality, and safety testing, and clinical validation. Each stage is a decision gate requiring product-specific evidence; progression through the pathway should not be assumed.

5. DISCUSSION

The evidence supports nanocarriers as enabling pharmaceutical technologies for selected phytochemicals when a defined physicochemical barrier is overcome by a compatible formulation (e.g., improved dissolution or prevention of degradation). The most convincing arguments begin with a mechanistic problem (such as poor dissolution or rapid degradation) and show how the exposure variable (relevant to the mechanism) is changed by the carrier and shows a biological effect at a comparable or clinically relevant dose. Novelty by

itself is not an outcome. A recurring weakness is an overreliance on in vitro assays and on a single animal model. Cell-based antioxidants or cytotoxicity assays can give misleading results if the nanoparticle causes light scattering, fluorescence quenching or adsorption of assay reagents or non-specific membrane injury. Blank-carrier controls, orthogonal assays, and proper analysis of the dose-response are needed. Improved plasma concentrations in animals must be related to unbound concentration at the target site and linked to a relevant pharmacodynamic endpoint. Positives and negatives should be reported.

Botanical quality is a fundamental issue. Correct species identification, plant part, extraction method, chromatographic fingerprint, marker compound ranges, contaminants, and stability must be defined before carrier optimization. A nano formulation may increase exposure not only of desired constituents but also of contaminants or unwanted constituents. Whole extract delivery raises questions of whether the active cocktail is stable during manufacturing and storage and whether the carrier preferentially partitions some constituents and thereby changes the original phytochemical profile [1–8,65–72]. The carrier itself can carry risks. Cationic surfaces can damage membranes, surfactants can be irritating or disrupt barrier integrity, inorganic components can be kept in tissue and polymers, or lipids can change degradation profiles, immune recognition, or biodistribution. The safety profile of the free phytochemical cannot be relied on as a surrogate for the final formulation. Appropriate evaluation would include route-relevant local tolerance, systemic toxicity, immunogenicity where relevant, reproductive or genotoxicity when indicated and potential interactions in the relevant population.

Clinical translation is still the outstanding challenge. Some phytosomal and enhanced-bioavailability botanical products are available; selected formulation-specific clinical studies are available; nevertheless, a commercial label, small trial or surrogate biomarker does not constitute broad therapeutic effectiveness. Human studies should use rigorous randomization, sufficient sample size, pre-specified outcomes, validated analytical assays, dose justification, clinically relevant comparator, and systematic adverse event reporting. A conventional extract and nano formulation should be compared directly if nanotechnology is claimed to enhance clinical benefit. The next generation of research should focus on quality-by-design, critical quality attributes, robust scale-up, continuous manufacturing where proper, stability-indicating analytical methods, realistic biorelevant testing, physiologically based pharmacokinetic modelling and early regulatory engagement. AI and computational screening may aid in prioritizing carrier compositions; however, predictions will need experimental verification. Sustainable sourcing and reduced solvent use are also important if a technology to enhance plant-derived medicine is to avoid creating an avoidable environmental burden.

5.1 Translational evidence and decision points

Table 4: Suggested stage-gate framework for translating nano-phytomedicines.

Development stage	Minimum evidence package	Decision question
Botanical / compound definition	Taxonomic authentication, fingerprint, marker assay, contaminants, stability	Is the active material reproducible and adequately defined?
Formulation optimization	Size distribution, morphology, loading, release, residuals, batch variation	Does the carrier solve a defined limitation?
Preclinical proof	Relevant controls, exposure measurements, efficacy model, route-specific toxicology	Does improved delivery produce a meaningful benefit at tolerable exposure?
Clinical translation	Human pharmacokinetics, dose	Is the specific product better

	finding, randomized efficacy trial, safety monitoring	than a suitable comparator?
Manufacturing/lifecycle	Validated process, specifications, stability, change control, pharmacovigilance	Can quality and safety be supported on a scale?

Each stage should be passed using product-specific data; evidence from another compound or carrier cannot substitute for validation of the candidate formulation [23, 40–48, 148–152].

5.2 Limitations of this review

Several limitations affect interpretation. The manuscript brings together a mix of compounds, carrier compositions, routes, models, and outcomes, which prevents a defensible quantitative synthesis without defining a narrower question and harmonizing the data. The provided source did not include archives of search histories, a verified search cutoff, deduplication and screening logs, reasons for full-text exclusion, a complete PRISMA count record or completed study-level risk-of-bias assessments. Therefore, the revised manuscript enhances structure and transparency but cannot honestly claim that these reproducibility steps have been completed. Publication bias and selective reporting could enhance positive findings on formulation, while incomplete characterizations make cross-study comparisons unreliable. Before submission, a subject librarian or experienced co-author should reproduce the searches independently, verify eligibility decisions, check the extracted data against original reports, and confirm each risk-of-bias judgement.

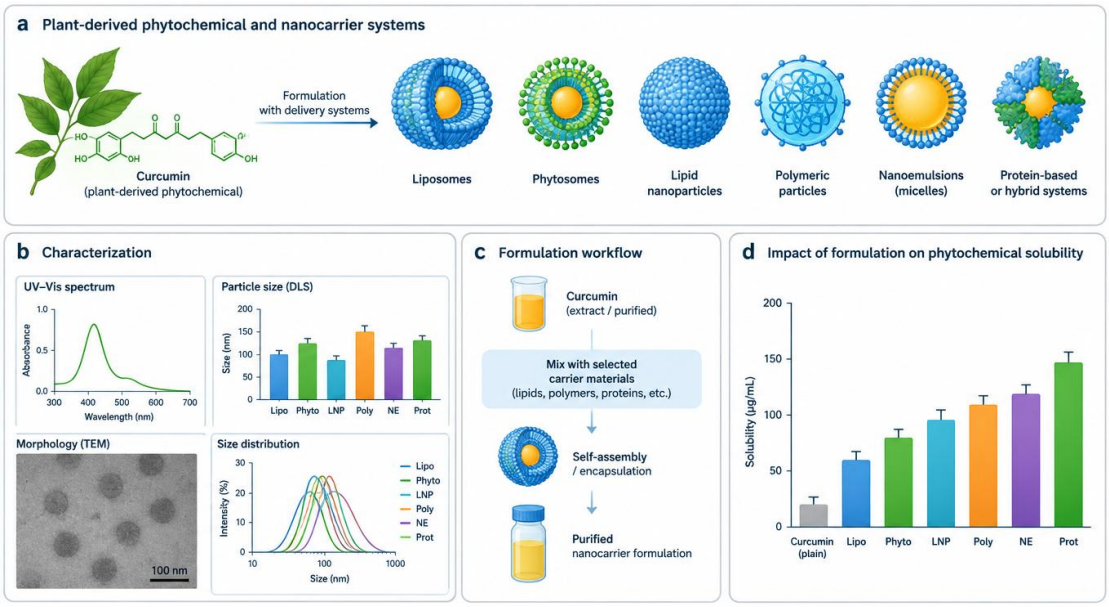


Figure 2: Overview of carrier classes investigated for phytochemical delivery.

Figure 2 Representative carrier families include liposomes, phytosomes, lipid nanoparticles, polymeric particles, nanoemulsions or micelles, and protein-based or hybrid systems. The diagram is conceptual and does not imply that one platform is universally superior.

6. FUTURE PERSPECTIVES

Future development should be focused on clinically relevant rather than purely technological advances, including oral carriers that are resistant to digestion and deliver their payloads at a desired site within the intestine, topical carriers with characterized skin deposition and tolerability, inhalation or parenteral systems with strict control over sterility, endotoxin and biodistribution, or disease-targeted platforms with

reproducible target engagement. Combination delivery of multiple phytochemicals may be a useful strategy, but it increases the burden of characterizing the components and their interactions.

A pragmatic translation strategy would be to choose a small number of well-characterized phytochemicals with an established exposure limitation, use a carrier with a compelling safety and manufacturing rationale and analytical comparability between batches, and continue through pharmacokinetic and dose-ranging investigations. Traditional medicines may guide compound choice and therapeutic domain, while modern chemistry, pharmacology, and clinical science define identity, quality, safety, and efficacy.

7. CONCLUSION

Novel carrier systems stand for a viable link between traditional botanical medicine and nanomedicine by addressing selected delivery limitations and challenges that phytochemicals face. Liposomes, phytosomes, lipid and polymeric nanoparticles, nanoemulsions, micelles and other systems can help to improve dispersion, protect unstable compounds, alter release and, in some cases, boost exposure or biological activity. The extent and importance of these benefits are compound-, carrier-, route- and product-specific. Preclinical improvements should not be extrapolated to proof of efficacy in humans, and carrier-related risks need to be assessed independently of the botanical ingredient. Advancement requires botanical authentication, chemical fingerprinting, thorough characterization, reproducible manufacturing, appropriate toxicology, rigorous human studies, and transparent regulatory evaluation. The field will realize its true potential when nanotechnology is used to solve a defined delivery problem and when every claim is backed up by evidence for the final formulation.

REFERENCES

1. World Health Organization. WHO traditional medicine strategy: 2014–2023. Geneva: WHO; 2013.
2. Atanasov AG, Waltenberger B, Pferschy-Wenzig EM, et al. Discovery and resupply of pharmacologically active plant-derived natural products: a review. Biotechnol Adv. 2015;33(8):1582-1614. doi:10.1016/j.biotechadv.2015.08.001.
3. Newman DJ, Cragg GM. Natural products as sources of new drugs over the four decades from 01/1981 to 09/2019. J Nat Prod. 2020;83(3):770-803. doi:10.1021/acs.jnatprod.9b01285.
4. Fabricant DS, Farnsworth NR. The value of plants used in traditional medicine for drug discovery. Environ Health Perspect. 2001;109 Suppl 1:69-75. doi:10.1289/ehp.01109s169.
5. Rates SMK. Plants as source of drugs. Toxicon. 2001;39(5):603-613. doi:10.1016/S0041-0101(00)00154-9.
6. Li JW, Vederas JC. Drug discovery and natural products: end of an era or an endless frontier? Science. 2009;325(5937):161-165. doi:10.1126/science.1168243.
7. Pan SY, Zhou SF, Gao SH, et al. New perspectives on how to discover drugs from herbal medicines: CAM's outstanding contribution to modern therapeutics. Evid Based Complement Alternat Med. 2013;2013:627375. doi:10.1155/2013/627375.
8. Booker A, Johnston D, Heinrich M. Value chains of herbal medicines—research needs and key challenges in the context of ethnopharmacology. J Ethnopharmacol. 2012;140(3):624-633. doi:10.1016/j.jep.2012.01.039.
9. Chavda VP, Vihol D, Mehta B, et al. Phytochemical-loaded liposomes for anticancer therapy: an updated review. Nanomedicine (Lond). 2022;17(8):547-568. doi:10.2217/nnm-2021-0463.
10. Singh M, Devi S, Rana VS, et al. Delivery of phytochemicals by liposome cargos: recent progress, challenges, and opportunities. J Microencapsul. 2019;36(3):215-235. doi:10.1080/02652048.2019.1617361.
11. Applications of Nanocarriers as Drug Delivery Vehicles for Active Phytoconstituents. Curr Pharm Des. 2020. doi:10.2174/1381612826666200610111013.

12. Chauhan D, Yadav PK, Sultana N, et al. Advancements in nanotechnology for the delivery of phytochemicals. J Integr Med. 2024;22(4):385-398. doi:10.1016/j.joim.2024.04.005.
13. Barani M, Bilal M, Rahdar A, et al. Phytosomes as innovative delivery systems for phytochemicals: a comprehensive review of literature. Int J Nanomedicine. 2021;16:6983-7022. doi:10.2147/IJN.S318416.
14. Li C, Wang Z, Lei H, Zhang D. Recent progress in nanotechnology-based drug carriers for resveratrol delivery. Drug Deliv. 2023;30(1):2174206. doi:10.1080/10717544.2023.2174206.
15. Santos AC, Pereira I, Pereira-Silva M, et al. Nanocarriers for resveratrol delivery: impact on stability and solubility concerns. Trends Food Sci Technol. 2019;91:483-497. doi:10.1016/j.tifs.2019.07.048.
16. Homayoonfal M, Aminianfar A, Asemi Z, Yousefi B. Application of nanoparticles for efficient delivery of quercetin in cancer cells. Curr Med Chem. 2024;31(9):1107-1141. doi:10.2174/0929867330666230301121611.
17. Silvestre F, Santos C, Silva V, et al. Pharmacokinetics of curcumin delivered by nanoparticles and the relationship with antitumor efficacy: a systematic review. Pharmaceuticals (Basel). 2023;16(7):943. doi:10.3390/ph16070943.
18. Li S, Yuan W, Deng G, Wang P, Yang P, Aggarwal BB. Chemical composition and product quality control of turmeric (Curcuma longa L.). Pharm Crops. 2011;2:28-54. doi:10.2174/2210290601102010028.
19. Anand Anubhav, Preety G, Smriti O. Application of nanotechnology for herbal medicine development: a review. Lett Drug Des Discov. 2024;21(8). doi:10.2174/1570180820666230308105723.
20. Khan MJ, Hafeez A, Siddiqui MA. Nanocarrier based delivery of berberine: a critical review on pharmaceutical and preclinical characteristics of the bioactive. Curr Pharm Biotechnol. 2023;24(11):1449-1464. doi:10.2174/1389201024666230112141330.
21. Chopra H, Bibi S, Singh I, et al. Emerging trends in the delivery of resveratrol by nanostructures: applications of nanotechnology in life sciences. J Nanomater. 2022;2022:3083728. doi:10.1155/2022/3083728.
22. Song Y, Zhang J, Zhu L, Zhang H, Wu G, Liu T. Recent advances in nanodelivery systems of resveratrol and their biomedical and food applications: a review. Food Funct. 2024;15:8629-8643. doi:10.1039/D3FO03892K.
23. FDA. Considering whether an FDA-regulated product involves the application of nanotechnology: guidance for industry. Silver Spring (MD): US Food and Drug Administration; 2014.
24. US Food and Drug Administration. Drug products, including biological products, that hold nanomaterials: guidance for industry. Silver Spring (MD): FDA; 2022.
25. European Medicines Agency. Reflection paper on nanotechnology-based medicinal products for human use. London: EMA; 2006.
26. European Medicines Agency. Reflection paper on the data requirements for intravenous liposomal products developed with reference to an innovator liposomal product. London: EMA; 2013.
27. International Organization for Standardization. ISO/TR 13014:2012 Nanotechnologies—guidance on physico-chemical characterization of engineered nanoscale materials for toxicologic assessment. Geneva: ISO; 2012.
28. International Organization for Standardization. ISO 21363:2020 Nanotechnologies—measurements of particle size and shape distributions by transmission electron microscopy. Geneva: ISO; 2020.
29. International Organization for Standardization. ISO 22412:2017 Particle size analysis—dynamic light scattering (DLS). Geneva: ISO; 2017.
30. International Organization for Standardization. ISO 10993-1:2018 Biological evaluation of medical devices—part 1: evaluation and testing within a risk management process. Geneva: ISO; 2018.

31. Mitchell MJ, Billingsley MM, Haley RM, Wechsler ME, Peppas NA, Langer R. Engineering precision nanoparticles for drug delivery. Nat Rev Drug Discov. 2021;20(2):101-124. doi:10.1038/s41573-020-0090-8.
32. Shi J, Kantoff PW, Wooster R, Farokhzad OC. Cancer nanomedicine: progress, challenges, and opportunities. Nat Rev Cancer. 2017;17(1):20-37. doi:10.1038/nrc.2016.108.
33. Peer D, Karp JM, Hong S, Farokhzad OC, Margalit R, Langer R. Nanocarriers as an emerging platform for cancer therapy. Nat Nanotechnol. 2007;2(12):751-760. doi:10.1038/nnano.2007.387.
34. Blanco E, Shen H, Ferrari M. Principles of nanoparticle design for overcoming biological barriers to drug delivery. Nat Biotechnol. 2015;33(9):941-951. doi:10.1038/nbt.3330.
35. Anselmo AC, Mitragotri S. Nanoparticles in the clinic. Bioeng Transl Med. 2016;1(1):10-29. doi:10.1002/btm2.10003.
36. Anselmo AC, Mitragotri S. Nanoparticles in the clinic: an update. Bioeng Transl Med. 2019;4(3):e10143. doi:10.1002/btm2.10143.
37. Bobo D, Robinson KJ, Islam J, Thurecht KJ, Corrie SR. Nanoparticle-based medicines: a review of FDA-approved materials and clinical trials to date. Pharm Res. 2016;33(10):2373-2387. doi:10.1007/s11095-016-195 nanoparticle.
38. Ventola CL. Progress in nanomedicine: approved and investigational nanodrugs. P T. 2017;42(12):742-755.
39. Wilhelm S, Tavares AJ, Dai Q, et al. Analysis of nanoparticle delivery to tumours. Nat Rev Mater. 2016;1:16014. doi:10.1038/natrevmats.2016.14.
40. Danhier F, Feron O, Préat V. To exploit the tumor microenvironment: passive and active tumor targeting of nanocarriers for anti-cancer drug delivery. J Control Release. 2010;148(2):135-146. doi:10.1016/j.jconrel.2010.08.027.
41. Jain RK, Stylianopoulos T. Delivering nanomedicine to solid tumors. Nat Rev Clin Oncol. 2010;7(11):653-664. doi:10.1038/nrclinonc.2010.139.
42. Maeda H, Wu J, Sawa T, Matsumura Y, Hori K. Tumor vascular permeability and the EPR effect in macromolecular therapeutics: a review. J Control Release. 2000;65(1-2):271-284. doi:10.1016/S0168-3659(99)00248-5.
43. Rosenblum D, Joshi N, Tao W, Karp JM, Peer D. Progress, and challenges towards targeted delivery of cancer therapeutics. Nat Commun. 2018;9:1410. doi:10.1038/s41467-018-03705-y.
44. Wilczewska AZ, Niemirowicz K, Markiewicz KH, Car H. Nanoparticles as drug delivery systems. Pharmacol Rep. 2012;64(5):1020-1037. doi:10.1016/S1734-1140(12)70901-5.
45. Allen TM, Cullis PR. Liposomal drug delivery systems: from concept to clinical applications. Adv Drug Deliv Rev. 2013;65(1):36-48. doi:10.1016/j.addr.2012.09.037.
46. Sercombe L, Veerati T, Moheimani F, Wu SY, Sood AK, Hua S. Advances and challenges of liposome assisted drug delivery. Front Pharmacol. 2015;6:286. doi:10.3389/fphar.2015.00286.
47. Akbarzadeh A, Rezaei-Sadabady R, Davaran S, et al. Liposome: classification, preparation, and applications. Nanoscale Res Lett. 2013;8:102. doi:10.1186/1556-276X-8-102.
48. Bozzuto G, Molinari A. Liposomes as nanomedical devices. Int J Nanomedicine. 2015;10:975-999. doi:10.2147/IJN.S68861.
49. Immordino ML, Dosio F, Cattel L. Stealth liposomes: review of the basic science, rationale, and clinical applications, existing, and potential. Int J Nanomedicine. 2006;1(3):297-315.
50. Bulbake U, Doppalapudi S, Kommineni N, Khan W. Liposomal formulations in clinical use: an updated review. Pharmaceutics. 2017;9(2):12. doi:10.3390/pharmaceutics9020012.
51. Edwards K, Baeumner A. Liposomes in analyses. Talanta. 2006;68(5):1432-1441. doi:10.1016/j.talanta.2005.08.041.
52. Riaz M. Liposomes preparation methods. Pak J Pharm Sci. 1996;9(1):65-77.

53. Gregoriadis G. Engineering liposomes for drug delivery: progress and problems. Trends Biotechnol. 1995;13(12):527-537. doi:10.1016/S0167-7799(00)89017-4.
54. Bangham AD, Standish MM, Watkins JC. Diffusion of univalent ions across the lamellae of swollen phospholipids. J Mol Biol. 1965;13(1):238-252. doi:10.1016/S0022-2836(65)80093-6.
55. New RRC, editor. Liposomes: a practical approach. Oxford: IRL Press; 1990.
56. Risselada HJ, Marrink SJ. The molecular face of lipids. Nat Rev Mol Cell Biol. 2009;10(10):739-750. doi:10.1038/nrm2745.
57. Gregoriadis G. Liposome technology. 3rd ed. Boca Raton: CRC Press; 2006.
58. Singh A, Neupane YR, Panda BP, Kohli K. Lipid-based nanocarriers for drug delivery: a review. J Drug Deliv Sci Technol. 2020;56:101549. doi:10.1016/j.jddst.2020.101549.
59. Barani M, Sangiovanni E, Angarano M, et al. Phytosomes as innovative delivery systems for phytochemicals: a comprehensive review of literature. Int J Nanomedicine. 2021;16:6983-7022. doi:10.2147/IJN.S318416.
60. Bombardelli E, Curri SB, Della Loggia R, Del NP, Tubaro A, Gariboldi P. Complexes between phospholipids and vegetal derivatives of biological interest. Fitoterapia. 1989;60:1-9.
61. Semalty A, Semalty M, Rawat MSM, Franceschi F. Supramolecular phospholipids-polyphenolics interactions: the phytosome strategy to improve the bioavailability of phytochemicals. Fitoterapia. 2010;81(5):306-314. doi:10.1016/j.fitote.2009.11.001.
62. Franceschi F, Giori A, Dall'Acqua S, et al. Phytosome: an unfamiliar approach for bioavailability and pharmacokinetic studies of silymarin. Fitoterapia. 2009;80(7):421-427.
63. Marena C, Lampertico M. Preliminary clinical development of silipide: a new complex of silybin in toxic liver disorders. Planta Med. 1991;57(2):A124-A125.
64. Bombardelli E, Spelta M. Phospholipid-polyphenol complexes: a new concept in skin care ingredients. Cosm Toil. 1991;106:69-76.
65. Singh RP, Gangadharappa HV, Mruthunjaya K. Phytosome complexation: a critical review. J Drug Deliv Sci Technol. 2016;35:201-210. doi:10.1016/j.jddst.2016.06.005.
66. Yanyu X, Yunmei S, Zhipeng C, Qineng P. The preparation of silybin-phospholipid complex and the study on its pharmacokinetics in rats. Int J Pharm. 2006;307(1):77-82. doi:10.1016/j.ijpharm.2005.10.001.
67. Freag MS, Elnaggar YSR, Abdallah OY. Lyophilized phytosomal nanocarriers as platforms for enhanced diosmin delivery: optimization and ex vivo permeation. Int J Nanomedicine. 2013;8:2385-2397. doi:10.2147/IJN.S44851.
68. Manach C, Scalbert A, Morand C, Rémésy C, Jiménez L. Polyphenols: food sources and bioavailability. Am J Clin Nutr. 2004;79(5):727-747. doi:10.1093/ajcn/79.5.727.
69. Scalbert A, Williamson G. Dietary intake and bioavailability of polyphenols. J Nutr. 2000;130(8S Suppl):2073S-2085S. doi:10.1093/jn/130.8.2073S.
70. Del Rio D, Rodriguez-Mateos A, Spencer JPE, Tognolini M, Borges G, Crozier A. Dietary (poly)phenolics in human health: structures, bioavailability, and evidence of protective effects against chronic diseases. Antioxid Redox Signal. 2013;18(14):1818-1892. doi:10.1089/ars.2012.4581.
71. Crozier A, Jaganath IB, Clifford MN. Dietary phenolics: chemistry, bioavailability, and effects on health. Nat Prod Rep. 2009;26(8):1001-1043. doi:10.1039/B802662A.
72. Williamson G, Manach C. Bioavailability and bioefficacy of polyphenols in humans. II. Review of 93 intervention studies. Am J Clin Nutr. 2005;81(1 Suppl):243S-255S. doi:10.1093/ajcn/81.1.243S.
73. Holst B, Williamson G. Nutrients, and phytochemicals: from bioavailability to bioefficacy beyond antioxidants. Curr Opin Biotechnol. 2008;19(2):73-82. doi:10.1016/j.copbio.2008.03.003.

74. Rein MJ, Renouf M, Cruz-Hernandez C, Actis-Goretta L, Thakkar SK, da Silva Pinto M. Bioavailability of bioactive food compounds: a challenging journey to bioefficacy. Br J Clin Pharmacol. 2013;75(3):588-602. doi:10.1111/j.1365-2125.2012.04425.x.
75. Parada J, Aguilera JM. Food microstructure affects the bioavailability of several nutrients. J Food Sci. 2007;72(2):R21-R32. doi:10.1111/j.1750-3841.2007.00274.x.
76. McClements DJ. Enhancing the bioavailability of hydrophobic nutraceuticals: the role of food structure and colloidal delivery systems. Food Funct. 2010;1(1):32-47. doi:10.1039/C0FO0016B.
77. McClements DJ, Li F, Xiao H. The nutraceutical bioavailability classification scheme: classifying nutraceuticals according to factors limiting their oral bioavailability. Annu Rev Food Sci Technol. 2015;6:299-327. doi:10.1146/annurev-food-032814-014043.
78. McClements DJ. Nanoemulsions versus microemulsions: terminology, differences, and similarities. Soft Matter. 2012;8:1719-1729. doi:10.1039/C2SM06903B.
79. McClements DJ, Rao J. Food-grade nanoemulsions: formulation, fabrication, properties, performance, biological fate, and potential toxicity. Crit Rev Food Sci Nutr. 2011;51(4):285-330. doi:10.1080/10408398.2011.559558.
80. Gupta A, Eral HB, Hatton TA, Doyle PS. Nanoemulsions: formation, properties, and applications. Soft Matter. 2016;12:2826-2841. doi:10.1039/C5SM02958A.
81. Solans C, Izquierdo P, Nolla J, Azemar N, Garcia-Celma MJ. Nano-emulsions. Curr Opin Colloid Interface Sci. 2005;10(3-4):102-110. doi:10.1016/j.cocis.2005.06.004.
82. Tadros T, Izquierdo P, Esquena J, Solans C. Formation, and stability of nano-emulsions. Adv Colloid Interface Sci. 2004;108-109:303-318. doi:10.1016/j.cis.2003.10.023.
83. Jaiswal M, Dudhe R, Sharma PK. Nanoemulsion: an advanced mode of drug delivery system. 3 Biotech. 2015;5(2):123-127. doi:10.1007/s13205-014-0214-0.
84. Anton N, Benoit JP, Saulnier P. Design, and production of nanoparticles formulated from nano-emulsion templates—a review. J Control Release. 2008;128(3):185-199. doi:10.1016/j.jconrel.2008.02.007.
85. Rao J, McClements DJ. Food-grade microemulsions and nanoemulsions: role of oil phase composition on formation and stability. Food Hydrocoll. 2011;25(6):1413-1423. doi:10.1016/j.foodhyd.2011.02.014.
86. Date AA, Desai N,á Nagarsenker M. Parenteral microemulsions: an overview. Int J Pharm. 2010;355(1-2):19-30.
87. Mehnert W, Mäder K. Solid lipid nanoparticles: production, characterization, and applications. Adv Drug Deliv Rev. 2001;47(2-3):165-196. doi:10.1016/S0169-409X(01)00105-3.
88. Müller RH, Mäder K, Gohla S. Solid lipid nanoparticles (SLN) for controlled drug delivery—a review of the state of the art. Eur J Pharm Biopharm. 2000;50(1):161-177. doi:10.1016/S0939-6411(00)00087-4.
89. Müller RH, Radtke M, Wissing SA. Nanostructured lipid matrices for improved microencapsulation of drugs. Int J Pharm. 2002;242(1-2):121-128. doi:10.1016/S0378-5173(02)00180-1.
90. Pardeike J, Hommoss A, Müller RH. Lipid nanoparticles (SLN, NLC) in cosmetic and pharmaceutical dermal products. Int J Pharm. 2009;366(1-2):170-184. doi:10.1016/j.ijpharm.2008.10.003.
91. Üner M, Yener G. Importance of solid lipid nanoparticles (SLN) in various administration routes and future perspectives. Int J Nanomedicine. 2007;2(3):289-300.
92. Naseri N, Valizadeh H, Zakeri-Milani P. Solid lipid nanoparticles and nanostructured lipid carriers: structure, preparation, and application. Adv Pharm Bull. 2015;5(3):305-313. doi:10.15171/apb.2015.043.

93. Severino P, Andreani T, Macedo AS, et al. Current state-of-art and current trends on lipid nanoparticles (SLN and NLC) for oral drug delivery. J Drug Deliv. 2012;2012:750891. doi:10.1155/2012/750891.
94. Fangueiro JF, Silva AM, Garcia ML, Souto EB. Advanced formulations for topical delivery of anti-inflammatory drugs. Expert Opin Drug Deliv. 2014;11(10):1609-1622.
95. Schwarz C, Mehnert W, Lucks JS, Müller RH. Solid lipid nanoparticles (SLN) for controlled drug delivery: I. Production, characterization, and sterilization. J Control Release. 1994;30(1):83-96. doi:10.1016/0168-3659(94)90047-7.
96. Radtke M, Müller RH. Nanostructured lipid drug carriers. New Drugs. 2001;2:48-52.
97. Jenning V, Gysler A, Schäfer-Korting M, Gohla SH. Vitamin A loaded solid lipid nanoparticles for topical use: drug release properties. J Control Release. 2000;66(2-3):115-126.
98. Freitas C, Müller RH. Effect of light and temperature on zeta potential and physical stability in solid lipid nanoparticle dispersions. Int J Pharm. 1998;168(2):221-229.
99. Fattal E, Barratt G. Nanotechnologies, and controlled release systems for the delivery of antisense oligonucleotides and siRNA. Adv Drug Deliv Rev. 2009;61(9):836-846.
100. Kamaly N, Yameen B, Wu J, Farokhzad OC. Degradable controlled-release polymers, and polymeric nanoparticles: mechanisms of controlling drug release. Chem Rev. 2016;116(4):2602-2663. doi:10.1021/acs.chemrev.5b00346.
101. Makadia HK, Siegel SJ. Poly lactic-co-glycolic acid (PLGA) as biodegradable controlled drug delivery carrier. Polymers (Basel). 2011;3(3):1377-1397. doi:10.3390/polym3031377.
102. Danhier F, Ansorena E, Silva JM, Coco R, Le Breton A, Préat V. PLGA-based nanoparticles: an overview of biomedical applications. J Control Release. 2012;161(2):505-522. doi:10.1016/j.jconrel.2012.01.043.
103. Jain RA. The manufacturing techniques of various drug loaded biodegradable poly(lactide-co-glycolide) (PLGA) devices. Biomaterials. 2000;21(23):2475-2490. doi:10.1016/S0142-9612(00)00115-0.
104. Freiberg S, Zhu XX. Polymer microspheres for controlled drug release. Int J Pharm. 2004;282(1-2):1-18. doi:10.1016/j.ijpharm.2004.04.013.
105. Vauthier C, Bouchemal K. Methods for the preparation and manufacture of polymeric nanoparticles. Pharm Res. 2009;26(5):1025-1058. doi:10.1007/s11095-008-9800-3.
106. Reis CP, Neufeld RJ, Ribeiro AJ, Veiga F. Nanoencapsulation I. Methods for preparation of drug-loaded polymeric nanoparticles. Nanomedicine. 2006;2(1):8-21. doi:10.1016/j.nano.2005.12.003.
107. Soppimath KS, Aminabhavi TM, Kulkarni AR, Rudzinski WE. Biodegradable polymeric nanoparticles as drug delivery devices. J Control Release. 2001;70(1-2):1-20. doi:10.1016/S0168-3659(00)00339-4.
108. Li Y, MacDowell N, Langer R, et al. Polymer nanoparticles for drug delivery. Nat Rev Mater. 2021.
109. Kamaly N, Xiao Z, Valencia PM, Radovic-Moreno AF, Farokhzad OC. Targeted polymeric therapeutic nanoparticles: design, development, and clinical translation. Chem Soc Rev. 2012;41(7):2971-3010. doi:10.1039/C2CS15344K.
110. Elsabahy M, Wooley KL. Design of polymeric nanoparticles for biomedical delivery applications. Chem Soc Rev. 2012;41(7):2545-2561. doi:10.1039/C1CS15219C.
111. Riley T, Govender T, Stolnik S, Xiong CD, Garnett MC, Illum L, Davis SS. Colloidal stability and drug incorporation aspects of micellar systems. Int J Pharm. 1999;191(2):147-156.
112. Jones MC, Leroux JC. Polymeric micelles—a new generation of colloidal drug carriers. Eur J Pharm Biopharm. 1999;48(2):101-111. doi:10.1016/S0939-6411(99)00039-9.

113. Blanazs A, Armes SP, Ryan AJ. Self-assembled block copolymer aggregates: from micelles to vesicles and their biological applications. Macromol Rapid Commun. 2009;30(4-5):267-277. doi:10.1002/marc.200800713.
114. Cabral H, Kataoka K. Progress of drug-loaded polymeric micelles into clinical studies. J Control Release. 2014;190:465-476. doi:10.1016/j.jconrel.2014.06.042.
115. Zhang L, Chan JM, Gu FX, et al. Self-assembled lipid-polymer hybrid nanoparticles: a robust drug delivery platform. ACS Nano. 2008;2(8):1696-1702. doi:10.1021/nn800275r.
116. Hu CMJ, Zhang L. Nanoparticle-based combination therapy toward overcoming drug resistance in cancer. Biochem Pharmacol. 2012;83(8):1104-1111.
117. Peer D, Lieberman J. Special delivery: targeted therapy with small RNAs. Gene Ther. 2011;18(12):1127-1133. doi:10.1038/gt.2011.56.
118. Yoo JW, Doshi N, Mitragotri S. Adaptive micro and nanoparticles: temporal control over carrier properties to facilitate drug delivery. Adv Drug Deliv Rev. 2011;63(14-15):1247-1256.
119. De Jong WH, Borm PJA. Drug delivery and nanoparticles: applications and hazards. Int J Nanomedicine. 2008;3(2):133-149.
120. Nel AE, Mädler L, Velegol D, et al. Understanding biophysicochemical interactions at the nano-bio interface. Nat Mater. 2009;8(7):543-557. doi:10.1038/nmat2442.
121. Monopoli MP, Åberg C, Salvati A, Dawson KA. Biomolecular coronas provide the biological identity of nanosized materials. Nat Nanotechnol. 2012;7(12):779-786. doi:10.1038/nnano.2012.207.
122. Tenzer S, Docter D, Kuharev J, et al. Rapid formation of plasma protein corona critically affects nanoparticle pathophysiology. Nat Nanotechnol. 2013;8(10):772-781. doi:10.1038/nnano.2013.181.
123. Salvati A, Pitek AS, Monopoli MP, et al. Transferrin-functionalized nanoparticles lose their targeting capabilities when a biomolecule corona adsorbs on the surface. Nat Nanotechnol. 2013;8(2):137-143. doi:10.1038/nnano.2012.237.
124. Fadeel B, Garcia-Bennett AE. Better safe than sorry: understanding the toxicological properties of inorganic nanoparticles manufactured for biomedical applications. Adv Drug Deliv Rev. 2010;62(3):362-374. doi:10.1016/j.addr.2009.11.008.
125. Nel A, Xia T, Mädler L, Li N. Toxic potential of materials at the nanolevel. Science. 2006;311(5761):622-627. doi:10.1126/science.1114397.
126. Donaldson K, Stone V, Tran CL, Kreyling W, Borm PJA. Nanotoxicology. Occup Environ Med. 2004;61(9):727-728. doi:10.1136/oem.2004.013243.
127. Monopoli MP, Aberg C, Salvati A, Dawson KA. Biomolecular coronas provide the biological identity of nanosized materials. Nat Nanotechnol. 2012;7(12):779-786. doi:10.1038/nnano.2012.207.
128. Johnston HJ, Hutchison G, Christensen FM, Peters S, Hankin S, Stone V. A review of the in vivo and in vitro toxicity of silver and gold particulates. Crit Rev Toxicol. 2010;40(4):328-346. doi:10.3109/10408440903453074.
129. Khlebtsov N, Dykman L. Biodistribution, and toxicity of engineered gold nanoparticles: a review of in vitro and in vivo studies. Chem Soc Rev. 2011;40(3):1647-1671. doi:10.1039/C0CS00018C.
130. European Commission. Commission recommendation of 10 June 2022 on the definition of nanomaterial. Off J Eur Union. 2022;C229:1-5.
131. International Council for Harmonisation. ICH Q8(R2): Pharmaceutical development. Geneva: ICH; 2009.
132. International Council for Harmonisation. ICH Q9(R1): Quality risk management. Geneva: ICH; 2023.
133. International Council for Harmonisation. ICH Q10: Pharmaceutical quality system. Geneva: ICH; 2008.
134. International Council for Harmonisation. ICH Q1A(R2): Stability testing of new drug substances and products. Geneva: ICH; 2003.

135. International Council for Harmonisation. ICH M3(R2): Nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals. Geneva: ICH; 2009.
136. International Council for Harmonisation. ICH S9: Nonclinical evaluation for anticancer pharmaceuticals. Geneva: ICH; 2009.
137. International Council for Harmonisation. ICH E6(R2): Good clinical practice. Geneva: ICH; 2016.
138. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. doi:10.1136/bmj.n71.
139. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898. doi:10.1136/bmj.l4898.
140. Hooijmans CR, Rovers MM, de Vries RBM, Leenaars M, Ritskes-Hoitinga M, Langendam MW. SYRCLE's risk of bias tool for animal studies. BMC Med Res Methodol. 2014;14:43. doi:10.1186/1471-2288-14-43.
141. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017;358:j4008. doi:10.1136/bmj.j4008.
142. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924-926. doi:10.1136/bmj.39489.470347.AD.

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