Pharmaceutical Sciences, 2024, 30(2), 153-186
doi:10.34172/PS.2023.27
https://ps.tbzmed.ac.ir/

Review Article

Harnessing Nanotechnology for Optimized Herbal Cancer Treatment: A Comprehensive Review of Nanoscale Drug Delivery Systems

Malihe Sadat Razavi[1,2], Fatemeh Ahmadi[1,2], Pedram Ebrahimnejad[1,2*], Abolfazl Akbarzadeh[3,4], Masoud Farokhrou[5], Ali Nokhodchi[6,7,8*]

[1]*Pharmaceutical Sciences Research Center, Hemoglobinopathy Institute, Mazandaran University of Medical Sciences, Sari, Iran.*
[2]*Department of Pharmaceutics, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran.*
[3]*Tuberculosis and Lung Disease Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.*
[4]*Universal Scientific Education and Research Network (USERN), Tabriz, Iran.*
[5]*Dental Professionals of Coral Springs, Coral Spring, Florida 33065, USA.*
[6]*Lupin Inhalation Research Center, Lupin Pharmaceuticals, 4006 NW 124th Ave., Coral Springs, FL 33065, USA.*
[7]*Pharmaceutics Research Laboratory, School of Life Sciences, University of Sussex, Brighton BN1 9QJ, UK.*
[8]*Daru Vira Iranian Pharmaceutical Group, Isfahan, Iran.*

Article Info

Article History:
Received: 28 Aug 2023
Accepted: 25 Nov 2023
ePublished: 19 Jan 2024

Keywords:
-Bioavailability
-Cancer treatment
-Drug delivery systems
-Herbal medicines
-Nanotechnology

Abstract

Cancer is widely recognized as the second leading cause of death on a global scale. In recent years, nanotechnology has emerged as a promising strategy in the field of cancer therapy. Nanoscale drug delivery systems, a category of innovative technologies, harness the potential of various nanoparticles and nanomaterials to efficiently transport chemotherapeutic drugs, revolutionizing cancer treatment. The use of natural products has shown substantial promise in both the prevention and therapy of cancer. Herbal medicines, in particular, have gained widespread use due to their inherent therapeutic advantages and notably fewer adverse effects compared to modern drugs. However, their hydrophobic nature has presented a challenge, limiting their bioavailability and therapeutic efficacy. To overcome these limitations, researchers have developed nanocarriers tailored for the delivery of therapeutic agents to specific target cells. The combination of nanocarriers with herbal remedies results in improved bioavailability, enhanced pharmacological activity, and increased stability, all while minimizing systemic toxicity in cancer treatment. This review provides a comprehensive discussion of novel nanocarriers that find application in cancer treatment, with a specific focus on herbal medicine. The amalgamation of these innovative approaches offers promising prospects for the future of cancer therapy.

Introduction

Cancer is considered one of the main destructive groups of disorders and a main cause of death.[1] In cancer, the presence of atypical cells signifies uncontrolled growth, and these abnormal cells may invade neighbouring tissues. Unrestrained division and expansion of these abnormal cells can pose a significant threat to the patient's health in most cases. Initially, cancer often begins as a localized ailment, but it has the potential to spread through the bloodstream and lymphatic system to various parts of the body.[2] This can result in cellular disorders and genetic changes in individuals.

The genetic material within a cell can become damaged or altered, leading to mutations that disrupt the normal regulation of cell growth and division. To sustain the rapid growth of a tumour, it requires a sufficient supply of nutrients and oxygen. This need for sustenance contributes to the highly heterogeneous vascularity of the tumour, with some areas exhibiting necrosis or haemorrhaging while others become highly vascularized. This shift towards increased vascularization makes the tumour's vasculature more permeable, a process regulated by various mediators.[3,4]

The tumour's microenvironment and molecular factors can introduce drug resistance. These factors encompass elements like hypoxic areas, irregular blood flow, the composition of the extracellular matrix, a high cell density within the tumour, and elevated interstitial fluid pressure. Together, they create pharmacological shelters or physical barriers that impede the proper diffusion of chemotherapeutic agents, limiting their penetration into the tumour.

One cause of drug resistance lies in the insufficient vascularization of the tumour region. This can

*Corresponding Authors: Pedram Ebrahimnejad, Email: pebrahimnejad@mazums.ac.ir & Ali Nokhodchi, Email: a.nokhodchi@sussex.ac.uk

significantly reduce the penetration of drugs into the tumour site, hindering their ability to exert cytotoxic effects on cancerous cells. Additionally, cellular mechanisms are involved in drug resistance, including alterations in apoptosis regulation, changes in enzymatic activity (such as topoisomerase activity), and transport mechanisms, like the P-glycoprotein efflux system that leads to multi-drug resistance (MDR) or the multi-drug resistance-related protein (MRP).[5,6]

The primary modalities for treating cancer typically revolve around chemotherapy, radiation therapy, and surgical interventions, which are the most commonly employed cancer treatment methods.[2,3] Despite remarkable advancements in current cancer therapies, several drawbacks continue to hinder optimal treatment outcomes.[4] In the case of chemotherapy, significant obstacles persist, including poor bioavailability of drugs, cytotoxicity, rapid clearance from the bloodstream, inadequate uptake by cancer cells, limited accumulation in tumours, the inability to differentiate between healthy and tumour cells, and most critically, insufficient inhibition of MDR cancer cells.[5] Furthermore, chemotherapy and radiotherapy are accompanied by adverse effects, including oral mucositis, gastrointestinal toxicity, hepatotoxicity, nephrotoxicity, hematopoietic system impairment, cardiotoxicity, and neurotoxicity.[6,7] Therefore, it is crucial to develop effective methods for anti-chemotherapeutic interventions that can overcome side effects.

In medicine, nanotechnology holds great promise, particularly in the field of cancer treatment.[8] Nanotechnology and the application of nanoscale formulations in cancer treatment and herbal medicine show great potential for revolutionizing therapeutic approaches, providing more effective and targeted treatments with reduced side effects.[9]

Nanoscale drug delivery systems (NDDS) represent a novel approach in pharmaceutical research aimed at overcoming limitations associated with traditional drug delivery systems.[10] These limitations include poor drug targeting and low drug loading capacity. NDDS, with their distinct dimensions and exceptional drug loading capability, offer improved drug targeting to specific tissues or cells, resulting in enhanced therapeutic outcomes. The nanoparticles (NPs) indicate certain sizes, shapes, and surface features. These three aspects greatly affect how well the NDDS works and ultimately influence its effectiveness in therapy. Nanocarriers can effectively transport drugs and help them stay in the targeted area for a longer time. They can escape from blood vessels and harm healthy cells. These particles are small enough to be filtered by the kidneys. On the other hand, larger particles are usually removed from the bloodstream by phagocytes.[11,12] Furthermore, surface modification of Nanocarriers can affect how easily they are absorbed by the body and how long they stay in the body. For example, when nanoparticles are covered with hydrophilic materials like polyethylene glycol (PEG), they decrease the chances of being detected by the immune system and cleared out of the body. So, drugs are often changed to be more hydrophilic to stay in the body longer and go into tumours better. Together, the different qualities of NPs determine how well they can treat cancer.[13-15]

In this regard, the accumulation of nanoparticles in cancer cells is determined by passive diffusion or convection through the leaky, hyperpermeable vasculature tumour. The high surface of nanoparticles, results in increased cellular uptake. The uptake may also derived from a special identification regarding ligand-labeled nanoparticles (active targeting). In the tumour interstitium, there will be extra retention of the colloidal particles (or macromolecules with a molecular weight above 50 kDa). This specific concept entitled 'enhanced permeability and retention effect' (EPR) causes an important intratumoral drug aggregation which is even higher than this observed in plasma and other tissues.[16,17]

In herbal medicine, nanotechnology has been employed to develop nanostructured formulations, which harness the potent active compounds present in various parts of medicinal plants, such as roots, rhizomes, and stem bark. The use of nanotechnology in engineering these herbal medications offers several advantages over traditional drug administration methods. These advantages may include improved bioavailability, controlled release of active compounds, increased stability, and enhanced targeting of specific sites.[18] The goal is to achieve optimal concentrations of therapeutic agents within the cancerous tissue, effectively destroying cancer cells while minimizing damage to healthy cells. The main focus of this review paper will be on herbal nanomedicines, highlighting their significance in drug delivery systems. By discussing these different systems, the review paper will present a more comprehensive understanding of the advancements and potential applications of nano-based drug delivery systems in cancer treatment, while emphasizing the unique features and benefits of herbal nanomedicines.

Methodology

Our quest for knowledge was fueled by an exhaustive online search, conducted across a spectrum of reputable sources, including PubMed, Scopus, Science Direct, Web of Science, and Google Scholar. Through these prominent databases, we embarked on a thorough exploration, delving into the realm of herbal medicine's potential in cancer treatment. This extensive inquiry spanned until October 2023, encompassing a wealth of contemporary research and insights. Our focus was trained on the intricate interplay of several key themes: cancer treatment, nanotechnology, drug delivery systems, herbal medicines, and the pivotal concept of bioavailability. Our goal was to unearth the latest findings, offering a comprehensive perspective on the cutting-edge advancements within

these domains, particularly in how herbal remedies can be harnessed to combat cancer.

Herbal-Based Drug Delivery Systems

Herbal remedies, which consist of plants or plant products, have been used for medicinal purposes for thousands of years, predating the development of modern drugs. Unlike conventional allopathic medicine, herbal medicines contain a multitude of components that work synergistically to combat diseases.[19] Phytochemicals derived from herbs have demonstrated anticancer properties with minimal side effects and low toxicity, offering a potential alternative to conventional cancer treatments and overcoming some of their limitations.[20] Herbal products offer a safe and cost-effective alternative with a diverse range of biological activities.[21] These activities include immune system stimulation, antibacterial and antiviral effects, anti-hepatotoxic and anti-ulcer properties, anti-inflammatory and antioxidant actions as well as antimutagenic and anticarcinogenic properties.[22] In Figure 1, the authors summarized the different applications of medicinal herbs.

In recent years, there has been a notable increase in research focused on NDDS specifically tailored for herbal medicines. These novel vehicles aim to fulfil two main requirements: delivering active compounds at a suitable rate within the body during the treatment period and directing the herbal medicinal substances to the target area. Various advantages can be achieved through the application of novel dosage forms such as polymeric nanoparticles, nanocapsules, liposomes, solid lipid nanoparticles, phytosomes, and nanoemulsions for herbal drugs. These advantages include improved solubility and bioavailability, reduced toxicity and physical/chemical degradation, enhanced pharmacological efficacy and stability, improved biodistribution, and sustained delivery.[23] Formulating plant medicines in nanocarriers holds great potential for increasing efficacy and addressing challenges associated with herbal medicines.[24] The structure of nano-carriers in cancer treatment is depicted in Figure 2. The bioavailability of herbal drugs, especially those that are poorly lipid-soluble, remains a challenge despite the advancements in phytochemical and phytopharmacological investigations. Many herbal drugs and extracts, despite showing promising results in vitro, exhibit poor bioavailability due to factors such as low solubility or inappropriate molecular size.[25] To address these issues, the application of NDDS for plant components is crucial. NDDS can improve patient compliance by enabling prolonged-release protocols, reducing the need for multiple-dose administrations, and enhancing the therapeutic value by reducing toxic side effects and increasing bioavailability.[26,27]

Nanoparticles offer several advantages in delivering herbal compounds, including their ability to target specific tissues or organs. Targeting is beneficial because it increases the proportion of the drug that reaches the target tissue, thereby improving bioavailability, and potentially reducing off-target effects. There are two general categories of targeting approaches using nanoparticles. The first is passive targeting, where nanoparticles reach the diseased site based on their intrinsic physical characteristics, such as size, shape, and surface charge, without specific chemical interactions.[28] The second is active targeting, which involves decorating the surface of nanoparticles with targeting ligands through physical or chemical attachment. This can be achieved using proteins, peptides, antibodies, or small molecules to functionalize the nanoparticles, enabling them to reach and be internalized by specific target areas. While the application of monoclonal antibodies connected to nanoparticles has shown promise in targeting the blood-brain barrier (BBB), this strategy has not been extensively explored in conjunction with natural

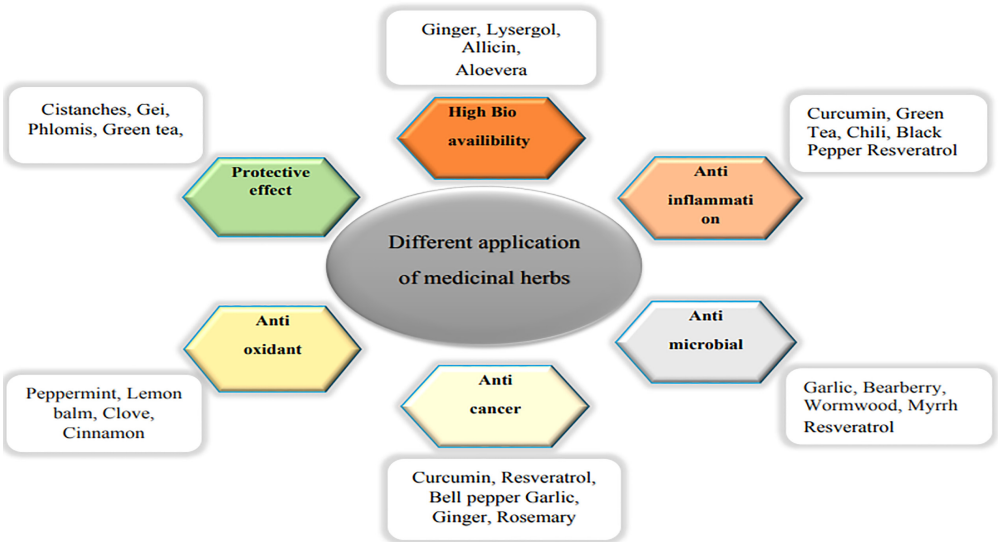


Figure 1. Different applications of medicinal herbs.

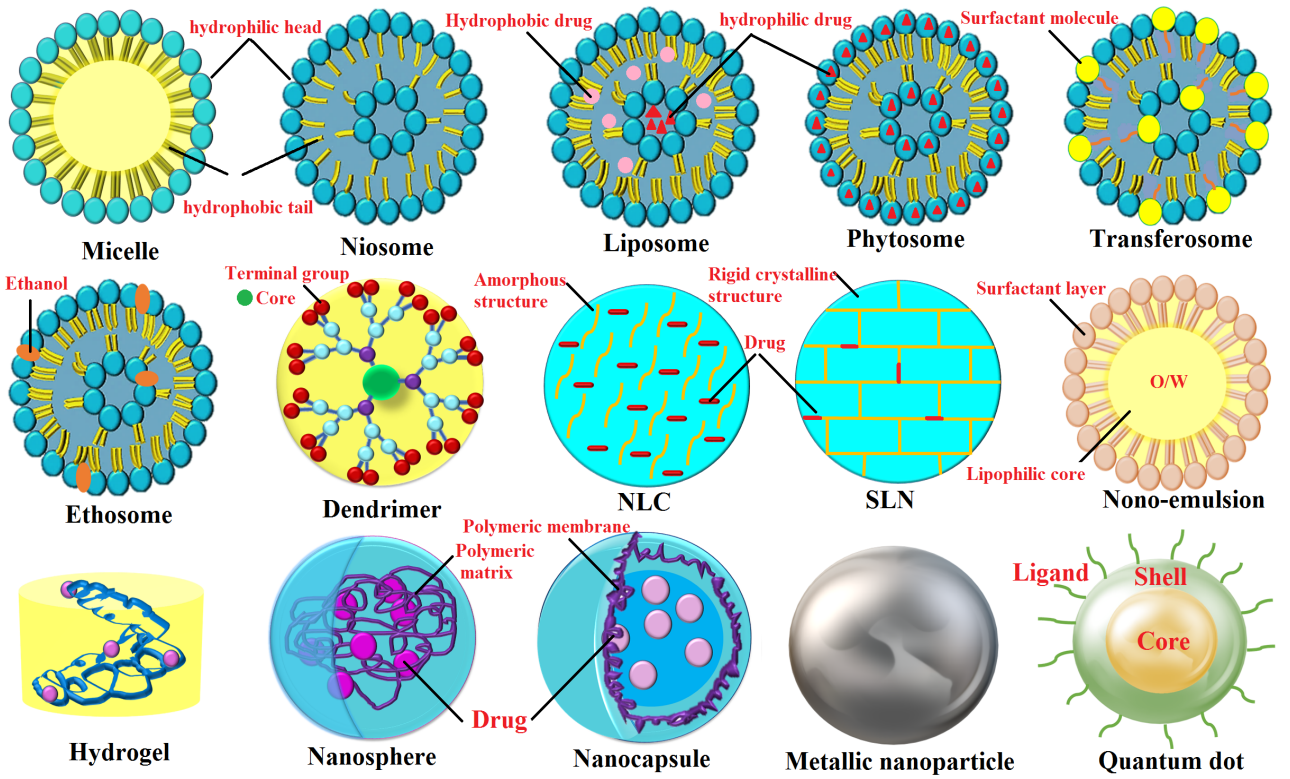


Figure 2. Structure of various nano-carriers in cancer drug delivery.

components.[29] In summary, the use of NDDS, particularly nanoparticles, holds great potential for improving the bioavailability of herbal drugs. These systems can enhance patient compliance, reduce toxic side effects, and increase the therapeutic value of herbal medicines. Additionally, the ability of nanoparticles to target specific tissues or organs offers further advantages in improving drug delivery and efficacy. Further research is needed to explore and optimize the application of NDDS in conjunction with natural components for targeted and efficient delivery of herbal drugs.

Nano herbals for cancer treatment

Here the authors summarized herbal nano drugs which are prepared as nanoparticles and applied in cancer therapy. Their chemical structures have been illustrated in Figure 3.

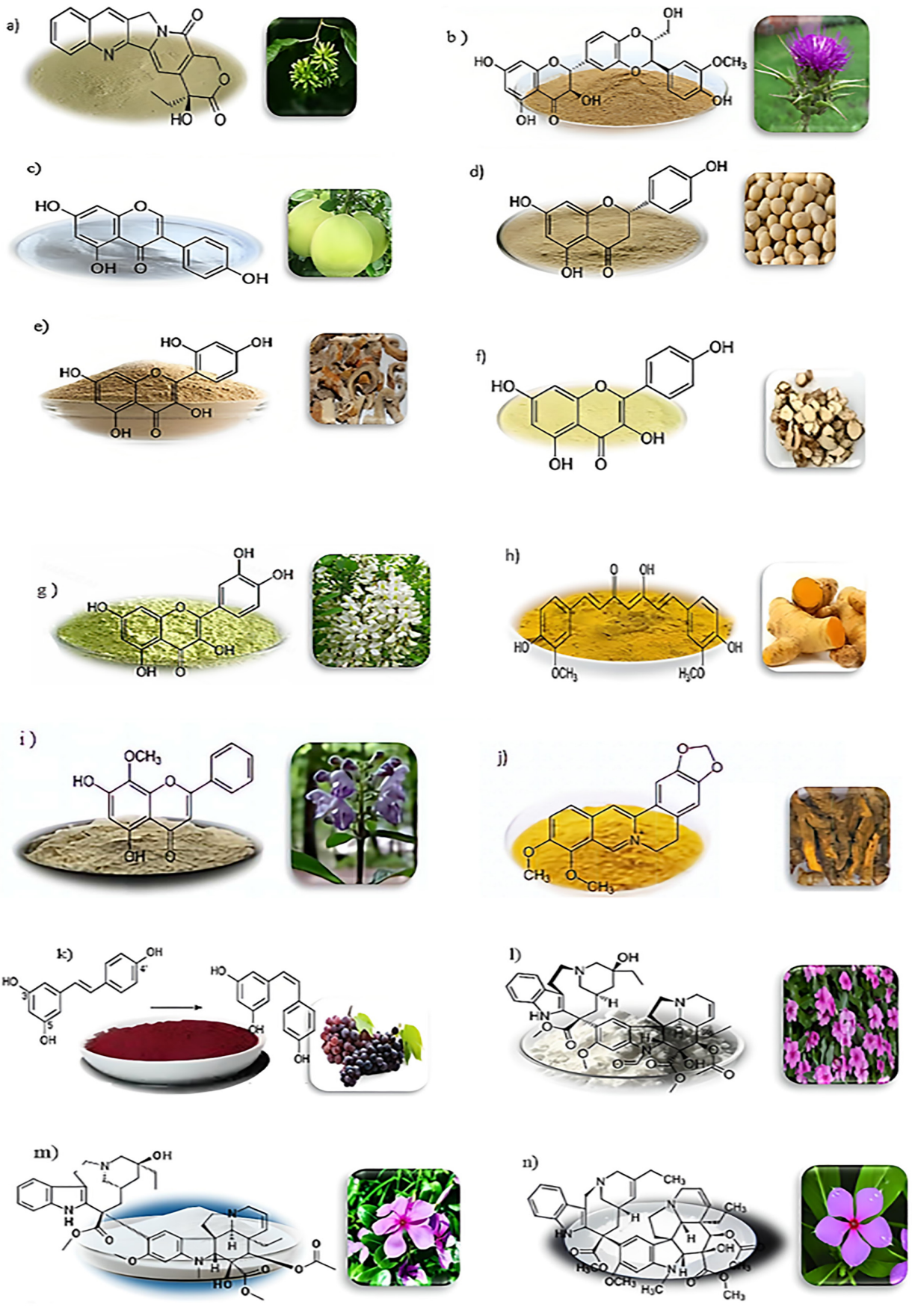
Camptothecin

Camptothecin (CPT was obtained from the bark and stem of *Camptotheca acuminata*, a plant native to China and commonly known as the "happy tree," used as a conventional Chinese Pharmaceutical agent for cancer therapy.[30] It has been widely utilized in many cancers, including breast, ovarian, primary and metastatic colon, lung, small pancreatic, and gastric cancers by inhibiting the DNA enzyme topoisomerase I.[31] However, the successful administration of CPTs is severely restricted in clinical use due to low solubility and stability in pharmaceutical solvents, short cycle time, rapid decomposition, fast clearance, and toxicity. To address these challenges, extensive endeavours have been undertaken to integrate Camptothecin or its analogues into conventional nanoparticle-based drug delivery systems, including polymeric nanoparticles, liposomes, micelles, dendrimers, mesoporous silica nanoparticles, carbon nanotubes, and graphene.[32] Utilizing nanoparticle-based drug delivery systems can enhance the efficacy of chemotherapy by leveraging the EPR effects, leading to the accumulation of these systems at the tumor site.[33-35] Figure 3a refers to the depiction of the chemical structure of CPT.

Landgraf and colleagues[36] leveraged porous silicon nanoparticles (pSiNP) to carry CPT and paired it with the epidermal growth factor receptor (EGFR)-targeting antibody, cetuximab, to create a more soluble and targeted cancer therapy. CPT-loaded pSiNP were evaluated in a humanized advanced breast cancer bone metastasis mouse model, using humanized tissue-engineered bone constructs (hTEBCs) in female NSG mice. The targeted CPT-loaded pSiNP not only reduced primary tumour growth but also increased survival rates and decreased metastases.

Silymarin

Silymarin (SM), derived from the *milk thistle* plant, has been extensively studied for its potential therapeutic benefits in various liver-related conditions.[37] The chemical structure


a)
b)
c)
d)
e)
f)
g)
h)
i)
j)
k)
l)
m)
n)

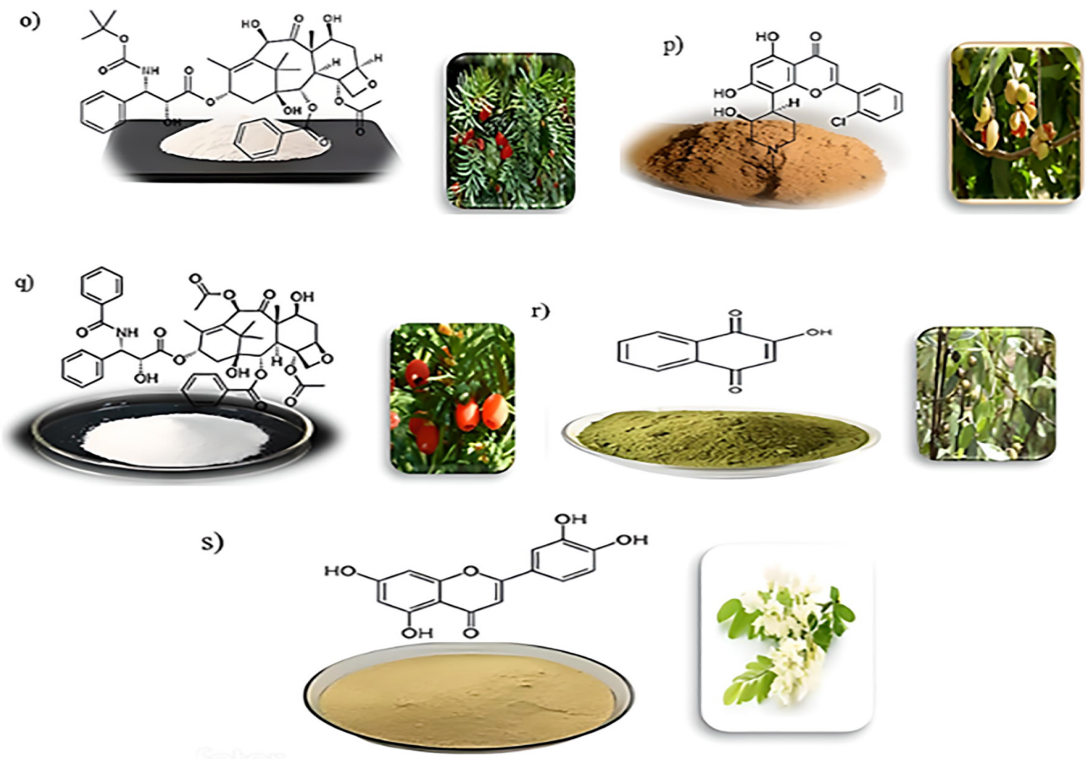


Figure 3. Chemical structure of (a) Camptotecin; (b) Silymarin; (c) Naringenin; (d) Genistein; (e) Morin; (f) Kaempferol; (g) Quercetin; (h) curcumin; (i) Wogonin; (j) Berberine; (k) Cis and trans Resveratrol; (l) Vincristine; (m) Vinblastine; (n) Vinorelbine; (o) Docetaxel; (p) Flavopiridol; (q) Paclitaxel; (r) Lawsone; (s) Luteolin.

of silymarin is depicted in Figure 3b Silymarin has been recognized for its hepatoprotective properties, which can be attributed to its antioxidant, anti-inflammatory, and anti-fibrotic effects.[38] SM is known for its antioxidant properties and has traditionally been used as an immunity booster, liver protector, and dietary supplement.[39] In addition to these applications, SM has shown potential for the prevention of cancer and exhibits valuable antitumor properties. It is particularly effective in inhibiting epidermal growth factor receptor (EGFR) signalling by suppressing the expression of cyclin-dependent kinases (CDKs) and up-regulating CDK-inhibitors p21CIP1 and p27KIP1, facilitating their binding to CDKs. This leads to growth arrest at the G1 and G2 checkpoints.[40] However, the bulky polycyclic structure of silymarin and its low oral bioavailability result in its poor solubility in water, which limits its clinical use. To overcome this challenge, several approaches have been employed to enhance the dissolution of silymarin. These include the formation of silibinin-phospholipid complexes,[41] solid dispersion,[42] encapsulated liposomes,[43] and microemulsification drug delivery systems.[44] However, each method has faced difficulties in different silymarin preparations, presenting challenges in terms of particle size, stability, manufacturing complexity, and storage. Zha and his team prepared silymarin nanoparticles (SMNs) using ESE technology.[45] Radu and his coworkers used 3-HydroxyButyrate-co-3-Hydroxyvalerate) (PHBHV) as a nanocarrier for curing colon cancer.[46] Mi *et al.*[47] created and tested selenized Si-SeNPs as an anticancer agent. Si-SeNPs demonstrated greater cytotoxicity against AGS gastric cancer cells compared to silymarin while leaving normal cells unharmed. The induction of apoptosis signalling in AGS cells by Si-SeNPs was substantiated through real-time PCR and Western blotting analyses. PI3K/AKT/mTOR pathways were inhibited, triggering both autophagy and apoptosis in AGS cells. They demonstrated promising effects of Si-SeNPs as a novel anticancer agent in apoptosis and autophagy.

Naringenin

Naringenin (NAR) (4,5,7-trihydroxy flavanone) with a chemical structure depicted in Figure 3c is a bitter colourless flavanone, a type of flavonoid that is present in citrus fruits and grapefruit.[48,49]

The sugar group of naringin which is responsible for its hydrophilic properties, does not permit its absorption in the digestive system, hence it must first be deglycosylated to naringenin to be passively diffused through biological membranes.[50] The other health benefits mentioned in the research article include antitumor potential, antibacterial effects, antiviral effects, and unique HCV inhibitory effects, as well as neuroprotective and anti-amniotic activities.[51-53] Key challenges in deploying naringin and naringenin hinge on the poor water solubility of NARs, precipitating

suboptimal bioavailability and permeability, instability, and a significant degree of first-pass metabolism before these compounds can access the circulatory system. To enhance the absorption and bioavailability of NARs, various strategies including the employment of cyclodextrin complexes, liposomes, and polymeric nanoparticles have been deployed.[54] Among them, polymeric nanoparticles have recently indicated considerable results as carriers for these drugs. These systems offer a host of benefits, such as precise drug targeting, improved bioavailability, controlled drug release at desired locations, solubilization for intravascular delivery, and protection against enzymatic degradation, especially in gastric acids.[55] In addition, these systems have the potential to accumulate at the tumour site through an EPR mechanism.[56] In recent work, Narendran Krishnakumar and his team applied naringenin-loaded nanoparticles (NARNP) using a nanoprecipitation technique with Eudragit® E, and polyvinyl alcohol (PVA) as carriers to study the effectiveness of this nanoparticle on human cervical cancer cells.[57]

In a piece of research carried out by Yıldırım *et al.*,[58] naringenin was incorporated into intelligent polymeric nanoparticles (NarSPNPs) that respond to variations in pH and temperature (Figure 4). Sensitive monomers, N-isopropyl acrylamide and Vinyl imidazole, were employed in the process. These NarSPNPs were evaluated and found to be both stable and potent in their action against breast cancer while posing no harm to human epithelial cells.

Genistein

Genistein (GEN) is an isoflavone, and its chemical structure is presented in Figure 3d. Genistein is characterized as both an angiogenesis inhibitor and a phytoestrogen.[59,60] They act as antioxidants and anthelmintics, and many isoflavones interact with estrogen receptors in animals and humans, producing estrogen-like effects. Many researches demonstrated the inhibitory effects of moderate doses of genistein on various cancer cells such as prostate, cervical, brain, breast, colon, stomach, and ovarian cancer cells.[61] Genistein works primarily as a tyrosine kinase inhibitor. Some studies have shown that genistein may be useful in treating leukemia It leads to induce G2/M arrest and apoptosis, which is considered to play the most important role in suppressing tumorigenesis.[62,63]

Further studies demonstrated that the induction of apoptosis in cancer treatment also occurs after the addition of 5-fluorouracil to colon cancer cells, 1,25-dihydroxyvitamin D to prostate cancer cells, daidzein to ovarian cancer cells, and cisplatin to malignant melanoma cells.[64,65]

The effectiveness of genistein is limited by its poor bioavailability. Novel formulations of genistein, such as diindolylmethane (BDIM) from Bio-response Inc, have shown higher bioavailability.[66] Researchers have explored various nanoscale approaches to enhance genistein's bioavailability. One approach involves formulating genistein in nanoemulsions containing lecithin, medium-chain triglycerides (MCTs), or octyl dodecanol (ODD) and water using a self-emulsification method.[67] Leonarduzzi and his team have developed flavonoid nanodrugs, demonstrating that incorporating flavonoids into lipid- or polymer-based nanoparticles significantly increases their oral bioavailability.[68-70] In a study by Patra *et al.*,[71] PLGA-PEG-folic acid (FA) nanoparticles (NPs) loaded with GEN were investigated for targeted delivery to ovarian cancer cells. Polymer conjugates of PLGA-PEG and PLGA-PEG-FA were synthesized and characterized. GEN-loaded nanoparticles of PLGA, PLGA-PEG, and PLGA-PEG-FA were prepared using a nano-precipitation method. The FA-modified PLGA-PEG nanoparticles showed increased uptake and stronger anti-cancer effects in SKOV-3 ovarian cancer cells compared to the non-targeted PLGA and PLGA-PEG nanoparticles.

Morin

Morin is a yellow chemical compound that can be isolated from the *foliage of Maclura pomifera* (Osage orange), Maclura tinctoria (old fustic), and *Psidium*

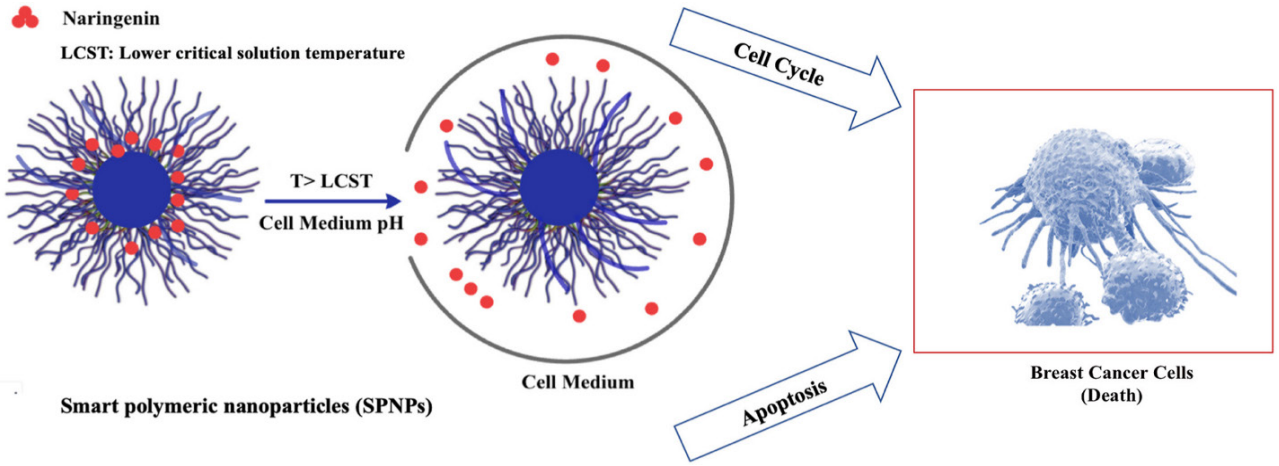


Figure 4. Effective anti-cancer properties of smart polymeric nanoparticles loaded with naringenin against breast cancer. Reprinted with permission from Ref. 58.

guajava (common guava).[72] The chemical structure of this compound is depicted in Figure 3e. Morin hydrate (MH) has been recognized as a natural antioxidant with antitumor properties and great potential for the treatment of different malignancies, including breast, lung cancer, human leukaemia, colon cancer, and others.[73,74] The main obstacles to using MH for oral administration, like other herbal medicines, are its limited solubility in water, low stability, and poor bioavailability.[75,76] To address these drawbacks, recent research has been conducted to explore novel carriers such as polymers, micelles, liposomes, niosomes, and others for the delivery of MH.[76,77] Nanoceria (CeO_2NPs) holds potential as a vehicle for transporting anti-cancer medications. In their research, Thakur and colleagues synthesized CeO_2-Amine (NH)-FA) nanoparticles specifically to target FA-overexpressing breast cancer cells and deliver Morin, a bioactive flavonoid with known anti-cancer properties.

The nanohybrids were cytotoxic toward breast cancer cells, inducing apoptosis via Reactive Oxygen Species (ROS) generation. Furthermore, they exhibited an anti-migratory effect and demonstrated superior anti-cancer effects in mice with tumours compared to free Morin and CeO_2-NH-FA. Notably, the Morin-CeO_2-NH-FA nanohybrids did not impact serum biochemistry. Additionally, a molecular docking study was conducted on Morin and the B-cell lymphoma-2 (Bcl-2) protein, demonstrating that Morin can bind to Bcl-2 with an affinity of -7.1 kCal/mol, revealing a potential mechanism of action. Overall, the Morin-CeO_2-NH-FA nanohybrids show significant anti-cancer effects on breast cancer cells due to the combined cytotoxic effects of Morin and nanoceria (Figure 5).[78]

Kaempferol

Kaempferol, a dietary flavonol and polyphenol antioxidant, is observed in fruits and vegetables, such as broccoli, leek, green beans, onion, Cissus quadrangularis, Bryophyllum pinnatum, and Ginko biloba.[79] It exhibits antioxidant, anti-inflammatory, and antimicrobial properties and has been studied for its potential to reduce the risk of chronic diseases, particularly cancer.[80] Various mechanisms have been identified through which kaempferol stimulates apoptosis in different cancer cell lines. It inhibits the expression of estrogen receptor-α in breast cancer (MDA-MB-453), activates the MEK-MAPK pathway in lung cancer (H460),[81] and demonstrates effectiveness against Hepatocellular carcinoma (Huh7), human colon cancer cells (HT29), human breast cancer cells (MCF-7), myeloma, human cervical cancer cells (HeLa),[82] chronic myelogenous leukaemia (K562), and promyelocytic leukaemia (U937),[81,83] as well as ovarian cancer.[84] Notably, kaempferol has a minimal cytotoxic effect on normal cells.[85,86] To enhance the bioavailability and solubility of kaempferol, Guterres

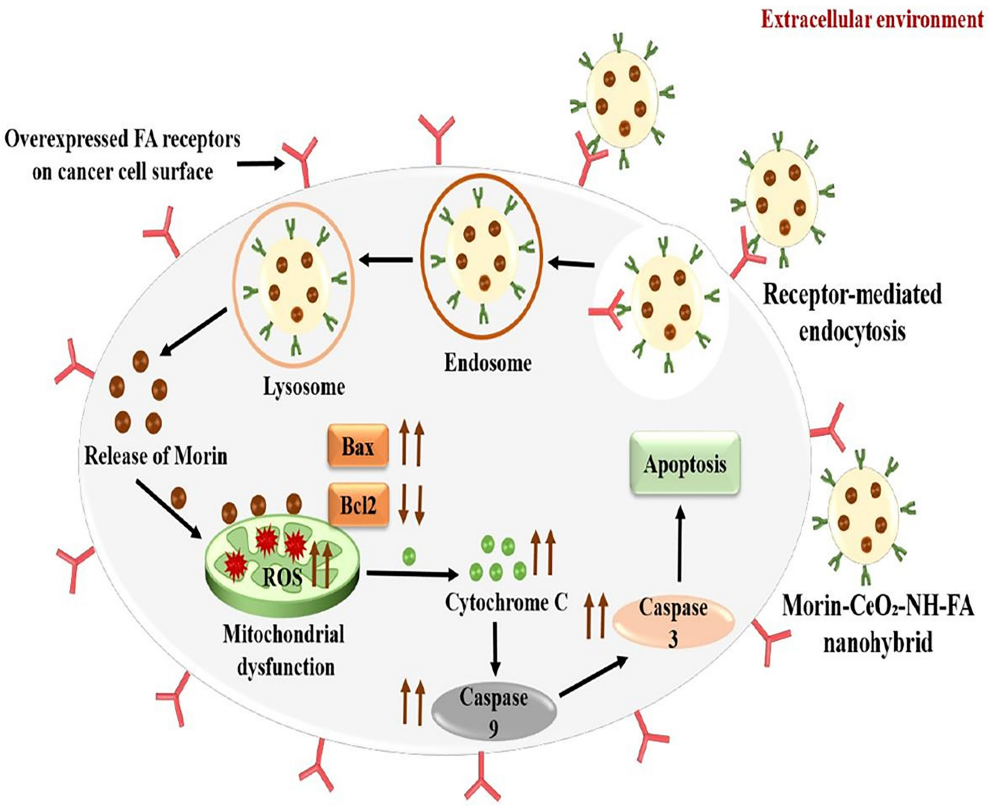


Figure 5. Folic acid-modified cerium oxide nanoparticles as an intelligent nanocarrier for the targeted and pH-sensitive delivery of Morin for the treatment of breast cancer. Reprinted with permission from Ref. 78.

and his coworkers studied various nanoparticles, including PEO-PPO-PEO, PLGA, PLGA-PEI, chitosan, and PAMAM nanoparticles. They used the nano-precipitation method to synthesize these nanoparticles, both with and without kaempferol and demonstrated their high biodegradability and biocompatibility.[87] The efficacy of the formulated nanoparticles containing kaempferol was studied against ovarian cancer cell lines, and their effectiveness in vitro was validated. The PLGA nanoparticle formulation showed promise for cancer treatment, as it effectively decreased the viability of tumour cells with minimal impact on the viability of ovarian normal cells. In comparison, kaempferol-embedded PEO-PPO-PEO nanoparticles exhibited even higher efficiency in preventing cancer cell survival.[88] The chemical structure of kaempferol is shown in Figure 3f.

Alyami and his team engineered silver nanoparticles (AgNPs) encapsulated with kaempferol, a compound derived from plants known for its health-promoting characteristics. They evaluated the anti-cancer efficacy of these particles against hepatocellular carcinoma (HepG2) cells, aiming to harness the advantages of both the nanometer size of nanoparticles and the biosafety of plant-based compounds. The kaempferol-coated AgNPs demonstrated concentration-dependent cytotoxic effects on HepG2 cells, as evidenced by reduced cell viability and increased lactate dehydrogenase (LDH) leakage, a marker of cell damage. These nanoparticles also increased ROS and lipid peroxidation, while reducing antioxidant glutathione (GSH) levels, leading to oxidative damage and apoptosis in HepG2 cells. This was supported by an increase in pro-apoptotic markers and a decrease in anti-apoptotic markers. Furthermore, the kaempferol-coated AgNPs inhibited HepG2 cell migration and invasion, suggesting an anti-metastatic effect. Through oxidative stress-induced apoptosis, the kaempferol-coated AgNPs demonstrated potential anti-cancer capabilities.[89]

Quercetin

Quercetin (3, 30, 40, 5, 7-pentahydroxylflavone, Mw: 302) is a potent antioxidant and anti-inflammatory agent that is abundant in various foods such as onions, apples, green tea, vegetables, fruits, and wine. Its molecular structure is depicted in Figure 3g. Quercetin belongs to a class of natural polyphenols known as flavonoids, which possess a diphenyl propane backbone with two benzene rings joined to three carbon chains, forming a closed pyran ring.

Despite its strong anticancer activity, quercetin faces challenges due to its low water solubility and limited bioavailability.[90] To address these limitations, nanotechnology-based formulations have been explored for the delivery of lipophilic drugs.[91] Jing and colleagues discovered that quercetin, a plant-derived flavonoid with anti-inflammatory and antioxidant properties, can inhibit Janus kinase 2 (JAK2) through its JH2 domain without forming covalent bonds. This inhibition leads to the suppression of osteosarcoma (OS) growth and immune evasion by targeting the JAK2-STAT3-PD-L1 signalling pathway. However, the poor water solubility and oral absorption of quercetin present challenges. To overcome these limitations, the researchers employed liposomes modified with folic acid to encapsulate quercetin. The folic acid modification allows for targeted delivery, as cancer cells often overexpress folic acid receptors. This approach offers a practical strategy for osteosarcoma treatment by utilizing folic acid-modified liposomes to deliver quercetin. This not only improves the delivery and bioavailability of quercetin but also enhances its effectiveness through targeted cancer therapy.[92]

Curcumin

Curcumin, a primary natural polyphenol found in the rhizome of the turmeric plant, possesses various beneficial properties such as antioxidant, anticancer, anti-inflammatory, chemo-preventive, and chemo- and radio-sensitization capabilities. The chemical structure of curcumin is depicted in Figure 3h. Despite its potent anticancer properties, curcumin faces challenges due to its low water solubility, leading to limited bioavailability. To overcome this limitation, researchers have developed curcumin nanoparticle formulations using cross-linked micellar aggregates and a random blend of copolymers. These formulations improve the solubility and bioavailability of curcumin, making it a promising candidate for the treatment of different cancers.[93,94]

Gholami and his team formulated liposomes using soybean phosphatidylcholine (SPC) and hydrogenated SPC (HSPC) to enhance the bioavailability of curcumin in bladder HTB9 cancer cells. These liposomal formulations improved curcumin uptake and its cytotoxic effect on bladder cancer HTB9 cells. Liposomal curcumin selectively induced apoptosis and DNA damage in cancer cells, indicating a targeted anti-cancer effect. The SPC and HSPC liposome nanoparticles improved the stability and bioavailability of curcumin, thereby enhancing its therapeutic potential.[95]

In pancreatic cancer (PC), curcumin has been shown to enhance the anti-cancer effect of gemcitabine, a chemotherapy drug. However, the limited water solubility and bioavailability of curcumin hinder its effectiveness. To address this issue, RS and colleagues developed a novel approach using mesoporous silica nanoparticles (MSN) as delivery vehicles for curcumin. The curcumin was loaded into the MSN, followed by coating with polyethylene glycol (PEG) and conjugation with transferrin (Tf). The resulting nanoparticles, MSN–NH2–Cur–PEG–Tf, exhibited three times higher cytotoxicity against MIA PaCa-2 pancreatic cancer cells compared to free curcumin. Tests demonstrated that both MSN–NH_2–Cur–PEG and MSN–NH_2–Cur–PEG–Tf nanoparticles reduced tumour growth, limited metastasis, and sensitized cancer cells to gemcitabine,

thereby enhancing its anti-cancer effect (Figure 6).[96]

Wogonin

Wogonin, a natural flavonoid obtained from Scutellaria baicalensis (Lamiaceae), has been shown to inhibit the PI3K-AKT signalling pathway. The chemical structure of wogonin is depicted in Fig. 3i. Despite its numerous advantages in cancer treatment, wogonin faces challenges due to its limited aqueous solubility, which restricts its use in clinical settings. In recent years, researchers have focused on overcoming this limitation by utilizing nanoparticles, such as magnetic nanoparticles, to improve the solubility and delivery of wogonin. Wogonin-loaded solid lipid nanoparticles (SLN) have shown promise as a carrier for delivering wogonin in breast cancer treatment.[97] Furthermore, Liu and colleagues reported that wogonin inhibits the Nrf2/GPX4 axis and induces ferroptosis in pancreatic cancer cells.[98] Ferroptosis is a type of regulated cell death that involves the accumulation of lipid peroxides and oxidative stress. By targeting the Nrf2/GPX4 axis, wogonin can promote ferroptosis in pancreatic cancer cells, potentially offering a novel approach to the treatment of this aggressive cancer.[99] These studies highlight the potential of wogonin as an anticancer agent, but further research and development are needed to address its limited solubility and enhance its therapeutic efficacy.

Berberine

Berberine, an isoquinoline alkaloid extracted from Chinese plants, particularly *Berberis vulgaris*, possesses various properties such as anti-viral, anti-bacterial, anti-diarrheal, anti-inflammatory, and anti-cancer effects. However, the clinical utilization of berberine has been limited by challenges such as poor water solubility, limited absorption, and low bioavailability. To overcome these obstacles, nanocarriers have emerged as a promising strategy for the delivery of berberine in cancer therapy. Various types of nanocarriers, including polymeric-based, magnetic mesoporous silica-based, lipid-based, dendrimer-based, graphene-based, silver, gold nanoparticles, and more, have been explored for the encapsulation of berberine.[100,101]

In a study by Paudel *et al.*,[102] berberine-loaded liquid crystalline nanoparticles (LCNs) were formulated and their effects on A549 cells (a lung cancer cell line) were investigated. The anti-proliferative activity of the LCNs was evaluated using MTT, trypan blue, and colony-forming assays, while the anti-migratory activity was assessed through wound healing and modified Boyden chamber assays. The researchers also examined the impact of berberine-loaded LCNs on lung cancer progression-associated proteins. The results showed that berberine-loaded LCNs effectively inhibited cancer progression by targeting proliferation-related proteins, inhibiting invasion, and suppressing colony formation.

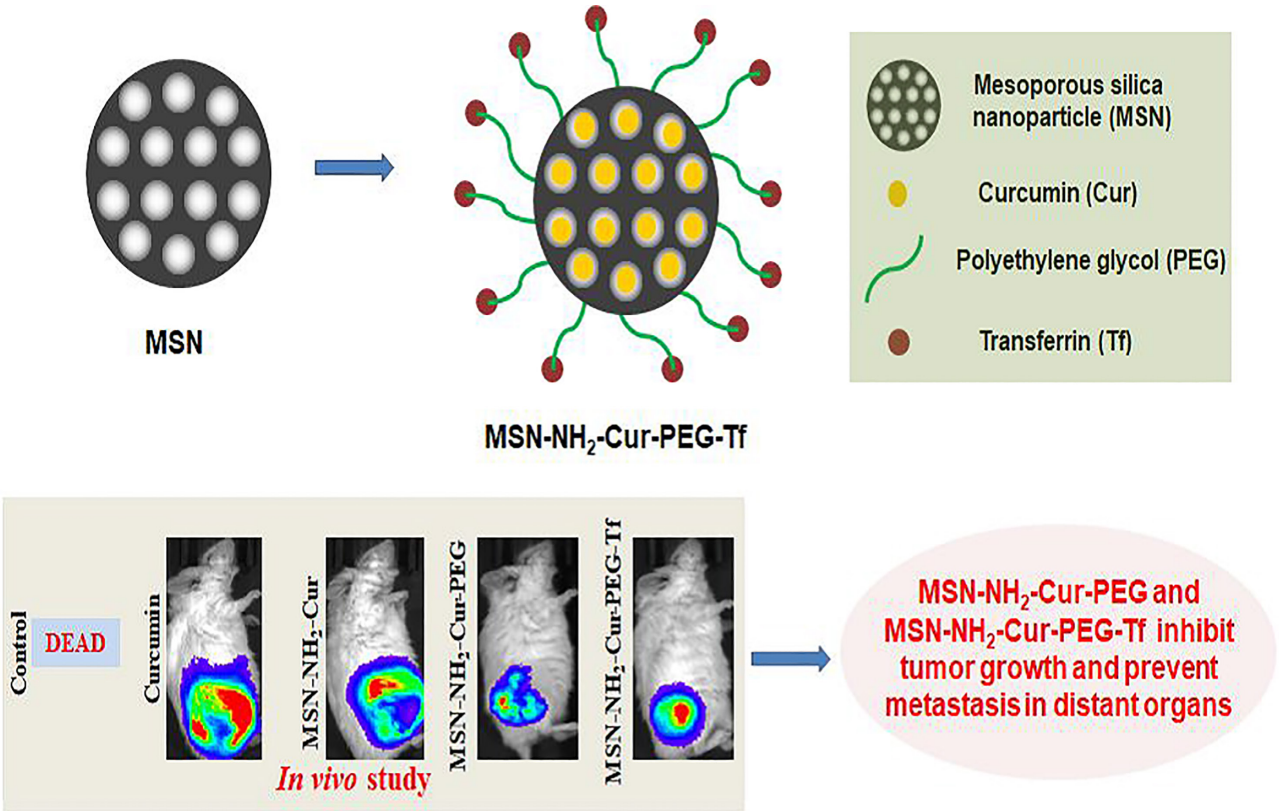


Figure 6. A preclinical assessment of nanoparticles specifically designed for delivering curcumin and treating pancreatic cancer using non-invasive methods. Reprinted with permission from Ref. 96.

It can be concluded that these studies highlight the potential of nanocarriers, such as liquid crystalline nanoparticles, in enhancing the therapeutic efficacy of berberine and overcoming its limitations in cancer therapy.[103]

Resveratrol

Resveratrol, a natural polyphenol, is known for its antioxidant properties and is found in various sources such as red wine, grapes, berries, peanuts, and pistachios.[104] It exists in nature as both cis and trans isomers, with the trans-isomer being the most abundant and biologically active form (Fig. 3k).[105] Resveratrol has been investigated for its potential prophylactic effects against several diseases including neurodegenerative processes, viral infections, vascular and cardiac diseases, and eye diseases. It also exhibits anti-inflammatory, anti-obesity, antioxidant, anti-ageing, and anti-carcinogenic effects.[106] In the context of cancer prevention, resveratrol has shown promise by inhibiting the proliferation of various cancer cell lines at different stages of cancer development, including initiation, promotion, and progression. It has demonstrated this effect in cancer cell lines such as lymphocytes, breast, glial, skin, and prostate tumour cells.[107]

A study conducted by Montalesi *et al.*[108] revealed that resveratrol can prevent the accumulation of Nuclear Golgi-Binding Protein (NGB) induced by estradiol/estrogen receptor alpha (E2/ERα) in specific cellular contexts. This modulation of NGB levels makes E2-dependent breast cancer cells more susceptible to apoptosis. Additionally, the researchers found that conjugating resveratrol with gold nanoparticles enhances its efficiency compared to resveratrol analogues. This enhancement leads to an increased pro-apoptotic action of paclitaxel and a reduction in NGB levels. Moreover, the conjugation of resveratrol with gold nanoparticles counteracts the anti-apoptotic action induced by E2 treatment in these cells.

Vinca alkaloids

Vincristine, Vinblastine, and Vinorelbine formerly referred to as leurocristine, is a compound classified as a vinca alkaloid. It is derived from the plant *Catharanthus roseus*, also known as *Madagascar periwinkle* or *Vinca rosea*. Vincristine particularly strongly blocks microtubule formation (Figure 3l). Vincristine is considered an anti-cancer drug for the treatment of a variety of cancers, but neurotoxicity is a common and dose-limiting side effect. Including vincristine in the composition of nanoparticles with high affinity for bone tissue can enhance the drug's effectiveness and minimize toxicity to healthy tissues.[109] Additionally, vincristine has been found to develop resistance in small cell lung cancer cell lines due to reduced uptake and increased drug efflux. To increase absorption, Murugan *et al.*[109] synthesized nanoparticles conjugated with folic acid and chitosan. Naseer *et al.*[110] developed a nanocomposition consisting of thiolated chitosan conjugated with hyaluronic acid and loaded with vincristine. The researchers investigated the in vitro anticancer properties of this formulation by conducting an MTT assay on cancerous prostate cells (PC3) and normal prostate epithelial cells (HPrEC). The results showed that the thiolated chitosan-hyaluronic acid nanocomposite loaded with vincristine exhibited significant cytotoxic effects on the cancer cells, with an IC_{50} value of 32 µg/ml for PC3 cells. Importantly, the nanocomposite demonstrated a superior safety profile for normal prostate epithelial cells, with an IC_{50} value of 16.2 µg/ml for HPrEC cells. This study highlighted the high cytotoxic efficacy of the synthesized nanocomposite at lower dosages while maintaining a safe profile for normal cells.

Vinblastine sulfate (Figure 3m), is an effective anticancer agent used in the treatment of various cancer types, including lymphoma, breast cancer, testicular cancer, non-small cell lung cancer, bladder cancer, head and neck cancer, and cervical cancer.[111-116] Au and colleagues aimed to enhance the cytotoxicity of vinblastine on tumour cells by loading it onto graphene quantum dots. The graphene quantum dots-vinblastine composite remarkably inhibited cancer growth in animals. The in vitro results showed that graphene quantum dots not only reduced its cytotoxicity towards normal cells but also enhanced the cytotoxicity of vinblastine towards cancer cells. The composite of graphene quantum dots-vinblastine with an aspect ratio of 1:5 demonstrated a higher cancer inhibition effect compared to raw vinblastine.[117]

Vinorelbine (Figure 3n) disrupts a set of microtubules and exerts its antitumor action by inhibiting the metaphase of mitosis through interaction with tubulin. Vinorelbine is considered to be more mitotic microtubule-specific than vincristine. It is approved for the treatment of various types of cancer, including breast cancer and non-small cell lung cancer, and has demonstrated effectiveness in combating these specific forms of cancer.[118,119] Combination therapy involving hidden vinorelbine liposomes and hidden parthenolide liposomes has been reported to possess beneficial pharmacological properties and is designed to target and eliminate cancer stem cells.[120] Metronomic oral vinorelbine has been extensively studied as a chemotherapy approach in non-small cell lung cancer and advanced breast cancer. Currently, metronomic oral vinorelbine is considered a promising treatment option for selected patients with non-small cell lung cancer or advanced breast cancer, both in the first-line and later-line settings, due to its efficacy and tolerability.[121]

Texans

Docetaxel (DTX) (Figure 3o), also known by its trade name *Taxotere*, is a semisynthetic taxane compound. It exerts its action by binding to the β-tubulin subunit of microtubules, leading to the inhibition of mitotic cell division between metaphase and anaphase, thereby preventing further cancer cell proliferation. DTX is a highly effective chemotherapy drug derived from plants and is used to treat various cancers, including breast cancer, head and neck cancer,

stomach cancer, prostate cancer, and non-small-cell lung cancer.[122-125] However, commercial formulations of DTX have limited ability to cross the blood-brain barrier (BBB). Additionally, the use of DTX is restricted by its various side effects, such as nephrotoxicity, allergic reactions, decreased white blood cell count, neurotoxicity, and fluid retention. In recent years, several alternative sub-micron delivery systems have been developed to improve the delivery of DTX to brain cells. Jurczyk *et al.*[126] prepared phospholipid nanocarriers for encapsulating DTX and investigated their ability to cross the BBB.These advancements aim to enhance the effectiveness and minimize the adverse effects of DTX in cancer treatment.

Paclitaxel (Figure 3q) is a potent anticancer drug that was initially extracted from the bark of the Pacific Yew tree (*Taxus brevifolia*) in 1971 and it was first explored by Wall and Mansukh.[127] It has been approved for the treatment of various cancers, including lung, ovarian, and breast cancer. However, paclitaxel can have significant side effects and limited solubility, which can affect its therapeutic efficacy. To overcome these limitations, researchers have explored the encapsulation of paclitaxel in nano-delivery systems. These systems, such as polymeric nanoparticles, liposomes, polymer complexes, inorganic nanoparticles, carbon nanotubes, nanocrystals, and cyclodextrin nanoparticles, have shown promising results in reducing cardiac toxicity, improving pharmacokinetic properties, and enhancing the therapeutic outcomes for cancer patients.[128-131]

In addition, combining chemotherapy with photothermal or photodynamic therapy has emerged as a promising strategy for overcoming drug-resistant cancers. To achieve effective combination therapy, simultaneous delivery of chemotherapeutics and infrared photosensitizers to cancer cells is crucial. Pan *et al.*[132] developed poly(caprolactone) (PCL) nanoparticles stabilized with bovine albumin and loaded with the infrared photosensitizer IR780 and the chemotherapeutic drug paclitaxel (PTX) for combined phototherapy and chemotherapy. These nanoparticles were further targeted towards ovarian cancer cells using a luteinizing hormone-releasing hormone (LHRH) peptide. The PCL-LHRH nanoparticles exhibited enhanced uptake in ovarian tumour cells and targeted delivery to tumour xenografts. Both paclitaxel and IR780 were successfully encapsulated within the nanoparticles. When combined with laser assistance, the PCL-LHRH/IR780-PTX nanoparticles showed effectiveness against drug-resistant ovarian tumours. This study suggests that targeted nanomaterials like these have the potential to revolutionize cancer treatment by improving the efficacy of combination therapies and overcoming drug resistance. Overall, the use of nanotechnology for paclitaxel delivery offers opportunities to enhance its therapeutic benefits, reduce side effects, and improve patient outcomes in the treatment of various cancers.

Flavopiridol

Flavopiridol (Figure 3p) is a synthetic flavonoid derived from the plant *Dysoxylum binectariferum*, which is native to India. It belongs to the class of cyclin-dependent kinase inhibitors and has shown potent activity in inducing apoptosis, or programmed cell death, in cancer cells.[133] Flavonoids, including flavopiridol, have been investigated as potential chemotherapeutic agents due to their ability to selectively target tumour cells while sparing normal cells from damage.[134] Despite its effectiveness against various cancer cells in laboratory studies, flavopiridol has shown limited efficacy in clinical trials for aggressive cancers. It has low solubility and a high tendency to bind to plasma proteins, which can hinder its clinical application. To address these challenges and improve its clinical effectiveness, researchers have explored encapsulating flavopiridol in liposomal carriers. Yang *et al.*[135] conducted studies to characterize the physicochemical and pharmacokinetic properties of flavopiridol encapsulated in liposomes. This approach aims to enhance the solubility and bioavailability of flavopiridol, potentially leading to improved therapeutic outcomes. By encapsulating flavopiridol in liposomes, researchers are exploring a novel strategy to overcome the limitations associated with its clinical use, enhance its efficiency, and improve its pharmacokinetic properties.

Zedoary turmeric oil

Zedoary turmeric oil (ZTO) is derived from the rhizomes of certain turmeric varieties and possesses several beneficial properties, including protection against liver injury, anti-tumour activity, anti-thrombotic effects, and antiviral properties. It can be considered an agent with potential anti-tumour, anti-inflammatory, or antiviral effects.[136-138] Zedoary oil contains bioactive compounds such as elemene, curcumol, curdione, germacrone, and pinene, which contribute to its pharmacological activities. Studies have shown that Zedoary oil and β-elemene can inhibit cell cycle progression, leading to G2/M and G0/G1 cell cycle arrests. Combining infrared photosensitizers with cisplatin, docetaxel, and taxanes has been found to enhance cytotoxic effects. However, the clinical application of these treatments is often hindered by challenges related to their hydrophobic nature, suboptimal stability, and limited bioavailability. These factors can impede effective delivery and limit the full therapeutic potential of these treatments in clinical settings. To address these challenges, various formulations have been developed for cancer therapy, including cervical and liver cancer. Lyophilized powder, aerosol, and parenteral formulations have been utilized, aiming to improve the solubility, stability, bioavailability, and pharmacological activity of these agents.[139,140] Additionally, nanoparticulate formulations such as liposomes, microemulsions, and microcapsules have been developed to enhance drug delivery, improve solubility, and prevent degradation.[141,142] By utilizing these formulations, researchers aim to optimize the

therapeutic efficacy of Zedoary turmeric oil and other anticancer agents, thereby improving treatment outcomes and overcoming the limitations associated with their hydrophobic properties and limited bioavailability. These advancements in formulation technology have the potential to enhance the clinical application of these agents and contribute to improved cancer treatment strategies.

Lawsone

Lawsonia inermis, commonly known as *Persian Henna*, is a tree that grows in various regions, including Australia, Asia, and coastal areas of Africa in the Mediterranean.[143] The crude extracts derived from the Henna plant have shown diverse biological activities, including anticancer, antioxidant, antibacterial, and anti-inflammatory properties.[144] Lawsone, the major component present in Henna, has been utilized in the synthesis of certain anticancer drugs, such as dichloroallyl and lapachol Lawsone.[145,146] However, the delivery of lawsone poses challenges due to its hydrophobic nature, which leads to low stability, limited bioavailability, poor permeability, and low solubility in biological systems.[147,148] Therefore, to overcome these challenges, researchers have explored different nanoparticle formulations to harness the therapeutic potential of Lawsone in the treatment of various diseases.

In a study by Barani *et al.*,[149] nanoniosomes loaded with Lawsone were developed using non-ionic surfactants and cholesterol. The niosomes were synthesized using the thin film hydration method. Characterization of the formulation revealed spherical-shaped particles with an average diameter of 250 nm and a negative zeta potential. The encapsulation efficiency of lawsone in the nanoniosomes was determined to be 70%, and the release profile exhibited sustained release properties. In vitro experiments demonstrated that the niosomal formulation of lawsone exhibited significantly enhanced anticancer activity against the MCF-7 cell line compared to the free lawsone solution. These findings highlight the potential of nanoniosomes as a delivery system for Lawsone, enabling improved stability, enhanced bioavailability, and controlled release of the compound. Such nanotechnology-based formulations hold promise for enhancing the therapeutic efficacy of Lawsone and overcoming its limitations, ultimately contributing to the development of more effective treatments for various diseases, including cancer.

Luteolin

Luteolin, a flavonoid compound found in various vegetables, fruits, and herbs, has demonstrated several biological properties, including anticancer, antidiabetic, and anti-inflammatory effects. Its anticancer properties have been extensively studied across different types of cancer, and it has shown the ability to inhibit cancer growth by targeting processes such as migration, angiogenesis, apoptosis, and cell cycle progression. In a study conducted by Sabzichi *et al.*,[150] luteolin-doxorubicin was loaded into phytosomes, which are advanced nanocomposite carriers. The researchers reported that the nano phytosomes sensitized MDA-MB 231 cells (a breast cancer cell line) to doxorubicin. Luteolin has the potential to inhibit Nrf2, a protein involved in cellular defence mechanisms, and sensitize tumour cells to the effects of chemotherapeutic agents at physiological concentrations. In this study, nano phytosomes of luteolin were developed to improve luteolin's bioavailability and enhance passive targeting in breast cancer cells. The researchers demonstrated that the co-treatment of cells with the nanocomposite containing luteolin and doxorubicin resulted in the highest percentage of cell death compared to other treatments.

Herbal Nanocarriers in Cancer Therapy

Numerous nanocarriers have been utilized in the field of delivering herbal anti-cancer products. In the subsequent sections, the authors provide a concise overview of various types of cancer and the corresponding nanocarriers employed for their targeted treatment using herbal remedies. Table 1 outlines the anticancer potential of nanoherbal drugs, the nanocarriers utilized, and the preparation techniques employed. Moreover, the summary of the patents according to herbal-based nano-formulations for cancer therapy is indicated in Table 2.

In addition, a range of herbal-based nanomaterials have already gained regulatory approval and have been deployed in the clinical setting to treat a variety of cancers are shown in Table 3.

Solid lipid nanoparticles

In the 1990s, researchers widely focused their attention on alternative nanoparticles made from SLNs. These SLNs, composed of solid lipids, were developed to address the limitations of traditional colloidal carriers such as liposomes and emulsions. Lipid nanoparticles, including SLNs, have gained significant attention in cancer treatment due to their ability to encapsulate lipophilic drugs and provide controlled drug release. One example of the application of SLNs in cancer treatment is the loading of curcumin to enhance the therapeutic efficiency in breast cancer. The curcumin-loaded SLNs achieved a high percentage of encapsulation efficiency (EE%) of 72.47% and a drug-loading content of 23.38%. These curcumin-SLNs demonstrated strong cytotoxicity against SKBR3 cells, as evidenced by in vitro cellular uptake data showing high uptake efficacy. Furthermore, the presence of curcumin in SLNs significantly induced higher apoptosis in SKBR3 cells compared to cells treated with the free drug.[204,205]

In another study, Jang *et al.*[206] improved the aqueous solubility and anti-cancer properties of camptothecin (CPT) by loading it into SLNs. The CPT-SLNs were prepared using the hot homogenization method and comprised a trilaurin-based lipid matrix containing pegylated phospholipid and poloxamer 188. The CPT-SLNs demonstrated a significant impact on in vitro

Table 1. Anticancer potential of nanoherbal drugs, the nanocarriers, and method of preparation.

Herbal	Nanocarrier	Cancer	Method of preparation	Therapeutic efficiency	Ref.
Camptothecin	Mixed micelles: poly(ethylene glycol)–phosphatidyl ethanolamine conjugate (PEG–PE) and d-α-tocopheryl polyetheyene glycol 1000 succinate (TPGS)	Murine Lewis lung carcinoma cells (LLC1), human colorectal adenocarcinoma cells (HT-29), and human breast adenocarcinomas cells (MCF7)	Solvent evaporation	Optimized formulations showed more stability and higher cytotoxicity against different cell lines In comparison with free drug.	[151]
Silymarin	Poly (3-HydroxyButyrate-co-3-HydroxyValerate) (PHBHV)	Colon cancer	Nanoprecipitation	Fabricated NPs decreased the viability of HT-29 cells, while enhanced the tumor penetration.	[46]
Silymarin	PLGA	Prostate cancer	Single-step emulsion	Optimized NPs indicated high blood concentrations of silybinin but the concentration of silibinin in prostate tissue was low.	[152]
Silymarin	Phytosome	Prostate cancer	Thin layer hydration	Optimized NPs indicated high blood concentrations of silybinin but the concentration of silibinin in prostate tissue was low.	[153,154]
Naringenin	Chitosan	Lung cancer	Ionic gelation	MTT results indicate no-toxicity of fabricated NPs CS-NPs/NAR against normal fibroblast 3T3	[155]
Naringenin	Poly caprolactone (PCL) and hyaluronic acid (HA)	Lung cancer	Nanoprecipitation	The fabricated formulation indicated efficient anti-cancer properties against urethane-induced lung carcinoma in rat.	[156]
Naringenin	Soluthin–maltodextrin	Colorectal cancer in mice	High speed homogenization	The cytotoxic effect of fabricated NPs indicated lower cytotoxicity in compare to pure drug while enhanced tumor suppression.	[157]
Naringenin	PLGA-PEG	Lung cancer and Mouse mammary	Double emulsion	The fabricated formulation indicated high toxic effect against cancer cells and anti-tumor effect.	[158]
Naringenin	Albumin-PEG nanoparticle conjugated-folic acid	Breast cancer	Double emulsion	Optimized NPs demonstrated anti-tumor by inhibiting breast cancer cells, cell cycle arrest, and apoptosis.	[159]
Genistein	Nanoemulsions (NEs) and Lipidic micelles	hepatic and colon carcinomas	Coarse homogenization	Optimized formulations indicated high cytotoxic effect in hepatic and colon carcinomas	[160]
Genistein	PLGA–TPGS	Liver cancer	Solvent evaporation	Genistein-loaded M-PLGA-TPGS indicated high anti-cancer effects and high tumor uptake in comparison to other formulations.	[161]
Genistein	Liposome	Prostate, breast, and ovarian carcinoma	Thin film hydration	Optimized NPs indicated anti-cancer efficiency against murine and human cell lines (murine breast carcinoma, 4T1, and human prostatic carcinoma, PC-3, and ovarian adenocarcinoma, OVCAR-3)	[162]
Genistein	PLA nanocapsules	Skin cancer	Nano-precipitation	Developed formulations indicated high permeation and low toxicity against skin cells	[163]

Table 1. Continued

Genistein	PLGA-PEG- (FA) NPs	Ovarian cancer	Nano-precipitation	Optimized NPs enhanced cellular uptake and anti-tumor activity and over-expression of folate receptor on ovarian cancer cell line (SKOV-3).	[71]
Morin	human serum albumin (HSA) nanoparticles (Mor-HSA-NPs)	Breast cancer	Desolvation technique	The MTT results demonstrated the cytotoxic effects of formulated NPs against MDA-MB-468 breast cancer cell line.	[164]
Morin	epicatechin loaded HSA nanoparticles (EC-HSA-NPs)	Breast cancer	-	-	
Morin	Lipid NP, Co-encapsuation of morin and quercetin	Breast cancer	Ultrasonication method	The optimized formulations demonstrated high cytotoxic effects and indicated promising effect in treating breast cancer.	[165]
Kaempferol	Poly (ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) (PEO-PPO-PEO)	Ovarian cancer	Nanoprecipitation	Fabricated NPs reduced cancer cell viability and indicated high toxicity.	[88]
Kaempferol	PLGA				
Quercetin	Lipid	Breast cancer	Phase inversion-based	Optimized NPs enhanced the cytotoxicity and apoptosis against MCF-7 and MDA-MB-231 breast cancer cells.	[166]
Quercetin	Nanoliposomes	Lung cancer	Thin-film hydration	Optimized NPs indicated an anti-cancer efficiency in mice with A549 tumors.	[167]
Quercetin	Co-encapsuation of Eelotinib and quercetin in SLN (chitosan-TPGS)	Non-small cell lung cancer (NSCLC)	Hot-homogenization	This formulation enhanced the uptake of quercetin, increased the apoptosis induction in A549/ER cells, and NPs accumulation in lung tissue, and reduction in EGFR expression.	[168]
Quercetin	Liposome	Colorectal cancer	Lipid thin-film hydration method	Nanoliposomes in comparison to quercetin indicated higher anti-proliferative, apoptotic, and anti-EGFR expression	[169]
Curcumin	Solid lipid nanoparticles	Liver cancer	Dissolution Co- precipitation	Fabricated NPs indicated SLN-cur and LDH-5-Fu enhanced the SMMC-7721 cells and demonstrated higher synergetic anticancer effects.	[170]
Curcumin	Liposome	Bladder cancer	Solvent evaporation	Fabricate formulation enhanced the cellular uptake and cytotoxicity of curcumin on bladder cancer HTB9 cells. And inhibited the cell proliferation.	[95]
Curcumin	PLGA NPs	Gastric cancer	Single emulsion solvent evaporation	Fabricated NPs inhibited tumor growth and reduced metastasis in pancreatic cancer patients.	[171]
Curcumin	SLN	Liver cancer	Thin-film ultrasonic dispersion	The optimized formulation inhibited the MHCC-97H cells proliferation the expression of NF-κB, COX-2, MMP-2, MMP-9, and uPA, while enhanced apoptosis. Meanwhile, decreased significantly.	[172]

Table 1. Continued.

Curcumin	Mesoporous silica NPs	Pancreatic cancer	Sol-gel method	Fabricated NPs inhibited tumor growth and reduced metastasis in pancreatic cancer patients.	96
Curcumin	Nanospheres	Hepatocellular carcinoma	Nanoprecipitation	Fabricated formulations were able to inhibit HepG2 cells proliferation.	172
Curcumin	Quantum dot	Breast cancer	Double emulsion method	Flow cytometry and MTT assay indicated cytotoxicity potential on MCF-7 cell lines.	173
Wogonin	Solid lipid nanoparticles	Breast cancer	Hot sonication	Optimized NPs improved cytotoxicity and attenuated the poly (ADP-ribose) polymerase in MCF-7 breast cancer cells.	97
Berberine	Liposome	Breast cancer	Film dispersion	The prepared liposomes inhibited ABC transporters (ABCC1, ABCC2, ABCC3, ABCG2) and enhanced the mitochondrial accumulation	174
Berberine	Liquid crystalline nanoparticles (LCNs)	Non-small cell lung cancer	Ultrasonication technique	Fabricated NPs suppressed colony formation and inhibited epithelial mesenchymal proliferation and indicated high therapeutic efficiency in NSCLC treatment option.	102
Berberine	Spherical NPs	Breast cancer	Loading berberine and Letrozole in colloidal gold NPs.	Fabricated NPs indicated cytotoxic effect against MDA-MB-231 cells.	175
Berberine	Liquid crystalline nanoparticles	Lung adenocarcinoma	ultrasonication technique	Fabricated NPs reduced the β-catenin gene expression	176
Resveratrol	Solid lipid nanoparticle	Colon cancer In combination with curcumin	Sonication and freeze-drying	Formulated NPs indicated high bioavailability and anti-cancer activity	177
Resveratrol	Glycyrrhizic acid-conjugated human serum albumin nanoparticles	Liver cancer	Emulsion solvent evaporation	The uptake rate of formulated NPs increased in comparison to pure drug and enhanced effective targeting to liver tumor.	178
Resveratrol	Liposome	Prostate cancer In combination with curcumin	Freeze-drying	In vivo study demonstrated the potency of formulated NPs in reduction prostatic adenocarcinoma and cell proliferation and induced apoptosis.	179
Resveratrol	Calcium alginate	Prostate cancer In combination with curcumin	Emulsification and cross-linking	The optimized NPs indicated cytotoxic effects against DU145 cells	180
Vincristine	Liposomes- gold nanoparticle	HeLa cancer cells	Thin film hydration and Turkevich–Frens	Formulated NPs demonstrated cytotoxicity and apoptosis against HeLa cells.	181
Vincristine -doxorubicin	Lipid carriers	Lymph cancer	Encapsulated into nanostructured lipid	Optimized NPs indicated high anti-cancer potency and cytotoxic effect on B-cell lymphoma cells and the best anti-tumor effect in vivo	182
Vinblastine	Nanoliposomal C6-ceramide	Colorectal cancer	Solvent evaporation	In vitro and in vivo demonstrated the antitumor efficiency of the formulated NPs, mediated by an autophagy mechanism	183

Table 1. Continued.

Vinorelbine	Nanomicellar	Breast and lung cancers	Co-precipitation and reconstitution	This study demonstrated the efficiency of formulated NPs in lung and cancer treatment.	184
Vinorelbine	PEGylated liposomes	Human hepatocellular carcinoma	lipid film hydration method	Formulated NPs enhanced the accumulation of drug in tumor and therapeutic activity in hepatocellular carcinoma and tissue distribution.	185
Docetaxel	Silica nanorattle	Liver Cancer	Selective-etching method	Optimized NPs enhanced antitumor activity and therapeutic activity with minimum toxicity.	186
Docetaxel	Shrapnel nanoparticles	Breast cancer	Self-assembled technique	The fabricated NPs enhanced cellular uptake and lung distribution, and cytotoxicity against 4T1 cells and inhibited tumor growth.	187
Docetaxel	PEG-PLGA nanoparticle	Brain cancer	Nanoprecipitation method	Fabricated NPs enhanced brain barrier permeation; and cell toxicity in glioma models.	188
Docetaxel	Micelles	Ovarian cancer	Solvent evaporation	Optimized NPs reduced hemolysis and cytotoxicity against SKVO-3 ovarian cancer cells	189
Paclitaxel	Lipid-dendrimer	Ovarian cancer	Desolvation technique	paclitaxel NPs enhance the survival of IGROV-1 ovarian	190
Paclitaxel	Titanium dioxide	Breast cancer	Modified propanol drying step	PTX-TiO_2 nanocomposite enhanced cell viability and indicated improved anti-tumor effect.	191
Paclitaxel	Lipid	Lung cancer	Melt-emulsification technique	Fabricated NPs indicated higher cytotoxic effect. In vivo study on animal models demonstrated the high tumor-targeting efficiency and anti-cancer effect.	192
Paclitaxel	PCL NPs (Co-delivery of PTX and IR 780 and modified with bovine serum albumin (BSA)	Ovarian cancer	Emulsion method	Fabricated NPs inhibited the growth of drug-resistant xenografts and enhanced the therapeutic efficiency on drug-resistant cancer.	191
Lawsone	Niosome	Breast cancer	Thin film hydration method	Optimized NPs enhanced cellular uptake and anti-tumor activity and over-expression of folate receptor on ovarian cancer cell line (SKOV-3). The optimized formulation indicated enhanced in cytotoxic effect against MCF-7 cell line.	149
Lawsone	Phosphine/diimine ruthenium complexes containing the lawsone	Prostate cancer	Precipitation method	Fabricated NPs enhanced the inhibition of 3D tumor spheroids growth, and cell viability of DU-145 cells	193
Lawsone	Liposome coated with chitosan-folate	Pancreatic cancer	-	Fabricated NPs enhanced the up-regulated the main apoptotic genes and cellular uptake.	194
Luteolin	Phytosomes	Human breast carcinoma	Thin film hydration method	Optimized NPs enhanced the toxicity and cell death against MDA-MB cells by reducing the expression of Nrf2 gene	150

Table 2. List of patents related to anti-cancer applications of herbals.

Title	Type of compound/ herbal/ excipients	Inventors	Patent number	Year	Ref
Therapeutic nanoparticles and methods thereof	Nitric oxide (NO), curcumin, nitrosothiols, melanin, plasmids, siRNA, (metal and rare earth); and ii) coated with polyethylene glycol (PEG)	Joel M. Friedman	US20170119814A1	2017	[195]
Delivery system for specifically targeting cancer cells and method of use thereof	Curcumin, polycaprolactone-polyethylene glycol copolymers, folate	James W. Lillard	US20130045162A1	2012	[196]
Carrier-Free Curcumin Nanoparticle for EGFR Positive Cancer Therapy	Curcumin, erlotinib, PEG	Peisheng Xu	US20210369861A1	2021	[197]
Berberine salts, ursodeoxycholic salts and combinations, and methods of preparation and application thereof	Berberine , ursodeoxycholic acid, organic bases, organic acids	Liping Liu	US10301303B2	2019	[198]
Albumin-PD-1 paclitaxel nanoparticle complex compositions and methods of making and using the same	Albumin-PD-1, paclitaxel, bevacizumab/ Avastin, rituximab/Rituxin, Trastuzumab/ Herceptin	Svetomir N. Markovic	US11433023B2	2022	[199]
Paclitaxel-albumin-binding agent compositions and methods for using and making the same	Paclitaxel, albumin, paclitaxel derivative	Svetomir N. Markovic	US11311631B2	2022	[199]
Nanoparticle complexes of albumin, paclitaxel, and anti-VEGF antibody for treatment of cancer	Paclitaxel, albumin, anti-VEGF polypeptide antibody such as AVASTIN®,	Svetomir N. Markovic	US10376579B2	2019	[200]
Docetaxel polymeric nanoparticles for cancer treatment.	Docetaxel, A poly (lactic acid) -poly (ethylene) glycol copolymer comprising poly (lactic acid), PEG	James Wright	KR20160024985A	2014	[201]
Docetaxel albumin nanoparticle pharmaceutical composition, preparation method thereof and use thereof	Docetaxel, albumin, amino acid	Zhengxing SU	US10493054B2	2019	[202]
Long-circulating solid lipid docetaxel nanoparticles and preparation method thereof	Docetaxel, dipalmitoyl phosphatidyl choline, DSPE, PEG, polycaprolactone	Li Yaping Chen	CN101653414B	2008	[203]

extended-release performance and effectively protected the CPT lactone form from hydrolysis under physiological conditions.

Quantum dots

Quantum dots (QDs) are semiconductor nanocrystals known for their small size, typically ranging from 2 to 10 nm in diameter. They possess unique luminescent properties, differentiating them from traditional organic dyes and fluorescent proteins. The use of QDs in nanomedicine has gained significant attention due to their potential for imaging and targeted delivery in biomedical applications. In particular, QDs have been extensively studied as contrast agents for *in vivo* tumour imaging. A novel drug delivery system was developed by conjugating glucosamine to graphene quantum dots and loading it with curcumin. This system was specifically designed to target breast cancer cells and assess their cytotoxic effects. The graphene quantum dots used in the study had sizes ranging from 20 to 30 nm and consisted of less than 10 layers. The curcumin-loaded nanocarrier exhibited sustained release properties and demonstrated pH sensitivity. Over 150 hours, the nanocarrier released 17% of curcumin at pH 7.4 and 37% at pH 5.5, indicating controlled and pH-dependent release behaviour. Furthermore, the cytotoxicity of the nanocarrier was evaluated using the MTT assay,

Table 3. Registered nanoclinical trials on https://clinicaltrials.gov focused on cancer.

Study Title	Track Number	Status	Interventions/Drug	Disease
Nanocurcumin for Prostate Cancer Patients Undergoing Radiotherapy (RT)	NCT02724618	Phase 2	Drug: Curcumin Radiation: RT Drug: Placebo	Prostate Cancer
Study Investigating the Ability of Plant Exosomes to Deliver Curcumin to Normal and Colon Cancer Tissue	NCT01294072	Phase 1	Dietary Supplement: curcumin Dietary Supplement: Curcumin conjugated with plant exosomes	Colon Cancer
Curcumin and Piperine in Reducing Inflammation for Ureteral Stent-Induced Symptoms in Patients With Cancer	NCT02598726	Phase 1	Drug: Curcumin Other: Laboratory Biomarker Analysis Dietary Supplement: Piperine Extract (Standardized) Other: Quality-of-Life Assessment	Patients with cancer
Evaluation of NanoDoce® in Participants With Urothelial Carcinoma	NCT03636256	Phase 1/2	Drug: NanoDoce (direct injection) Drug: NanoDoce (intravesical instillation) - Visit 2 Instillation Other: Institutional Standard of Care Drug: NanoDoce (intravesical instillation) - Induction and Maintenance Instillations	Bladder cancer
A Study to Evaluate the Efficacy and Safety of Nanosomal Docetaxel Lipid Suspension in Triple Negative Breast Cancer Patients	NCT03671044	Phase 3	Drug: Nanosomal Docetaxel Lipid Suspension (75 mg/m2) Drug: Nanosomal Docetaxel Lipid Suspension (100 mg/m2)Drug: Taxotere® (100 mg/m2)	Triple-negative breast cancer
Nanosomal Docetaxel Lipid Suspension in Treating Patients With Advanced Solid Tumors	NCT01957995	Phase 1	Drug: nanosomal docetaxel lipid suspension Other: pharmacological study	Advanced Solid Tumors
Carboplatin and Paclitaxel Albumin-Stabilized Nanoparticle Formulation Before Surgery in Treating Patients With Locally Advanced or Inflammatory Triple Negative Breast Cancer	NCT01525966	Phase 2	Drug: carboplatinDrug: paclitaxel albumin-stabilized nanoparticle formulationOther: laboratory biomarker analysis	Triple-negative breast cancer
Nab-paclitaxel and Carboplatin Followed by Response-Based Local Therapy in Treating Patients With Stage III or IV HPV-Related Oropharyngeal Cancer (OPTIMA)	NCT02258659	Phase 2	Drug: paclitaxel albumin-stabilized nanoparticle formulation Drug: carboplatin Radiation: radiation therapy	Oropharyngeal cancer
Intraperitoneal Paclitaxel Albumin-Stabilized Nanoparticle Formulation in Treating Patients With Advanced Cancer of the Peritoneal Cavity	NCT00825201	Phase 1	Drug: paclitaxel albumin-stabilized nanoparticle formulation Other: liquid chromatography Other: mass spectrometry	Advanced Cancer of the Peritoneal Cavity
Paclitaxel Albumin-Stabilized Nanoparticle Formulation in Treating Patients of Different Ages With Metastatic Breast Cancer	NCT00609791	Phase 2	Drug: paclitaxel albumin-stabilized nanoparticle formulation Other: pharmacological study Other: physiologic testing	Metastatic breast cancer
Trial of NanoPac® in Subjects With Locally Advanced Pancreatic Adenocarcinoma	NCT03077685	Phase 2	Drug: NanoPac®	Advanced pancreatic adenocarcinoma
Paclitaxel Albumin-Stabilized Nanoparticle Formulation in Treating Patients With Advanced or Refractory Solid Tumors	NCT00499291	-	Drug: paclitaxel albumin-stabilized nanoparticle formulation Procedure: gene expression analysis Procedure: laboratory biomarker analysis Procedure: pharmacological study Procedure: polymerase chain reaction	Advanced or Refractory Solid Tumors

which confirmed its non-toxicity. The cell viability of the nanocarrier remained above 94% even at concentrations of 50 µg/ml against MCF-7 cells. Comparatively, the curcumin/glucosamine-graphene quantum dots exhibited higher cytotoxicity compared to curcumin/graphene quantum dots.[207]

Dendrimers

Dendrimers are nano-sized molecules with radially symmetric, three-dimensional structures. They possess characteristics such as high branching, well-defined submicron globular structures, variable chemical composition, multivalency, structural uniformity, and good biological compatibility, making them highly suitable for drug delivery applications. Various types of dendrimers have been reported by researchers, depending on their functionalization moieties, including core-shell (tecto), chiral, liquid crystalline, PAMAM, peptide, PPI, glycodendrimers, and more. Loading of drugs into dendrimers can be achieved through methods such as hydrophobic interaction, simple encapsulation, electrostatic interaction, covalent conjugation, or hydrogen bonding.[155] The unique chemistry and advances in nanotechnology make dendrimers applicable in various drug delivery systems, including oral, ocular, intravenous, nasal, transdermal, pulmonary, colon, and rectal delivery.

Gupta *et al.*[208] described a method for delivering berberine using G4 PAMAM dendrimers through encapsulation (BPE) and conjugation (BPC) methods. The resulting formulations of encapsulated and conjugated berberine had an average particle size of 100-200 nm. The EE% in BPE was approximately 29.9%, while the EE% in BPC was found to be 37.49%, indicating a high drug burden in the attachment. The study observed that about 72% and 98% of the drug was released from BPC within 24 hours, respectively, while around 80% and 98% of the drug was released from BPE within 24 hours, respectively. This intravenous sustained-release approach helps reduce the hemolytic toxicity associated with PAMAM dendrimers and mitigates the hypoglycemic disadvantage of berberine.

Liposome

Liposomes are spherical particles composed of a bilayer membrane surrounding a water compartment. They possess unique characteristics such as small size, biodegradability, biocompatibility, amphiphilic properties, and low toxicity.[209] Liposomes are versatile drug delivery systems that consist of small vesicles capable of encapsulating drugs with varying lipophilicities. These drugs can be accommodated within the phospholipid bilayer or in the entrapped aqueous volume at the bilayer interface of the liposome. Liposomes, typically prepared from phospholipids, have found applications as carriers for delivering active compounds in nanomedicine, adjuvants in vaccination, and signal enhancers/vehicles in biological diagnostics, herbs, enzymes, and more. Recent studies highlight the crucial role of liposomes in cancer therapy, as they can reduce side effects by increasing specificity for cancer cells. Several liposomal formulations of herbal medicines have been investigated as drug delivery systems, where liposomes improve drug solubility and dissolution rate, thereby enhancing bioavailability.[210]

For targeted anti-cancer therapy, Tia *et al.*[211] developed a glycyrrhetinic acid (GA)-modified WG liposome (WG-Lip). Attachment of GA to the liposomes did not decrease the EE% of the liposomes without GA. Furthermore, GA-WG-Lip exhibited the highest uptake, and the IC50 value was 1.46 times greater than that of WG-Lip. The GA-attached liposomes rapidly accumulated in the tumour region with a prolonged retention time. Compared to unmodified liposomes, GA-attached liposomes demonstrated a better tumour inhibitory ratio. The GA-WG composite showed improvements in therapeutic efficacy, tumour accumulation, and biodistribution, possibly due to enhanced receptor-mediated uptake of liposomes in liver cells.

Zheng *et al.*[212] prepared 9NC-loaded liposomes (9NC-LP) by incorporating 9NC into liposomes, which increased solubility and stability. 9NC-LP had an average size of 190 nm with a zeta potential of 211 mV, making it a suitable reagent for cancer treatment via intravenous administration. Both 9NC-LP and 9NC induced cell cycle arrest and apoptosis, as evidenced by the expression of p53 protein.

Niosomes

There are some drawbacks of liposome technology, such as its time-consuming, chemical instability, impure phospholipid content, and high manufacturing cost. Niosomes are preferred to liposomes, so remain to be more extensively considered delivery system.[213] Niosomes are microscopic lamellar structures prepared by mixing nonionic surfactants to form vesicles capable of loading both hydrophilic and hydrophobic agents. Niosomes can be prepared using various methods such as the transmembrane pH gradient uptake process, ether injection method, thin film hydration method, sonication, bubble method, microfluidization, and reverse phase technique.

Niosomes are a novel drug delivery system with numerous therapeutic applications, including anticancer and anti-infective treatments,[214] gen delivery,[215] carriers of anti-inflammatory drugs,[216] delivery of peptide drugs, imaging agents for diagnostic purposes, and various administration routes. A novel co-encapsulation of curcumin and quercetin was achieved using hyaluronan-containing niosomes,[217,218] Hemati *et al.*[219] focused on optimizing cationic PEGylated niosomes containing siRNA (a chemosensitizer), quercetin, and doxorubicin (a chemotherapeutic drug) to enhance therapeutic effects. The commonly used 1,2-dioleoyl-3-trimethylammonium-propane (DOTAP) was used for loading siRNA onto niosomes. Under optimal conditions,

with cholesterol:tween-60:DOTAP:DPPC:DSPE-PEG2000 ratio of 5.5:49.5:25:15:5, vesicles with a size of 52.8 nm and zeta potential of +27.4 mV were obtained. The EE% of quercetin and doxorubicin was 94.9% and 86.4%, respectively.

Phytosome

Many herbal drugs have hydrophilic constituents, which often suffer from limited bioavailability and poor absorption due to their large molecular size or low permeability through lipid membranes. The clinical efficacy of multi-constituent herbal extracts can be compromised by their susceptibility to degradation in the gastric environment when administered orally. This compromises the bioavailability of these compounds and reduces their therapeutic effectiveness. To improve the pharmacokinetic and pharmacodynamic profiles and enhance bioavailability, herbal products can be complexed with medically beneficial nutrients such as phospholipids, typically lecithin. This complexation significantly improves the bioavailability of these compounds. The compounds can be transformed into lipid-compatible complexes using a lipid bilayer composed of phosphatidylcholine, forming small cell-like structures called phytosomes. Several manufacturing approaches have been described for the production of phytosomes in drug delivery systems.[220] Phytosomes offer higher stability due to the formation of chemical bonds between phosphatidylcholine and water-soluble active herbal ingredients.

In a study conducted by Marjaneh *et al.*,[221] formulated phytosomal curcumin was developed for therapeutic applications and its effects were investigated when combined with 5-Fluorouracil (5-FU) in a mouse model of colitis-associated colon cancer. The combination of curcumin and 5-FU showed efficacy in reducing the size and number of tumours in both the middle and distal portions of the colon. Furthermore, this combination treatment resulted in a decrease in the disease activity index (DAI), indicating a positive impact on colitis-associated colon cancer.

Metallic nanoparticles

Nanoparticles can be classified into different groups based on their specific attributes, shapes, or sizes. These inherent characteristics of nanoparticles can be easily manipulated to customize drug delivery systems for various applications.[222] In recent decades, there has been an increasing interest in the application of metallic nanoparticles in various biomedical applications, such as targeted drug delivery, biosensors, bioimaging, hyperthermia, photoablation therapy, bioimaging, and biosensors.[223,224] Nanoparticles can be surface-modified with specific functional groups to allow them to attach to drugs, antibodies, or other ligands, making them promising candidates for medical applications. The most extensively studied metal oxide and metal nanoparticles include silver, gold, lead, platinum, iron, copper, zinc oxide, and titanium oxide.[224,225]

Lou *et al.*[226] developed a poly (DL-lactide-co-glycolide) nanocomposite containing gold-quercetin to enhance drug delivery and minimize side effects in cancer therapy. The quercetin nanoparticles induced apoptosis and cell autophagy in human neuroglioma cells. Treatment with quercetin nanoparticles down-regulated the expression of activated Bcl-2 and PI3K/AKT in human neuroglioma cells. The expression levels of cytoplasmic p53, ERK, LC3, PARP, and cleaved Caspase-3 were positively correlated with the concentration of quercetin nanoparticles. Moreover, in a dose-dependent therapy, GAIP and p-mTOR were down-regulated through quercetin nanoparticles.

Microspheres

Microspheres refer to spherical particles with diameters ranging from 1 to 1000 μm. They can be prepared from various natural, inorganic, or synthetic polymeric materials. Different polymers have been used to create these biodegradable carriers, including albumin, gelatin, modified starch, polylactic acid, polypropylene dextran, and others. Microspheres are commonly employed as vehicles for controlled drug delivery systems due to their high bioavailability, biocompatibility, and sustained release characteristics, making them suitable for achieving desired release profiles.[32]

Tong *et al.*[227] investigated PLGA microspheres as delivery vehicles for CPT, a chemotherapeutic agent. The microspheres were composed of poly (lactic-co-glycolic acid) (PLGA) and exhibited different surface characteristics based on the drug loading. High-loading microspheres (1:10 MS) showed a slightly rough surface while low drug-loading microspheres (1:40 MS, 1:20 MS, blank MS) had a smooth surface. Stability analysis confirmed that CPT was released from the microspheres while maintaining its active lactone conformation. MTT assay demonstrated that CPT encapsulated in PLGA microspheres retained its anticancer activity, highlighting the potential of these microspheres for cancer therapy.

Dai *et al.*[228] developed PCL–PEG–PCL (PCEC) microspheres to prevent the hydrolysis of CPT. This nanocomposite extended the release time of CPT and improved its therapeutic effect in tumour growth and colorectal peritoneal carcinomatosis in mice. CPT-loaded PCEC microspheres were prepared using the oil-in-water emulsion solvent evaporation method. The CPT–PCEC microspheres exhibited significant inhibition of progressive tumour growth, reduced toxic side effects, and improved survival rate.

Nanoemulsion

Nanoemulsion is a submicrometer-sized material that is being extensively studied as a carrier for enhancing

the delivery of active compounds. It is composed of an aqueous phase and an oil phase, with the submicron droplets stabilized by surfactant and co-surfactant agents.[229] Nanoemulsion, which falls under the category of multi-phase colloidal systems, is expected to be stable and clear. It can be classified into three types: water-in-oil (W/O), oil-in-water (O/W), and bicontinuous emulsions. O/W or W/O emulsions hold promise as drug delivery systems and various herbal compositions have been formulated as emulsions for different applications.

Ahmad *et al.*[230] developed a nanoemulsion using an aqueous titration method. The optimized formulation consisted of 65.22% v/v distilled water and 28.99% v/v Smix (a mixture of PEG 400 and kolliphor RH40 in a ratio of 1:2) as the aqueous phase. This formulation exhibited a mean particle size of 21.2 nm and achieved a maximum drug release of 97.7% within 24 hours. The viscosity of the optimized formulation was measured to be 9.59 cps. Compared to the conventional suspension system, the NE9 formulation demonstrated significantly shorter Tmax (time to reach maximum concentration) ($p < 0.05$), higher Cmax (maximum concentration) ($p < 0.01$), and higher AUC (area under the curve) ($p < 0.01$). Moreover, recent studies have indicated that optimized nanoformulations increased ROS (reactive oxygen species) intensity and chromatin condensation ($p < 0.05$) and reduced cell viability against liver cancer cells without damaging normal cells.

Tranfersome

Transfersomes are a novel vesicular vehicle that has been recently utilized for the delivery of active agents. They function as carriers or artificial vesicles designed to mimic the characteristics of a cell vesicle during exocytosis, making them suitable for drug delivery.[231] One of the main challenges in transdermal drug delivery is the low permeability of the skin, as well as issues such as carrier breakage, leakage of active molecules, carrier fusion, and aggregation. To overcome these challenges, transfersomes have been developed as a type of drug carrier that enables the transdermal delivery of both high and low molecular weight drugs.

Jangdey *et al.*[232] conducted a study on apigenin-loaded transfersomes, which demonstrated a sustained-release profile compared to the pure drug. The EE% of the transfersomes was found to be 84.24%, with a drug loading of 8.042% and an average size of 35.41 nm. This study highlights a novel approach to formulating transfersomes containing apigenin, which shows efficacy in penetrating the layers of the skin, particularly the melanocytes layers, for efficient drug delivery.

Ethosome

Ethosomes are soft and flexible nanocarriers composed primarily of phospholipids, a high concentration of alcohol (such as isopropyl or ethanol) at relatively high concentrations (20-45%), and water. They were introduced by Ainbinder *et al.*[233] and have gained significant interest in comparison to liposomes due to their high deformability, efficient entrapment, and enhanced drug penetration capabilities in drug delivery systems. Ethosomes are particularly suitable for topical or transdermal administration as they are non-invasive vehicles. These novel lipid carriers have a highly deformable structure, high entrapment efficiency, and promote the penetration of active molecules through the skin, although the underlying mechanisms are not yet fully understood. Ethosomes can accommodate active agents with various physicochemical properties, including hydrophilic, lipophilic, or amphiphilic agents.

In a study conducted by Eskolaky *et al.*,[234] Paclitaxel® loaded pegylated ethosomes were synthesized using the reverse-phase evaporation method. The cytotoxic effect of these particles was evaluated on cancer cells (SK-MEL-3). The blank pegylated ethosomes exhibited a mean particle size of 102.3 ± 2.1 nm and a zeta potential of -19.2 mV, while the drug-loaded pegylated ethosomes had a mean particle size of 138.1 ± 2.7 nm and a zeta potential of -13.1 mV. The encapsulation efficiency was determined to be 96 ± 1.2%, and the drug loading was 2.82 ± 0.2. A comparison of the release profiles between the nanodrug and the free drug showed that the half-life (t1/2) of the nanodrug was approximately twice as long. Moreover, toxicological data indicated approximately 4.5 times higher cytotoxicity against the SK-MEL-3 cell line compared to the free drug.

In another study by Paolino *et al.*,[235] ethosomes loaded with paclitaxel were synthesized and evaluated for their therapeutic potential in squamous cell carcinoma. The findings revealed improved anti-proliferative activity in a squamous cell carcinoma model and enhanced skin penetration through the human stratum corneum. The results suggested that paclitaxel-loaded ethosomes hold promise as a therapeutic option for squamous cell cancer, which is a malignant transformation of actinic keratoses. The ethosomes exhibited significant promotion of apoptotic activity induced by the delivered paclitaxel and played a crucial role in modulating actinic keratosis, thus maintaining a balance between cell death and cellular proliferation in skin disorders.

Nanocapsules

Nanocapsules are vesicular structures in which active molecules are entrapped within a cavity containing a liquid or solid core, surrounded by a natural or synthetic polymer. They have attracted significant attention due to their protective coating, particularly for pyrophoric and easily oxidized agents, and their ability to control drug release. Nanocapsules can be

prepared using various methods, including interfacial polymerization, nanoprecipitation, emulsification/solvent diffusion, solvent evaporation, dialysis, salting out, and supercritical fluid technology. The morphology of micro/nanocapsules, including size, size distribution, inner morphology, core composition, and release mechanism, plays a crucial role in determining the effectiveness and efficiency of drug delivery systems. Nanocapsules can be administered to the body through various routes, such as intravenous or oral injection. By carefully considering these characteristics, researchers can optimize drug delivery platforms to achieve desired therapeutic outcomes.[236]

In a study by Song *et al.*,[237] smart reduction-responsive camptothecin nanocapsules were developed using nanoprecipitation and in situ polymerization with a polymerized surface ligand. Drug release experiments showed that the nanocapsules exhibited robust drug release behaviours in the presence of glutathione due to the cleavage of the disulfide bond crosslinker, leading to rapid release of the encapsulated camptothecin in the cell cytoplasm. In vitro examinations confirmed that the camptothecin nanocapsules could effectively be taken up by cells via cytotoxicity and endocytosis pathways in squamous cell cancer. Guo *et al.*[238] prepared a series of disulfide structures with 10-hydroxycamptothecin (HCPT) molecules. The toxicities and anti-cancer activities of these conjugates (13a–14d) were evaluated through in vitro MTT assay using HepG2, HT-29, K562, and HUVECs cell lines. The conjugates showed significantly improved anti-cancer activity with reduced toxicity compared to the parental molecule, HCPT. Among the various conjugates, DLS and TEM analysis revealed that compound 13a formed nano-sized spherical micelles with a mean size of about 200 nm in an aqueous solution. Furthermore, the EPR effect of nanoparticles contributed to the improved efficacy and reduced toxicity of these conjugates.

Hydrogels

Hydrogels have gained significant attention in biomedicine for various applications, including pharmaceutical and cell vehicles, tissue engineering matrices, cell culture, and self-healing.[239] These materials consist of a hydrophilic polymer three-dimensional network that can be adjusted by controlling the density of cross-links and the affinity of the hydrogels for the aqueous environment in which they are swollen. Hydrogels can be formed through permanent covalent cross-links, ionic interactions, hydrogen bonding, bio-recognition or affinity interactions, hydrophobic interactions, polymeric chains, or a combination of these interactions.[240] Hydrophobic monomers are also used in hydrogel fabrication to tailor their properties for specific applications. They can be prepared from natural or synthetic polymers. Hydrogels can hold large amounts of water within their 3D networks, making them suitable for loading herbal medicines, which are generally aqueous in nature.[241]

In a study by Nazlı *et al.*,[242] alginate-chitosan composite beads were prepared using the drip technique and the polyelectrolyte complex formation between alginate and chitosan. Resveratrol, a compound used in cancer therapy, was incorporated into the hybrid beads. The encapsulation efficiency of resveratrol in the hybrid beads reached 74% when a mass ratio of chitosan-alginate of 2:1 and 70 mg of resveratrol were used. The cumulative release of resveratrol from the beads was approximately 97% at pH 5.5 and 6.8 after 48 hours. The maximum cumulative release of 70 mg resveratrol-loaded Ca-alginate beads in PBS media at pH 6.8 and 5.5 was 95.9% and 81.2%, respectively.

In another study conducted by Teong *et al.*,[243] the anticancer behaviour of curcumin-loaded hydrogel nanocomposite aggregates was investigated on A549 lung adenocarcinoma cells. The biopolymeric nanoparticles had an average diameter of approximately 4 nm, which increased to a range of 26-55 nm upon the incorporation of curcumin. The incorporation efficiencies of curcumin into gelatin, hyaluronan chitosan, and nanoparticles were measured at 67%, 78%, and 81%, respectively. At a low concentration of curcumin (13.6 μM), the aggregates exhibited a significant reduction in the viability of A549 cells after 6 hours of incubation. The nanocomposite aggregates showed enhanced anti-cancer proliferation behaviour compared to curcumin alone, attributed to the improved dispersion of curcumin in aqueous media achieved by combining it with hydrophilic compounds.

Conclusion

Nanotechnology presents exciting opportunities for addressing challenges associated with herbal medicine and improving cancer treatment. In this context, nanocarriers play a pivotal role, particularly in the delivery of anticancer drugs. They offer enhanced therapeutic outcomes compared to conventional chemotherapy by effectively targeting affected cells while minimizing side effects. Furthermore, nanocarriers have the advantage of prolonged circulation in the body, allowing for controlled and targeted drug release upon stimulation.

One of the primary limitations of herbal bioactive compounds is their hydrophobic nature, which affects their oral bioavailability. To overcome this hurdle, nanocarriers have proven successful in encapsulating these bioactive compounds. Additionally, nanocarriers increase the circulation time of active substances in the blood due to their high surface area-to-volume ratio. The utilization of nanocarriers for cancer treatment and diagnosis holds significant promise in improving cancer therapy. As these methods continue to advance, they are likely to find broader applications in cancer treatment, making it more accessible and effective.

While there have been concerns about the environmental, safety, and potential health impacts of industrial nanotechnologies, ongoing research can

address these issues over time. To realize the future potential of nanotechnology in herbal therapy, it's crucial to focus on new research studies and works on nanoformulations-based herbals. Recent developments in nanotechnology indicate a promising future for natural remedies as ongoing investigations in this field progress.

The use of plant extracts is favoured for their distinct advantages, including low side effects, therapeutic effectiveness, and cost-efficiency compared to synthetic products. Nanoformulations-based herbals exhibit significantly higher anticancer properties than free herbals, suggesting novel applications in the commercialization of nanomedicines. Clinical and pre-clinical trials, along with laboratory research, should continue to explore the numerous variables in therapeutic applications.

The review suggests that a wide range of herbals can be formulated into suitable nanomedicine forms, potentially introducing many herbals as pharmaceutical products in the market in the near future. In conclusion, the integration of nanotechnology with multifunctional nanocarriers that possess tumour-specific targeting capabilities and carry natural products holds great promise for advancing cancer therapy in the near future.

Author Contributions

Malihe Sadat Razavi: Conceptualization, Methodology, Validation, Writing - Original Draft , Visualization, Project administration. Fatemeh Ahmadi: Conceptualization, Methodology, Validation, Writing - Original Draft, Visualization, Project administration. Pedram Ebrahimnejad: Conceptualization, Supervision, Project administration, Funding acquisition. Abolfazl Akbarzadeh: Writing - Review & Editing, Investigation. Masoud Farokhrou: Writing - Review & Editing, Ali Nokhodchi: Conceptualization, Supervision, Project administration, Writing - Review & Editing,.

Conflict of Interest

The authors declare that they have no competing interests.

References

1. Misra R, Acharya S, Sahoo SK. Cancer nanotechnology: Application of nanotechnology in cancer therapy. Drug Discov Today. 2010;15(19-20):842-50. doi:10.1016/j.drudis.2010.08.006.
2. Singhal S, Nie S, Wang MD. Nanotechnology applications in surgical oncology. Annu Rev Med. 2010;61:359-73. doi:10.1146/annurev.med.60.052907.094936
3. Razavi MS, Abdollahi A, Malek-Khatabi A, Ejarestaghi NM, Atashi A, Yousefi N, et al. Recent advances in plga-based nanofibers as anticancer drug delivery systems. J Drug Del Sci Technol. 2023;85:104587. doi:10.1016/j.jddst.2023.104587
4. Wang X, Yang L, Chen ZG, Shin DM. Application of nanotechnology in cancer therapy and imaging. CA Cancer J Clin. 2008;58(2):97-110. doi:10.3322/CA.2007.0003
5. Lee SM, Park H, Yoo KH. Synergistic cancer therapeutic effects of locally delivered drug and heat using multifunctional nanoparticles. Adv Mater. 2010;22(36):4049-53. doi:10.1002/adma.201001040
6. Zhang QY, Wang FX, Jia KK, Kong LD. Natural product interventions for chemotherapy and radiotherapy-induced side effects. Front Pharmacol. 2018;9:1253. doi:10.3389/fphar.2018.01253
7. Zhou M, Zhang X, Yang Y, Liu Z, Tian B, Jie J, et al. Carrier-free functionalized multidrug nanorods for synergistic cancer therapy. Biomater. 2013;34(35):8960-7. doi:10.1016/j.biomaterials.2013.07.080
8. Majidinia M, Mirza-Aghazadeh-Attari M, Rahimi M, Mihanfar A, Karimian A, Safa A, et al. Overcoming multidrug resistance in cancer: Recent progress in nanotechnology and new horizons. IUBMB Life. 2020;72(5):855-71. doi:10.1002/iub.2215
9. Malek-Khatabi A, Sadat Razavi M, Abdollahi A, Rahimzadeghan M, Moammeri F, Sheikhi M, et al. Recent progress in plga-based microneedle-mediated transdermal drug and vaccine delivery. Biomater Sci. 2023;11(16):5390-409. doi:10.1039/d3bm00795b
10. Lamichhane S, Lee S. Albumin nanoscience: Homing nanotechnology enabling targeted drug delivery and therapy. Arch Pharm Res. 2020;43(1):118-33. doi:10.1007/s12272-020-01204-7
11. Owens III DE, Peppas NA. Opsonization, biodistribution, and pharmacokinetics of polymeric nanoparticles. Int J Pharm. 2006;307(1):93-102. doi:10.1016/j.ijpharm.2005.10.010
12. Mirkasymov AB, Zelepukin IV, Nikitin PI, Nikitin MP, Deyev SM. In vivo blockade of mononuclear phagocyte system with solid nanoparticles: Efficiency and affecting factors. J Control Release. 2021;330:111-8. doi:10.1016/j.jconrel.2020.12.004
13. Suk JS, Xu Q, Kim N, Hanes J, Ensign LM. Pegylation as a strategy for improving nanoparticle-based drug and gene delivery. Adv Drug Del Rev. 2016;99:28-51. doi:10.1016/j.addr.2015.09.012
14. Hoang Thi TT, Pilkington EH, Nguyen DH, Lee JS, Park KD, Truong NP. The importance of poly(ethylene glycol) alternatives for overcoming peg immunogenicity in drug delivery and bioconjugation. Polym (Basel). 2020;12(2):298. doi:10.3390/polym12020298
15. Raju GSR, Benton L, Pavitra E, Yu JS. Multifunctional nanoparticles: Recent progress in cancer therapeutics. Chem Commun. 2015;51(68):13248-59. doi:10.1039/C5CC04643B
16. Kalyane D, Raval N, Maheshwari R, Tambe V, Kalia K, Tekade RK. Employment of enhanced permeability and retention effect (epr): Nanoparticle-based precision tools for targeting of therapeutic and diagnostic

agent in cancer. Mater Sci Eng C Mater Biol Appl. 2019;98:1252-76. doi:10.1016/j.msec.2019.01.066
17. Subhan MA, Yalamarty SSK, Filipczak N, Parveen F, Torchilin VP. Recent advances in tumor targeting via epr effect for cancer treatment. J Pers Med. 2021;11(6):571. doi:10.3390/jpm11060571
18. Ebrahimnejad P, Sodagar Taleghani A, Asare-Addo K, Nokhodchi A. An updated review of folate-functionalized nanocarriers: A promising ligand in cancer. Drug Discov Today. 2022;27(2):471-89. doi:10.1016/j.drudis.2021.11.011
19. Tavakkoli A, Ahmadi A, Razavi BM, Hosseinzadeh H. Black seed (*Nigella sativa*) and its constituent thymoquinone as an antidote or a protective agent against natural or chemical toxicities. Iranian J Pharm Res. 2017;16(Suppl):2-23.
20. Adhikari K, Uprety Y, Pyakurel D, Thagunna K, Bhatta L, Chaudhary R. Healthcare Choices and Use of Medicinal Plants: An Ethnobotanical Study in Kanda Area of Bajhang District, Kailash Sacred Landscape, Nepal. In: Abbasi AM, Bussmann RW, editors. Ethnobiology of Mountain Communities in Asia. Ethnobiology. Cham: Springer; 2021. doi:10.1007/978-3-030-55494-1_18
21. Razavi MS, Ebrahimnejad P, Fatahi Y, D'Emanuele A, Dinarvand R. Recent developments of nanostructures for the ocular delivery of natural compounds. Front Chem. 2022;10:850757. doi:10.3389/fchem.2022.850757
22. Brodowska KM. Natural flavonoids: Classification, potential role, and application of flavonoid analogues. Eur J Biol Res. 2017;7(2):108-23.
23. Saraf S. Applications of novel drug delivery system for herbal formulations. Fitoterapia. 2010;81(7):680-9.
24. Sofowora A. Research on medicinal plants and traditional medicine in africa. J Altern Complement Med. 1996;2(3):365-72. doi:10.1089/acm.1996.2.365
25. 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
26. Mirzaeei S, Taghe S, Alany RG, Nokhodchi A. Eudragit® l100/polyvinyl alcohol nanoparticles impregnated mucoadhesive films as ocular inserts for controlled delivery of erythromycin: Development, characterization and in vivo evaluation. Biomedicines. 2022;10(8):1917. doi:10.3390/biomedicines10081917.
27. Moazeni M, Kelidari HR, Saeedi M, Morteza-Semnani K, Nabili M, Gohar AA, et al. Time to overcome fluconazole resistant candida isolates: Solid lipid nanoparticles as a novel antifungal drug delivery system. Colloids Surf B 2016;142:400-7. doi:10.1016/j.colsurfb.2016.03.013
28. Muhamad II, Selvakumaran S, Lazim NAM. Designing polymeric nanoparticles for targeted drug delivery system. In: Seifalian A, Mel A, Kalaskar DM, editors. Nanomedicine. Altrincham, Cheshire: One Central Press; 2014.
29. Zhang T-T, Li W, Meng G, Wang P, Liao W. Strategies for transporting nanoparticles across the blood–brain barrier. Biomater Sci. 2016;4(2):219-29. doi:10.1039/c5bm00383k
30. Sharma BK. Synthetic and natural compounds as anti-cancer agents–a review. Asian J Res Chem. 2017;10(5):699-707. doi:10.5493/wjem.v2.i3.45
31. Garcia-Carbonero R, Supko JG. Current perspectives on the clinical experience, pharmacology, and continued development of the camptothecins. Clin Cancer Res. 2002;8(3):641-61.
32. Cheetham AG, Zhang P, Lin YA, Lock LL, Cui H. Supramolecular nanostructures formed by anticancer drug assembly. J Am Chem Soc. 2013;135(8):2907-10. doi:10.1021/ja3115983
33. Andtbacka RH, Kaufman HL, Collichio F, Amatruda T, Senzer N, Chesney J, et al. Talimogene laherparepvec improves durable response rate in patients with advanced melanoma. J Clin Oncol. 2015;33(25):2780-8. doi:10.1200/JCO.2014.58.3377
34. Li Y, Lin J, Huang Y, Li Y, Yang X, Wu H, et al. Self-targeted, shape-assisted, and controlled-release self-delivery nanodrug for synergistic targeting/anticancer effect of cytoplasm and nucleus of cancer cells. ACS Appl Mater Interfaces. 2015;7(46):25553-9. doi:10.1021/acsami.5b07348
35. Peer D, Karp JM, Hong S, Farokhzad OC, Margalit R, Langer R. Nanocarriers as an emerging platform for cancer therapy. Nat Nanotechnol. 2007;2(12):751.
36. Landgraf M, Lahr CA, Kaur I, Shafiee A, Sanchez-Herrero A, Janowicz PW, et al. Targeted camptothecin delivery via silicon nanoparticles reduces breast cancer metastasis. Biomaterials. 2020;240:119791. doi:10.1016/j.biomaterials.2020.119791
37. Hahn G, Lehmann HD, Kurten M, Uebel H, Vogel G. [On the pharmacology and toxicology of silymarin, an antihepatotoxic active principle from *Silybum marianum* (L.) gaertn]. Arzneimittelforschung 1968;18(6):698-704.
38. Kvasnička F, Bıba B, Ševčık R, Voldřich M, Kratka J. Analysis of the active components of silymarin. J Chromatogr A. 2003;990(1-2):239-45. doi:10.1016/s0021-9673(02)01971-4
39. Boigk G, Stroedter L, Herbst H, Waldschmidt J, Riecken EO, Schuppan D. Silymarin retards collagen accumulation in early and advanced biliary fibrosis secondary to complete bile duct obliteration in rats. Hepatology. 1997;26(3):643-9. doi:10.1002/hep.510260316
40. Ramasamy K, Agarwal R. Multitargeted therapy of cancer by silymarin. Cancer Lett. 2008;269(2):352-62. doi:10.1016/j.canlet.2008.03.053
41. Song Y, Zhuang J, Guo J, Xiao Y, Ping Q. Preparation and properties of a silybin-phospholipid complex. Pharmazie. 2008;63(1):35-42.

42. Sun N, Wei X, Wu B, Chen J, Lu Y, Wu W. Enhanced dissolution of silymarin/polyvinylpyrrolidone solid dispersion pellets prepared by a one-step fluid-bed coating technique. Powder Technol. 2008;182(1):72-80. doi:10.1016/j.powtec.2007.05.029
43. El-Samaligy MS, Afifi NN, Mahmoud EA. Increasing bioavailability of silymarin using a buccal liposomal delivery system: Preparation and experimental design investigation. Int J Pharm. 2006;308(1-2):140-8. doi:10.1016/j.ijpharm.2005.11.006
44. Wu W, Wang Y, Que L. Enhanced bioavailability of silymarin by self-microemulsifying drug delivery system. Eur J Pharm Biopharm. 2006;63(3):288-94. doi:10.1016/j.ejpb.2005.12.005
45. Zhao X, Deng Y, Zhang Y, Zu Y, Lian B, Wu M, et al. Silymarin nanoparticles through emulsion solvent evaporation method for oral delivery with high antioxidant activities, bioavailability, and absorption in the liver. RSC Adv. 2016;6(95):93137-46. doi:10.1039/C6RA12896C
46. Radu I-C, Hudita A, Zaharia C, Stanescu PO, Vasile E, Iovu H, et al. Poly (hydroxybutyrate-co-hydroxyvalerate)(phbhv) nanocarriers for silymarin release as adjuvant therapy in colo-rectal cancer. Frontiers Pharmacol. 2017;8:508. doi:10.3389/fphar.2017.00508
47. Mi XJ, Choi HS, Perumalsamy H, Shanmugam R, Thangavelu L, Balusamy SR, et al. Biosynthesis and cytotoxic effect of silymarin-functionalized selenium nanoparticles induced autophagy mediated cellular apoptosis via downregulation of pi3k/akt/mtor pathway in gastric cancer. Phytomedicine. 2022;99:154014. doi:10.1016/j.phymed.2022.154014
48. Belitz HD, Grosch W, Schieberle P. Coffee, Tea, Cocoa. In: Food Chemistry. Berlin: Springer; 2004. doi:10.1007/978-3-662-07279-0_22
49. Cavia-Saiz M, Muñiz P, Ortega N, Busto M. Effect of enzymatic debittering on antioxidant capacity and protective role against oxidative stress of grapefruit juice in comparison with adsorption on exchange resin. Food Chem. 2011;125(1):158-63. doi:10.1016/j.foodchem.2010.08.054
50. Scalbert A, Williamson G. Dietary intake and bioavailability of polyphenols. J Nutr. 2000;130(8S Suppl):2073S-85S. doi:10.1093/jn/130.8.2073S
51. Ratnam DV, Ankola DD, Bhardwaj V, Sahana DK, Kumar MN. Role of antioxidants in prophylaxis and therapy: A pharmaceutical perspective. J Control Release. 2006;113(3):189-207. doi:10.1016/j.jconrel.2006.04.015
52. Shulman M, Cohen M, Soto-Gutierrez A, Yagi H, Wang H, Goldwasser J, et al. Enhancement of naringenin bioavailability by complexation with hydroxypropyl-beta-cyclodextrin. [corrected]. PLoS One. 2011;6(4):e18033. doi:10.1371/journal.pone.0018033
53. Paredes A, Alzuru M, Mendez J, Rodriguez-Ortega M. Anti-sindbis activity of flavanones hesperetin and naringenin. Biol Pharm Bull. 2003;26(1):108-9. doi:10.1248/bpb.26.108
54. Jain AK, Swarnakar NK, Godugu C, Singh RP, Jain S. The effect of the oral administration of polymeric nanoparticles on the efficacy and toxicity of tamoxifen. Biomaterials. 2011;32(2):503-15. doi:10.1016/j.biomaterials.2010.09.037
55. Ge H, Hu Y, Jiang X, Cheng D, Yuan Y, Bi H, et al. Preparation, characterization, and drug release behaviors of drug nimodipine-loaded poly(epsilon-caprolactone)-poly(ethylene oxide)-poly(epsilon-caprolactone) amphiphilic triblock copolymer micelles. J Pharm Sci. 2002;91(6):1463-73. doi:10.1002/jps.10143
56. Acharya S, Sahoo SK. PLGA nanoparticles containing various anticancer agents and tumour delivery by epr effect. Adv Drug Del Rev. 2011;63(3):170-83. doi:10.1016/j.addr.2010.10.008
57. Krishnakumar N, Sulfikkarali N, RajendraPrasad N, Karthikeyan S. Enhanced anticancer activity of naringenin-loaded nanoparticles in human cervical (hela) cancer cells. Biomed Prev Nutr. 2011;1(4):223-31. doi:10.1016/j.bionut.2011.09.003
58. Yıldırım M, Acet Ö, Yetkin D, Acet BÖ, Karakoç V, Odabası M. Anti-cancer activity of naringenin loaded smart polymeric nanoparticles in breast cancer. J Drug Del Sci Technol. 2022;74:103552. doi:10.1016/j.jddst.2022.103552
59. Coward L, Barnes NC, Setchell KD, Barnes S. Genistein, daidzein, and their. Beta.-glycoside conjugates: Antitumor isoflavones in soybean foods from american and asian diets. J Agri Food Chem. 1993;41(11):1961-7. doi:10.1021/jf00035a027
60. Wang BS, Juang LJ, Yang JJ, Chen LY, Tai HM, Huang MH. Antioxidant and antityrosinase activity of flemingia macrophylla and glycine tomentella roots. Evid Based Complement Alternat Med. 2012;2012:431081. doi:10.1155/2012/431081
61. El Touny LH, Banerjee PP. Identification of a biphasic role for genistein in the regulation of prostate cancer growth and metastasis. Cancer Res. 2009;69(8):3695-703. doi:10.1158/0008-5472.CAN-08-2958
62. Li W, Frame LT, Hoo KA, Li Y, D'Cunha N, Cobos E. Genistein inhibited proliferation and induced apoptosis in acute lymphoblastic leukemia, lymphoma and multiple myeloma cells in vitro. Leuk Lymphoma. 2011;52(12):2380-90. doi:10.3109/10428194.2011.598251
63. Yan GR, Xiao CL, He GW, Yin XF, Chen NP, Cao Y, et al. Global phosphoproteomic effects of natural tyrosine kinase inhibitor, genistein, on signaling pathways. Proteomics. 2010;10(5):976-86. doi:10.1002/pmic.200900662
64. Manthey JA, Grohmann K, Guthrie N. Biological properties of citrus flavonoids pertaining to cancer

and inflammation. Curr Med Chem. 2001;8(2):135-53. doi:10.2174/0929867013373723
65. Yan GR, Zou FY, Dang BL, Zhang Y, Yu G, Liu X, et al. Genistein-induced mitotic arrest of gastric cancer cells by downregulating kif 20A, a proteomics study. Proteomics. 2012;12(14):2391-9. doi:10.1002/pmic.201100652
66. Azmi AS, Ahmad A, Banerjee S, Rangnekar VM, Mohammad RM, Sarkar FH. Chemoprevention of pancreatic cancer: Characterization of par-4 and its modulation by 3,3' diindolylmethane (DIM). Pharm Res. 2008;25(9):2117-24. doi:10.1007/s11095-008-9581-8
67. Silva AP, Nunes BR, De Oliveira MC, Koester LS, Mayorga P, Bassani VL, et al. Development of topical nanoemulsions containing the isoflavone genistein. Pharmazie 2009;64(1):32-5.
68. Bhadoriya SS, Mangal A, Madoriya N, Dixit P. Bioavailability and bioactivity enhancement of herbal drugs by "nanotechnology": A review. J Curr Pharm Res. 2011;8:1-7.
69. Leonarduzzi G, Testa G, Sottero B, Gamba P, Poli G. Design and development of nanovehicle-based delivery systems for preventive or therapeutic supplementation with flavonoids. Curr Med Chem. 2010;17(1):74-95. doi:10.2174/092986710789957760
70. Mir M, Ebrahimnejad P. Preparation and characterization of bifunctional nanoparticles of vitamin e tpgs-emulsified plga-peg-fol containing deferasirox. Nanosci Nanotechnol Asia. 2014;4(2):80-7.
71. Patra A, Satpathy S, Naik PK, Kazi M, Hussain MD. Folate receptor-targeted PLGA-PEG nanoparticles for enhancing the activity of genistein in ovarian cancer. Artif Cells Nanomed Biotechnol. 2022;50(1):228-39. doi: 10.1080/21691401.2022.2118758
72. Rattanachaikunsopon P, Phumkhachorn P. Bacteriostatic effect of flavonoids isolated from leaves of *Psidium guajava* on fish pathogens. Fitoterapia 2007;78(6):434-6. doi:10.1016/j.fitote.2007.03.015
73. Pal S, Roy SG, De P. Synthesis via raft polymerization of thermo-and ph-responsive random copolymers containing cholic acid moieties and their self-assembly in water. Poly Chem. 2014;5(4):1275-84. doi:10.1039/C3PY01317K
74. Zheng Y, Chen H, Zeng X, Liu Z, Xiao X, Zhu Y, et al. Surface modification of TPGS-b-(PCL-ran-PGA) nanoparticles with polyethyleneimine as a co-delivery system of trail and endostatin for cervical cancer gene therapy. Nanoscale Res lett. 2013;8(1):161. doi:10.1186/1556-276X-8-161
75. Dou J, Zhang H, Liu X, Zhang M, Zhai G. Preparation and evaluation in vitro and in vivo of docetaxel loaded mixed micelles for oral administration. Colloids Surf B Biointerfaces. 2014;114:20-7. doi:10.1016/j.colsurfb.2013.09.010
76. Ouahab A, Cheraga N, Onoja V, Shen Y, Tu J. Novel ph-sensitive charge-reversal cell penetrating peptide conjugated peg-pla micelles for docetaxel delivery: In vitro study. Int J Pharm. 2014;466(1-2):233-45. doi:10.1016/j.ijpharm.2014.03.009
77. Kim GT, Lee SH, Kim JI, Kim YM. Quercetin regulates the sestrin 2-ampk-p38 mapk signaling pathway and induces apoptosis by increasing the generation of intracellular ros in a p53-independent manner. Int J Mol Med. 2014;33(4):863-9. doi:10.3892/ijmm.2014.1658
78. Thakur N, Sadhukhan P, Kundu M, Singh TA, Hatimuria M, Pabbathi A, et al. Folic acid-functionalized cerium oxide nanoparticles as smart nanocarrier for ph-responsive and targeted delivery of morin in breast cancer therapy. Inorganic Chem Commu. 2022;145:109976. doi:10.1016/j.inoche.2022.109976
79. Raghavan BS, Kondath S, Anantanarayanan R, Rajaram R. Kaempferol mediated synthesis of gold nanoparticles and their cytotoxic effects on mcf-7 cancer cell line. Process Biochem. 2015;50(11):1966-76. doi:10.1016/j.procbio.2015.08.003
80. Chen AY, Chen YC. A review of the dietary flavonoid, kaempferol on human health and cancer chemoprevention. Food Chem. 2013;138(4):2099-107. doi:10.1016/j.foodchem.2012.11.139
81. Leung HW, Lin CJ, Hour MJ, Yang WH, Wang MY, Lee HZ. Kaempferol induces apoptosis in human lung non-small carcinoma cells accompanied by an induction of antioxidant enzymes. Food Chem Toxicol. 2007;45(10):2005-13. doi:10.1016/j.fct.2007.04.023
82. Filomeni G, Desideri E, Cardaci S, Graziani I, Piccirillo S, Rotilio G, et al. Carcinoma cells activate amp-activated protein kinase-dependent autophagy as survival response to kaempferol-mediated energetic impairment. Autophagy. 2010;6(2):202-16. doi:10.4161/auto.6.2.10971
83. Choi EJ, Ahn WS. Kaempferol induced the apoptosis via cell cycle arrest in human breast cancer mda-mb-453 cells. Nutr Res Pract. 2008;2(4):322-5. doi:10.4162/nrp.2008.2.4.322
84. Gates MA, Tworoger SS, Hecht JL, De Vivo I, Rosner B, Hankinson SE. A prospective study of dietary flavonoid intake and incidence of epithelial ovarian cancer. Int J Cancer. 2007;121(10):2225-32. doi:10.1002/ijc.22790
85. Song M, Liu T, Shi C, Zhang X, Chen X. Bioconjugated manganese dioxide nanoparticles enhance chemotherapy response by priming tumor-associated macrophages toward m1-like phenotype and attenuating tumor hypoxia. ACS Nano. 2016;10(1):633-47. doi:10.1021/acsnano.5b06779
86. Tu LY, Bai HH, Cai JY, Deng SP. The mechanism of kaempferol induced apoptosis and inhibited proliferation in human cervical cancer siha cell: From macro to nano. Scanning 2016;38(6):644-53. doi:10.1002/sca.21312

87. Guterres SS, Fessi H, Barratt G, Puisieux F, Devissaguet JP. Poly(d,l-lactide) nanocapsules containing non-steroidal anti-inflammatory drugs: Gastrointestinal tolerance following intravenous and oral administration. Pharm Res. 1995;12(10):1545-7. doi:10.1023/a:1016208125979
88. Luo H, Jiang B, Li B, Li Z, Jiang BH, Chen YC. Kaempferol nanoparticles achieve strong and selective inhibition of ovarian cancer cell viability. Int J Nanomed. 2012;7:3951-9. doi:10.2147/IJN.S33670
89. Alyami NM, Alyami HM, Almeer R. Using green biosynthesized kaempferol-coated sliver nanoparticles to inhibit cancer cells growth: An in vitro study using hepatocellular carcinoma (HepG2). Cancer Nanotechnol. 2022;13(1):26. doi:10.1186/s12645-022-00132-z
90. Karasawa MMG, Mohan C. Fruits as prospective reserves of bioactive compounds: A review. Nat Prod Bioprospec. 2018;8:335-46. doi:10.1007/s13659-018-0186-6
91. Razavi MS, Ebrahimnejad P, Javar HA, Weppelmann TA, Akbari J, Amoli FA, et al. Development of dual-functional core-shell electrospun mats with controlled release of anti-inflammatory and anti-bacterial agents for the treatment of corneal alkali burn injuries. Biomater Adv. 2023:154;213648. doi:10.1016/j.bioadv.2023.213648
92. Jing D, Wu W, Chen X, Xiao H, Zhang Z, Chen F, et al. Quercetin encapsulated in folic acid-modified liposomes is therapeutic against osteosarcoma by non-covalent binding to the JH2 domain of JAK2 Via the JAK2-STAT3-PDL1. Pharmacol Res. 2022;182:106287. doi:10.1016/j.phrs.2022.106287
93. Ahmadi F, Ghasemi-Kasman M, Ghasemi S, Tabari MG, Pourbagher R, Kazemi S, et al. Induction of apoptosis in HeLa cancer cells by an ultrasonic-mediated synthesis of curcumin-loaded chitosan-alginate-STPP nanoparticles. Int J Nanomed. 2017;12:8545. doi:10.2147/IJN.S146516
94. Hashemian M, Anissian D, Ghasemi-Kasman M, Akbari A, Khalili-Fomeshi M, Ghasemi S, et al. Curcumin-loaded chitosan-alginate-STPP nanoparticles ameliorate memory deficits and reduce glial activation in pentylenetetrazol-induced kindling model of epilepsy. Prog Neuropsychopharmacol Biol Psychiatry. 2017;79(Pt B):462-71. doi:10.1016/j.pnpbp.2017.07.025
95. Gholami L, Momtazi-Borojeni AA, Malaekeh-Nikouei B, Nikfar B, Amanolahi F, Mohammadi A, et al. Selective cellular uptake and cytotoxicity of curcumin-encapsulated spc and hspc liposome nanoparticles on human bladder cancer cells. Curr Pharm Des. 2023;29(13):1046-58. doi:10.2174/1381612829666230331084848
96. RS P, Mal A, Valvi SK, Srivastava R, De A, Bandyopadhyaya R. Noninvasive preclinical evaluation of targeted nanoparticles for the delivery of curcumin in treating pancreatic cancer. ACS Applied Bio Mat. 2020;3(7):4643-54. doi:10.1021/acsabm.0c00515
97. Baek JS, Na YG, Cho CW. Sustained cytotoxicity of wogonin on breast cancer cells by encapsulation in solid lipid nanoparticles. Nanomater (Basel). 2018;8(3):159. doi:10.3390/nano8030159
98. Liu X, Peng X, Cen S, Yang C, Ma Z, Shi X. Wogonin induces ferroptosis in pancreatic cancer cells by inhibiting the Nrf2/GPX4 axis. Front Pharmacol. 2023;14:1129662. doi:10.3389/fphar.2023.1129662
99. Lee J, Roh JL. Targeting Nrf2 for ferroptosis-based therapy: Implications for overcoming ferroptosis evasion and therapy resistance in cancer. Biochim Biophys Acta Mol Basis Dis. 2023;1869(7):166788. doi:10.1016/j.bbadis.2023.166788
100. Devarajan N, Nathan J, Mathangi R, Mahendra J, Ganesan SK. Pharmacotherapeutic values of berberine: A chinese herbal medicine for the human cancer management. J Biochem Mol Toxicol. 2023;37(3):e23278. doi:10.1002/jbt.23278
101. Meschi M, Khorsandi K, Kianmehr Z. The effect of berberine follow by blue light irradiation and valproic acid on the growth inhibition of mda-mb-231 breast cancer cells. Appl Biochem Biotechnol. 2023;195:6752-67. doi:10.1007/s12010-023-04395-z
102. Paudel KR, Mehta M, Yin GHS, Yen LL, Malyla V, Patel VK, et al. Berberine-loaded liquid crystalline nanoparticles inhibit non-small cell lung cancer proliferation and migration in vitro. Environ Sci Pollut Res Int. 2022;29(31):46830-47. doi:10.1007/s11356-022-19158-2
103. Javed Iqbal M, Quispe C, Javed Z, Sadia H, Qadri QR, Raza S, et al. Nanotechnology-based strategies for berberine delivery system in cancer treatment: Pulling strings to keep berberine in power. Front Mol Biosci. 2020;7:624494. doi:10.3389/fmolb.2020.624494
104. Ahmad I, Hoda M. Attenuation of diabetic retinopathy and neuropathy by resveratrol: Review on its molecular mechanisms of actions. Life Sci. 2020;245:117350. doi:10.1016/j.lfs.2020.117350
105. Dong Y, Wan G, Yan P, Qian C, Li F, Peng G. Fabrication of resveratrol coated gold nanoparticles and investigation of their effect on diabetic retinopathy in streptozotocin induced diabetic rats. J Photochem Photobiol B. 2019;195:51-7. doi:10.1016/j.jphotobiol.2019.04.012
106. Chimento A, D'Amico M, De Luca A, Conforti FL, Pezzi V, De Amicis F. Resveratrol, epigallocatechin gallate and curcumin for cancer therapy: Challenges from their pro-apoptotic properties. Life. 2023;13(2):261. doi:10.3390/life13020261
107. Guo W, Wu X, Li Y, Gao J, Wang F, Jin Y, et al. Evaluation of biophysical as well as biochemical potential of curcumin and resveratrol during prostate cancer. J Drug Targeting 2020;28(1):41-5. doi:10.1080/1061186X.2019.1601199
108. Montalesi E, Cracco P, Acconcia F, Fiocchetti M,

Iucci G, Battocchio C, et al. Resveratrol analogs and prodrugs differently affect the survival of breast cancer cells impairing estrogen/estrogen receptor alpha/neuroglobin pathway. Int J Mol Sci. 2023;24(3):2148. doi:10.3390/ijms24032148

109. Murugan C, Sharma V, Murugan RK, Malaimegu G, Sundaramurthy A. Two-dimensional cancer theranostic nanomaterials: Synthesis, surface functionalization and applications in photothermal therapy. J Control Release. 2019;299:1-20. doi:10.1016/j.jconrel.2019.02.015
110. Naseer F, Ahmad T, Kousar K, Kakar S, Gul R, Anjum S. Formulation of surface-functionalized hyaluronic acid-coated thiolated chitosan nano-formulation for the delivery of vincristine in prostate cancer: A multifunctional targeted drug delivery approach. J Drug Del Sci. Technol. 2022;74:103545.
111. Cannava C, De Gaetano F, Stancanelli R, Venuti V, Paladini G, Caridi F, et al. Chitosan-hyaluronan nanoparticles for vinblastine sulfate delivery: Characterization and internalization studies on k-562 cells. Pharmaceutics. 2022;14(5):942. doi:10.3390/pharmaceutics14050942
112. Albukhaty S, Al-Musawi S, Abdul Mahdi S, Sulaiman GM, Alwahibi MS, Dewir YH, et al. Investigation of dextran-coated superparamagnetic nanoparticles for targeted vinblastine controlled release, delivery, apoptosis induction, and gene expression in pancreatic cancer cells. Molecules. 2020;25(20):4721. doi:10.3390/molecules25204721
113. Khaki-Khatibi F, Zeinali M, Ramezani B, Sabzichi M, Mohammadian J, Hamishehkar H. Harnessing wye-132 as an inhibitor of the mtor signaling enriches the cytotoxicity effect of vinblastine in b16f10 melanoma cancer cells. Process Biochem. 2020;99:123-30. doi:10.1016/j.procbio.2020.08.026
114. Passer BJ, Cheema T, Wu S, Wu CL, Rabkin SD, Martuza RL. Combination of vinblastine and oncolytic herpes simplex virus vector expressing il-12 therapy increases antitumor and antiangiogenic effects in prostate cancer models. Cancer Gene Ther. 2013;20(1):17-24. doi:10.1038/cgt.2012.75
115. Yu C, Hequn C, Jinbo C, Feng Z, Xiongbing Z, Jian D. Gemcitabine/cisplatin versus methotrexate/vinblastine/doxorubicin/cisplatin for muscle-invasive bladder cancer: A systematic review and meta-analysis. J Cancer Res Ther. 2018;14(6):1260-5. doi:10.4103/0973-1482.188434
116. Chung DY, Kang DH, Kim JW, Ha JS, Kim DK, Cho KS. Comparison of oncologic outcomes of dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (ddMVAC) with gemcitabine and cisplatin (GC) as neoadjuvant chemotherapy for muscle-invasive bladder cancer: Systematic review and meta-analysis. Cancers. 2021;13(11):2770. doi:10.3390/cancers13112770
117. Au TH, Nguyen BN, Nguyen PH, Pethe S, Vo-Thanh G, Vu Thi TH. Vinblastine loaded on graphene quantum dots and its anticancer applications. J Microencapsul. 2022;39(3):239-51. doi:10.1080/02652048.2022.2060361
118. Dhyani P, Quispe C, Sharma E, Bahukhandi A, Sati P, Attri DC, et al. Anticancer potential of alkaloids: A key emphasis to colchicine, vinblastine, vincristine, vindesine, vinorelbine and vincamine. Cancer Cell Int. 2022;22(1):206. doi:10.1186/s12935-022-02624-9
119. Ni M, Wang H, Wang M, Zhou W, Zhang J, Wu J, et al. Investigation on the efficiency of chinese herbal injections for treating non-small cell lung cancer with vinorelbine and cisplatin based on multidimensional bayesian network meta-analysis. Front Pharmacol. 2020;11:631170. doi:10.3389/fphar.2020.631170
120. Liu Y, Lu W-L, Guo J, Du J, Li T, Wu J-W, et al. A potential target associated with both cancer and cancer stem cells: A combination therapy for eradication of breast cancer using vinorelbine stealthy liposomes plus parthenolide stealthy liposomes. J Controlled Release. 2008;129(1):18-25. doi:10.1016/j.jconrel.2008.03.022
121. Xu B, Sun T, Wang S, Lin Y. Metronomic therapy in advanced breast cancer and nsclc: Vinorelbine as a paradigm of recent progress. Expert Rev Anticancer Ther. 2021;21(1):71-9. doi:10.1080/14737140.2021.1835478
122. Stoicescu EA, Burcea M, Iancu RC, Zivari M, Popa Cherecheanu A, Bujor IA, et al. Docetaxel for breast cancer treatment-side effects on ocular surface, a systematic review. Processes. 2021;9(7):1086. doi:10.3390/pr9071086
123. SA AR, Mohd Gazzali A, Fisol FA, I MA, Parumasivam T, Mohtar N, et al. Advances in nanocarriers for effective delivery of docetaxel in the treatment of lung cancer: An overview. Cancers (Basel). 2021;13(3):400. doi:10.3390/cancers13030400
124. Imran M, Saleem S, Chaudhuri A, Ali J, Baboota S. Docetaxel: An update on its molecular mechanisms, therapeutic trajectory and nanotechnology in the treatment of breast, lung and prostate cancer. J Drug Del Sci Technol. 2020;60:101959. doi:10.1016/j.jddst.2020.101959
125. Jurczyk M, Kasperczyk J, Wrześniok D, Beberok A, Jelonek K. Nanoparticles loaded with docetaxel and resveratrol as an advanced tool for cancer therapy. Biomedicines. 2022;10(5):1187. doi:10.3390/biomedicines10051187
126. Satapathy BS, Mukherjee B, Baishya R, Debnath MC, Dey NS, Maji R. Lipid nanocarrier-based transport of docetaxel across the blood brain barrier. RSC Adv. 2016;6(88):85261-74. doi:10.1039/C6RA16426A
127. Bonifacio BV, Silva PB, Ramos MA, Negri KM, Bauab TM, Chorilli M. Nanotechnology-based drug delivery systems and herbal medicines: A review. Int J Nanomed. 2014;9:1-15. doi:10.2147/IJN.S52634
128. Chen Q, Xu S, Liu S, Wang Y, Liu G. Emerging nanomedicines of paclitaxel for cancer treatment.

J Control Release. 2022;342:280-94. doi:10.1016/j.jconrel.2022.01.010
129. Sharifi-Rad J, Quispe C, Patra JK, Singh YD, Panda MK, Das G, et al. Paclitaxel: Application in modern oncology and nanomedicine-based cancer therapy. Oxid Med Cell Longev. 2021;2021:3687700. doi:10.1155/2021/3687700
130. Ashrafizadeh M, Ahmadi Z, Mohamadi N, Zarrabi A, Abasi S, Dehghannoudeh G, et al. Chitosan-based advanced materials for docetaxel and paclitaxel delivery: Recent advances and future directions in cancer theranostics. Int J Biol Macromol. 2020;145:282-300. doi:10.1016/j.ijbiomac.2019.12.145
131. Pourkarim F, Rahimpour E, Alvani S, Jouyban A. Solubilization methods for paclitaxel and docetaxel: An overview. Pharm Sci. 202;28(2):208-23. doi:10.34172/ps.2021.30
132. Pan Q, Tian J, Zhu H, Hong L, Mao Z, Oliveira JM, et al. Tumor-targeting polycaprolactone nanoparticles with codelivery of paclitaxel and ir780 for combinational therapy of drug-resistant ovarian cancer. ACS Biomater Sci Eng. 2020;6(4):2175-85. doi:10.1021/acsbiomaterials.0c00163
133. Deep A, Marwaha RK, Marwaha MG, Nandal R, Sharma AK. Flavopiridol as cyclin dependent kinase (CDK) inhibitor: A review. New J Chem. 2018;42(23):18500-7. doi:10.1039/C8NJ04306J
134. Bisol Â, de Campos PS, Lamers ML. Flavonoids as anticancer therapies: A systematic review of clinical trials. Phytother Res. 2020;34(3):568-82. doi:10.1002/ptr.6551
135. Yang X, Zhao X, Phelps MA, Piao L, Rozewski DM, Liu Q, et al. A novel liposomal formulation of flavopiridol. Int J Pharm. 2009;365(1-2):170-4. doi:10.1016/j.ijpharm.2008.08.008
136. Jaiswal SG, Naik SN. Turmeric oil: Composition, extraction, potential health benefits and other useful applications. Avicenna J Med Biochem. 2021;9(2):93-106. doi:10.34172/ajmb.2021.15
137. Stohs SJ, Chen O, Ray SD, Ji J, Bucci LR, Preuss HG. Highly bioavailable forms of curcumin and promising avenues for curcumin-based research and application: A review. Molecules. 2020;25(6):1397. doi:10.3390/molecules25061397
138. Sohn S-I, Priya A, Balasubramaniam B, Muthuramalingam P, Sivasankar C, Selvaraj A, et al. Biomedical applications and bioavailability of curcumin—an updated overview. Pharmaceutics. 2021;13(12):2102. doi:10.3390/pharmaceutics13122102
139. Nair A, Amalraj A, Jacob J, Kunnumakkara AB, Gopi S. Non-curcuminoids from turmeric and their potential in cancer therapy and anticancer drug delivery formulations. Biomolecules. 2019;9(1):13. doi:10.3390/biom9010013
140. Li Z, Hao E, Cao R, Lin S, Zou L, Huang T, et al. Analysis on internal mechanism of zedoary turmeric in treatment of liver cancer based on pharmacodynamic substances and pharmacodynamic groups. Chin Herb Med. 2022;14(4):479-93. doi:10.1016/j.chmed.2022.06.007
141. Zheng B, McClements DJ. Formulation of more efficacious curcumin delivery systems using colloid science: Enhanced solubility, stability, and bioavailability. Molecules. 2020;25(12):2791. doi:10.3390/molecules25122791
142. Chen W-T, Kuo Y-L, Chen C-H, Wu H-T, Chen H-W, Fang W-P. Improving the stability and bioactivity of curcumin using chitosan-coated liposomes through a combination mode of high-pressure processing. LWT. 2022;168:113946. doi:10.1016/j.lwt.2022.113946
143. Muhammad H, Muhammad S. The use of *Lawsonia inermis* Linn.(Henna) in the management of burn wound infections. African J Biotechnol. 2005;4(9):934-7.
144. Hosein HKM, Zinab D. Phenolic compounds and antioxidant activity of henna leaves extracts (*Lawsonia inermis*). World J Dairy Food Sci. 2007;2(1):38-41.
145. Udapurkar P, Bhusnure O, Kamble S, Biyani K. Phyto-phospholipid complex vesicles for phytoconstituents and herbal extracts: A promising drug delivery system. Int J Herbal Med. 2016;4(5):14-20.
146. Singh RP, Ramakant N. Preparation and evaluation of phytosome of lawsone. Int J Pharm Sci Res. 2015;6(12):5217-26.
147. Chaudhary G, Goyal S, Poonia P. Lawsonia inermis linnaeus: A phytopharmacological review. Int J Pharm Sci Drug Res. 2010;2(2):91-8.
148. López López LI, Nery Flores SD, Silva Belmares SY, Sáenz galindo A. Naphthoquinones: Biological properties and synthesis of lawsone and derivatives-a structured review. Vitae. 2014;21(3):248-58.
149. Barani M, Mirzaei M, Torkzadeh-Mahani M, Nematollahi MH. Lawsone-loaded niosome and its antitumor activity in mcf-7 breast cancer cell line: A nano-herbal treatment for cancer. Daru. 2018;26(1):11-7. doi:10.1007/s40199-018-0207-3
150. Sabzichi M, Hamishehkar H, Ramezani F, Sharifi S, Tabasinezhad M, Pirouzpanah M, et al. Luteolin-loaded phytosomes sensitize human breast carcinoma mda-mb 231 cells to doxorubicin by suppressing nrf2 mediated signalling. Asian Pac J Cancer Prev. 2014;15(13):5311-6. doi:10.7314/apjcp.2014.15.13.5311
151. Mu L, Elbayoumi T, Torchilin V. Mixed micelles made of poly (ethylene glycol)–phosphatidylethanolamine conjugate and d-α-tocopheryl polyethylene glycol 1000 succinate as pharmaceutical nanocarriers for camptothecin. Int J Pharm. 2005;306(1-2):142-9. doi:10.1016/j.ijpharm.2005.08.026
152. Maya S, Sabitha M, Nair SV, Jayakumar R. Phytomedicine-loaded polymeric nanomedicines: Potential cancer therapeutics. In: Dutta P, Dutta J, editors. Multifaceted Development and Application

of Biopolymers for Biology, Biomedicine and Nanotechnology. Advances in Polymer Science, vol 254. Berlin, Heidelberg: Springer; 2013. doi:10.1007/12_2012_195.
153. Babazadeh A, Zeinali M, Hamishehkar H. Nano-phytosome: A developing platform for herbal anti-cancer agents in cancer therapy. Curr Drug Targets. 2018;19(2):170-80. doi:10.2174/1389450118666170508095250
154. Flaig TW, Glode M, Gustafson D, van Bokhoven A, Tao Y, Wilson S, et al. A study of high-dose oral silybin-phytosome followed by prostatectomy in patients with localized prostate cancer. Prostate. 2010;70(8):848-55. doi:10.1002/pros.21118
155. Kumar SP, Birundha K, Kaveri K, Devi KR. Antioxidant studies of chitosan nanoparticles containing naringenin and their cytotoxicity effects in lung cancer cells. Int J Biol Macromol. 2015;78:87-95. doi:10.1016/j.ijbiomac.2015.03.045
156. Parashar P, Rathor M, Dwivedi M, Saraf SA. Hyaluronic acid decorated naringenin nanoparticles: Appraisal of chemopreventive and curative potential for lung cancer. Pharmaceutics. 2018;10(1):33. doi:10.3390/pharmaceutics10010033
157. Chaurasia S, Patel RR, Vure P, Mishra B. Oral naringenin nanocarriers: Fabrication, optimization, pharmacokinetic and chemotherapeutic efficacy assessments. Nanomedicine (Lond). 2017;12(11):1243-60. doi:10.2217/nnm-2016-0436
158. Amiri A, Rahimipour M. Determination of anti-cancer effects of poly (dl-lactide-co-glycolide)-block-poly (ethylene glycol) nanocarrier loaded with naringenin. Biquarterly Iranian J Anal Chem. 2015;3(1):38-41.
159. Firouzabadi K, Karimi E, Tabrizi MH. Fabrication of bovine serum albumin-polyethylene glycol nanoparticle conjugated-folic acid loaded-naringenin as an efficient carrier biomacromolecule for suppression of cancer cells. Biotechnol App Biochem. 2023;70(2):790-7. doi:10.1002/bab.2399
160. Pham J, Brownlow B, Elbayoumi T. Mitochondria-specific pro-apoptotic activity of genistein lipidic nanocarriers. Mol Pharm. 2013;10(10):3789-800. doi:10.1021/mp4004892
161. Wu B, Liang Y, Tan Y, Xie C, Shen J, Zhang M, et al. Genistein-loaded nanoparticles of star-shaped diblock copolymer mannitol-core PLGA–TPGS for the treatment of liver cancer. Mater Sci Eng C Mater Biol Appl. 2016;59:792-800. doi:10.1016/j.msec.2015.10.087
162. Phan V, Walters J, Brownlow B, Elbayoumi T. Enhanced cytotoxicity of optimized liposomal genistein via specific induction of apoptosis in breast, ovarian and prostate carcinomas. J Drug Target. 2013;21(10):1001-11. doi:10.3109/1061186X.2013.847099
163. Zampieri AL, Ferreira FS, Resende EC, Gaeti MP, Diniz DG, Taveira SF, et al. Biodegradable polymeric nanocapsules based on poly(dl-lactide) for genistein topical delivery: Obtention, characterization and skin permeation studies. J Biomed Nanotechnol. 2013;9(3):527-34. doi:10.1166/jbn.2013.1555
164. Ghosh P, Bag S, Roy AS, Subramani E, Chaudhury K, Dasgupta S. Solubility enhancement of morin and epicatechin through encapsulation in an albumin based nanoparticulate system and their anticancer activity against the MDA-MB-468 breast cancer cell line. RSC Adv. 2016;6(103):101415-29. doi:10.1039/C6RA20441D
165. Palei NN, Mounika G, Mohanta BC, Rajangam J. Quercetin and morin dual drug loaded nanostructured lipid carriers: Formulation and in vitro cytotoxicity study on mcf7 breast cancer cells. J Dispers Sci Technol. 2023. doi:10.1080/01932691.2023.2248261
166. Sun M, Nie S, Pan X, Zhang R, Fan Z, Wang S. Quercetin-nanostructured lipid carriers: Characteristics and anti-breast cancer activities in vitro. Colloids Surf B Biointerfaces. 2014;113:15-24. doi:10.1016/j.colsurfb.2013.08.032
167. Zhou X, Liu HY, Zhao H, Wang T. Rgd-modified nanoliposomes containing quercetin for lung cancer targeted treatment. Onco Targets Ther. 2018;11:5397-405. doi:10.2147/OTT.S169555
168. Ganthala PD, Alavala S, Chella N, Andugulapati SB, Bathini NB, Sistla R. Co-encapsulated nanoparticles of Erlotinib and Quercetin for targeting lung cancer through nuclear EGFR and PI3K/AKT inhibition. Colloids Surf B: Biointerfaces. 2022;211:112305. doi:10.1016/j.colsurfb.2021.112305
169. Keshavarz F, Dorfaki M, Bardania H, Khosravani F, Nazari P, Ghalamfarsa G. Quercetin-loaded liposomes effectively induced apoptosis and decreased the epidermal growth factor receptor expression in colorectal cancer cells: An in vitro study. Iranian J Med Sci. 2023;48(3):321-8. doi:10.30476/IJMS.2022.95272.2658
170. Zhu R, Wu X, Xiao Y, Gao B, Xie Q, Liu H, et al. Synergetic Effect of SLN-Curcumin and LDH-5-Fu on SMMC-7721 Liver Cancer Cell Line. Cancer Biother Radiopharm. 2013;28(8):579-87. doi:10.1089/cbr.2012.1445
171. Alam J, Dilnawaz F, Sahoo SK, Singh DV, Mukhopadhyay AK, Hussain T, et al. Curcumin encapsulated into biocompatible co-polymer plga nanoparticle enhanced anti-gastric cancer and anti-helicobacter pylori effect. Asian Pac J Cancer Prev. 2022;23(1):61-70. doi:10.31557/APJCP.2022.23.1.61
172. Elnawasany S, Haggag YA, Shalaby SM, Soliman NA, El Saadany AA, Ibrahim MAA, et al. Anti-cancer effect of nano-encapsulated boswellic acids, curcumin and naringenin against hepg-2 cell line. BMC Complement Med Ther. 2023;23(1):270. doi:10.1186/s12906-023-04096-4
173. Zoghi M, Pourmadadi M, Yazdian F, Nigjeh MN, Rashedi H, Sahraeian R. Synthesis and characterization of chitosan/carbon quantum dots/

fe2o3 nanocomposite comprising curcumin for targeted drug delivery in breast cancer therapy. Int J Biolog Macromol. 2023;249:125788. doi:10.1016/j.ijbiomac.2023.125788

174. Ma X, Zhou J, Zhang CX, Li XY, Li N, Ju RJ, et al. Modulation of drug-resistant membrane and apoptosis proteins of breast cancer stem cells by targeting berberine liposomes. Biomaterials. 2013;34(18):4452-65. doi:10.1016/j.biomaterials.2013.02.066
175. Foudah AI, Alam A, Salkini MA, Ross SA, Kumar P, Aldawsari MF, et al. Synergistic combination of letrozole and berberine in ascorbic acid-stabilized aunps: A promising solution for breast cancer. Pharmaceuticals (Basel). 2023;16(8):1099. doi:10.3390/ph16081099
176. Malyla V, De Rubis G, Paudel KR, Chellappan DK, Hansbro NG, Hansbro PM, et al. Berberine nanostructures attenuate ß-catenin, a key component of epithelial mesenchymal transition in lung adenocarcinoma. Naunyn-Schmiedeberg's Archives Pharmacol. 2023;396(12):3595-603. doi:10.1007/s00210-023-02553-y
177. Gumireddy A, Christman R, Kumari D, Tiwari A, North EJ, Chauhan H. Preparation, characterization, and in vitro evaluation of curcumin- and resveratrol-loaded solid lipid nanoparticles. AAPS PharmSciTech. 2019;20(4):145. doi:10.1208/s12249-019-1349-4
178. Wu M, Lian B, Deng Y, Feng Z, Zhong C, Wu W, et al. Resveratrol-loaded glycyrrhizic acid-conjugated human serum albumin nanoparticles wrapping resveratrol nanoparticles: Preparation, characterization, and targeting effect on liver tumors. J Biomater Appl. 2017;32(2):191-205. doi:10.1177/0885328217713357
179. Narayanan NK, Nargi D, Randolph C, Narayanan BA. Liposome encapsulation of curcumin and resveratrol in combination reduces prostate cancer incidence in pten knockout mice. Int J Cancer. 2009;125(1):1-8. doi:10.1002/ijc.24336
180. Saralkar P, Dash AK. Alginate nanoparticles containing curcumin and resveratrol: Preparation, characterization, and in vitro evaluation against du145 prostate cancer cell line. AAPS PharmSciTech. 2017;18(7):2814-23. doi:10.1208/s12249-017-0772-7
181. Liu Y, He M, Niu M, Zhao Y, Zhu Y, Li Z, et al. Delivery of vincristine sulfate-conjugated gold nanoparticles using liposomes: A light-responsive nanocarrier with enhanced antitumor efficiency. Int J Nanomedicine. 2015;10:3081-95. doi:10.2147/IJN.S79550
182. Dong X, Wang W, Qu H, Han D, Zheng J, Sun G. Targeted delivery of doxorubicin and vincristine to lymph cancer: Evaluation of novel nanostructured lipid carriers in vitro and in vivo. Drug Deliv. 2016;23(4):1374-8. doi:10.3109/10717544.2015.1041580
183. Adiseshaiah PP, Clogston JD, McLeland CB, Rodriguez J, Potter TM, Neun BW, et al. Synergistic combination therapy with nanoliposomal c6-ceramide and vinblastine is associated with autophagy dysfunction in hepatocarcinoma and colorectal cancer models. Cancer Lett. 2013;337(2):254-65. doi:10.1016/j.canlet.2013.04.034
184. Bahadori F, Topcu G, Eroglu MS, Onyuksel H. A new lipid-based nano formulation of vinorelbine. AAPS PharmSciTech. 2014;15(5):1138-48. doi:10.1208/s12249-014-0146-3
185. Wu CH, Lan CH, Wu KL, Wu YM, Jane WN, Hsiao M, et al. Hepatocellular carcinoma-targeted nanoparticles for cancer therapy. Int J Oncol. 2018;52(2):389-401. doi:10.3892/ijo.2017.4205
186. Li L, Tang F, Liu H, Liu T, Hao N, Chen D, et al. In vivo delivery of silica nanorattle encapsulated docetaxel for liver cancer therapy with low toxicity and high efficacy. ACS Nano. 2010;4(11):6874-82. doi:10.1021/nn100918a
187. Xu P, Meng Q, Sun H, Yin Q, Yu H, Zhang Z, et al. Shrapnel nanoparticles loading docetaxel inhibit metastasis and growth of breast cancer. Biomaterials. 2015;64:10-20. doi:10.1016/j.biomaterials.2015.06.017
188. Grover A, Hirani A, Pathak Y, Sutariya V. Brain-targeted delivery of docetaxel by glutathione-coated nanoparticles for brain cancer. AAPS PharmSciTech. 2014;15(6):1562-8. doi:10.1208/s12249-014-0165-0
189. Patil KS, Hajare AA, Manjappa AS, Dol HS. Vacuum foam drying of docetaxel mixed micelles for improved stability and ovarian cancer treatment. J Drug Del Sci Technol. 2023;86:104747. doi:10.1016/j.jddst.2023.104747
190. Liu Y, Ng Y, Toh MR, Chiu GN. Lipid-dendrimer hybrid nanosystem as a novel delivery system for paclitaxel to treat ovarian cancer. J Control Release. 2015;220:438-46. doi:10.1016/j.jconrel.2015.11.004
191. Mund R, Panda N, Nimesh S, Biswas A. Novel titanium oxide nanoparticles for effective delivery of paclitaxel to human breast cancer cells. J Nanopart Res. 2014;16(12):2739. doi: 10.1007/s11051-0142739-x
192. Wang Y, Zhang H, Hao J, Li B, Li M, Xiuwen W. Lung cancer combination therapy: Co-delivery of paclitaxel and doxorubicin by nanostructured lipid carriers for synergistic effect. Drug Deliv. 2016;23(4):1398-403. doi:10.3109/10717544.2015.1055619
193. De Grandis RA, Santos P, Oliveira KM, Machado ART, Aissa AF, Batista AA, et al. Novel lawsone-containing ruthenium(ii) complexes: Synthesis, characterization and anticancer activity on 2d and 3d spheroid models of prostate cancer cells. Bioorg Chem. 2019;85:455-68. doi:10.1016/j.bioorg.2019.02.010
194. Naeeni NB, Tabrizi MH, Karimi E, Ghafaripour H. Synthesis and characterization of liposomal nanoparticles coated with chitosan–folate for efficient delivery of lawsone to pancreatic cancer cells. Polym Bull. 2023. doi:10.1007/s00289-023-04860-z
195. Friedman JM, Navati MS, Friedman AJ, Nacharaju P, Krausz A. United States patent US20170119814A1.

2015.
196. Lillard Jr JW, Singh S, Singh R. United States patent US20130045162A1. 2012.
197. Xu P. United States patent US20210369861A1. 2021.
198. Liu L. United States patent US10301303B2. 2015.
199. Markovic LE, Scansen BA, Ames MK, Coleman AE. Transcatheter closure of patent ductus arteriosus in 11 dogs and one cat after incomplete or aborted surgical ligation. J Vet Cardiol. 2022;41:1-10. doi:10.1016/j.jvc.2021.12.001.
200. Markovic SN, Nevala WK. United States patent US10376579B2. 2013.
201. Wright J. WIPO patent. WO2014210485A1. 2014.
202. Zhengxing SU, Likai YANG., Zhao D, Zhou J, Fengying SHAN, Wang L, et al. United States patent US10493054B2.2015.
203. Li YP Chen LL, Gu WW. Long-circulating solid lipid docetaxel nanoparticles and preparation method thereof. Chinese patent CN101653414B. 2008.
204. Singhal GB, Patel RP, Prajapati B, Patel NA. Solid lipid nanoparticles and nano lipid carriers: As novel solid lipid based drug carrier. Int Res J Pharm 2011;2(2):20-52.
205. 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
206. Jang DJ, Moon C, Oh E. Improved tumor targeting and antitumor activity of camptothecin loaded solid lipid nanoparticles by preinjection of blank solid lipid nanoparticles. Biomed Pharmacother. 2016;80:162-72. doi:10.1016/j.biopha.2016.03.018
207. Ghanbari N, Salehi Z, Khodadadi AA, Shokrgozar MA, Saboury AA. Glucosamine-conjugated graphene quantum dots as versatile and ph-sensitive nanocarriers for enhanced delivery of curcumin targeting to breast cancer. Mater Sci Eng C Mater Biol Appl. 2021;121:111809. doi:10.1016/j.msec.2020.111809
208. Gupta L, Sharma AK, Gothwal A, Khan MS, Khinchi MP, Qayum A, et al. Dendrimer encapsulated and conjugated delivery of berberine: A novel approach mitigating toxicity and improving in vivo pharmacokinetics. Int J Pharm. 2017;528(1-2):88-99. doi:10.1016/j.ijpharm.2017.04.073
209. Mozafari MR, Pardakhty A, Azarmi S, Jazayeri JA, Nokhodchi A, Omri A. Role of nanocarrier systems in cancer nanotherapy. J Liposome Res. 2009;19(4):310-21. doi:10.3109/08982100902913204
210. Allen TM, Cullis PR. Liposomal drug delivery systems: From concept to clinical applications. Adv Drug Deliv Rev. 2013;65(1):36-48. doi:10.1016/j.addr.2012.09.037
211. Tian J, Wang L, Wang L, Ke X. A wogonin-loaded glycyrrhetinic acid-modified liposome for hepatic targeting with anti-tumor effects. Drug Deliv. 2014;21(7):553-9. doi:10.3109/10717544.2013.853850
212. Zheng S, Chang S, Lu J, Chen Z, Xie L, Nie Y, et al. Characterization of 9-nitrocamptothecin liposomes: Anticancer properties and mechanisms on hepatocellular carcinoma in vitro and in vivo. PLoS One. 2011;6(6):e21064. doi:10.1371/journal.pone.0021064
213. Barani M, Nematollahi MH, Zaboli M, Mirzaei M, Torkzadeh-Mahani M, Pardakhty A, et al. In silico and in vitro study of magnetic niosomes for gene delivery: The effect of ergosterol and cholesterol. Mater Sci Eng C Mater Biol Appl. 2019;94:234-46. doi:10.1016/j.msec.2018.09.026
214. Zamboni WC. Liposomal, nanoparticle, and conjugated formulations of anticancer agents. Clin Cancer Res. 2005;11(23):8230-4. doi:10.1158/1078-0432.CCR-05-1895
215. Lasic DD. Liposomes in gene delivery. Boca Raton: CRC press; 1997.
216. Shaw IH, Knight CG, Dingle JT. Liposomal retention of a modified anti-inflammatory steroid. Biochem J. 1976;158(2):473-6. doi:10.1042/bj1580473
217. Ghadi ZS, Dinarvand R, Asemi N, Amiri FT, Ebrahimnejad P. Preparation, characterization and in vivo evaluation of novel hyaluronan containing niosomes tailored by box-behnken design to co-encapsulate curcumin and quercetin. Eur J Pharm Sci. 2019;130:234-46. doi:10.1016/j.ejps.2019.01.035
218. Sadeghi Ghadi Z, Ebrahimnejad P. Curcumin entrapped hyaluronan containing niosomes: Preparation, characterisation and in vitro/in vivo evaluation. J Microencapsul. 2019;36(2):169-79. doi:10.1080/02652048.2019.1617360
219. Hemati M, Haghiralsadat F, Yazdian F, Jafari F, Moradi A, Malekpour-Dehkordi Z. Development and characterization of a novel cationic pegylated niosome-encapsulated forms of doxorubicin, quercetin and sirna for the treatment of cancer by using combination therapy. Artif Cells Nanomed Biotechnol. 2019;47(1):1295-311. doi:10.1080/21691401.2018.1489271
220. Jain N, Gupta BP, Thakur N, Jain R, Banweer J, Jain DK, et al. Phytosome: A novel drug delivery system for herbal medicine. Int J Pharm Sci Drug Res. 2010;2(4):224-8.
221. Marjaneh RM, Rahmani F, Hassanian SM, Rezaei N, Hashemzehi M, Bahrami A, et al. Phytosomal curcumin inhibits tumor growth in colitis-associated colorectal cancer. J Cell Physiol. 2018;233(10):6785-98. doi:10.1002/jcp.26538
222. Ma P, Mumper RJ. Paclitaxel nano-delivery systems: A comprehensive review. J Nanomed Nanotechnol. 2013;4(2):1000164. doi:10.4172/2157-7439.1000164
223. Debnath S, Swetha D, Babu MN. Green synthesis of nanoparticles using herbal extract. In: Sen S, Chakraborty R, editors. Herbal medicine in India. Singapore: Springer; 2020. doi:10.1007/978-981-13-7248-3_14.
224. Chandrasekaran R, Yadav SA, Sivaperumal S. Phytosynthesis and characterization of copper oxide

nanoparticles using the aqueous extract of beta vulgaris l and evaluation of their antibacterial and anticancer activities. J Cluster Sci. 2020;31(1):221-30. doi:10.1007/s10876-019-01640-6
225. Kudr J, Haddad Y, Richtera L, Heger Z, Cernak M, Adam V, et al. Magnetic nanoparticles: From design and synthesis to real world applications. Nanomaterials (Basel). 2017;7(9):243. doi:10.3390/nano7090243
226. Lou M, Zhang LN, Ji PG, Feng FQ, Liu JH, Yang C, et al. Quercetin nanoparticles induced autophagy and apoptosis through AKT/ERK/Caspase-3 signaling pathway in human neuroglioma cells: In vitro and in vivo. Biomed Pharmacother. 2016;84:1-9. doi:10.1016/j.biopha.2016.08.055
227. Tong W, Wang L, D'Souza MJ. Evaluation of PLGA microspheres as delivery system for antitumor agent-camptothecin. Drug Dev Ind Pharm. 2003;29(7):745-56. doi:10.1081/ddc-120021774
228. Dai M, Xu X, Song J, Fu S, Gou M, Luo F, et al. Preparation of camptothecin-loaded pcec microspheres for the treatment of colorectal peritoneal carcinomatosis and tumor growth in mice. Cancer Lett. 2011;312(2):189-96. doi:10.1016/j.canlet.2011.08.007
229. Sobhani H, Tarighi P, Ostad SN, Shafaati A, Nafissi-Varcheh N, Aboofazeli R. Formulation development and toxicity assessment of triacetin mediated nanoemulsions as novel delivery systems for rapamycin. Iranian J Pharm Res. 2015;14(Suppl): 3-21.
230. Ahmad U, Akhtar J, Singh SP, Ahmad FJ, Siddiqui S. Silymarin nanoemulsion against human hepatocellular carcinoma: Development and optimization. Artif Cells Nanomed Biotechnol. 2018;46(2):231-41. doi:10.1080/21691401.2017.1324465
231. Jahangir MA, Muheem A, Anand C, Imam SS. Recent advancements in transdermal drug delivery system. Pharmaceutical drug product development and process optimization. In: Beg S, Al Robaian M, Rahman M, Imam SS, Alruwaili N, Panda KS. New York: Apple Academic Press; 2020.
232. Jangdey MS, Gupta A, Saraf S, Saraf S. Development and optimization of apigenin-loaded transfersomal system for skin cancer delivery: In vitro evaluation. Artif Cells Nanomed Biotechnol. 2017;45(7):1452-62. doi:10.1080/21691401.2016.1247850
233. Ainbinder D, Paolino D, Fresta M, Touitou E. Drug delivery applications with ethosomes. J Biomed Nanotechnol. 2010;6(5):558-68. doi:10.1166/jbn.2010.1152
234. Eskolaky EB, Ardjmand M, Akbarzadeh A. Evaluation of anti-cancer properties of pegylated ethosomal paclitaxel on human melanoma cell line SKMEL-3. Tropical J Pharm Res. 2015;14(8):1421-5.
235. Paolino D, Celia C, Trapasso E, Cilurzo F, Fresta M. Paclitaxel-loaded ethosomes®: Potential treatment of squamous cell carcinoma, a malignant transformation of actinic keratoses. Eur J Pharm Biopharm. 2012;81(1):102-12. doi:10.1016/j.ejpb.2012.02.008
236. Kothamasu P, Kanumur H, Ravur N, Maddu C, Parasuramrajam R, Thangavel S. Nanocapsules: The weapons for novel drug delivery systems. BioImpacts. 2012;2(2):71-81. doi:10.5681/bi.2012.011
237. Song XQ, Tao C, Li W, Wang JX, Le Y, Zhang JJ. Preparation of reduction-responsive camptothecin nanocapsules by combining nanoprecipitation and in situ polymerization for anticancer therapy. Pharmaceutics. 2018;10(4):173. doi:10.3390/pharmaceutics10040173
238. Guo N, Hao T, Shang X, Zhang T, Liu H, Zhang Q, et al. Novel amphiphilic PEG-hydroxycamptothecin conjugates as glutathione-responsive prodrug nanocapsules for cancer chemotherapy. J Nanoparticle Res. 2017;19(6):205. doi:10.1007/s11051-017-3897-4
239. Abdollahi A, Malek-Khatabi A, Razavi MS, Sheikhi M, Abbaspour K, Rezagholi Z, et al. The recent advancement in the chitosan-based thermosensitive hydrogel for tissue regeneration. J Drug Del Sci Technol. 2023;86:104627. doi:10.1016/j.jddst.2023.104627
240. Alavi M, Nokhodchi A. An overview on antimicrobial and wound healing properties of zno nanobiofilms, hydrogels, and bionanocomposites based on cellulose, chitosan, and alginate polymers. Carbohydr Polym. 2020;227:115349. doi:10.1016/j.carbpol.2019.115349
241. Wang H, Yang Z. Molecular hydrogels of hydrophobic compounds: A novel self-delivery system for anti-cancer drugs. Soft Mater 2012;8(8):2344-7. doi:10.1039/C2SM06923G
242. Nazlı AB, Açıkel YS. Loading of cancer drug resveratrol to pH-sensitive, smart, alginate-chitosan hydrogels and investigation of controlled release kinetics. J Drug Del Sci Technol. 2019;53:101199. doi:10.1016/j.jddst.2019.101199
243. Teong B, Lin CY, Chang SJ, Niu GC, Yao CH, Chen IF, et al. Enhanced anti-cancer activity by curcumin-loaded hydrogel nanoparticle derived aggregates on a549 lung adenocarcinoma cells. J Mater Sci Mater Med. 2015;26(1):5357. doi:10.1007/s10856-014-5357-3