Review
Sciences of Pharmacy

Solid Lipid Nanoparticles as Delivery Systems for Plant-Derived Phytochemicals in Cancer Therapy: A Systematic Review

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Abstract: Solid lipid nanoparticles (SLNs) have been investigated as lipid-based delivery systems to improve the solubility, stability, bioavailability, and delivery of plant-derived phytochemicals to tumors for cancer therapy. However, the available evidence remains heterogeneous and predominantly preclinical. This systematic review aimed to evaluate the formulation strategies, physicochemical characteristics, and therapeutic applications of phytochemical-loaded SLNs in cancer therapy. The review followed the PRISMA 2020 guidelines. Original research articles in English investigating phytochemical-loaded SLNs for cancer therapy were included. Data on formulation composition, preparation methods, physicochemical properties, drug release, *in vitro* anticancer activity, pharmacokinetics, biodistribution, and *in vivo* antitumor efficacy were extracted. Risk of bias was assessed using the SYRCLE tool for animal studies and an adapted checklist for *in vitro* studies. Thirty one articles were included in the qualitative synthesis. Most SLNs had particle sizes in the nanoscale range, approximately 50-350 nm, with encapsulation efficiencies of 43-99% and sustained-release profiles. Encapsulation generally improved cellular uptake and *in vitro* cytotoxicity in several cancer models. However, evidence of improved bioavailability, active tumor targeting, and *in vivo* antitumor efficacy remained limited and heterogeneous. Surface modification enhanced cellular uptake or organ accumulation in some studies, but validated tumor-specific targeting was not consistently demonstrated. Overall, phytochemical-loaded SLNs demonstrate potential as delivery platforms; however, clinical translation requires standardized formulations, robust *in vivo* studies, comprehensive safety evaluations, and clinical trials.

Introduction

Cancer remains one of the leading causes of morbidity and mortality worldwide despite significant advances in diagnosis and treatment. However, conventional anticancer therapies are still limited by poor drug solubility, nonspecific biodistribution, rapid systemic clearance, multidrug resistance, dose-limiting toxicity, and inadequate drug accumulation in tumor tissues. In addition, the complex tumor microenvironment hinders efficient drug penetration, reducing therapeutic efficacy. These challenges have accelerated the development of nanotechnology-based drug delivery systems to improve pharmacokinetic profiles, potentially enhance drug delivery to tumor tissues, and reduce systemic adverse effects (1).

Among nanotechnology-based carriers, solid lipid nanoparticles (SLNs) have attracted considerable attention as lipid-based delivery systems. SLNs are colloidal carriers composed mainly of solid lipids and stabilising surfactants, with particle sizes generally in the nanometer range. SLNs have been investigated to improve formulation stability, protect incorporated compounds from degradation, and modify drug release and delivery characteristics. Depending on their composition and formulation design, SLNs may offer improved apparent solubility, enhanced bioavailability, controlled release, and incorporation of both hydrophilic and lipophilic compounds. Although some components may be classified as generally recognised as safe (GRAS), the safety of the final formulation depends on the specific lipid, surfactant, surface modifier, dose, route of administration, and duration of exposure. Therefore, the GRAS status of individual ingredients does not automatically guarantee the safety of the final SLN formulation (2–4).

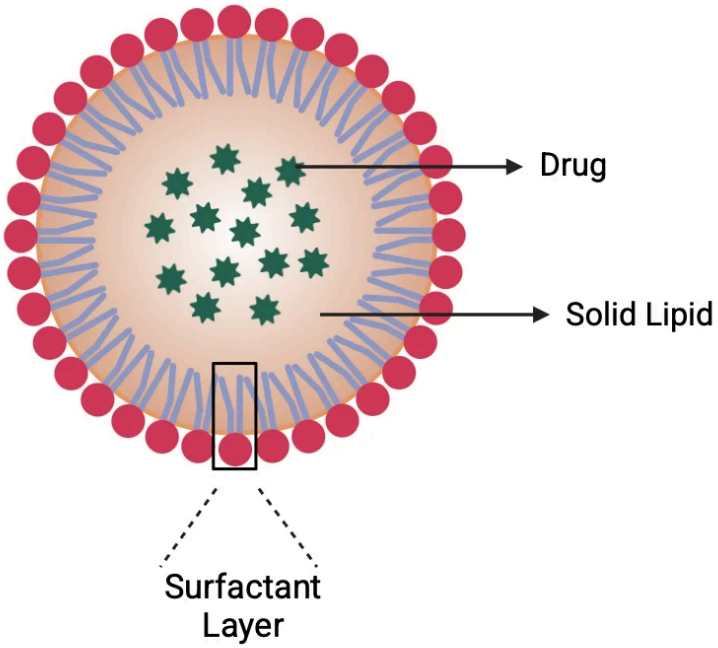


Figure 1. Structure of a solid lipid nanoparticle (SLN).

SLNs should also be distinguished from other lipid-based and polymeric nanocarriers because differences in composition and structure may influence drug incorporation, release behaviour, and physical stability. Nanostructured lipid carriers (NLCs) contain a combination of solid and liquid lipids, whereas SLNs primarily consist of a solid lipid matrix. Conventional liposomes are vesicular systems composed of one or more phospholipid bilayers surrounding an aqueous compartment. At the same time, SLNs are generally described as matrix-based lipid nanoparticles containing a solid lipid phase. Lipid emulsions consist of liquid lipid droplets dispersed in an aqueous phase and stabilized by emulsifying agents, whereas polymeric nanoparticles are formed from natural or synthetic polymers. However, the biological performance, biodistribution, and targeting potential of these systems depend on several factors, including formulation composition, surface characteristics, route of administration, and experimental conditions. Therefore, this review focuses specifically on SLN-based delivery systems containing plant-derived phytochemicals or plant extracts for cancer-related applications (5 – 7).

Among the various therapeutic agents incorporated into SLNs, plant-derived phytochemicals have attracted considerable interest as potential anticancer agents because they can regulate multiple stages of carcinogenesis, including cancer initiation, progression, and metastasis. These bioactive compounds exhibit antioxidant, antiinflammatory, antiproliferative, proapoptotic, and antiangiogenic activities while modulating molecular pathways involved in tumor development and cell survival. Despite their promising therapeutic potential, the clinical application of many phytochemicals is limited by poor aqueous solubility, low bioavailability, rapid metabolism, and insufficient accumulation at tumor sites. Therefore, SLNs have been investigated as potential delivery systems to address these limitations and improve the delivery characteristics of phytochemicals in cancer-related applications (8).

In general, an SLN formulation consists of a solid lipid, a surfactant, an active pharmaceutical ingredient (API), and other formulation components, depending on the preparation method, as illustrated in **Figure 1**. The active compound may be dissolved, dispersed, or incorporated within the solid lipid matrix, while surfactants contribute to the stabilization of the particle interface. The distribution of the active compound within the lipid matrix depends on its physicochemical properties and the composition and preparation conditions of the formulation. These characteristics may influence drug incorporation, release behavior, and formulation stability. Although SLNs may be designed to modify drug distribution or facilitate delivery to specific tissues, their targeting potential requires appropriate experimental validation. SLNs have been investigated for various routes of administration, including oral, parenteral, topical, and ocular delivery (9, 10).

Their formulation components and preparation methods largely influence the performance of SLNs. A variety of solid lipids, including fatty acids, triglycerides, and acylglycerols, have been used in SLN formulations. Several preparation techniques have been developed, including high-shear homogenization, high-pressure homogenization, solvent emulsification, solvent evaporation, ultrasonication, and the microemulsion method. These techniques require energy input to produce nanoparticles with the desired particle size, while surfactants play a crucial role in maintaining dispersion stability and preventing particle aggregation (11, 12).

Previous reviews have examined plant-derived bioactive compounds delivered through solid lipid

nanoparticles (SLNs) and nanostructured lipid carriers (NLCs), including formulation strategies, production methods, and preclinical applications (13, 14). However, these reviews cover both SLNs and NLCs, whereas this review focuses specifically on SLNs containing plant-derived phytochemicals or plant extracts for cancer-related applications. Differences in lipid composition and structural characteristics between SLNs and NLCs may influence the incorporation, release, and stability of active compounds. Therefore, a focused synthesis of evidence concerning phytochemical-and plant extract-loaded SLNs is warranted.

Accordingly, this systematic review addressed the following research questions: (1) What formulation components and preparation methods have been reported for phytochemical- and plant extract-loaded SLNs in cancer-related applications? (2) What physicochemical characteristics and release profiles have been reported for these formulations? and (3) What biological and pharmacological findings have been reported, including *in vitro* anticancer activity, pharmacokinetic or biodistribution outcomes, and *in vivo* antitumor effects, where available?

The objective of this review was to evaluate the formulation strategies, physicochemical characteristics, release profiles, and biological applications of phytochemical- and plant extract-loaded SLNs in cancer-related research. This review focused on distinguishing physicochemical findings, *in vitro* biological activity, pharmacokinetic and biodistribution outcomes, and *in vivo* antitumor efficacy to provide a balanced assessment of the current evidence and identify areas for further investigation.

Methodology

Study Design and Eligibility Criteria

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines. Study eligibility was structured using the PICOS framework.

Population: Studies involving cancer-related biological models, including cancer cell lines, experimental animals, and other relevant models used to assess safety, cellular uptake, pharmacokinetics, or biodistribution.

Intervention: SLN-based formulations containing plant-derived bioactive compounds, including isolated phytochemicals and plant extracts, for cancer-related applications.

Comparison: Free or non-encapsulated active substances, blank SLNs, uncoated formulations, untreated controls, or other reference formulations were recorded when available. Studies without a comparator were eligible when they provided relevant formulation or biological data.

Outcomes: Outcomes included formulation composition, preparation methods, physicochemical characteristics, drug release, cellular uptake, *in vitro* cytotoxicity, apoptosis, pharmacokinetics, biodistribution, *in vivo* antitumor effects, and safety outcomes.

Study design: Original experimental studies using *in vitro*, *in vivo*, or *ex vivo* models were eligible when they provided relevant formulation or biological data. Studies focused on formulation development and physicochemical characterization were also included when relevant to the review objectives.

Original experimental studies using *in vitro*, *in vivo*, or *ex vivo* models were included. Original research articles published in English with sufficient full-text information were eligible. Review articles were used only as supporting references and excluded from the qualitative synthesis. Editorials, conference proceedings, letters, book chapters, patents, and studies lacking sufficient methodological or experimental information were excluded(15).

Literature Search and Study Selection

A systematic literature search was conducted in PubMed, ScienceDirect, and Scopus between 16 and 18 September 2026. The search was restricted to studies published between 16 September 2016 and 16 September 2026 to identify relevant evidence from the previous ten years. The primary search strategy combined terms related to solid lipid nanoparticles, phytochemicals or plant-derived bioactive compounds, and cancer-related applications:

("solid lipid nanoparticles" OR SLN OR "solid lipid nanocarrier") AND (phytochemical OR "plant extract") AND (cancer OR anticancer)

The search strategy was adapted to the syntax of each database, including the use of the `TITLE-ABS-KEY` field in Scopus. All retrieved records were exported to Mendeley Reference Manager for the identification and removal of duplicates. Full-text articles were sought through institutional access, publisher platforms, and other legally available sources. The remaining records were screened based on their titles and abstracts, followed by a full-text assessment according to predefined eligibility criteria.

Studies were excluded if they were not original research articles, did not investigate solid lipid nanoparticles containing plant-derived bioactive compounds for cancer-related applications, or did not provide sufficient methodological and experimental information relevant to the objectives of this review. Articles for which the full text could not be obtained after reasonable retrieval attempts were also excluded. The study selection process was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines.

Data Collection and Extraction

Data were extracted from the included studies using a standardized data extraction form developed in align with the objectives of this review. Extracted information included the first author, publication year, plant-derived bioactive compound or extract, cancer type, formulation composition (including lipid, surfactant, and surface-coating components when applicable), and preparation method. Physicochemical characteristics, including particle size, polydispersity index (PDI), zeta potential, encapsulation efficiency (EE), drug loading (DL), morphology, and relevant characterization findings obtained through FTIR, XRD, DSC, SEM, or TEM, were collected when available. Information on *in vitro* drug release, release kinetics, and therapeutic evaluation, including cytotoxicity, cellular uptake, apoptosis, pharmacokinetics, biodistribution, or *in vivo* antitumor activity, was also extracted when reported. The main findings of each study were organized into summary

tables and synthesized narratively, with emphasis on formulation strategies, physicochemical characteristics, drug release performance, and therapeutic outcomes of SLNs containing plant-derived bioactive compounds or extracts for cancer-related applications (16).

Results and Discussion

Database Search and Included Studies

A systematic literature search was conducted in Scopus, PubMed, and ScienceDirect to identify studies investigating solid lipid nanoparticles (SLNs) containing plant-derived bioactive compounds for cancer-related applications. The search covered publications from 2016 to 2026 using keywords related to solid lipid nanoparticles, phytochemicals or plant extracts, and cancer-related applications.

A comprehensive systematic literature search was conducted across Scopus, PubMed, and ScienceDirect to identify studies investigating solid lipid nanoparticles (SLNs) containing plant-derived bioactive compounds specifically for cancer-related applications. The comprehensive search covered publications spanning from 2016 to 2026. The initial database search identified 2,559 total records (Scopus: 154; PubMed: 24; ScienceDirect: 2,381). After successfully removing duplicates (n = 8) and non-research articles such as reviews, editorials, book chapters, and conference abstracts (n = 2,210), 341 records were carefully screened based on titles and abstracts. Of these, 76 records were excluded, leaving 265

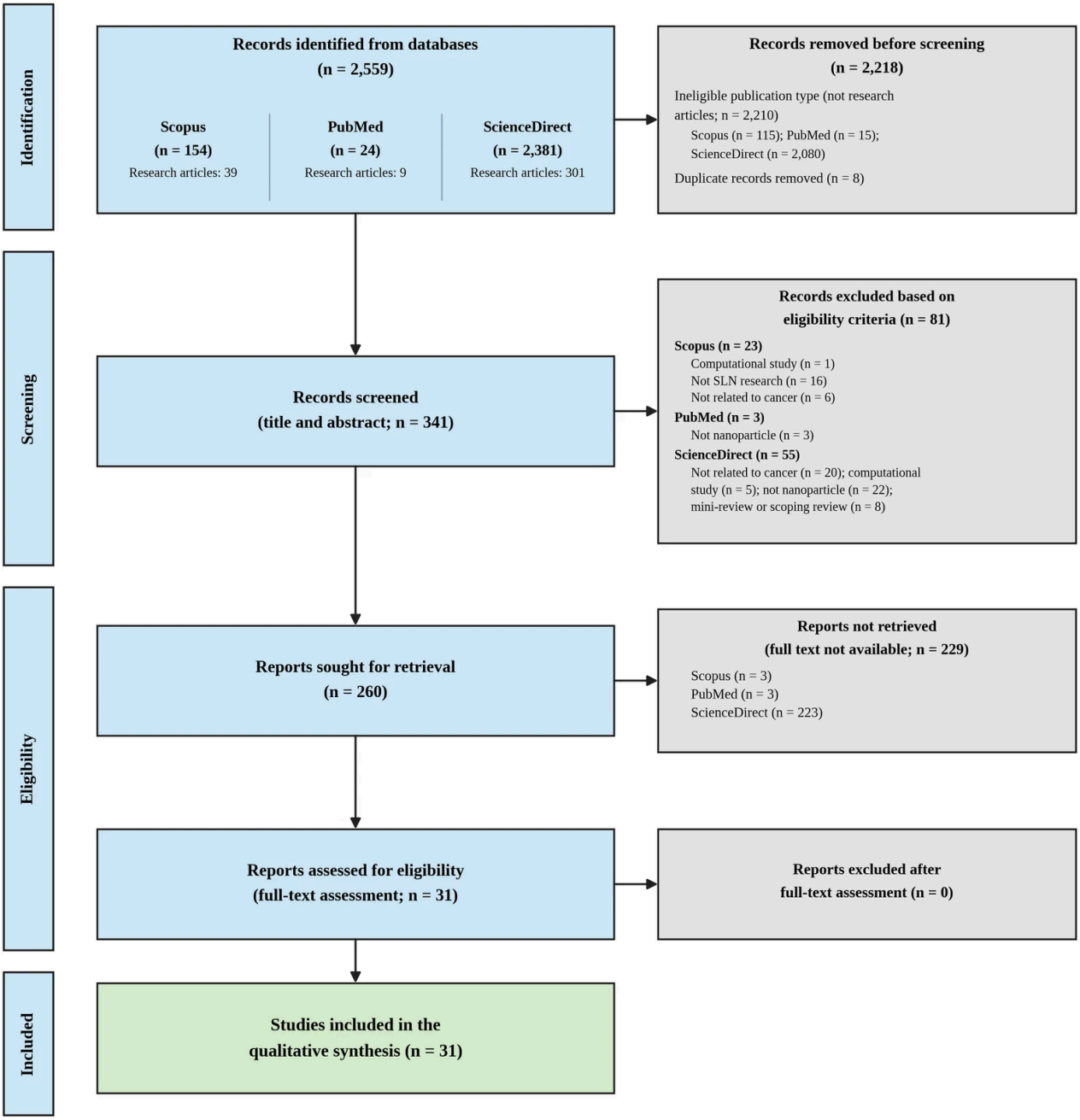


Figure 2. PRISMA flowchart displaying relevant publications in this review.

Table 1. Formulation strategies and physicochemical characteristics of phytochemical-loaded SLNs.

No.	Plant-derived compound / preparation	Formulation composition	Preparation method	Physicochemical characteristics	Release profile	Reference
1.	Resveratrol from *Vitis vinifera* derivative (polyphenolic compound)	Resveratrol, stearic acid as solid lipid, lecithin, Myrj 52 as surfactant, chloroform as organic solvent, and distilled water as aqueous phase	Solvent injection followed by emulsification and low-temperature solidification. Resveratrol, stearic acid, and lecithin were dissolved in chloroform, injected into hot Myrj 52 solution (75 ± 2 °C) under stirring, then cooled, centrifuged, and lyophilized.	Spherical nanoparticles without aggregation observed by TEM. Particle size: 168 ± 10.7 nm, PDI: 0.26 ± 0.03, zeta potential: -23.5 ± 1.6 mV, drug loading capacity: 25.2 ± 1.7%. UV-Vis showed characteristic Res absorption peak at 304 nm.	NR	Wang *et al.* (2017) (17)
2.	Curcumin from *Curcuma longa* (turmeric)-loaded solid lipid nanoparticles (NCC-SLN)	Curcumin-loaded SLN composed of GMS, soy lecithin, poloxamer 188, stearylamine, and NCC as surface coating.	Modified hot homogenization and ultrasonication method	NCC-SLN showed spherical morphology with particle size 245.1 ± 5.4 nm, PDI 0.295 ± 0.16, zeta potential -10.4 ± 3.9 mV, and EE 78.5 ± 3.1%. NCC coating increased size and altered surface charge.	NCC-SLN reduced burst release in SGF (6.7% vs 40.4% at 2 h) and showed sustained release in SIF up to 24 h.	Baek & Cho (2017) (18)
3.	Cinnamon (*Cinnamomum cassia*) and oregano (*Origanum vulgare*) extracts-loaded chitosan-coated SLNs	Compritol® 888 ATO, Gelucire® 44/14, Poloxamer 407, chitosan coating, cinnamon and oregano extracts	Hot melt emulsification-homogenization followed by ultrasonication and chitosan coating	Particle size: 254.77 nm, PDI: 0.28, zeta potential: +15.26 mV, EE: 77.3% (cinnamon), 69.1% (oregano)	Sustained release up to 72 h; 100% release of cinnamaldehyde and rosmarinic acid	Kamel *et al.* (2017) (19)
4.	Curcumin from *Curcuma longa* (turmeric)-loaded Solid Lipid Nanoparticles	Curcumin, stearic acid, lecithin, Myrj 52 as surfactant	Emulsification and low-temperature solidification method, followed by cooling and lyophilization	Spherical nanoparticles (~40 nm). Zeta potential: -25.3 ± 1.3 mV, drug loading: 23.38%, encapsulation efficiency: 72.47%	NR	Wang *et al.* (2018) (20)
5.	Citral-loaded solid lipid nanoparticles from *Cymbopogon citratus*	Citral, Imwitor® 900, Poloxamer 188	Hot high-pressure homogenization (HPH) optimized by factorial design	Particle size: 97.7 ± 1.2 nm, PDI: 0.249 ± 0.013.	NR	Zielińska *et al.* (2018) (21)
6.	Pomegranate extract from *Punica granatum*	Pomegranate extract, stearic acid as lipid, Tween 80 as surfactant, and lecithin as cosurfactant	Hot homogenization followed by probe ultrasonication, optimized using Box-Behnken design	Optimized PE-SLNs: particle size 280 nm, PDI 0.32, zeta potential −41.9 mV, encapsulation efficiency 62.56%, drug loading capacity 1.86%	Sustained release up to 48 h, cumulative release 72.5% from optimized formulation	Badawi *et al.* (2018) (22)
7.	Vietlife-Antican (VLA): curcumin-SLNs, ginger oleoresin-SLNs, and rutin-SLNs	Nanocurcumin, nanoginger, nanorutin	Combination of individual phytochemical-loaded SLNs formulated into softgel capsule	Nanoformulation containing three phytochemicals with enhanced bioavailability and low toxicity	NR	Thao *et al.* (2019) (23)

Table 1. Continued.

No.	Plant-derived compound / preparation	Formulation composition	Preparation method	Physicochemical characteristics	Release profile	Reference
8.	Beta-carotene (BC-SLNs) from plant carotenoid	Beta-carotene, glyceryl monostearate (GMS), Gelucire® 50/13, phospholipid S-100, Tween 80, and Pluronic F68	Hot homogenization followed by dialysis and lyophilization	Particle size: 203 ± 7.23 nm, PDI: 0.185 ± 0.009, zeta potential: -7.21 ± 0.82 mV, EE: 68.3 ± 3.4%, DL: 12.89 ± 1.03%	Sustained release up to 48 h with initial burst release (28.34 ± 2.1% at 1 h)	Jain *et al.* (2019) (24)
9.	*Annona muricata* fruit extract	*A. muricata* ethanolic fruit extract, stearic acid (SA), lecithin (LEC), and poloxamer 188 (POL)	High-pressure homogenization followed by ultrasonication	Optimized formulation (F4): particle size 134.8 nm, entrapment efficiency 83.26%, zeta potential −27.34 mV, desirability factor 0.94	Sustained release with cumulative drug release 79.83% after 48 h	Sabapati *et al.* (2019) (25)
10.	*Croton argyrophyllus* Kunth essential oil (CAEO-SLN)	*Croton argyrophyllus* Kunth essential oil, cetyl palmitate as solid lipid, and Poloxamer® 407 as surfactant	Hot high-pressure homogenization followed by cooling to form SLNs	Mean particle size 201.4 ± 2.3 nm, polydispersity index 0.211, encapsulation efficiency 89.63 ± 1.02%, loading capacity 0.43 ± 0.07%	Sustained release, release followed the Korsmeyer-Peppas model, with approximately 70% essential oil released after 24 h	Souto *et al.* (2020) (26)
11.	Resveratrol (RV-c-SLNs)	Resveratrol, Capmul® MCM C10 as solid lipid, CTAB as cationic lipid, and Tween 80 as surfactant	Hot high-pressure homogenization optimized using Box-Behnken design	Particle size: 139 nm, PDI: 0.271, zeta potential: +50.25 mV, EE: 83.8%; LC: 24.3%	Biphasic release, > 60% drug release within 6 h, followed by sustained release	Rahman *et al.* (2020) (27)
12.	*Zataria multiflora* essential oil (ZMSLN)	*Z. multiflora* essential oil, stearic acid, Span 60, and Tween 80	High-pressure homogenization method	Particle size: 176 ± 8 nm, PDI: 0.22 ± 0.1, spherical morphology, EE: 67 ± 5%	NR	Valizadeh *et al.* (2021) (28)
13.	Soluble curcumin-loaded pectin co-functionalized dual-layered solid lipid nanoparticles (DL-SLN)	Soluble curcumin, cetyl palmitate lipid core, Tween 80, Span 80, pectin, and skimmed milk powder coating	Hot homogenization followed by pectin-SMP coating and lyophilization	Particle size: 347.9 ± 10.81 nm, PDI: 0.388 ± 0.053, zeta potential: -36.9 ± 1.7 mV, EE: 83.94 ± 6.16%	Sustained and colon-targeted release up to 72 h under gastrointestinal conditions	Mohamed *et al.* (2021) (29)
14.	*Cuminum cyminum* essential oil	Cumin essential oil, glyceryl monostearate (GMS), Precirol, stearic acid, Tween 80, and Poloxamer 188	High-shear homogenization followed by probe ultrasonication	Z-average: 1252 ± 21.4 nm, PDI: 0.423 ± 0.03, zeta potential: 17 ± 0.52 mV, EE: 23.00-96.21%, LC: 0.00–7.05%	Sustained nano-encapsulation improved stability and biological activity of essential oil	Tavassolirajaee *et al.* (2022) (30)
15.	Pomegranate extract (PE-SLNs) transdermal emulgel	Pomegranate extract, stearic acid, Tween 80, lecithin, and carbopol 940, propylene glycol, and ethanol	PE-SLNs prepared using a previously reported method, followed by incorporation of the optimized SLN dispersion into	Particle size: 280 nm, PDI: 0.32, zeta potential: −41.9 mV, encapsulation efficiency: 62.56%.	*Ex vivo* permeation through mouse skin for up to 48 h, non-Fickian transport mechanism	Teaima *et al.* (2022) (31)

Table 1. Continued.

No.	Plant-derived compound / preparation	Formulation composition	Preparation method	Physicochemical characteristics	Release profile	Reference
			Carbopol 940 emulgel containing propylene glycol and ethanol as penetration enhancers			
16.	Myricetin (MCN-SLNs)	Myricetin (MCN), Compritol 888 ATO, Gelucire 44/14, oleic acid, Tween 80, and Vitamin E	Prepared using ultra-sonication/high-speed homogenization method.	Particle size: 108.3 ± 6.3 nm, spherical morphology, drug loading efficiency (DL) = 28.3%, encapsulation efficiency (EE) = 90%	MCN-SLNs showed sustained release: initial burst release (~35% within 5 h) followed by gradual release reaching ~76% within 48 h	Alidadi *et al.* (2022) (32)
17.	Diosgenin-loaded stearic acid solid lipid nanoparticles (Dio-SLNPs)	Diosgenin, stearic acid, lecithin, and Tween 80 (polysorbate-80) coating	Prepared using solvent emulsification/evaporation	Particle size mainly ranged from 20-200 nm. Average zeta size of Dio-SLNPs was 15.92 nm with zeta potential -26.0 mV, indicating improved stability, monodispersity and Spherical morphology.	Diosgenin encapsulation efficiency: 56%, unentrapped diosgenin in solvent: 19%, residue: 25%. Diosgenin release increased in a dose-dependent manner after 1 h	Khan *et al.* (2022) (33)
18.	Resveratrol-loaded SLNs (RSV-SLN)	Resveratrol, tristearin, soya phosphatidylcholine, DSPE-PEG 2000	Solvent emulsification-evaporation method	Size: 126.85 ± 12.09 nm, PDI: 0.386, zeta potential: -24.23 mV, EE: 74.67%	Sustained release (67.21% at 48 h)	Sharma *et al.* (2022) (34)
19.	Quercetin (QCT-SLNs)	Quercetin, stearic acid/Precirol lipid, Poloxamer 188, and chitosan coating	Probe ultrasonication followed by chitosan coating and incorporation into mucoadhesive *in situ* gel	Particle size: ~250–275 nm, spherical morphology, EE: > 97%; positive zeta potential after coating	Biphasic sustained release up to 142 h	Shawky *et al.* (2022) (35)
20.	Xanthohumol (XH) from hops (*Humulus lupulus*)	Compritol E ATO (solid lipid), Lipoid E 80 SN (surfactant), and Pluronic F-68 (co-surfactant)	High-shear homogenization followed by probe ultrasonication, optimized using Box-Behnken design and lyophilization	Particle size: 108.60 ± 3.21 nm, PDI: 0.22 ± 0.04, zeta potential, −12.70 mV, EE: 80.20 ± 2.95%, DL: 12.40 ± 1.63%, yield: 85.54 ± 2.98%, assay: 97.68%, pH: 6.65, amorphous structure (DSC/PXRD), spherical morphology (FE-SEM/HRTEM)	Sustained release: 28.42% (12 h), 37.2% (24 h), 60.25% (36 h), and 80.56% (92 h). First-order and Higuchi kinetics (R^2 = 0.975)	Harish *et al.*, (2022) (36)
21.	Phyllanthi tannin fraction (PTF) from	GMS, lecithin, Brij®58, PTF, and purified water	Thin-film hydration followed by probe sonication and freeze drying using sucrose	Particle size: 51.36 ± 0.51 nm (suspension) and 118.9 ± 0.66 nm	Sustained release for > 72 h with no initial burst, release	Wang *et al.* (2023) (37)

Table 1. Continued.

No.	Plant-derived compound / preparation	Formulation composition	Preparation method	Physicochemical characteristics	Release profile	Reference
	Phyllanthus emblica			(freeze-dried), PDI: 0.14 ± 0.01 and 0.21 ± 0.02, zeta potential: −20.37 ± 0.76 and −33.57 ± 1.50 mV, EE: 73.83%, DL: 5.00%; spherical morphology (TEM), TPC: 42%.	increased with pH. Free PTF showed rapid release within 8 h	
22.	Curcumin	GMS, soy lecithin, Tween 80, chitosan, HPMC K4M, Carbopol-974, and TEA	Cold emulsification-probe sonication, chitosan coating, and incorporation into HPMC/Carbopol gel	Particle size: 356.14 ± 8.89 nm (SLN) and 444.8 ± 6.9 nm (coated), PDI: 0.291 ± 0.010 and 0.299 ± 0.009, zeta potential: -34.32 ± 2.45 and +42.23 ± 1.54 mV, EE: 57.08 ± 0.09%. Spherical morphology (TEM). Gel pH: 6.34 ± 0.43 and 6.58 ± 0.5, spreadability: 5.87 ± 0.25 and 6.38 ± 0.19 cm^2/g, viscosity: 29.98 ± 1.87 and 33.49 ± 2.43 Pa·s	Sustained release for 24 h without burst release. Free curcumin reached approximately 88% release within 12 h.	Singhai *et al.* (2023) (38)
23.	Allicin (AC) from garlic	Stearic acid, lecithin, Tween 80, chitosan folic acid coating, and allicin.	High-pressure homogenization, centrifugation, surface functionalization, and lyophilization	Particle size: 86.7 ± 9.4 nm, PDI: 0.31, zeta potential: +21.3 ± 7.9 mV, EE: 86.3%; folic acid binding: 63%; spherical morphology (FESEM); FTIR confirmed surface modification	Burst release followed by sustained release, 70.5% cumulative release after 5 days	Alyasiri *et al.* (2023) (39)
24.	Curcumin from *Curcuma longa*	Glyceryl monostearate, Tween 80, curcumin, and trehalose	Emulsification-ultrasonication, homogenization, cooling, and freeze-drying	Particle size: 114.9 ± 1.36 nm, PDI: 0.112 ± 0.005, zeta potential: -32.3 ± 0.30 mV, EE: 69.74 ± 2.03%, DL: 0.81 ± 0.04%, spherical morphology (TEM). After reconstitution: particle size 119.5 ± 2.17 nm, PDI 0.124, zeta potential −34.6 ± 0.32 mV, EE 71.43 ± 1.53%, and DL 0.77 ± 0.03%	Initial burst release (32.85% within 2 h), followed by sustained release for 120 h, approximately 99% cumulative release at 120 h	Rahman *et al.* (2023) (40)
25.	Pterostilbene (PTS)	Compritol® 888 ATO, Poloxamer 407, lactoferrin, and chondroitin sulfate.	Hot emulsification, ultrasonication, ice bath cooling, and layer by layer coating with lactoferrin and chondroitin sulfate	Optimized CS/Lf/PTS-SLNs: particle size 223.42 ± 18.71 nm, PDI 0.33 ± 0.017, zeta potential -11.85 ± 0.07 mV, EE 98.54 ± 0.3% (uncoated PTS-SLNs), spherical morphology (TEM), FTIR confirmed PTS incorporation and polymer coating	Controlled release: 72.93 ± 2.93% after 24 h for CS/Lf/PTS-SLNs at pH 7.4, similar profiles at pH 5.5	Aly *et al.* (2023) (41)
26.	Herniarin (7-methoxycoumarin)	Stearic acid, lecithin, Tween 80, and herniarin.	Homogenization, incubation, and centrifugation	Particle size: 61.93 nm (DLS), PDI: 0.30, zeta potential: -31.65 mV, EE: 91.199%, SEM: spherical particles, 71.5-128.4 nm, FTIR confirmed herniarin	NR	Delkhah *et al.* (2023) (42)

Table 1. Continued.

No.	Plant-derived compound / preparation	Formulation composition	Preparation method	Physicochemical characteristics	Release profile	Reference
				encapsulation		
27.	Quercetin (QC)	Glyceryl dibehenate (Compritol 888 ATO), oleic acid, lecithin, PVA, and QC (100 mg)	Ultrasonication, homogenization, and centrifugation	Particle size: 104 ± 12.5 nm (TEM) and 112 nm (DLS), PDI: 0.50 ± 0.04, zeta potential: -25.8 mV, spherical morphology, FTIR confirmed formulation.	65% release within 12 h and approximately 90% over 3 days	Afarin *et al.* (2024) (43)
28.	β-Carotene	Palmitic acid and Poloxamer-407, optimized concentration: 1.55 mg/mL lipid and 0.80% surfactant	Solvent diffusion, high-speed homogenization and lyophilization	Particle size: 111.78 nm, PDI: 0.24, zeta potential: −26.3 ± 1.3 mV, EE: 66.46%, drug loading: 11.13%, recovery: 70.61 ± 1.60%, spherical morphology (SEM), FTIR and DSC confirmed drug entrapment, stability: EE 58.93 ± 1.37% and drug loading 9.82 ± 2.18% after 6 months	62.5% release after 12 h and 89.7% after 48 h, first-order kinetics (R^2 = 0.965) and Higuchi model (R^2 = 0.931).	Dutta *et al.* (2024) (44)
29.	*Artemisia vulgaris* essential oil (AVEO)	Stearic acid, lecithin, Tween 80, chitosan-folic acid coating, and mannitol	Hot homogenization, surface modification, centrifugation, and lyophilization	Particle size: 253.67 nm, PDI: 0.26, zeta potential: +39.96 mV, EE: 99.09%, folic acid binding efficiency: 46.25%, spherical morphology, FTIR confirmed surface modification	NR	Aghabagherzadeh *et al.* (2024) (45)
30.	Bitter apple fruit extract (BAFE) from *Citrullus colocynthis*	Glyceryl monostearate, Span 80, caprylic/capric triglyceride, BAFE, and Tween 80.	High-shear homogenization and probe ultrasonication, followed by freezing at -80 °C and lyophilization	Average particle size: 121.2 nm (DLS), particle morphology analyzed by TEM.	NR	Alali *et al.* (2025) (46)
31	Geniposide (GE) from *Gardenia jasminoides* Ellis	Glyceryl monostearate, stearic acid, soya lecithin, and TPGS; GE loading 5% w/w	Double emulsion-solvent evaporation, homogenization, and probe ultrasonication	Particle size: 103.4 ± 1.7 nm, PDI: 0.297 ± 0.03, zeta potential: -21.6 ± 1.2 mV, EE: 81.4 ± 1.8%, spherical morphology, FTIR, DSC, and XRD characterization	67% release in PBS and 81% in acidic buffer after 72 h, Higuchi model	Bora *et al.* (2026) (47)

Table 2. Biological findings reported in the included studies.

No.	Compound / extract / oil	Cancer model or application	Cancer line	Biological, pharmacokinetic, biodistribution, or safety findings as reported	Reference
1.	Resveratrol (Res)	Breast cancer	MDA-MB-231	Res-SLNs showed enhanced anticancer activity compared with free resveratrol, with lower IC_{50} (40.82 ± 3.92 μg/mL vs 72.06 ± 7.85 μg/mL), increased apoptosis (25.6%), enhanced G0/G1 cell cycle arrest (25.5 ± 1.38%), and inhibition of migration/invasion through Bax/Bcl-2, Cyclin D1, and c-Myc regulation. Blank SLNs showed no significant cytotoxicity.	Wang *et al.* (2017) (17)
2.	Curcumin from *Curcuma longa*	Breast cancer	MCF-7	NCC-SLN enhanced cytotoxicity and cellular uptake compared with free curcumin. Blank SLN showed no cytotoxicity. NCC-SLN improved oral bioavailability (AUC: 4.98 ± 2.28 μg·h/mL vs 0.56 ± 0.14 μg·h/mL for curcumin solution) and increased	Baek & Cho (2017) (18)

Table 2. Continued.

No.	Compound / extract / oil	Cancer model or application	Cancer line	Biological, pharmacokinetic, biodistribution, or safety findings as reported	Reference
				intestinal lymphatic uptake after oral administration in rats.	
3.	Cinnamon (*Cinnamomum cassia*) and oregano (*O. vulgare*)	Colorectal cancer	HCT-116 human colon carcinoma cells	SLN-Cs encapsulating cinnamon and oregano extracts enhanced anticancer activity in combination with 5-Fluorouracil (5-FU). Cytotoxicity evaluation showed IC_{50} values of 19.9 µg/mL (cinnamon extract), 29.8 µg/mL (oregano extract), 26.4 µg/mL (cinnamon-loaded SLN-Cs), and 37.2 µg/mL (oregano-loaded SLN-Cs).	Kamel *et al.* (2017) (19)
4.	Curcumin from *Curcuma longa*	Breast cancer	SKBR3	Cur-SLNs showed enhanced anticancer activity compared with free curcumin, with lower IC_{50} (18.78 µM vs 28.42 µM after 48 h), increased cellular uptake, enhanced ROS generation, apoptosis induction (36.7% apoptosis), G1/S cell cycle arrest, and regulation of Bax/Bcl-2, Cyclin D1, and CDK4 proteins.	Wang *et al.* (2018) (20)
5.	Citral-loaded solid lipid nanoparticles (Citral-SLN) from *Cymbopogon citratus*	Skin cancer	A431	Citral showed strong cytotoxic activity, reducing A431 cell viability to approximately 4% after exposure to high concentration (400 µg/mL). Citral-SLN showed improved physical stability with low instability index (0.032 after production; 0.042 after 1 month at 25 °C). Pharmacokinetic and biodistribution studies were not reported.	Zielińska *et al.* (2018) (21)
6.	Pomegranate extract (PE)	Breast cancer, prostate cancer, hepatocellular carcinoma	MCF-7, PC-3, HepG-2; normal HFB-4 cells	Optimized PE-SLNs showed enhanced antiproliferative activity compared with free PE. IC_{50} values were 1.05 µg/mL (MCF-7), 2.63 µg/mL (PC-3), 5.68 µg/mL (HepG-2), while showing lower toxicity toward normal HFB-4 cells (19.34 µg/mL). PE-SLNs improved selective anticancer activity compared with free extract.	Badawi *et al.* (2018) (22)
7.	Vietlife-Antican (VLA): curcumin-SLNs, ginger oleoresin-SLNs, and rutin-SLNs	Breast cancer, hepatocarcinoma, lung cancer, colorectal cancer, leukemia; LLC tumor model	MCF7, HepG2, SK-LU-1, SW480, HL-60; LLC-bearing mice	VLA showed cytotoxic activity against cancer cells with IC_{50} values of 181.64–227.05 µg/mL and lower toxicity toward HEK-293 normal cells (IC_{50} 249.18 µg/mL). In LLC-bearing mice, VLA 600 mg/kg inhibited tumor growth (29.57% reduction) and increased mean survival time (34.05 days). Combination of VLA 200 mg/kg with cisplatin enhanced tumor suppression (49.67% inhibition) and increased IL-2 and IL-10 production.	Thao *et al.* (2019) (23)
8.	Beta-carotene-loaded solid lipid nanoparticles (BC-SLNs)	Breast cancer	MCF-7	BC-SLNs showed improved anticancer activity compared with free beta-carotene in MCF-7 cells. Nanoencapsulation maintained anticancer efficacy and enhanced cytotoxic effects. Oral administration in rats increased beta-carotene bioavailability, with Cmax 59.1 µg/mL, AUCtotal 1215.32 µg/mL·h, and approximately 1.92-fold higher exposure compared with free BC.	Jain *et al.* (2019) (24)
9.	*A. muricata* fruit extract-loaded SLNs	Breast cancer	MCF-7	SLNs showed enhanced cytotoxicity and apoptosis compared with free extract. Extract-loaded SLNs reduced IC50 from 30 µg/mL (free extract) to 12 µg/mL, indicating improved anticancer efficacy. Total apoptosis	Sabapati *et al.* (2019) (25)

Table 2. Continued.

No.	Compound / extract / oil	Cancer model or application	Cancer line	Biological, pharmacokinetic, biodistribution, or safety findings as reported	Reference
				increased from 71.34% (extract) to 86.0% (SLNs).	
10.	*Croton argyrophyllus* Kunth essential oil-loaded SLNs (CAEO-SLN)	Neurodegenerative/oxidative stress model	SH-SY5Y	CAEO-SLN preserved antioxidant activity by reducing lipid peroxidation and scavenging DPPH radicals. The formulation showed low cytotoxicity with cell viability up to 88.84 ± 0.86%, indicating reduced toxicity compared with free essential oil.	Souto *et al.* (2020) (26)
11.	Resveratrol-loaded cationic SLNs (RV-c-SLNs)	Hepatocellular carcinoma	HepG2 cells and DEN-induced HCC rat model	RV-c-SLNs showed enhanced cytotoxicity against HepG2 cells compared with resveratrol solution. *In vivo*, RV-c-SLNs reduced tumor incidence (11.1% vs 100% in DEN control), decreased tumor volume (0.3 ± 0.1), increased tumor accumulation (2.6-fold vs RV solution), reduced inflammatory markers, and improved hepatic histopathological changes.	Rahman *et al.* (2020) (27)
12.	*Z. multiflora* essential oil-loaded SLNs (ZMSLN)	Breast cancer and melanoma	MDA-MB-468 breast cancer cells and A-375 melanoma cells	ZMSLN showed stronger antiproliferative activity than free essential oil. Cell viability decreased to < 13% at 75 µg/mL treatment. Significant cytotoxic effects were observed against both cancer cell lines ($P < 0.001$).	Valizadeh *et al.* (2021) (28)
13.	Soluble curcumin (DL-SLN)	Colorectal cancer	SW480	DL-SLN enhanced curcumin anticancer activity, induced apoptosis and cell cycle arrest, improved oral bioavailability, and showed colon-targeted delivery. Pharmacokinetic improvement: Cmax 5.78 ± 3.26 µg/mL. Tmax 24 h.	Mohamed *et al.* (2021) (29)
14.	*Cuminum cyminum* essential oil (CEO)	Breast cancer, lung cancer, and prostate cancer	MCF7, A549, and PC3	NECEO showed enhanced cytotoxic activity compared with free CEO. IC50 values after 48 h were 108 µg/mL (MCF7), 213 µg/mL (A549), and 124 µg/mL (PC3). Nanoencapsulation improved anticancer activity.	Tavassolirajaee *et al.* (2022) (30)
15.	Pomegranate extract (PE)-(PE-SLNs)	Solid Ehrlich ascites carcinoma (breast carcinoma model)	Swiss albino mice bearing Ehrlich solid tumor	PE-SLNs emulgel significantly reduced tumor growth compared with control. Tumor inhibition rate reached 59.71%, with tumor volume reduced to 237.42 ± 93.77 mm^3 after treatment. Histopathological analysis showed increased tumor necrosis (> 50%).	Teaima *et al.* (2022) (31)
16.	Myricetin-loaded solid lipid nanoparticles (MCN-SLNs)	Colorectal cancer	HT-29	MCN-SLNs significantly reduced cell viability and colony formation compared with free MCN. The formulation increased apoptosis, elevated Bax and AIF expression, reduced Bcl-2 expression, increased ROS generation, and decreased mitochondrial membrane potential	Alidadi *et al.* (2022) (32)

Table 2. Continued.

No.	Compound / extract / oil	Cancer model or application	Cancer line	Biological, pharmacokinetic, biodistribution, or safety findings as reported	Reference
				(MMP), indicating mitochondrial-mediated apoptosis.	
17.	Diosgenin-loaded solid lipid nanoparticles (Dio-SLNPs)	Human glioblastoma and Concanavalin-A-induced sickness behavior mouse model (BALB/c mice)	U87-MG	Dio-SLNPs inhibited cancer cell proliferation and improved depression-like behavioral symptoms. The formulation enhanced diosgenin delivery toward the brain and reduced inflammatory alterations.	Khan *et al.* (2022) (33)
18.	Resveratrol-loaded SLNs (RSV-SLN)	Prostate cancer	PC3	RSV-SLN maintained cytotoxic activity, improved cellular uptake, prolonged circulation (t½ 8.22 h), and increased prostate accumulation (7.56-fold vs RSV solution).	Sharma *et al.* (2022) (34)
19.	Quercetin-loaded cationic solid lipid nanoparticles (QCT-SLNs)	Bladder cancer	T-24	QCT-SLNs showed concentration-dependent cytotoxicity (IC50: 1.6-8.9 µg/mL), enhanced bladder tissue retention and penetration, and prolonged local drug exposure.	Shawky *et al.* (2022) (35)
20.	Xanthohumol-loaded SLNs	Prostate cancer	PC-3	MTT assay: XH-SLNs showed dose and time dependent cytotoxicity (6-48 h), with enhanced inhibition at 24-48 h. Caco-2 permeability: XH-SLNs achieved 6.2 ± 0.98 nmol *versus* 1.34 ± 0.087 nmol for free XH at 5 h (4.62-fold higher). Pharmacokinetics (free XH vs. XH-SLNs): Cmax: 20,730 vs. 22,350 ng/mL; AUC_0–t: 71,360 vs. 341,900 ng/mL·h; $t_1/_2$: 1.975 vs. 12.76 h, MRT: 3.58 vs. 21.97 h. Relative bioavailability: 20.80% (free XH) and 4,791% (XH-SLNs).	Harish *et al.*, (2022) (36)
21.	Phyllanthi tannin fraction (PTF)	Lung cancer	Lewis lung cancer cells; Lewis lung cancer tumor-bearing mice	CCK-8 assay: IC_{50} values were 67.43 µg/mL (free PTF) and 20.74 µg/mL (PTF-SLNs). Apoptosis reached 15% at 20 µg/mL. *In vivo*: Tumor inhibition was 59.97% (PTF, 2 g/kg) and 64.55% (PTF-SLNs, 0.4 g/kg), with reduced tumor volume and weight. PTF-SLNs maintained stable AST, ALT, creatinine, and urea levels and improved organ histopathology compared with free PTF.	Wang *et al.* (2023) (37)
22.	Curcumin-loaded chitosan-coated SLNs	Cervical cancer (intended application)	EAC	MTT assay: IC_{50} values were 37.71 µM (free curcumin), 3.57 µM (SLNPs), and 4.92 µM (chitosan-coated SLNP gel) at 48 h. Mucoadhesion increased particle size from 310.07 ± 21.56 to 1108.76 ± 56.43 nm. Hemolysis at 100, 200, and 300 µg/mL was 4.54 ± 0.31%, 4.84 ± 0.31%, and 5.46 ± 0.32%, respectively. TNF-α levels ranged from 278 ± 25 to 479 ± 19 pg/mL (day 1) and 299 ± 14 to 498 ± 26 pg/mL (day 7) at 100-500 µg/mL.	Singhai *et al.* (2023) (38)
23.	Allicin (AC)	Breast cancer	MCF-7 and HFF (normal cells)	MTT assay: IC_{50} = 20 µg/mL (MCF-7), with no detectable HFF toxicity. ABTS and DPPH IC_{50} values were 165.72 and 36.05 µg/mL, respectively. Flow cytometry showed increased Sub-G1 population without cell-cycle arrest. Apoptotic cells increased with concentration; qPCR: BAX increased, Bcl-2 decreased, and caspase-8 showed no significant change.	Alyasiri *et al.* (2023) (39)
24.	Curcumin	Lung cancer	A549	MTT assay: IC_{50} values were 26.12 ± 1.24 µM (Cur-SLNs) and 35.12 ± 2.33 µM (free curcumin). Cellular uptake: 682.08 ± 6.33 vs. 162.4 ± 4.2 ng/µg (5.2-fold increase). Hemolysis: 9.26 ± 1.31% vs. 7.15 ± 0.47% at 50 µg/mL. Cur-SLNs retained 89%	Rahman *et al.* (2023) (40)

Table 2. Continued.

No.	Compound / extract / oil	Cancer model or application	Cancer line	Biological, pharmacokinetic, biodistribution, or safety findings as reported	Reference
				curcumin after 12 h in PBS (free curcumin: 40%) and remained stable for 90 days at 25 °C/60% RH.	
25.	Pterostilbene (PTS)	Triple negative breast cancer	MDA-MB-231, HGF (normal cells), and orthotopic breast cancer mouse model	*In vitro*: IC_{50} values were 79.5 ± 6.36, 48.45 ± 4.88, 31.56 ± 2.12, and 30.22 ± 3.13 µg/mL for PTS, PTS-SLNs, Lf/PTS-SLNs, and CS/Lf/PTS-SLNs, respectively. Uptake increased 1.8-fold, with wound closure of 0% (24 h) and 3.69 ± 0.7% (48 h). *In vivo*: Necrosis reached 77.5 ± 2.5%, VEGF decreased 2.33-fold, caspase-3 and BAX increased 1.68 and 2-fold, and Bcl-2 decreased to 10.33 ± 1.52%. No significant biochemical or histological abnormalities were observed.	Aly *et al.* (2023) (41)
26.	Herniarin	Gastric, colorectal, and pancreatic cancer	HT-29, AGS, Panc-1 and HFF (normal cells)	MTT assay: Dose-dependent cytotoxicity with IC_{50} values of 138.34 (HT-29), 123.46 (AGS), and 83.744 (Panc-1), HFF cells remained unaffected. Apoptosis and DNA fragmentation increased with concentration. Flow cytometry showed an increased Sub-G1 population without cell-cycle arrest. qPCR: CASP3, CASP8, and CASP9 increased, while BCL-2 and MMP2 decreased; MMP9 decreased nonsignificantly.	Delkhah *et al.* (2023) (42)
27.	Quercetin-loaded SLNs (QC-SLNs) combined with etoposide (ETO)	Breast cancer (triple-negative breast cancer)	MDA-MB-231	MTT assay: The QC-SLN/etoposide combination exhibited dose and time-dependent cytotoxicity at 24 and 48 h, with synergistic effects (CI: 0.49-0.89; DRI: 2-8). The combination increased apoptosis (36.2%), caspase-9 (76.5%), and caspase-3 activity (82%), upregulated Bax (4.8-fold) and p53 (3.42-fold), and downregulated Bcl-2 (0.36-fold). P21 expression increased 3.9 fold.	Afarin *et al.* (2024) (43)
28.	β-Carotene	Breast cancer	MCF-7	MTT assay: IC_{50} of β-carotene-loaded SLNs = 14.89 ± 0.02 µg/mL, compared with pure β-carotene = 182.6 ± 0.25 µg/mL. The SLN formulation showed enhanced cytotoxicity against MCF-7 cells.	Dutta *et al.* (2024) (44)
29.	*Artemisia vulgaris* essential oil (AVEO)	Breast, colorectal, and prostate cancer	CF-7, HT-29, PC-3, HFF (normal cells)	Cytotoxicity (MTT): IC_{50} values of 48.87 µg/mL (MCF-7), 88.48 µg/mL (HT-29), and 121.34 µg/mL (PC-3), no toxicity observed in HFF cells. Antioxidant: ABTS IC_{50} = 203.83 µg/mL, DPPH IC_{50} = 680.86 µg/mL. Apoptosis: increased SubG1 population and caspase-3/9 expression, decreased TNF-α expression. Antiangiogenic: reduced blood vessel formation and VEGF/VEGF-R expression. Antibacterial: *Pseudomonas aeruginosa* MIC = 1 mg/mL and MBC = 2 mg/mL.	Aghabagherzadeh *et al.* (2024) (45)
30.	Bitter apple fruit extract (BAFE)	Skin cancer	A431	MTT assay: 85% inhibition at 24 h, 72% at 48 h, and 58% at 72 h. Antioxidant activity: DPPH IC_{50} = 20.49 µg/mL. Biocompatibility: EC_{50} > 100. Wound healing: 52.25% wound closure after 48 h *versus* 40.37% in the control.	Alali *et al.* (2025) (46)
31.	Geniposide (GE)	Non-small cell lung cancer (NSCLC)	A549	GSLN showed enhanced cytotoxicity compared with free GE. IC_{50}: free GE 196.2 ± 2.7 µg/mL, GSLN 44.1 ± 1.5 µg/mL. Increased apoptosis, reduced colony formation, and enhanced cellular uptake were reported.	Bora *et al.* (2026) (47)

Table 3. Composition and formulation components of solid lipid nanoparticles (SLNs).

Component	Function in SLN Formulation	Representative Examples	References
Solid lipid	Forms the solid lipid matrix and serves as the drug carrier, influencing drug loading, release behaviour, and nanoparticle stability.	Beeswax, stearic acid, cholesterol, caprylic/capric triglyceride, cethyl palmitate, glyceryl stearate (mono- and tri-), glyceryl trilaurate, glyceryl trimyristate, glyceryl behenate (Compritol® 888 ATO), glyceryl tripalmitate, Witepsol® E85/H5/W35, monostearate monocitrate, solid paraffin, behenic acid	Mishra *et al.*, 2018; Satapathy *et al.*, 2021 (48, 49)
Surfactant (Emulsifier)	Reduces interfacial tension between the aqueous phase and lipid core, stabilizes nanoparticles, and prevents aggregation.	Phosphatidylcholine, soy lecithin, egg lecithin, poloxamer, poloxamine, polysorbate 80 (Tween 80)	Mishra *et al.*, 2018; Satapathy *et al.*, 2021 (48, 49)
Co-surfactant	Improves emulsion stability, facilitates particle size reduction, and enhances formulation homogeneity.	Sodium dodecyl sulphate, tyloxapol, sodium oleate, sodium taurocholate, sodium glycocholate, butanol	Mishra *et al.*, 2018; Satapathy *et al.*, 2021 (48, 49)
Aqueous phase	Serves as the continuous dispersion medium during SLN preparation.	Purified water	Satapathy *et al.*, 2021 (48)
Preservative	Prevents microbial contamination during storage.	Thiomersal	Mishra *et al.*, 2018; Satapathy *et al.*, 2021 (48, 49)
Cryoprotectant	Protects nanoparticles from aggregation during freeze-drying and improves storage stability.	Gelatine, glucose, mannose, maltose, lactose, sorbitol, mannitol, glycine, polyvinyl alcohol, polyvinyl pyrrolidone	Mishra *et al.*, 2018; Satapathy *et al.*, 2021 (48, 49)
Charge modifier	Alters surface charge to improve colloidal stability, cellular interaction, and drug delivery performance.	Dipalmitoyl phosphatidylcholine, stearylamine, dicetyl phosphate, dimyristoyl phosphatidyl glycerol	Mishra *et al.*, 2018; Satapathy *et al.*, 2021 (48, 49)

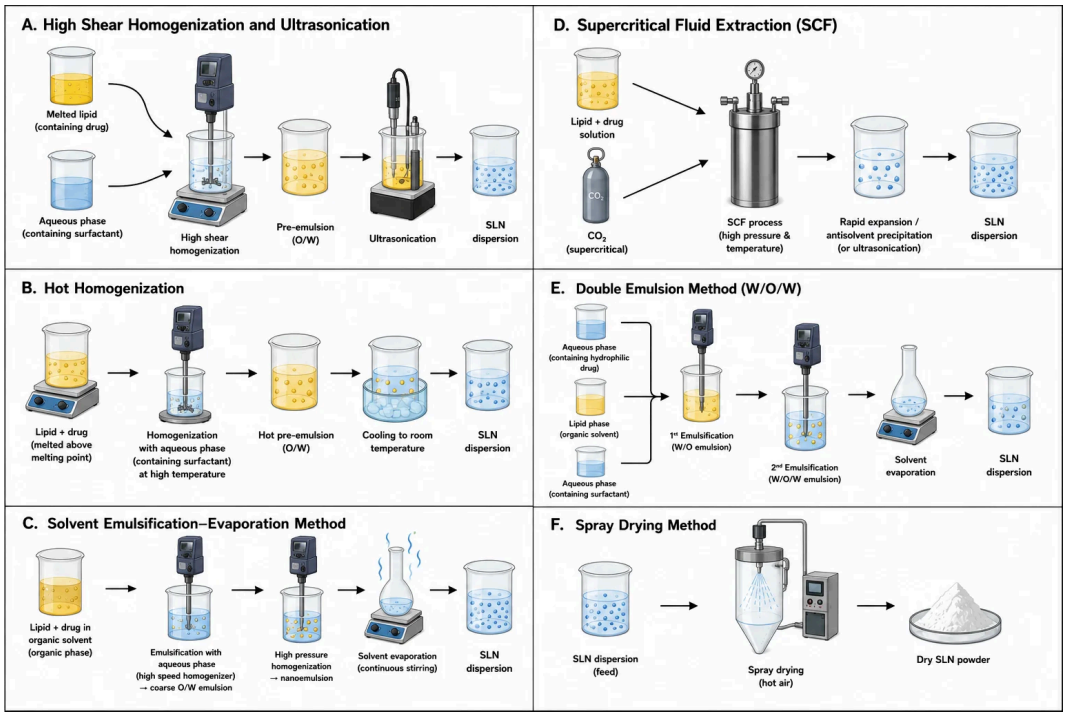


Figure 3. Schematic illustration of the major preparation methods of Solid Lipid Nanoparticles (SLNs), including (A) High shear homogenization and ultrasonication, (B) Hot homogenization, (C) Solvent emulsification-evaporation, (D) Supercritical fluid extraction, (E) Double emulsion (W/O/W), and (F) Spray drying.

reports sought for full retrieval. All 265 reports were retrieved and thoroughly assessed for eligibility. After full-text assessment, 234 reports were excluded for specific reasons: not related to SLN (n = 16), not related to cancer (n = 20), not related to phytochemicals (n = 6), computational study only (n = 5), review or scoping review (n = 8), full text not available (n = 35), and other reasons (n = 144). Finally, 31 studies met all inclusion criteria and were included in the qualitative synthesis. The complete study selection process is presented in the PRISMA 2020 flow diagram (**Figure 2**).

SLN Composition and Formulation Components

The formulation of solid lipid nanoparticles (SLNs) primarily consists of a solid lipid matrix and surfactants, which are often complemented by co-surfactants, preservatives, cryoprotectants, and charge-modifying agents (**Table 3**). These components collectively contribute to the physicochemical stability and performance of SLNs. In particular, surfactants play a crucial role in lowering the interfacial tension between the lipid core and the surrounding aqueous phase, thereby promoting nanoparticle stabilization (48).

Preparation Methods of Solid Lipid Nanoparticles

Several techniques have been developed for the preparation of Solid Lipid Nanoparticles (SLNs), each with distinct principles, advantages, and limitations that influence the physicochemical properties of the resulting nanoparticles. The preparation methods most frequently employed in SLN formulations are summarized below (**Figure 3**).

High-shear Homogenization and Ultrasonication

High-shear homogenization is one of the most widely used techniques for preparing SLNs, particularly through the melt emulsification approach. The properties of the resulting nanoparticles, including particle size, zeta potential, and polydispersity index (PDI), depend on processing parameters such as homogenization speed, processing time, and cooling conditions. This technique is relatively simple and can produce high-quality SLN dispersions, as demonstrated in formulations containing Witepsol® W35. However, the formation of microparticles remains a major limitation, as it may reduce dispersion quality. To overcome this drawback, high-shear homogenization is commonly combined with ultrasonication, which improves particle size uniformity and enhances the overall quality of the nanoparticles. Nevertheless, ultrasonication may also promote physical instability during storage and introduce metal contamination from the homogenization equipment (8, 48, 49).

Hot Homogenization

In hot homogenization technique, the lipid is heated above its melting point and mixed with the drug to form a pre-emulsion, which is subsequently homogenized with the aqueous phase before cooling to produce SLNs. The characteristics of the nanoparticles are strongly influenced by the composition of the pre-emulsion and the type and concentration of surfactant. Increasing the processing temperature generally reduces particle size by lowering lipid viscosity; however, excessive temperatures may also promote microparticle formation and increase the risk of drug and lipid degradation (48).

Solvent Emulsification-evaporation

The solvent emulsification-evaporation method is commonly applied to formulate SLNs, particularly for thermolabile drugs. In this process, the lipid and drug dissolved in an organic solvent and emulsified into an aqueous phase. The organic solvent is then removed by evaporation, leading to the formation of SLN dispersions. The final nanoparticle properties depend on the composition of the lipid matrix, surfactant, and co-surfactant. This technique is capable of producing nanoparticles with high encapsulation efficiency and is considered suitable for large-scale manufacturing (48, 50).

Supercritical Fluid Extraction

Supercritical fluid (SCF) technology utilizes fluids above their critical temperature and pressure to facilitate nanoparticle production. Supercritical carbon dioxide (CO_2) is the most frequently used medium because it is non-toxic, readily removed from the final product, and exhibits excellent solubility for lipophilic compounds. In SLN preparation, SCF technology is often integrated with ultrasonication or rapid expansion, atomization, and antisolvent precipitation techniques to obtain nanoparticles with desirable physicochemical properties (8, 51).

Double Emulsion Method

The double emulsion method is particularly suitable for encapsulating hydrophilic drugs, including peptides and insulin. This technique involves the formation of a water-in-oil-in-water (W/O/W) emulsion through sequential emulsification and solvent evaporation. Stabilizing agents are incorporated to minimize drug diffusion into the external aqueous phase during processing. Although this method is widely used for hydrophilic compounds, it often produces relatively larger particles, making additional surface modification necessary to improve nanoparticle performance (48, 51).

Spray Drying

Although spray drying is currently less common than freeze-drying, it remains a cost-effective alternative for converting SLN suspensions into solid dosage forms. The main limitation of this technique is particle aggregation caused by elevated temperatures, shear stress, and partial melting of the lipid matrix during processing. Consequently, spray drying is generally suitable only for lipids with melting points above 70°C. The process converts SLN dispersions into dry powders through atomization, followed by rapid drying with heated air, thereby improving storage stability (48, 50).

Conclusion

This systematic review indicates that plant-derived phytochemical-loaded SLNs can significantly improve physicochemical properties, including nanosized particle distribution, encapsulation efficiency, and sustained

release profiles. Through comprehensive evaluation, in several *in vitro* models, this encapsulation also improved cellular uptake and cytotoxicity significantly compared with free phytochemicals. However, evidence for bioavailability enhancement, active tumor targeting, and *in vivo* antitumor efficacy remains limited, heterogeneous, and predominantly preclinical. Although surface modification improved cellular uptake or organ accumulation, these studies did not consistently demonstrate validated tumor-specific targeting. Therefore, phytochemical-loaded SLNs are promising delivery platforms, but they are not yet clinically effective. To address these gaps, future studies should use standardized formulations, robust *in vivo* models, risk-of-bias assessment, safety evaluation, and clinical trials. The main limitations of this review include the limited number of databases, language restrictions, heterogeneous study designs, and the lack of a formal meta-analysis.

Abbreviations

SLNs = Solid Lipid Nanoparticles; API = Active Pharmaceutical Ingredient; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

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Conflict of Interest

The authors declare that there are no conflicts of interest related to this study.

Data Availability

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethics Statement

Ethical approval was not required for this study because it is a systematic review based on published literature and did not involve human participants, animals, or identifiable personal data.

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Additional Information

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