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Review Article

Current Advances in Nanotechnology-Mediated Delivery of Herbal and Plant-Derived Medicines

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Abstract

Phytomedicine has been used by humans since ancient times to treat a variety of diseases. However, herbal medicines face significant challenges, including poor water and lipid solubility and instability, which lead to low bioavailability and insufficient therapeutic efficacy. Recently, it has been shown that nanotechnology-based drug delivery systems are appropriate

to overcome the above-mentioned limitations. The present review study first discusses herbal medicines and the challenges involved in the formulation of these drugs. The different types of nano-based drug delivery systems used in herbal delivery and their potential to improve therapeutic efficacy are summarized, and common techniques for preparing nanocarriers used in herbal drug delivery are also discussed. Finally, a list of nanophyto medicines that have entered clinical trials since 2010, as well as those that the FDA has approved, is presented.

Keywords: Phytomedicine, Herbal drug, Nanotechnology, Drug delivery systems, Nanophytomedicine

Introduction

Phytomedicines also called herbal medicines, are mixtures of plant metabolites containing pharmacologically active compounds with some healing and therapeutic properties. due to the benefits such as fewer adverse effects and low cost, herbal medicines have been used since ancient times as therapeutic agents in various diseases. In addition, over one-third of all FDA-approved new molecular entities are natural products and their derivatives.[1,2] The first plant-derived drug was painkiller morphine, with a mechanism of inhibiting the discharge of neurotransmitters from presynaptic neurons and was authorized for utilization in 1827.[3] Later, many other products were developed, including paclitaxel, which is used today as an anticancer agent in ovarian, breast, lung, and other cancers and extracted from the pacific yew plant (Taxus brevifolia).[4,5]

The significant steps to obtain herbal extracts or oils from plant materials generally include harvesting (to suppress plant metabolism at the right time), drying (to protect the active substance by inhibiting enzymes), size reduction (to increase the surface area and thus the improvement of solvent extraction) and extraction (in order to obtain therapeutic portion and omission of inert parts). Finally, the resulting extract can be traditionally formulated in various dosage forms such as solid, liquid, and semi-solid, or encapsulated in novel drug delivery systems such as liposomes, pyrosomes, polymeric NPs, etc.[6-8]

Despite the prominent pharmacological actions of herbal drugs in various diseases, several challenges, including pharmacokinetic drawbacks such as low bioavailability and limited absorption and physicochemical challenges like poor water and lipid solubility, large molecular size, and instability, can reduce their efficacy, primarily upon oral administration.[9,10] An effective drug delivery system is needed to overcome the abovementioned barriers, reduce repeated administration, and increase patient compliance.[11]

In recent decades, nanotechnology-based delivery systems have received much attention in phytomedicine. The encapsulation of herbal drugs in nanocarriers and overcoming the above-mentioned limitations provides benefits such as improved solubility, protection from degradation, reduction of side effects, controlled release, and consequently optimal bioavailability and therapeutic efficacy.[12-14]

This review outlines the challenges of phyto/herbal medicines, including physicochemical and pharmacokinetic drawbacks. Different types of nanocarriers are also discussed as novel and efficient strategies in herbal drug delivery with the potential to overcome the above-mentioned challenges. Some of the common techniques used for the formulation of nanoparticles (NPs) have been reviewed. Therefore, an overview of FDA-approved nanophytomedicines as well as those being used in clinical trials since 2010, has been provided.

Herbal medicines: Challenges

Herbal medicines are a mixture of various ingredients with different physicochemical properties.[15] In addition, poor gastrointestinal (GI) absorption and consequent low oral bioavailability of herbal drugs are due to various factors, including high molecular weight, poor solubility in GI fluids, limited permeability through cell membranes, degradation in the GI tract, hepatic presystemic metabolism, and P-glycoprotein (P-GP/MDR1/ABCB1)]-mediated gut efflux.[16,17] Therefore, the development and preparation of herbal formulations face various challenges.

Nanotechnology-based techniques have been developed to overcome the above-mentioned limitations and increase the bioavailability of herbal medicines.

Nanotechnology for herbal drug delivery

The importance of nanotechnology

Nanotechnology can be used to develop products with novel and improved actions and physicochemical properties particularly in the medical field.[18] Nanocarriers protect their payload from degradation, improve bioavailability, reduce the therapeutic dose and side effects, and provide targeted therapy and controlled release of phytomedicine.[19-21] Different classes of nanocarriers, including lipid-based NPs, polymer-based NPs, and inorganic NPs, have been used for drug delivery in phytomedicine, which will be discussed in detail below. A schematic of common nanocarriers is shown in Figure 1.

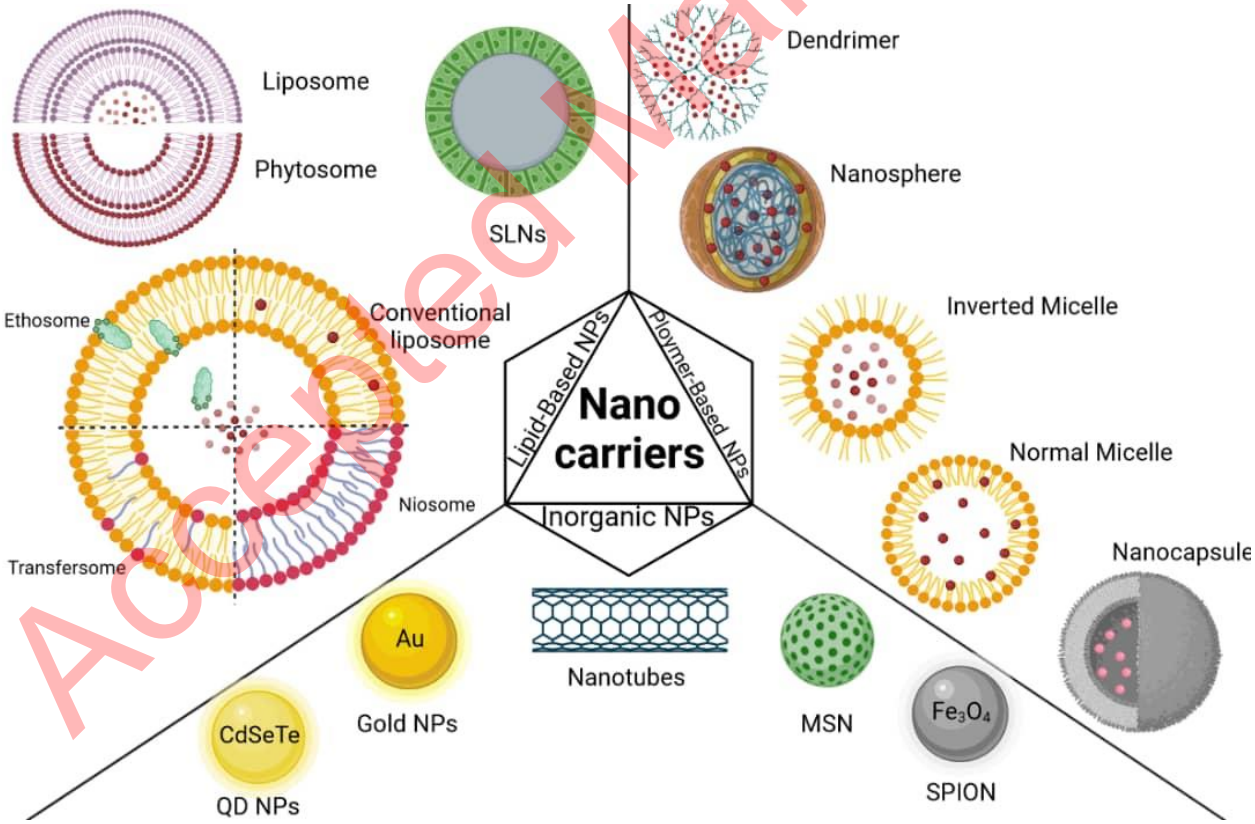

Figure 1. Schematic representation of common nanocarriers for herbal drug delivery.

Lipid-based nanocarriers for herbal drug delivery

In addition to the benefits mentioned in the previous section, lipid-based NPs such as solid lipid nanoparticles (SLNs), liposomes, and phytosomes also have the advantages of biocompatibility

and the ability to improve the aqueous solubility of poorly soluble herbal drugs.[22] Lipid-based nanocarriers are prepared using various materials and methods depending on their target. Challenges like scale-up and physical instability such as aggregation must be considered in the choice of preparation method.[23] Following the preparation of NPs, parameters such as size, morphology, and surface properties should be determined because they play an essential role in the cellular uptake and pharmacological effects of NPs.[24]

Liposomes are vesicular NPs which consist of concentric lipid bilayers made of amphipathic phospholipid molecules that assemble to create spherical structures in aqueous media and surround part of the solvent.[25] In addition to increasing the solubility of the loaded drug, the liposome has been considered as a suitable carrier in herbal delivery in terms of its ability to load both hydrophilic and lipophilic drugs besides improving bioavailability and therapeutic efficacy.[26,27]

In 1989, an Italian pharmaceutical and nutraceutical company, Indena, successfully generated complexes of phospholipids (phosphatidylcholine) and plant actives called phytosome® and then patented the innovation.[28] Phytosomes (refer to Figure 1), also called phytolipid delivery systems, are more stable than liposomes. Because, unlike liposomes, they have a chemical bond in their structure. Phytosomes increase the bioavailability of poorly soluble herbal medicines by increasing their absorption in GI. Some of the phytosomes comprising various phytoconstituents such as grape seed, hawthorn, Ginkgo biloba, milk thistle, ginseng, and green tea are commercialized in the USA.[29,30]

In 1990, SLNs as colloidal NPs which containing lipids that are in solid state at room and body temperature were developed. SLNs have advantages such as excellent physicochemical stability and higher protection compared to other NPs such as liposomes and polymeric NPs. In addition, due to biocompatibility and small size (50 to 1000 nm), it is possible to use SLN herbal formulations in various routes of administration.[31,32] Table 1 summarizes the studies performed on the most common herbal medicines loaded in lipid-based NPs in the last 5 years.

Table 1. A summary of lipid-based herbal nanoformulations.

Nanocarrier type	Active ingredients/Product	Therapeutic activity/Disease	Results (benefits of nanotechnology)	Ref.
Liposome	Triptolide	Anticancer activity	Significant antitumor ability on breast cancer	33
	Curcumin	Anti-inflammatory activity	Improved antioxidant and behavioral responses in inflamed mice	34
		Anticancer activity	Higher therapeutic efficiency	35
			Significant cytotoxic effect on MCF-7 cells	36
			Prolonged release of curcumin Improved antitumor effect	37
		Anti-inflammatory activity	Prolonged release of curcumin Reduced inflammatory markers	38
	Capsaicin	Anticancer activity	Enhanced anticancer activity Improved pharmacokinetics properties	39
	Usnic acid	Antimicrobial activity	Increased antimicrobial activity	40
		Antimycobacterial activity	Effective antimycobacterial activity against infected macrophages	41
	Catechins	Anticancer activity	Significantly higher inhibition activity	42

		Antioxidant activity	Higher stability and antioxidant and antibacterial effects	43
Phytosome	Quercetin	Anticancer activity	Significantly increased apoptosis	44
	Naringenin	Acute lung injury	Sustained release of Naringenin Enhanced pulmonary bioavailability of Naringenin	45
	Silybin	Hepatoprotection activity	Higher hepatoprotection efficacy Higher drug bioavailability	46
	Epigallocatechin-3-gallate	Anti-Inflammatory activity	Significant anti-inflammatory activity of epigallocatechin-3-gallate	47
	Curcumin	Inflammation and anxiety	Reduction of adverse effects of stress on anxiety and inflammation parameters	48
	Ginsenosides	Antioxidant activity	Improved efficacy and bioavailability of the ginsenosides	49
SLN	Triptolide	Rheumatoid arthritis	Remarkable inhibition of inflammation and reduction of knee edema	50
		Antige+n-induced arthritis	Better therapeutic effect	51
	Berberine	Anticancer activity	Prolonged release of berberine	52
	Wogonin		Enhanced cytotoxicity Sustained and controlled release	53
	Epigallocatechin gallate	Antioxidant and anticancer activities	Enhanced stability	54
	Curcumin	Anticancer activity	Stronger cytotoxicity Higher uptake efficiency	55
		Pgp inhibitor	Effective reduction of the sensitivity to doxorubicin against drug-resistant TNBC tumors	56
		CNS diseases	Increased brain accumulation	57
		Anticancer activity	Increased bioavailability	58
		Hodgkin's lymphoma	Enhanced growth inhibitory effect	59
		Antioxidant activity	Improved stability	60
	Hibiscus rosa sinensis extract	Antidepressant activity	Greater antidepressant activity	61
	Myricetin	Anticancer activity	Significant increase in necrosis percentage	62
	Silybin	Type 2 diabetes	Enhanced absorption of silybin after oral administration	63
	Linalool	Anticancer activity	Higher tumor inhibitory effects	64

Polymeric nanocarriers for herbal drug delivery

Recently, polymeric NPs have attracted more attention as a drug delivery system in phytomedicine. These NPs have a particle size of 10 to 1000 nm and are divided into two categories of nanospheres and nanocapsules based on structure. Nanospheres are polymeric matrices in which the active substance is uniformly dispersed, while nanocapsules have a core-shell structure with a polymeric shell, and the active ingredient is encapsulated in the core or is adsorbed on the polymeric membrane. Biodegradable and biocompatible synthetic or natural polymers are used to prepare polymeric NPs. These particles allow the controlled release of the drug and target it to a specific site in the body.[65-67]

Dendrimers have been extensively studied in herbal delivery among polymers due to their unique polyvalency, monodispersity, and controllable structure.[68] Dendrimers consist of three

parts: the central core, the generations, and the terminal groups. The drug can be attached to the terminal group either covalently or non-covalently and it can be encapsulated in the hydrophobic core. Polyamidoamine (PAMAM) is the first commercialized dendrimer, which is also used to increase the absorption of poorly water-soluble drugs.[69,70]

Polymeric micelles with a core-shell structure (10-100 nm) are another polymeric NPs that are formed by self-assembly of block copolymers consisting of both a hydrophilic block and a hydrophobic block in an aqueous medium. The hydrophobic core provides benefits such as increased solubility and protection against degradation and intracellular accumulation of the drug. The outer hydrophilic layer can achieve improved biocompatibility and active targeting. In general, the stability of polymeric micelles is higher than that of surfactant micelles.[71-73] The studies conducted on the delivery of most common herbal medicines using different polymeric NPs during the last 5 years are summarized in Table 2.

Table 2. Polymer-based herbal nanoformulations.

Nanocarrier type	Active ingredients/Product	Therapeutic activity/Disease	Results (benefits of nanotechnology)	Ref.
Nanospheres	Curcumin	Anticancer activity	Higher anticancer activity and apoptosis in HepG2 cells	74
			Increased growth inhibition and apoptosis in breast cancer cells	75
			Improved serum stability Enhanced apoptotic effects on tumor cells	76
		Skin wound healing process	Enhanced potential in cutaneous wound repair	77
	Berberine	Anticancer activity	Increased dissolution rate and bioavailability	78
	Artemether	Antimalarial activity	Sustained release of artemether	79
Nanocapsules	Berberine	Anticancer activity	Improved efficiency and controlled release of berberine	80
	Curcumin	Neuroprotective activity	Improvement in the blockade of apomorphine-induced behavioral changes	81
		Antimalarial activity	Controlled release of curcumin	82
Dendrimer	Quercetin	Antibacterial efficacy	Sustained drug release Enhanced therapeutic potential of quercetin	83
	Silybin	Antioxidant activity	Extended-release time and improved solubility and stability	84
	Curcumin	Anticancer activity	Reduction of the viability of glioblastoma cell lines	85
			Improved antitumor effect	86
Polymeric micelles	Berberine	Anticancer activity	Enhanced cellular uptake and improved solubility and delivery	87
			Higher cellular uptake Enhanced cytotoxic effect against HCT116 cells	80
	10-Hydroxycamptothecin		Improved liver targeting and absorption	88
	Curcumin	Antibacterial activity	Enhanced penetration into the biofilms and antibacterial activity	89

Inorganic nanoparticles

Recently, various types of inorganic NPs, such as metal NPs, mesoporous silica nanoparticles (MSNs), carbon nanotubes (CNTs), and magnetic NPs, have been used for applications in drug delivery.

Metal NPs, the most important of which are quantum dots (QDs), gold, silver, platinum, iron (II, III) oxide, titanium dioxide, and zinc oxide, were discovered by Faraday in 1908. Recently, metal NPs have attracted attention in herbal drug delivery due to their unique properties, like the high surface area to volume ratio, many low coordination sites, the transition between metallic and molecular states, and high surface energies.[90-92]

MSNs are capable of carrying large amounts of cargo due to their large surface area and porosity. In addition, they are widely used in both oral and parenteral drug delivery due to because of unique properties such as excellent chemical stability and biocompatibility.[93,94]

CNTs are relatively more compatible than other inorganic NPs. These NPs, which have a tubular structure, are obtained by curling up graphite sheets and are divided into two categories: single-walled carbon nanotubes (SWCNTs) and multi-walled carbon nanotubes (MWCNTs). SWCNTs can increase the solubility and bioavailability of herbal medicines. In addition, due to their hollow structure and the possibility of surface functionalization, they play an essential role in improving the physical and chemical properties of herbal drugs.[95,96]

Magnetic NPs are another group of inorganic NPs, among which Fe_2O_3 in the form of superparamagnetic NPs is not sensitive to oxidation compared to other magnetic NPs such as nickel and cobalt, so it has the potential application in biomedicine, mainly targeted drug delivery. In fact, the possibility of accumulation of magnetic NPs in the target tissue by applying an external magnetic field leads to target therapy.[97]

The studies performed during the last 5 years on the delivery of most common herbal medicines using different types of an inorganic nanocarriers are summarized in Table 3.

Table 3. Inorganic NPs used in herbal nanoformulations.

Inorganic nanocarrier	Nanocarrier type	Active ingredients/Product	Therapeutic activity/Disease	Results (benefits of nanotechnology)	Ref.
Metal NP	Gold	Berberine	Anticancer activity	Remarkable reduction of tumor weight	98
			Spinal cord injury	Higher anti-apoptotic and anti-inflammatory effects	99
		Curcumin	Anticancer activity	Higher inhibition of tumor cell growth	100
	Silver	Curcumin	Antibacterial activity	Improved curcumin photostability and antibacterial activity	101
			Carbon tetrachloride induced hepatic injury	Significant antioxidant activity	102
			Anticancer activity	Promoted cytotoxic effect on the tumor cells	103
	QD	Curcumin	Anticancer activity	Better inhibitory effect on tumor cells	104
MSN	folic acid–conjugated MSN	Curcumin	Antioxidant, Anticancer activity	Enhanced cellular uptake and sustained release Induction of apoptosis in vitro. Enhanced in vitro antioxidant activity	105
	PEGylated lipid bilayer-coated MSN	Paclitaxel and curcumin		Improved stability, solubility, and sustained release in vitro	106

				Enabled iv administration of hydrophobic drugs Promoted in vitro cytotoxic activity against breast cancer cells	
Magnetic NP	Fe_2O_3/chitosan/montmorillonite	Quercetin	Anticancer activity	Decreased toxicity Controlled and targeted release of the quercetin	107
	α-Fe_2O_3	Sida cordifolia plant extract	Antibacterial activity	Enhanced antimicrobial activity through targeted delivery	108
	Fe_3O_4	Gallic acid	Anticancer activity	Higher anticancer activity	109
		Quercetin		Improved anticancer activity	110
	Fe_3O_4–β-cyclodextrin		Epilepsy disorder	Improved therapeutic efficacy	111
	Fe_3O_4	Silymarin	Anticancer activity	Higher antioxidant activity	112
CNT	MWCNT	Curcumin, Glycyrrhizin and Rutin	Anticancer activity	Increased stability of suspension of CNTs in aqueous media Decreased toxicity of delivery system	113
		Curcumin		Prolonged-release property High adsorption capacity for curcumin	114
	SWCNT	Curcumin		Increase in population of necrotic cells	115
				Improved inhibition of cancer cell proliferation	116
	Cancer cell membrane-modified SWCNT	Berberine		Increased accumulation in liver cancer tissue Prolonged circulation time	117

Techniques used for the formulation of nanophytomedicines

High-pressure homogenization method

In the high-pressure homogenization (HPH) method, lipid particles are converted into nanoscale particles using high pressure and high shear stress. This method, divided into hot and cold homogenization, is widely used to produce lipid-based NPs, including emulsions, liposomes, and SLNs at large scales. In both cases, the first step involves dissolving of the drug in the molten lipid. In hot homogenization, homogenization is applied to the pre-emulsion at a higher temperature than the melting point of lipid. In contrast, in cold homogenization, homogenization of suspension is performed at room temperature.[118,119]

Solvent emulsification–diffusion method

In this method, the polymer or lipid is dissolved in an organic solvent and then emulsified into an aqueous phase containing an emulsifier. Finally, the solvent is evaporated under a vacuum to form polymeric or lipid-based NPs. The advantage of this method over the homogenization method is the lack of high temperature, so it is a suitable method for formulating temperature-sensitive drugs. However, organic solvents may cause toxicological problems.[120,121]

Co-precipitation method

Co-precipitation is the most used method for the preparation of metal oxide and core-shell NPs. It is a cost-effective, fast, straightforward, and easily transposable on a larger scale method for

industrial applications. This method gives nanomaterials via high purity and doesn't require high pressure or temperature and hazardous organic solvents.[122]

Phase coacervation

Coacervation is one of the common methods of microencapsulation and is divided into two categories: simple and complex. In simple coacervation, a colloidal solute such as ethyl cellulose or chitosan is used, while in the case of complex coacervation, a polymer solution is prepared by the interaction between two oppositely charged agents such as gelatin and chitosan. Generally, this method involves the phase-separation of two separate liquid phases to form a polymer-rich phase (coacervate) and a polymer-depleted phase (equilibrium solution).[123,124]

Salting out method

Both the drug and polymer are first dissolved in a solvent in this method. Then, the solubility of the polymer is reduced by adding an electrolyte, and as a result, it precipitates and encapsulates the drug. This technique is primarily used for the preparation of nanospheres.[125,126]

Supercritical fluid-based methods

The supercritical fluid technique with the potential to produce NPs with a narrow size distribution without solvent residues in the final product is considered an essential tool for preparing a wide range of biomedical nanomaterials. Carbon dioxide and water are most commonly used supercritical solvents in this method.[127] The basis of this method is the dissolution of the drug and carrier materials (e.g., polymer) in the supercritical solvent at critical temperature and pressure and then its expansion by spraying in the expansion chamber at lower pressures, which leads to the deposition of materials and the formation of NPs.[128]

Nanoprecipitation technique

Nanoprecipitation techniques, also called solvent displacement methods, were developed by Fessi, et al.[129] Usually, in this method, the polymer and drug are dissolved in a water-miscible solvent and then added to a non-solvent. The solubility of the polymer decreases as soon as it enters the nonsolvent and the polymer precipitates encapsulate the drug. The presence of an emulsifier or stabilizer, such as poloxamers is vital to avoid the aggregation of NPs during the nanoprecipitation process.[130]

Self-assembly methods

Self-assembly is the spontaneous arrangement of individual units to create well-defined structures, which is more suitable for preparing two-dimensional nanostructures such as nanosheets. Self-assembly can occur under the influence or in the absence of external intervention, which is called dynamic and static processes, respectively.[131,132]

Clinical trials and FDA-approved herbal drug delivery nanoformulations

Cosmetochem Company specialized in the production of a range of botanical extracts in a liposomal powder named Liposome Herbasec®. Similarly, a line of Phytosome® technology-based products has been developed and commercialized by the Indena Company. Both liposomal and phytosomal NPs are very efficient penetration enhancers, so they are used as drug carriers for skin with the ability to increase the bioavailability of plant extracts.[15,133]

In addition, different companies have offered various nanoformulations of anticancer phytomedicines. A summary of anticancer nanophytomedicines, which have entered clinical trials and have also been approved by the FDA, is given in Table 4.

Table 4. Clinical trials and FDA-approved anticancer nanophytomedicines

Phytomedicine	Brand name	Nanocarrier	FDA approved	Clinical trials (phase)	Govt. Clinical trials
Docetaxel	DoceAqualip	Lipid nanosuspension	Approved in India	I/II/ III	NCT01957995 NCT03671044
	SYP-0709	Polymeric NPs	-	I	NCT02274610 NCT01103791
	LE-DT/ ATI-1123	Liposome	-	I/II	NCT01151384
	CriPec® docetaxel/ CPC634	CriPec NPs	-	I/II	NCT02442531 NCT03742713 NCT03712423
	DocetaxelPM/ SYP-0704A/ NANOXEL- M	Polymeric micelle	-	II/III	NCT02639858 NCT02982395 NCT03585673
Irinotecan	Onivyde®	Liposome	Yes	-	NCT00702182 NCT01494506 ChiCTR-IPR- 15005856
Vincristine	Marqibo®	Liposome	Yes	-	-
Vinorelbine tartrate	Navelbine/ NanoVNB®	Liposome	Yes	-	NCT03518606 NCT02925000
Curcumin	IMX-110	Curcumin/doxorubicin-encapsulating nanoparticle	Yes	I/II	NCT03382340
	Lipocurc™	Liposome	-	I/II	NCT02138955
Camptothecin	CRLX101/ NLG207	Polymeric nanoparticle	-	I/II	NCT02010567 NCT01380769 NCT01612546
Paclitaxel	NK105	Micellar nanoparticle	-	III	NCT01644890
	Genexol-PM/ IG-001/ Cynviloq	Polymeric micelle	-	I/II/ III/IV	NCT03618758
	Lipusu®	Liposome	-	I/II/ III/IV	NCT02142790 NCT02996214
	Abraxane®	Albumin-stabilized nanoparticle	Yes	-	NCT02555696 NCT02151149

Conclusion

Despite the potential use of plant-derived drugs in the treatment of various diseases, they have considerable limitations due to their high molecular weight, high required dose, poor solubility, and high toxicity. Novel nanotechnology-based drug delivery systems, including polymeric, lipid, and inorganic nanocarriers are beneficial in overcoming these limitations. Nanocarriers containing herbal medicines provide benefits such as increased therapeutic efficacy and bioavailability. Today, many herbal and plant-derived nanoformulations have been approved by the FDA, and many clinical studies are underway in this field.

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Conflict of Interest Statement

All authors declare that they have no conflicts of interest.

Author Contributions

RB and AJ designed the work, collected data, and wrote the manuscript. AJ and RB designed and regenerated the conceptual pictures. AN, BC and YJ checked and revised the article. All authors read and approved the final manuscript**.**

References

1. Hafez DA, Elkhodairy KA, Teleb M, Elzoghby AO. Nanomedicine-based approaches for improved delivery of phyto-therapeutics for cancer therapy. *Expert Opin Drug Deliv* 2020;17(3):279-85. doi: 10.1080/17425247.2020.1723542
2. Sharma R, Hazra J, Prajapati P. Nanophytomedicines: A Novel Approach to Improve Drug Delivery and Pharmacokinetics of Herbal Medicine. *Bio Bull* 2017;3(1):132-5.
3. Patridge E, Gareiss P, Kinch MS, Hoyer D. An analysis of FDA-approved drugs: natural products and their derivatives. *Drug Discov Today* 2016;21(2):204-7.
4. Wani M. Plant antitumor agents. VI. The isolation and structure of taxol, a novel antileukemic and antitumor agent from Taxus brevifolia. *J Am Chem Soc* 1972;19:2325-6.
5. Foa R, Norton L, Seidman AD. Taxol (paclitaxel): a novel anti-microtubule agent with remarkable anti-neoplastic activity. *Int J Clin Lab Res* 1994;24(1):6-14. doi: 10.1007/BF02592403
6. Bart H-J, Pilz S. Industrial scale natural products extraction: John Wiley & Sons; 2011.
7. Vlietinck A, Pieters L, Apers S. Legal requirements for the quality of herbal substances and herbal preparations for the manufacturing of herbal medicinal products in the European union. *Planta Med* 2009;75(7):683-8. doi: 10.1055/s-0029-1185307
8. Singh J. Maceration, percolation and infusion techniques for the extraction of medicinal and aromatic plants. *Extraction technologies for medicinal and aromatic plants* 2008;67:32-5.
9. Kumar K, Rai A. Miraculous therapeutic effects of herbal drugs using novel drug delivery systems. *International Research Journal of Pharmacy* 2012;3(2):27-30.
10. Gunasekaran T, Haile T, Nigusse T, Dhanaraju MD. Nanotechnology: an effective tool for enhancing bioavailability and bioactivity of phytomedicine. *Asian Pac J Trop Biomed* 2014;4(Suppl 1):S1-7. doi: 10.12980/APJTB.4.2014C980
11. Sandhiya V, Ubaidulla U. A review on herbal drug loaded into pharmaceutical carrier techniques and its evaluation process. *Future Journal of Pharmaceutical Sciences* 2020;6(1):1-16.
12. Rahman HS, Othman HH, Hammadi NI, Yeap SK, Amin KM, Samad NA, et al. Novel drug delivery systems for loading of natural plant extracts and their biomedical applications. *International journal of nanomedicine* 2020;15:2439.
13. Aqil F, Munagala R, Jeyabalan J, Vadhanam MV. Bioavailability of phytochemicals and its enhancement by drug delivery systems. *Cancer Lett* 2013;334(1):133-41. doi: 10.1016/j.canlet.2013.02.032
14. Thakur L, Ghodasra U, Patel N, Dabhi M. Novel approaches for stability improvement in natural medicines. *Pharmacogn Rev* 2011;5(9):48-54. doi: 10.4103/0973-7847.79099
15. Saraf S. Applications of novel drug delivery system for herbal formulations. *Fitoterapia* 2010;81(7):680-9.
16. Zhang W, Yang S, He H, Liu C, Chen W, Tang X. Technology for improving the bioavailability of small molecules extracted from traditional Chinese medicines. *Expert Opin Drug Deliv* 2009;6(11):1247-59. doi: 10.1517/17425240903206963
17. He SM, Chan E, Zhou SF. ADME properties of herbal medicines in humans: evidence, challenges and strategies. *Curr Pharm Des* 2011;17(4):357-407. doi: 10.2174/138161211795164194
18. Bagherifar R, Kiaie SH, Hatami Z, Ahmadi A, Sadeghnejad A, Baradaran B, et al. Nanoparticle-mediated synergistic chemoimmunotherapy for tailoring cancer therapy: recent advances and perspectives. *Journal of nanobiotechnology* 2021;19(1):1-18.
19. Alexander A, Ajazuddin, Patel RJ, Saraf S, Saraf S. Recent expansion of pharmaceutical nanotechnologies and targeting strategies in the field of phytopharmaceuticals for the delivery of herbal extracts and bioactives. *J Control Release* 2016;241:110-24. doi: 10.1016/j.jconrel.2016.09.017
20. Etheridge ML, Campbell SA, Erdman AG, Haynes CL, Wolf SM, McCullough J. The big picture on nanomedicine: the state of investigational and approved nanomedicine products. *Nanomedicine* 2013;9(1):1-14. doi: 10.1016/j.nano.2012.05.013
21. Istrati D, Lacatusu I, Bordei N, Badea G, Oprea O, Stefan LM, et al. Phyto-mediated nanostructured carriers based on dual vegetable actives involved in the prevention of cellular damage. *Mater Sci Eng C Mater Biol Appl* 2016;64:249-59. doi: 10.1016/j.msec.2016.03.087
22. Chen ML. Lipid excipients and delivery systems for pharmaceutical development: a regulatory perspective. *Adv Drug Deliv Rev* 2008;60(6):768-77. doi: 10.1016/j.addr.2007.09.010
23. Devi VK, Jain N, Valli KS. Importance of novel drug delivery systems in herbal medicines. *Pharmacogn Rev* 2010;4(7):27-31. doi: 10.4103/0973-7847.65322
24. Shi F, Zhao JH, Liu Y, Wang Z, Zhang YT, Feng NP. Preparation and characterization of solid lipid nanoparticles loaded with frankincense and myrrh oil. *Int J Nanomedicine* 2012;7:2033-43. doi: 10.2147/IJN.S30085

25. Kiaie SH, Mojarad-Jabali S, Khaleseh F, Allahyari S, Taheri E, Zakeri-Milani P, et al. Axial pharmaceutical properties of liposome in cancer therapy: recent advances and perspectives. *International Journal of Pharmaceutics* 2020;581:119269.
26. Xi J, Guo R. Studies on molecular interactions between puerarin and PC liposomes. *Chinese Science Bulletin* 2007;52(19):2612-7.
27. Sarangi MK, Padhi S. Novel herbal drug delivery system: An overview. *Archives of Medicine and Health Sciences* 2018;6(1):171.
28. Gnananath K, Sri Nataraj K, Ganga Rao B. Phospholipid Complex Technique for Superior Bioavailability of Phytoconstituents. *Adv Pharm Bull* 2017;7(1):35-42. doi: 10.15171/apb.2017.005
29. Awasthi R, Kulkarni G, Pawar VK. Phytosomes: an approach to increase the bioavailability of plant extracts. *International journal of pharmacy and pharmaceutical sciences* 2011;3(2):1-3.
30. Manach C, Williamson G, Morand C, Scalbert A, Remesy C. Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. *Am J Clin Nutr* 2005;81(1 Suppl):230S-42S. doi: 10.1093/ajcn/81.1.230S
31. Martins S, Costa-Lima S, Carneiro T, Cordeiro-da-Silva A, Souto E, Ferreira D. Solid lipid nanoparticles as intracellular drug transporters: an investigation of the uptake mechanism and pathway. *International journal of pharmaceutics* 2012;430(1-2):216-27.
32. Pople PV, Singh KK. Development and evaluation of topical formulation containing solid lipid nanoparticles of vitamin A. *AAPS PharmSciTech* 2006;7(4):91. doi: 10.1208/pt070491
33. Zheng W, Wang C, Ding R, Huang Y, Li Y, Lu Y. Triptolide-loaded nanoparticles targeting breast cancer in vivo with reduced toxicity. *Int J Pharm* 2019;572:118721. doi: 10.1016/j.ijpharm.2019.118721
34. Baradaran S, Hajizadeh Moghaddam A, Khanjani Jelodar S, Moradi-Kor N. Protective Effects of Curcumin and its Nano-Phytosome on Carrageenan-Induced Inflammation in Mice Model: Behavioral and Biochemical Responses. *J Inflamm Res* 2020;13:45-51. doi: 10.2147/JIR.S232462
35. Zhang T, Chen Y, Ge Y, Hu Y, Li M, Jin Y. Inhalation treatment of primary lung cancer using liposomal curcumin dry powder inhalers. *Acta Pharm Sin B* 2018;8(3):440-8. doi: 10.1016/j.apsb.2018.03.004
36. Mahmoudi R, Ashraf Mirahmadi-Babaheidri S, Delaviz H, Fouani MH, Alipour M, Jafari Barmak M, et al. RGD peptide-mediated liposomal curcumin targeted delivery to breast cancer cells. *J Biomater Appl* 2021;35(7):743-53. doi: 10.1177/0885328220949367
37. Wang WY, Cao YX, Zhou X, Wei B. Delivery of folic acid-modified liposomal curcumin for targeted cervical carcinoma therapy. *Drug Des Devel Ther* 2019;13:2205-13. doi: 10.2147/DDDT.S205787
38. Ng ZY, Wong J-Y, Panneerselvam J, Madheswaran T, Kumar P, Pillay V, et al. Assessing the potential of liposomes loaded with curcumin as a therapeutic intervention in asthma. *Colloids and surfaces B: Biointerfaces* 2018;172:51-9.
39. Al-Samydai A, Alshaer W, Al-Dujaili EAS, Azzam H, Aburjai T. Preparation, Characterization, and Anticancer Effects of Capsaicin-Loaded Nanoliposomes. *Nutrients* 2021;13(11):3995. doi: 10.3390/nu13113995
40. Francolini I, Giansanti L, Piozzi A, Altieri B, Mauceri A, Mancini G. Glucosylated liposomes as drug delivery systems of usnic acid to address bacterial infections. *Colloids and Surfaces B: Biointerfaces* 2019;181:632-8.
41. Lima Salviano T, Dos Santos Macedo DC, de Siqueira Ferraz Carvalho R, Pereira MA, de Arruda Barbosa VS, Dos Santos Aguiar J, et al. Fucoidan-Coated Liposomes: A Target System to Deliver the Antimicrobial Drug Usnic Acid to Macrophages Infected with Mycobacterium tuberculosis. *J Biomed Nanotechnol* 2021;17(8):1699-710. doi: 10.1166/jbn.2021.3139
42. Hong S-C, Park K-M, Hong CR, Kim J-C, Yang S-H, Yu H-S, et al. Microfluidic assembly of liposomes dual-loaded with catechin and curcumin for enhancing bioavailability. *Colloids and Surfaces A: Physicochemical and Engineering Aspects* 2020;594:124670.
43. Wu J, Guan R, Cao G, Liu Z, Wang Z, Shen H, et al. Antioxidant and Antimicrobial Effects of Catechin Liposomes on Chinese Dried Pork. *J Food Prot* 2018;81(5):827-34. doi: 10.4315/0362-028X.JFP-17-452
44. Alhakamy NA, Fahmy UA, Eldin SMB, Ahmed OAA, Aldawsari HM, Okbazghi SZ, et al. Scorpion Venom-Functionalized Quercetin Phytosomes for Breast Cancer Management: In Vitro Response Surface Optimization and Anticancer Activity against MCF-7 Cells. *Polymers (Basel)* 2021;14(1):93. doi: 10.3390/polym14010093
45. Yu Z, Liu X, Chen H, Zhu L. Naringenin-Loaded Dipalmitoylphosphatidylcholine Phytosome Dry Powders for Inhaled Treatment of Acute Lung Injury. *J Aerosol Med Pulm Drug Deliv* 2020;33(4):194-204. doi: 10.1089/jamp.2019.1569
46. Chi C, Zhang C, Liu Y, Nie H, Zhou J, Ding Y. Phytosome-nanosuspensions for silybin-phospholipid complex with increased bioavailability and hepatoprotection efficacy. *Eur J Pharm Sci* 2020;144:105212. doi: 10.1016/j.ejps.2020.105212

47. H Shariare M, Afnan K, Iqbal F, A Altamimi M, Ahamad SR, S Aldughaim M, et al. Development and optimization of epigallocatechin-3-gallate (egcg) nano phytosome using design of experiment (DoE) and their in vivo anti-inflammatory studies. *Molecules* 2020;25(22):5453.
48. Nemati Karimooy F, Vaez A, Asadi I, Fereidouni A, Saadat M. Therapeutic Effects of Nano-Phytosome of Curcumin on Anxiety-like Behaviors, Neuroinflammation and Biochemical Parameters in Rats Exposed to Stress. *Chemical Methodologies* 2021;5(3):219-26.
49. Merchant NA, Kavya T, Srinivasa R, Rao P, Narayanan P, Bhat S, editors. Ginsenoside Rg1 Nanophytosome synthesis and their characterization: An initiative towards the treatment of Amyotrophic Lateral Sclerosis. 2021 IEEE 21st International Conference on Nanotechnology (NANO); 2021: IEEE.
50. Gu Y, Tang X, Yang M, Yang D, Liu J. Transdermal drug delivery of triptolide-loaded nanostructured lipid carriers: Preparation, pharmacokinetic, and evaluation for rheumatoid arthritis. *Int J Pharm* 2019;554:235-44. doi: 10.1016/j.ijpharm.2018.11.024
51. Li S, Su L, Lv G, Luo W, Kang Y. Ultrasound Guided Intra-Articular Injection of Triptolide-loaded Solid Lipid Nanoparticle for Treatment of Antigen-Induced Arthritis in Rabbits. *Front Pharmacol* 2022;13:824015. doi: 10.3389/fphar.2022.824015
52. Kabary DM, Helmy MW, Elkhodairy KA, Fang JY, Elzoghby AO. Hyaluronate/lactoferrin layer-by-layer-coated lipid nanocarriers for targeted co-delivery of rapamycin and berberine to lung carcinoma. *Colloids Surf B Biointerfaces* 2018;169:183-94. doi: 10.1016/j.colsurfb.2018.05.008
53. Baek JS, Na YG, Cho CW. Sustained Cytotoxicity of Wogonin on Breast Cancer Cells by Encapsulation in Solid Lipid Nanoparticles. *Nanomaterials (Basel)* 2018;8(3):159. doi: 10.3390/nano8030159
54. Shtay R, Keppler JK, Schrader K, Schwarz K. Encapsulation of (−)-epigallocatechin-3-gallate (EGCG) in solid lipid nanoparticles for food applications. *Journal of Food Engineering* 2019;244:91-100.
55. Wang W, Chen T, Xu H, Ren B, Cheng X, Qi R, et al. Curcumin-Loaded Solid Lipid Nanoparticles Enhanced Anticancer Efficiency in Breast Cancer. *Molecules* 2018;23(7):1578. doi: 10.3390/molecules23071578
56. Fathy Abd-Ellatef GE, Gazzano E, Chirio D, Hamed AR, Belisario DC, Zuddas C, et al. Curcumin-Loaded Solid Lipid Nanoparticles Bypass P-Glycoprotein Mediated Doxorubicin Resistance in Triple Negative Breast Cancer Cells. *Pharmaceutics* 2020;12(2):96. doi: 10.3390/pharmaceutics12020096
57. Sadegh Malvajerd S, Azadi A, Izadi Z, Kurd M, Dara T, Dibaei M, et al. Brain Delivery of Curcumin Using Solid Lipid Nanoparticles and Nanostructured Lipid Carriers: Preparation, Optimization, and Pharmacokinetic Evaluation. *ACS Chem Neurosci* 2019;10(1):728-39. doi: 10.1021/acschemneuro.8b00510
58. Minafra L, Porcino N, Bravata V, Gaglio D, Bonanomi M, Amore E, et al. Radiosensitizing effect of curcumin-loaded lipid nanoparticles in breast cancer cells. *Sci Rep* 2019;9(1):11134. doi: 10.1038/s41598-019-47553-2
59. Guorgui J, Wang R, Mattheolabakis G, Mackenzie GG. Curcumin formulated in solid lipid nanoparticles has enhanced efficacy in Hodgkin's lymphoma in mice. *Archives of biochemistry and biophysics* 2018;648:12-9.
60. Santonocito D, Sarpietro MG, Carbone C, Panico A, Campisi A, Siciliano EA, et al. Curcumin Containing PEGylated Solid Lipid Nanoparticles for Systemic Administration: A Preliminary Study. *Molecules* 2020;25(13):2991. doi: 10.3390/molecules25132991
61. Vijayanand P, Jyothi V, Aditya N, Mounika A. Development and Characterization of Solid Lipid Nanoparticles Containing Herbal Extract: In Vivo Antidepressant Activity. *J Drug Deliv* 2018;2018:2908626. doi: 10.1155/2018/2908626
62. Khorsandi L, Mansouri E, Rashno M, Karami MA, Ashtari A. Myricetin loaded solid lipid nanoparticles upregulate MLKL and RIPK3 in human lung adenocarcinoma. *International Journal of Peptide Research and Therapeutics* 2020;26(2):899-910.
63. Piazzini V, Cinci L, D'Ambrosio M, Luceri C, Bilia AR, Bergonzi MC. Solid lipid nanoparticles and chitosan-coated solid lipid nanoparticles as promising tool for silybin delivery: formulation, characterization, and in vitro evaluation. *Current Drug Delivery* 2019;16(2):142-52.
64. Rodenak-Kladniew B, Islan GA, de Bravo MG, Durán N, Castro GR. Design, characterization and in vitro evaluation of linalool-loaded solid lipid nanoparticles as potent tool in cancer therapy. *Colloids and Surfaces B: Biointerfaces* 2017;154:123-32.
65. Khuda-Bukhsh AR, Bhattacharyya SS, Paul S, Boujedaini N. Polymeric nanoparticle encapsulation of a naturally occurring plant scopoletin and its effects on human melanoma cell A375. *Zhong xi yi jie he xue bao= Journal of Chinese integrative medicine* 2010;8(9):853-62.
66. Mainardes RM, Gremião MPD, Evangelista RC. Thermoanalytical study of praziquantel-loaded PLGA nanoparticles. *Revista Brasileira de Ciências Farmacêuticas* 2006;42:523-30.

67. Sureshkumar R, Munikumar M, Ganesh G, Jawahar N, Nagasamyvenkatesh D, Senthil V, et al. Formulation and evaluation of pectin-hydroxypropyl methylcellulose coated curcumin pellets for colon delivery. *Asian Journal of Pharmaceutics (AJP): Free full text articles from Asian J Pharm* 2014;3(2).
68. Tolia GT, Choi HH. The role of dendrimers in topical drug delivery. *Pharmaceutical technology* 2008;32(11):88-98.
69. Klajnert B, Bryszewska M. Dendrimers: properties and applications. *Acta Biochim Pol* 2001;48(1):199-208.
70. D'Emanuele A, Attwood D. Dendrimer–drug interactions. *Advanced drug delivery reviews* 2005;57(15):2147-62.
71. Biswas S, Kumari P, Lakhani PM, Ghosh B. Recent advances in polymeric micelles for anti-cancer drug delivery. *Eur J Pharm Sci* 2016;83:184-202. doi: 10.1016/j.ejps.2015.12.031
72. Zou F, Wei K, Peng X. Thermodynamics of micellization and sustained release of folate targeted capecitabine loaded nanomicelles. *Journal of Nanoscience and Nanotechnology* 2016;16(8):8519-27.
73. Wang Z, Yu Y, Ma J, Zhang H, Zhang H, Wang X, et al. LyP-1 modification to enhance delivery of artemisinin or fluorescent probe loaded polymeric micelles to highly metastatic tumor and its lymphatics. *Mol Pharm* 2012;9(9):2646-57. doi: 10.1021/mp3002107
74. Rajasekar A, Devasena T, Suresh S, Senthil B, Sivaramakrishnan R, Pugazhendhi A. Curcumin nanospheres and nanorods: Synthesis, characterization and anticancer activity. *Process Biochemistry* 2022;112:248-53.
75. Afzali E, Eslaminejad T, Yazdi Rouholamini SE, Shahrokhi-Farjah M, Ansari M. Cytotoxicity Effects of Curcumin Loaded on Chitosan Alginate Nanospheres on the KMBC-10 Spheroids Cell Line. *Int J Nanomedicine* 2021;16:579-89. doi: 10.2147/IJN.S251056
76. Duse L, Agel MR, Pinnapireddy SR, Schafer J, Selo MA, Ehrhardt C, et al. Photodynamic Therapy of Ovarian Carcinoma Cells with Curcumin-Loaded Biodegradable Polymeric Nanoparticles. *Pharmaceutics* 2019;11(6):282. doi: 10.3390/pharmaceutics11060282
77. Kim DW, Choi CH, Park JP, Lee SJ. Nanospheres Loaded with Curcumin Improve the Bioactivity of Umbilical Cord Blood-Mesenchymal Stem Cells via c-Src Activation During the Skin Wound Healing Process. *Cells* 2020;9(6):1467. doi: 10.3390/cells9061467
78. Jia J, Zhang K, Zhou X, Zhou D, Ge F. Precise Dissolution Control and Bioavailability Evaluation for Insoluble Drug Berberine via a Polymeric Particle Prepared Using Supercritical CO(2). *Polymers (Basel)* 2018;10(11):1198. doi: 10.3390/polym10111198
79. Bhide AR, Jindal AB. Fabrication and evaluation of artemether loaded polymeric nanorods obtained by mechanical stretching of nanospheres. *International Journal of Pharmaceutics* 2021;605:120820.
80. Ghaffarzadegan R, Khoee S, Rezazadeh S. Fabrication, characterization and optimization of berberine-loaded PLA nanoparticles using coaxial electrospray for sustained drug release. *Daru* 2020;28(1):237-52. doi: 10.1007/s40199-020-00335-y
81. de Oliveira Pacheco C, de Gomes MG, da Silva Neto MR, Parisotto AJM, Dos Santos RB, Maciel TR, et al. Surface-functionalized curcumin-loaded polymeric nanocapsules could block apomorphine-induced behavioral changes in rats. *Pharmacological Reports* 2021:1-13.
82. Dos Santos RB, Nakama KA, Pacheco CO, de Gomes MG, de Souza JF, de Souza Pinto AC, et al. Curcumin-loaded nanocapsules: Influence of surface characteristics on technological parameters and potential antimalarial activity. *Materials Science and Engineering: C* 2021;118:111356.
83. Rehman K, Ali I, El-Haj BM, Kanwal T, Maharjan R, Saifullah S, et al. Synthesis of novel biocompatible resorcinarene based nanosized dendrimer-vesicles for enhanced anti-bacterial potential of quercetin. *Journal of Molecular Liquids* 2021;341:116921.
84. Diaz C, Guzmán J, Jiménez VA, Alderete JB. Partially PEGylated PAMAM dendrimers as solubility enhancers of Silybin. *Pharmaceutical development and technology* 2018;23(7):689-96.
85. Gallien J, Srinageshwar B, Gallo K, Holtgrefe G, Koneru S, Otero PS, et al. Curcumin Loaded Dendrimers Specifically Reduce Viability of Glioblastoma Cell Lines. *Molecules* 2021;26(19):6050. doi: 10.3390/molecules26196050
86. Mohammadpour K, Salahvarzi S, Dadgar Z. Connection of poly (Propylene imine) dendrimer to curcumin and investigation into anti-cancer effects of its products. *Asian Journal of Nanosciences and Materials* 2020;3(4):340-50.
87. Abdelmoneem MA, Mahmoud M, Zaky A, Helmy MW, Sallam M, Fang J-Y, et al. Dual-targeted casein micelles as green nanomedicine for synergistic phytotherapy of hepatocellular carcinoma. *J Control Release* 2018;287:78-93. doi: 10.1016/j.jconrel.2018.08.026
88. Wu H, Yu T, Tian Y, Wang Y, Zhao R, Mao S. Enhanced liver-targeting via coadministration of 10-Hydroxycamptothecin polymeric micelles with vinegar baked Radix Bupleuri. *Phytomedicine* 2018;44:1-8. doi: 10.1016/j.phymed.2018.04.022

89. Barros CHN, Hiebner DW, Fulaz S, Vitale S, Quinn L, Casey E. Synthesis and self-assembly of curcumin-modified amphiphilic polymeric micelles with antibacterial activity. *J Nanobiotechnology* 2021;19(1):104. doi: 10.1186/s12951-021-00851-2
90. Jain S, Saxena N, Sharma MK, Chatterjee S. Metal nanoparticles and medicinal plants: present status and future prospects in cancer therapy. *Materials Today: Proceedings* 2020;31:662-73.
91. Singla R, Guliani A, Kumari A, Yadav SK. Metallic nanoparticles, toxicity issues and applications in medicine. Nanoscale materials in targeted drug delivery, theragnosis and tissue regeneration: Springer; 2016. p. 41-80.
92. Kiaie S, Karami C, Khodadadian A, Taher M, Soltanian S. A facile method for detection of N-acetylcysteine and L-cysteine with silver nanoparticle in aqueous environments. *J Bioequiv Availab* 2016;8:197-203.
93. Zhang Y, Wang J, Bai X, Jiang T, Zhang Q, Wang S. Mesoporous silica nanoparticles for increasing the oral bioavailability and permeation of poorly water soluble drugs. *Mol Pharm* 2012;9(3):505-13. doi: 10.1021/mp200287c
94. Hao N, Jayawardana KW, Chen X, Yan M. One-step synthesis of amine-functionalized hollow mesoporous silica nanoparticles as efficient antibacterial and anticancer materials. *ACS Appl Mater Interfaces* 2015;7(2):1040-5. doi.org/10.1021/am508219g
95. Li YL, Li J, Yan CY, Lai ZF, Hu GJ. Chinese medicine single-walled carbon nanotube targeting compound for antitumor therapy: a feasible way? *Chin J Integr Med* 2014;20(1):63-7. doi: 10.1007/s11655-012-1080-4
96. Jogi H, Maheshwari R, Raval N, Kuche K, Tambe V, Mak KK, et al. Carbon nanotubes in the delivery of anticancer herbal drugs. *Nanomedicine (Lond)* 2018;13(10):1187-220. doi: 10.2217/nnm-2017-0397
97. Varadan VK, Chen L, Xie J. Nanomedicine: design and applications of magnetic nanomaterials, nanosensors and nanosystems: John Wiley & Sons; 2008.
98. Chiu CF, Fu RH, Hsu SH, Yu YA, Yang SF, Tsao TC, et al. Delivery Capacity and Anticancer Ability of the Berberine-Loaded Gold Nanoparticles to Promote the Apoptosis Effect in Breast Cancer. *Cancers (Basel)* 2021;13(21):5317. doi: 10.3390/cancers13215317
99. Zhou Z, Li D, Fan X, Yuan Y, Wang H, Wang D, et al. Gold nanoclusters conjugated berberine reduce inflammation and alleviate neuronal apoptosis by mediating M2 polarization for spinal cord injury repair. *Regen Biomater* 2022;9:rbab072. doi: 10.1093/rb/rbab072
100. Fu C, Ding C, Sun X, Fu A. Curcumin nanocapsules stabilized by bovine serum albumin-capped gold nanoclusters (BSA-AuNCs) for drug delivery and theranosis. *Mater Sci Eng C Mater Biol Appl* 2018;87:149-54. doi: 10.1016/j.msec.2017.12.028
101. Azeez L, Lateef A, Adebisi SA. Silver nanoparticles (AgNPs) biosynthesized using pod extract of Cola nitida enhances antioxidant activity and phytochemical composition of Amaranthus caudatus Linn. *Applied Nanoscience* 2017;7(1-2):59-66.
102. Ebaid H, Habila M, Hassan I, Al-Tamimi J, Omar MS, Rady A, et al. Curcumin-containing Silver Nanoparticles Prevent Carbon Tetrachloride- induced Hepatotoxicity in Mice. *Comb Chem High Throughput Screen* 2021;24(10):1609-17. doi: 10.2174/1386207323666201211100830
103. Garg S, Garg A. Encapsulation of curcumin in silver nanoparticle for enhancement of anticancer drug delivery. *Int J Pharm Sci Res* 2018;9(3):1160-6. doi: 10.13040/IJPSR.0975-8232.9(3).1160-66
104. Khan FA, Lammari N, Muhammad Siar AS, Alkhater KM, Asiri S, Akhtar S, et al. Quantum dots encapsulated with curcumin inhibit the growth of colon cancer, breast cancer and bacterial cells. *Nanomedicine (Lond)* 2020;15(10):969-80. doi: 10.2217/nnm-2019-0429
105. AbouAitah K, Swiderska-Sroda A, Farghali AA, Wojnarowicz J, Stefanek A, Gierlotka S, et al. Folic acid–conjugated mesoporous silica particles as nanocarriers of natural prodrugs for cancer targeting and antioxidant action. *Oncotarget* 2018;9(41):26466. doi: 10.18632/oncotarget.25470
106. Lin J, Cai Q, Tang Y, Xu Y, Wang Q, Li T, et al. PEGylated Lipid bilayer coated mesoporous silica nanoparticles for co-delivery of paclitaxel and curcumin: Design, characterization and its cytotoxic effect. *Int J Pharm* 2018;536(1):272-82. doi: 10.1016/j.ijpharm.2017.10.043
107. Ahmadi M, Pourmadadi M, Ghorbanian SA, Yazdian F, Rashedi H. Ultra pH-sensitive nanocarrier based on Fe(2)O(3)/chitosan/montmorillonite for quercetin delivery. *Int J Biol Macromol* 2021;191:738-45. doi: 10.1016/j.ijbiomac.2021.09.023
108. Pallela PNVK, Ummey S, Ruddaraju LK, Gadi S, Cherukuri CS, Barla S, et al. Antibacterial efficacy of green synthesized α-Fe2O3 nanoparticles using Sida cordifolia plant extract. *Heliyon* 2019;5(11):e02765. doi: 10.1016/j.heliyon.2019.e02765
109. Rosman R, Saifullah B, Maniam S, Dorniani D, Hussein MZ, Fakurazi S. Improved Anticancer Effect of Magnetite Nanocomposite Formulation of GALLIC Acid (Fe(3)O(4)-PEG-GA) Against Lung, Breast and Colon Cancer Cells. *Nanomaterials (Basel)* 2018;8(2):83. doi: 10.3390/nano8020083

110. Ghafelehbashi R, Yaraki MT, Saremi LH, Lajevardi A, Haratian M, Astinchap B, et al. A pH-responsive citric-acid/α-cyclodextrin-functionalized Fe3O4 nanoparticles as a nanocarrier for quercetin: An experimental and DFT study. *Mater Sci Eng C Mater Biol Appl* 2020;109:110597. doi: 10.1016/j.msec.2019.110597
111. Hashemian M, Ghasemi-Kasman M, Ghasemi S, Akbari A, Moalem-Banhangi M, Zare L, et al. Fabrication and evaluation of novel quercetin-conjugated Fe3O4–β-cyclodextrin nanoparticles for potential use in epilepsy disorder. *Int J Nanomedicine* 2019;14:6481. doi: 10.2147/IJN.S218317
112. Zare M, Sarkati MN. Chitosan-functionalized Fe3O4 nanoparticles as an excellent biocompatible nanocarrier for silymarin delivery. *Polymers for Advanced Technologies* 2021;32(10):4094-100. doi:10.1002/pat.5416
113. Ohadi M, Rezaei P, Mehrabani M, Behnam B, Ansari M. Synthesis, characterization and toxicity assessment of the novel non covalent functionalized multi-walled carbon nanotubes with glycyrrhizin, curcumin and rutin. *J Clust Sci* 2021:1-10. doi: 10.1007/s10876-021-02026-3
114. Malek SK, Gabris MA, Jume BH, Baradaran R, Aziz M, Abd Karim KJB, et al. Adsorption and in vitro release study of curcumin form polyethyleneglycol functionalized multi walled carbon nanotube: kinetic and isotherm study. *DARU Journal of Pharmaceutical Sciences* 2019;27(1):9-20.
115. Tiwari J, Garg A, Jain AP. Synthesis and characterization of single walled carbon nanotubes (SWCNTs) anchored curcumin for breast cancer targeting. 2020.
116. Singh N, Sachdev A, Gopinath P. Polysaccharide functionalized single walled carbon nanotubes as nanocarriers for delivery of curcumin in lung cancer cells. *J Nanosci Nanotechnol* 2018;18(3):1534-41. doi: 10.1166/jnn.2018.14222
117. Yue J, Wang Z, Shao D, Chang Z, Hu R, Li L, et al. Cancer cell membrane-modified biodegradable mesoporous silica nanocarriers for berberine therapy of liver cancer. *RSC Adv* 2018;8(70):40288-97. doi: 10.1039/c8ra07574c
118. Sahni JK, Baboota S, Ali J. Promising role of nanopharmaceuticals in drug delivery. *Pharma Times* 2011;43(10):16-8.
119. Ansari SH, Islam F, Sameem M. Influence of nanotechnology on herbal drugs: A Review. *J Adv Pharm Technol Res* 2012;3(3):142-6. doi: 10.4103/2231-4040.101006
120. Trotta M, Debernardi F, Caputo O. Preparation of solid lipid nanoparticles by a solvent emulsification–diffusion technique. *International journal of pharmaceutics* 2003;257(1-2):153-60.
121. Siekmann B, Westesen K. Melt-homogenized solid lipid nanoparticles stabilized by the nonionic surfactant tyloxapol. I. Preparation and particle size determination. *Pharm Pharmacol Lett* 1994;3:194-7.
122. Cruz IF, Freire C, Araújo JP, Pereira C, Pereira AM. Multifunctional ferrite nanoparticles: from current trends toward the future. Magnetic Nanostructured Materials: Elsevier; 2018. p. 59-116.
123. Chadha S. Recent advances in nano-encapsulation technologies for controlled release of biostimulants and antimicrobial agents. *Advances in Nano-Fertilizers and Nano-Pesticides in Agriculture* 2021:29-55. doi: 10.1016/B978-0-12-820092-6.00002-1
124. Salaün F. Microencapsulation technology for smart textile coatings. Active coatings for smart textiles: Elsevier; 2016. p. 179-220.
125. Yoo HS, Oh JE, Lee KH, Park TG. Biodegradable nanoparticles containing doxorubicin-PLGA conjugate for sustained release. *Pharm Res* 1999;16(7):1114-8. doi: 10.1023/a:1018908421434
126. Kumari B. A Review on Nanoparticles: Their Preparation method and applications. *Ind Res J Pharm Sci* 2018;5(2):1420.
127. Pathak K. Effective formulation strategies for poorly water soluble drugs. Advances and Challenges in Pharmaceutical Technology: Elsevier; 2021. p. 181-228.
128. Blasi P, Giovagnoli S, Schoubben A, Ricci M, Rossi C. Solid lipid nanoparticles for targeted brain drug delivery. *Adv Drug Deliv Rev* 2007;59(6):454-77. doi: 10.1016/j.addr.2007.04.011
129. Fessi H, Puisieux F, Devissaguet JP, Ammoury N, Benita S. Nanocapsule formation by interfacial polymer deposition following solvent displacement. *International journal of pharmaceutics* 1989;55(1):R1-R4.
130. Quintanar-Guerrero D, Allemann E, Fessi H, Doelker E. Preparation techniques and mechanisms of formation of biodegradable nanoparticles from preformed polymers. *Drug Dev Ind Pharm* 1998;24(12):1113-28. doi: 10.3109/03639049809108571
131. Ghalia MA, Dahman Y. Advanced nanobiomaterials in tissue engineering: Synthesis, properties, and applications. Nanobiomaterials in soft tissue engineering: Elsevier; 2016. p. 141-72. doi: 10.1016/B978-0-323-42865-1.00006-4
132. Yadav S, Sharma AK, Kumar P. Nanoscale Self-Assembly for Therapeutic Delivery. *Front Bioeng Biotechnol* 2020;8:127. doi: 10.3389/fbioe.2020.00127

133. 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):306-14. doi: 10.1016/j.fitote.2009.11.001