Novel Drug Delivery In Cancer Treatment

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Abstract:

Delivery of drugs using nanoparticles systems are revolutionizing cancer treatment by addressing the limitations of traditional treatment methods.NDDS utilize various nanoscale carriers, including microsphere,liposomes,phytosomes,and ethosomes,microemulsion, solid lipid nanoparticle to improve the efficacy & security of anticancer representatives. Collectively, these nanoparticle systems enable targeted delivery, controlled release,and enhanced therapeutic effects, representing a significant advancement in personalized cancer treatment.Ongoing research into these innovative carriers is essential for further improving their performance and clinical applications in oncology. Nanoparticle drug delivery systems (NDDS) are transforming cancer treatment by improving the specificity as well as effectiveness of chemotherapeutic agents.The combination of these advanced delivery systems with conventional therapies has the capacity to get better clinical results and reduce adverse effects in individuals with cancer. The integration of nanoparticle mechanisms for delivering drugs (NDDS) in cancer treatment has created new opportunities for targeted and effective treatment.

Keywords:nanoparticle,microsphere,liposomes,phytosomes,ethosomes,microemulsion,solid lipid nanoparticles,targeted delivery.

Introduction:

As the other greatest cause of death globally and among the most prevalent reasons for illness and mortality, Cancer is a severe public health concern. concern.In the 2015, it was the cause of 8.8 million fatalities. About 70% of fatalities attributed to cancer take place in middle-class and low-income nations. By 2030, there will likely be 21.6 million new cases yearly, up from 14.1 million in 2012. Cancer also has a significant financial impact; in 2010, it was estimated that the disease will cost the US economy $1.16 trillion annually. Thus, cancer can devastate individuals and families and pose a threat to economies at all socioeconomic levels.[1]

In recent years, there has been a rise in interest in the subject use of the delivery of various anti-cancer drugs via nanocarriers medications due to its precise targeting, enhanced therapeutic effectiveness, less systemic poisoning, cells absorption, and growth inside the tumor. Its effect known as enhanced permeability and retention (EPR) particularly noteworthy within this regard.[2] In the meanwhile, disease monitoring, biomedical imaging, and cancer detection all employ nanotechnology.[3] Chemotherapy for cancer patients usually has harmful adverse consequences, that restricts the quantity of the medication that may given to the patient. Consequently, the medicine may not reach a deadly dose in all of the tumor tissue.The pharmacological characteristics of conventional chemotherapeutics can be enhanced by the introduction of nanocarriers such liposomes and micelles.[4]Patients with cancer may not receive as much medication during chemotherapy because of the often dangerous side effects. Consequently, not every piece of tumor tissue could receive a lethal dose of the medication. By adding nanocarriers such liposomes and micelles, traditional chemotherapeutics'

pharmacological properties can be improved.Because they have such enormous potential in the area of medication delivery, in recent decades, a lot of study has been conducted on nanocarriers.Due of their high volume to surface area ratio ratio,nanocarriers have the ability to alter a drug's basic properties and bioactivity.Improved pharmacokinetics and biodistribution, decreased toxicities, improved solubility and stability, controlled release, and site-specific administration of pharmaceutical agents are all possible with nanocarriers in drug delivery systems.[5,6]

Anticancer medications should ideally be able to pass through the body's barriers they arrive at the targeted tissues of tumors with the least amount volume loss or blood circulation actions possible after being administered.Second, medications should be able to destroy cancerous cells only although avoiding normal cells once they have reached the intended location. Because these two fundamental strategies concurrently decrease dose-limiting toxicities and increase drug intracellular concentration, they are also linked to increases in patient longevity and quality of life. Nanoparticles appear to have the capacity to meet both of these needs for efficient systems for delivering drugs more and more.[7] One of the important novel drug delivery techniques is the use of nanoparticles. Innovative formulations of nanoparticles, such as liposomes, solid-lipid nanoparticles, microemulsions, ethosomes, and polymeric nanoparticles with herbal molecules, can be used to effectively deliver herbal medicines. These formulations can improve therapeutic effect, selectivity, effectiveness, and drug bioavailability at the target site, which lowers the frequency of dosing and, consequently, healthcare costs.One of the important novel drug delivery techniques is the use of nanoparticles.Innovative formulations of various nanoparticles, including polymeric nanoparticles containing herbal compounds, ethosomes, microemulsions, liposomes, and solid-lipid nanoparticles, can be used to effectively deliver herbal medicines.These formulations can improve efficacy, selectivity, and therapeutic impact, and drug bioavailability at the target location, that lowers the regularity of dosing and, consequently, healthcare costs.[8]

A lot of emphasis been paid throughout the previous few decades to the development of innovative drug delivery systems (NDDS) for medicines made from herbs. Two requirements should preferably be met by the innovative carriers. First, over the course of therapy, it should administer the medication at a pace based on the body's requirements. Secondly, it ought to take the herbal medicine's active component to the area of action.Conventional dose forms, including prolonged-release dosage forms, cannot satisfy any of these.Conventional dose forms, including prolonged-release dosage forms, cannot satisfy any of these.Developing nanodosage forms (polymeric nanoparticles and nanocapsules, liposomes, solid lipid nanoparticles, phytosomes and nanoemulsion, etc.) has several benefits of herbal medications in phyto-formulation research, including enhanced dispersion and sustained administration of tissue macrophages, protection from deterioration both chemical and physical, enhanced bioavailability and solubility, as well as toxicity prevention, enhanced pharmaceutical action, enhanced consistency, etc.[9]

Innovative drug delivery involves either changing the drug's molecular structure or integrating it into a carrier system to regulate its dispersion. The new drug delivery system allows for increased bioavailability, stability, better solubility, protection against toxicity, sustained distribution, and protection against physical and chemical degradation.[10]

Nanocarriers

The pharmacological qualities of conventional chemotherapeutics can be enhanced by the application of nanocarriers. Considering their little structure (less than 100 nm), they can easily spread from circulation through vascular abnormalities that are frequently seen at tumor locations as a result of continuing angiogenesis[11] where encapsulated cytotoxic medicines can be administered to the tissue of tumors. This, along with the fact that lymphatic drainage is typically inadequate at tumor locations, produces an effect known as the increased effect of permeability and retention (EPR), which contributes to their therapeutic efficacy.[12,13] When administered using traditional drug delivery methods, cancer-fighting chemotherapy pose a variety of particular challenges, like low selectivity, excessive toxicities and the emergence of medication resistance.[14] A lot of anticancer drugs lose some of their healing effectiveness as a result of these barriers. By taking advantage of the pathophysiology of the tumor microenvironment, Platforms based on nanocarriers have enabled the delivery of anticancer drugs into tumors efficiently, greatly improving the therapeutic outcomes for cancer disorders.[15] Moreover, systems for nanocarriers embellished with targeting ligands also been applied to the overexpressed receptors superficially of tumor cell.Many medicines predicated on nanocarrier technology obtained approval to treat different types of cancers, and numerous others are going through different phases of clinical studies.[16]

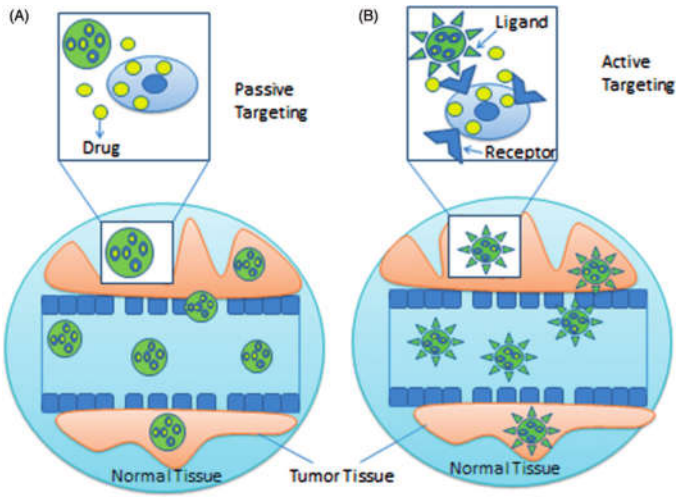

Diagram 1. Diagram illustrating the various ways that medications can be delivered by nanocarriers to tumours. (A) Tissue targeting via passive means and (B) active targeting of cells.

Active targeting

Active tumor targeting is used to overcome multiple drug resistance, avoid passive tumor targeting's drawbacks, and lessen the amount of chemotherapeutic medicines that are delivered off-target.[17] The efficient use of the active targeting technique requires that the selected targeting moiety only bind to a receptor that is overexpressed by tumor cells.The intended target receptor needs to be consistently expressed in every target cell.Active targeting's

objective is to target either the tumor cells or the tumor vasculature and microenvironment with a ligand-adorned nanocarrier.[18]

Both of these cellular targets have received a lot of attention recently in the field of active targeting in an effort to lessen the side effects and increase the effectiveness of chemotherapy drugs. By using ligand-anchored nanocarriers to target overexpressed cell surface receptors through ligand-receptor interactions, tumor cells can be actively targeted.[19]

Passive targeting

Because blood carrying tumors arteries are naturally leaky, the nanocarriers can readily pass through the endothelium barrier and enter the interstitial space. The size of the tumor's endothelial cell linings vary depending on the type of tumor and can reach up to 700 nm, which is 50–70 times larger than the normal and characteristic endothelium (up to 10 nm).[20] Moreover, the lymphatic drainage system of solid tumors is often weak, which results in an inadequate circulatory repossession of the extravasated molecules and the aggregation of nanocarriers at the tumor site. We refer to this as the EPR effect[21],It is thought to be an excellent method for successfully targeting tumors. However, due to the diffusion phenomena, nanocarriers with low molecular weight medications rejoin the bloodstream and are unable to remain at the tumor site for an extended amount of time.

These medications' "passive targeting" effect is entirely dependent on the pathophysiological and immunochemical features of the tumor tissues."[21] Using the EPR effect, the usage of nanocarriers not only improves the targeting of tumor cells but also increases the systemic circulation of medications.[22] Drugs are retained for extended periods of time using a variety of methods, such as pH-dependent and polymeric-based nanocarrier systems. Furthermore, the unique and different microenvironment surrounding tumor cells compared to normal cells plays a role in passive targeting.[23]

On their path to the target, nanocarriers encounter a variety of obstacles, including mucosal barriers and non-specific uptake.[24] It is crucial to integrate a basic understanding of tumor biology with the logical design of nanocarriers in order to report on the difficulties associated with using nanotechnology to target tumors. Leaky blood arteries and poor lymphatic drainage are two common characteristics of tumors. The enhanced permeability and retention effect (EPR effect) allows a nanocarrier to enter tumor tissues through leaky arteries, while free medicines may diffuse non-specifically.[25] Increased permeability of blood vessels in tumor cells is caused by angiogenesis, which is the fast and abnormal creation of new blood vessels from preexisting ones.[26]

Novel drug delivery in cancer treatment

Liposomes:

Since their initial approval in 1965, liposomes have been regarded as a key component of sophisticated drug delivery systems. The encapsulation of pharmaceuticals that exhibit reduced toxicity, biodegradability, targeted drug delivery, and enhanced pharmacokinetics effect is one of the many characteristics of liposomes' significance. [27] Liposomes are lipid carriers at the nanoscale that are created when phospholipid molecules self-assemble in an aqueous solution. Because liposomes are composed of lipids, their effectiveness is diminished by the liver's quick absorption of the particles and the uptake by macrophages. This can be prevented by adding ligands like monosialoganglioside to the lipid surface of liposomes, or by adding phospholipids like distearoylphosphatidylcholine (DSPC), cholesterol, polyvinylpyrrolidone polyacrylamide lipids, glucuronic acid lipids, or polyvinylpyrrolidone to liposomes to lengthen their half-lives in the body. Stealth liposomes are those that have been coated with monosialoganglioside. These liposomes are approximately 100 nm in size.[28] A phospholipid bilayer envelops the interior aqueous core of liposomes, which is utilized for medication encapsulation. When it comes to the biocompatibility of these nanocarriers, using phospholipids is optimal. The phospholipid bilayer enables the encapsulation of hydrophobic chemotherapy agents, whereas the interior aqueous core is ideal for the administration of hydrophilic medications.[29]

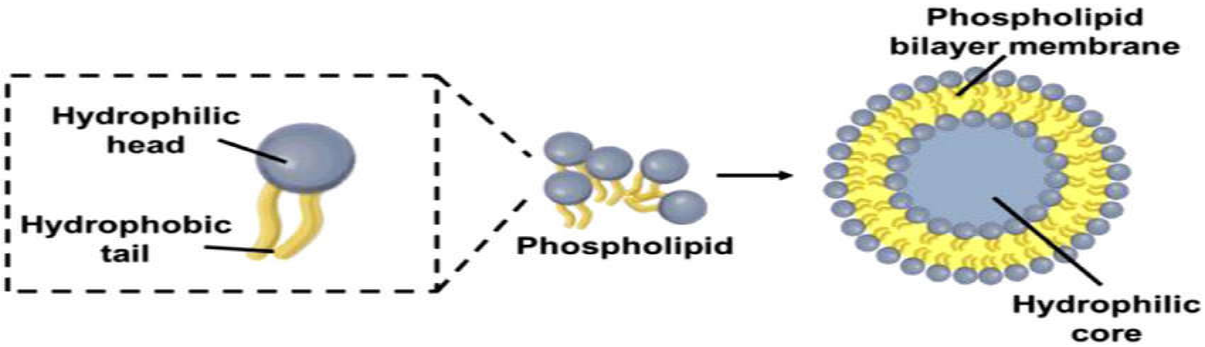

Figure 2.The basic structure of liposome.

Antitumor medications typically cause substantial side effects, which has limited their clinical use. Liposomes have been extensively utilized and researched in tumors due to their remarkable qualities, which allow them to be an excellent medication carrier in the field of tumor therapy.

Many liposome-based pharmacological preparations have been successfully converted into clinical applications in recent years due to the rapid advancement of liposome technology, and numerous liposome medicines are currently undergoing clinical trials.[30] Doxil®, the first liposome medication, was introduced to the US market in 1995 to treat patients with AIDS-related Kaposi's sarcoma and ovarian cancer31. NeXstar Pharmaceuticals then created DaunoXome® to administer daunomycin. Later, an increasing number of liposome products, including Mepact®, Marqibo®, Depocyt®, and Vyxeos®, were created and used in therapeutic settings.[32]

Table 1.Herbal formulations based on liposomal drug delivery systems.

Sr. no	Plant/constituent used	Derived from plant	Biological activity	Application of technology	Ref
1	Ampelopsin	Ampelopsis species grossedentata, megalophylla, and japonica	anticancer enhanced treatment	enhanced results from therapy	[33]
2	*Atractylodes macrocephaa* roots	Sunflower family member *Atractylodes macrocephala*	Intestinal problems and anticancer drugs	Improvement of bioavailability and solubility	[34]
3	Curcumin	Curry powder (*Curcuma longa*)	anti-tumor	Entrapment efficiency is great and the systemic residence period is long.	[35]
4	Nux Vomica	Neptune nux-vomica	anti-neoplastic	Enhanced steadiness	[36]
5	Paclitaxel	sourced from the Pacific yew tree's (Taxus brevifolia) bark	anti-tumor	pH sensitivity and increased entrapment effectiveness	[37]
6	Triptolide	Skinned *Tripterygium wilfordi* root	anti-tumor	Enhanced steadiness	[38]
7	Wogonin	*Scutellaria baicalensis Georgi*	anti-tumor	extended period of time	[39]

Generally speaking, it is essential that a targeting agent binds to molecules that are specifically expressed on the surface of cancer cells with high selectivity in order to deliver nanocarriers to these cells via targeting. Below is a list of additional crucial factors. A surface marker, such as an antigen or receptor, should be overexpressed on target cells in comparison to normal cells in order to maximize specificity.[40] Liposomes have the innate capacity to specifically target cancer. Endothelial cells, connected by tight junctions, enclose the endothelial walls of all healthy human blood arteries.These tight connections aid in preventing the big blood particle from seeping out of the channel. Tumor vessels lack this kind of organization, making them

diagnostically "leaky." This capacity is called improved retention and permeability impact. Liposomes smaller than 400 nm have the ability to infiltrate tumor locations quickly from blood, while in healthy tissue, the endothelium wall keeps the liposomes in the bloodstream.[41,42,43] Because liposomes increase selectivity for cancer cells, they can lessen the adverse effects of cancer therapy approaches that are not selective. This makes liposomes a promising drug delivery mechanism for cancer treatment. It can encourage cancer cells to be passively targeted. Larger molecules can enter tumor-specific cells because of their increased permeability and retention effect. Because of this property, liposomes containing anticancer medications can enter cancer cells, but they cannot enter healthy cells because of endothelial walls. This causes the drug-loaded liposomes to selectively target tumor cells rather than healthy cells; this characteristic is known as passive targeting.[44]

Advantages of liposomes include,

- Increased Solubility.
- Non-destructive.
- Enhanced Absorbency.
- Sustained delivery.
- Improved Steadiness.
- Increasing Bioavailability.
- Exceptionally biocompatible.

Phytosomes:

Phytosomes are a sophisticated type of herbal preparation that resemble tiny cells. It is composed of phosphotydicholine-containing lipid bilayer that envelops bioactive phytoconstituents of herbal extract. Because of the chemical link between the phosphatidylcholine molecules and the phytoconstituents, phytosomes have a superior stability profile. Bioactive phytoconstituents, which include terpenoids, glycosides, and flavonoids (the main type), have a variety of therapeutic applications.[45] Because phosphotydylcholine has gastro-protective qualities, it prevents plant extracts—drugs—from being destroyed in the gastrointestinal tract. As a result, these extracts have better pharmacokinetic and pharmacodynamic profiles and higher bioavailability than traditional herbal extracts. It is capable of carrying both hydrophilic and lipophilic drug domains. Since flavonoids have anti-inflammatory, anti-allergic, antiviral, and anti-cancer qualities, they are sometimes referred to as nature's biological response modifiers. Flavonoids are a significant and important class of phytochemicals.[46] This phytosome technology is a game-changer for markedly improved bioavailability, far greater therapeutic value, guaranteed tissue delivery, and nutritional safety without sacrificing any of these other benefits.[47] Their enhanced pharmacokinetic and pharmacological characteristics are beneficial not only for treating acute illnesses but also for pharmaceutical and cosmetic formulations.[48]

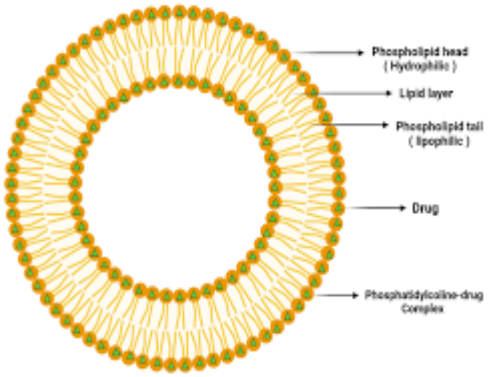

Figure 3.The basic structure of phytosome.

Originally investigated for cosmetic purposes, phytosomes have over the past 20 years shown increasing evidence of their potential for drug administration, with positive effects in the fields of cardiovascular, anti-inflammatory, hepatoprotective, and anticancer applications.[49]

Table 2.Herbal formulations based on phytosomal drug delivery systems.

Sr.no	Plant /constituent used	Derived from plant	Biological activity	Application of technology	Ref.
1	Curcumin	Turmeric (*Curcuma longa)*	anti-oxidant and anti-tumor	increased antioxidant activity and bioavailability	50
2	Epigallocatechin	Verdant tea	anti-oxidant and anticancer	Enhancement of absorption	51
3	Naringenin	Grape and orange juice	Anti-inflammatory and anti-cancer	Long-lasting effects and improved bioavailability	52
4	Procyanidins	Grape seed	antioxidant and anticancer	Improvement of bioavailability	53

Recent preclinical and clinical research has demonstrated that an anticancer plant-derived compound, when encapsulated in a suitable herbal delivery vehicle such as nano phytosomes, may be able to overcome the limitations imposed by the limited absorption of herbal extracts, which limit their clinical utility in the treatment of cancer.[54] Few research have been done employing phytosomes as a carrier in cancer therapy, despite the apparent promise of phytosome technology. As a result, very few goods like Siliphos® (Silybin phytosomes) and Meriva® (curcumin phytosomes)have made it onto the market.[55] Phytosomes can be used as an advantageous delivery system for anti-cancer medications since they are abundant, biocompatible, and affordable. They can also be taken orally. This strategy might avoid the negative consequences linked to the clinical use of well-known anti-cancer chemotherapy medications. The most popular and successful anti-cancer medications are taxanes, which

include the naturally occurring paclitaxel (PTX, brand name Taxol®) and the semi-synthetic analogue docetaxel (DTX, brand name Taxotere®). Taxanes are FDA-approved.[56]

Phytosomes are defined by their size, stability, and ability to carry drugs. The establishment of chemical bonds between phospholipid molecules and phytoactive substances is what gives phytosomes their stability. Because of their enlarged permeability and retention effect, phytosomes, which have a size range of 50–200 nm, can concentrate at the tumor site without going through the reticuloendothelial system.[57] Combining phytochemicals from herbal plant extract with a phospholipid carrier to increase the pharmacological benefits of conventional chemotherapy while reducing its side effects has resulted in the development of a unique cancer therapeutic strategy.[58]

Advantages of Phytosome include:

- A rise in lipophilicity.
- Enhanced bioavailability.
- Improved stability.

Solid lipid nanoparticles:

Solid-lipid nanoparticles are 50–100 nm in size and belong to the sub-micron colloidal system. It is made by dispersing physiological solid lipid particles in an aqueous surfactant solution or water at nanoscales. These are monolayer phospholipid carriers with a stable hydrophobic core, so that hydrophilic or lipophilic medications can be carried by them. For example, SLNPs are non-toxic, biodegradable, and biocompatible. Long-term stability and improved control over the encapsulated compound's release kinetics are features of SLNPs.[59] As a carrier system for correcting dynamic medication and successfully water dissolvable medication, solid lipid nanoparticles (SLNs) are presented. Nanoparticles are colloidal particles with sizes between 10 and 1000 nm. They are made from synthetic distinctive polymers and can improve the delivery of medications and reduce lethality.[60] Solid biodegradable lipids make up the matrix of solid lipid nanoparticles (SLN), which are aqueous colloidal dispersions. The advantages of a few colloidal carriers of its class are combined by SLNs, who strategically avoid their drawbacks. These advantages include physical stability, the guarantee that fused labile medications will be protected from degradation, the assurance that incorporated labile drugs will be released under controlled release, and excellent tolerability. In-vitro and in-vivo characterizations of SLN formulations for different application routes (parenteral, oral, dermal, ocular, pulmonar, and rectal) have been completed.[61]

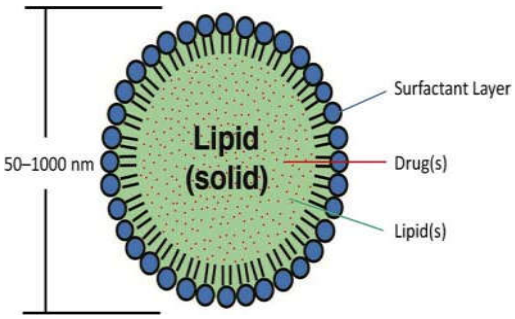

Figure 4.The basic structureof solidlipid nanoparticle.

Because most lipids are biodegradable, SLNs have excellent biocompatibility.Drugs that are both lipophilic and hydrophilic can be integrated into SLNs, which also provide regulated and targeted release. Moreover, SLNs are less expensive than polymeric or surfactant-based carriers.[62].

Table 3.Herbal formulations based on solid-lipid nanoparticulate drug delivery systems.

Sr. no	Plant used/ constituents	Derived from plant	Biological activity	Application of technology	Ref.
1	The triptoplide	extract from the Chinese herb Tripterygium wilfordii Hook F.	used as a treatment for autoimmune illnesses, especially those including leukemia and anti-tumor properties.	Increasing bioavailability	63,64
2	Curcuminoids	*Curcuma longa.*	antioxidant, anticancer, and antiplatelet aggregation.	Reduction in the toxicity of medications and enhancement of their bioavailability	65
3	Podophyllotoxin	derived from *Podophyllum pellatum's* dried roots.	antiviral and antitumor effects.	Increasing bioavailability	66

The most prevalent cancer in women is breast carcinoma, whose prevalence is steadily increasing over time.Effective breast cancer chemotherapies are significantly hampered by systemic toxicity, side effects, rapid elimination, and insufficient drug concentrations approaching the tumor. When used in conjunction with MDR chemotherapy, SLNs have the potential to overcome current chemotherapeutic limits and other related problems in the treatment of breast cancer.[67]

Worldwide, lung cancer (LuC) is the leading cause of cancer-related mortality and the most common malignancy in both men and women to receive a diagnosis. Even while radiation and chemotherapy work well to treat lung cancer, a large percentage of individuals experience a return of the disease that is more resistant to further treatment. Therefore, a unique therapeutic approach is needed to improve the prognosis of this type of cancer. A study with SLNs loaded with the anticancer chemical naringenin revealed that, in accordance with the drug's pharmacokinetic characteristics, such as mean residence time and maximum plasma concentration, rats that received naringenin-laden SLNs intratracheally showed an enhanced cellular absorption pattern.[68] SLNs may prove to be a successful colon cancer treatment. By increasing apoptotic activation, SLNs were observed to suppress cell growth in HT-29 and

GCT116 adenocarcinoma cells more than free fatty acid.[69] The difficulty to target medicines to neoplastic cells has increased the incidence of prostate cancer; however, SLNs (e.g., LNCap) have been shown to be successful in suppressing prostate cancer cells as a drug delivery mechanism.[70] A successful nanoscale lipid-based strategy for brain cancer medication delivery is the usage of SLNs. Although the precise mechanism by which the delivery system crosses the blood-brain barrier is unknown, endothelial cells are considered to aid in internalization (pinocytosis). Endocytosis and pinocytosis result in the efficient absorption of circulating plasma proteins onto the surface of the SLN.[71]

Microemulsion:

Microemulsions are a transparent, isotropic mixture of water and oil that is thermodynamically stable and stabilized by surfactants and sub-surfactants. Small-scale emulsions, like droplet-type dispersions, consist of either water in oil (W/O) or oil in water (O/W). The size of a microemulsion varies from 5 to 100 nm. Salt and other components are present in the aqueous phase, whereas a combination of olefins and hydrocarbons is present in the oil phase. W/O or W/O/W emulsions are generated for water-soluble pharmaceuticals, whereas O/W or O/W/O emulsions are made for oily or lipophilic medications.[72]

Microemulsions exhibit strong absorption and penetration due to their small droplet size and extremely low surface tension. There is growing interest in these adaptable carriers, and their uses have expanded beyond the traditional oral route to include other methods of administration. This is explained by their distinct solubilization characteristics and thermodynamic stability, which have attracted interest in their application as drug delivery vehicles intended for the brain. Since peripheral circulation and the olfactory pathway connect the brain and nose compartments, intranasal drug delivery is one of the targeted delivery methods for brain targeting.Testicular and small cell lung cancers can both benefit from the anticancer medication etoposide, an epipodophyllotoxin. Because the drug must be diluted in the infusion fluid before delivery, its low water solubility poses a challenge to the formulation of its parenteral dosage form. This characteristic causes medication precipitation in the infusion fluid, which can be harmful to the patient's health because it may cause capillary blockage.[73] Because a microemulsion can enhance drug solubilization, it is a promising option for the oral delivery of medications that are poorly soluble in water. When a drug's thermodynamic activity in the vehicle increases, so does its absorption rate.[74]

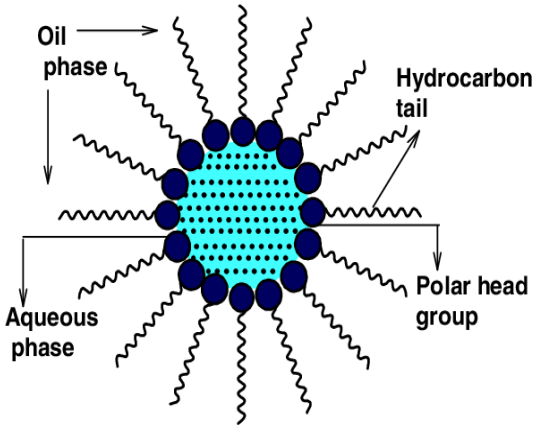

Figure 5.The basic structure of microemulsion.

A medication's effectiveness can be raised by employing microemulsion as a delivery method, which lowers the dosage and side effects overall. Additionally, hydrophilic and lipophilic medications can be delivered by microemulsions.Additionally, microemulsions are easy to produce, need no energy, and allow for regulated or reversible synthesis due to their thermodynamic stability.When the temperature returns to within the stability range after being unstable at low or high temperatures, the microemulsion reforms.[75]

Table 4. Herbal formulations based on microemulsion drug delivery systems.

Sr.no	Plant /constituent used	Derived from plant	Biological activity	Application of technology	Ref.
1	Curcumin	Turmeric (*Curcuma longa)*	antioxidant, anti-tumor, and anti-platelet aggregation properties	Increase the anti-inflammatory response	[76,77]
2	Triptolide	Triepoxide diterpenoid derived from Chinese medicine Hook F of Tripterygium Wilfondil	used to treat leukemia and other autoimmune diseases, as well as antitumor activities	Cut down on the toxicity	[78]
3	Berberine	*Berberis vulgaris*	anti-tumor	longer period spent inside the body	[79,80]
4	Docetaxel	European yew tree Taxus baccata	anti-tumor	lengthier time spent internalizing	[81,82]

One of the antineoplastic agents now in use, methotrexate (MTX), has drawbacks including drug resistance and hazardous side effects to normal cells. It is an analogue of folic acid that interferes with the activity of the enzyme dihydrofolate reductase, preventing the conversion of dihydrofolate to tetrahydrofolate and therefore interfering with the synthesis of components of DNA and RNA.[83] However, rather than altering the inherent mechanism of antitumor activity, traditional microemulsion-based chemotherapeutic delivery systems primarily rely on enhanced drug internalization into targeted cells to maximize their therapeutic impact. Recently, by modifying signaling pathways, a synergistic drug combination method has significantly increased the apoptosis rate in order to further improve the efficacy of anticancer medications.[84]

Advantages of micro-emulsion:

- Ability to Solubilize.
- Extended medication release.

- Elevated stability.
- Ease of production.
- Enhancement of bioavailability.

Microsphere:

The controlled release drug delivery system uses microspheres as its delivery method. It is a matrix-based drug encapsulating device that can hold a range of medications and distributes drugs equally across the polymer matrix.[85] Protein and polymers make up the majority of it; acceptable polymers include polylactic acid (PLA), polylactic-co-glycolic acid (PLGA), gelatine, albumin, and polylactic. Polymers can be synthetic or natural. Drugs dissolved in polymers are released by a first-order mechanism. The amount of medication release is inversely correlated with the polymeric concentration.[86] Microspheres are one of the NDDSs that provide a uniform dispersion of drug in polymer matrix, with first order kinetics for drug release. Microspheres are discrete spherical particles with sizes ranging from 1 to 1000 μm. The drug that is entrapped comes into touch with the media when the matrix diffuses to the outside dissolving media. After the drug is dissolved, it is released into the various bodily systems. When a polymer is added, surface erosion occurs, which facilitates the drug's release.[87] Microspheres can be made using a variety of natural (albumin, gelatin, modified starches, etc.) and synthetic (polypropylene, dextran, polylactic acid, and polylactide-co-glycolide, etc.) polymers using different techniques.[88] There are several benefits to using microspheres as a medication delivery vehicle, including increased efficacy and decreased toxicity of the integrated drugs to non-targeted cells and tissues. Nevertheless, there are drawbacks as well. For example, microspheres are difficult to mass-produce and become relatively unstable as they denature over a few weeks.[89]

They are the mechanism for delivering colloidal drugs. Microspheres are characterized as freely flowing powders made of biodegradable proteins or synthetic polymers with a particle size of less than 200 μm. Drugs can be directed to an organ or organs by using biodegradable microspheres that are inserted into the end vessels of the organs. The size of the microsphere employed and the method of administration (intravenous vs. intra-arterial) determine its success.[90]

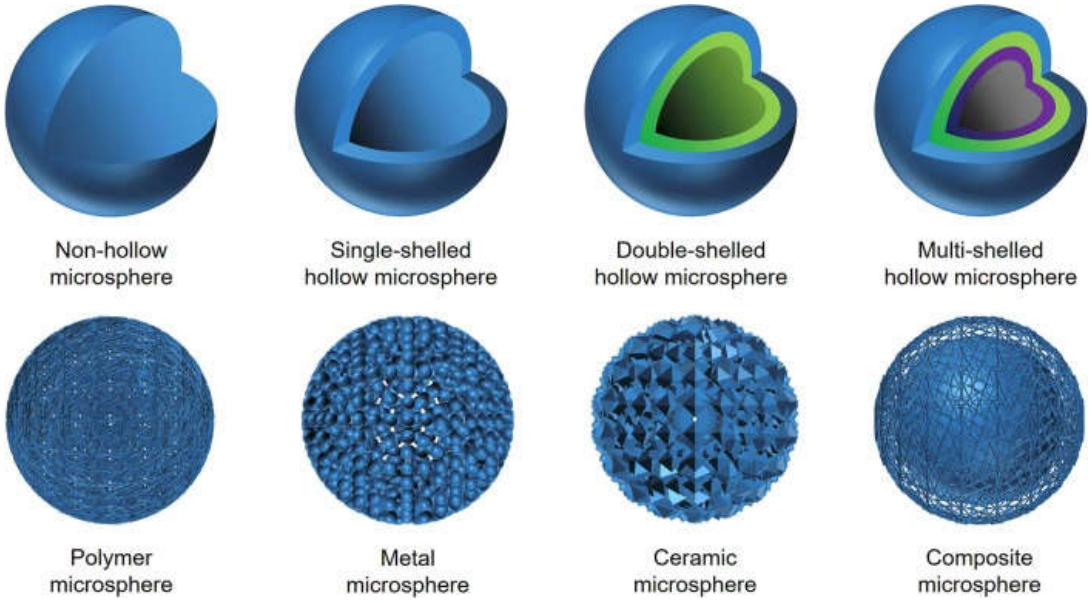

Figure 6.The basic structure of various microsphere

Microspheres are employed in radiation therapy to treat liver cancer or as a stopgap measure before surgery or transplantation. A bad prognosis is indicated by the development of liver metastases from any solid tumor, unless the cancer can be surgically resected. Hepatic metastases account for the majority of mortality in patients with colorectal cancer.[91] Cytotoxin-loaded microspheres are injected into the breast by a catheter that is surgically placed into the subclavian artery or one of its branches, most commonly the thyrocervical trunk. However, angiographic insertion of catheters directly into the internal mammary artery can result in more selective perfusion. These microspheres are transported by blood flow to the capillary bed upon intraarterially delivered medication, where they embolize and release their therapeutic payload into the intended organ. A single pulse of albumin microspheres laden with adriamycin has been used to target breast cancer cells via an internal mammary artery catheter positioned radiologically. Adriamycin-loaded albumin microspheres have been demonstrated in animal experiments to be more effective at suppressing tumor growth than free medications in a solution.[92]

Because the medication does not reach the target location in effective concentrations, conventional chemotherapy is less effective in treating colon cancer than it is in treating other malignancies. Therefore, larger dose sizes are necessary for effective treatment, which could have unintended consequences. Pharmaceutical technologists have been developing ways to more effectively transfer the medication to the colon, where it can target the tumor tissues, in an effort to ameliorate the condition.[93] Therapeutic medicines can now be delivered to brain tumors using a technique based on microspheres. In order to treat malignant brain tumors through local delivery of anti-neoplastic agents, the polymer poly(methylidene malonate) has been used to create 5-fluorouracil-sustained release biodegradable microspheres. This polymer has a slow degradation rate, which results in a long-term local delivery system.[94] Exocrine pancreatic insufficiency with steatorrhea and creatorrhea is the result of impaired pancreatic juice flow brought on by a mechanical blockage of the pancreatic duct in individuals with pancreatic head cancer. This could be a factor in the significant weight reduction these individuals frequently experience. Enteric-coated pancreatin microsphere treatment, combined with dietary counseling and high-dose enteric-coated pancreatin enzyme supplementation,

prevents weight loss and pancreatic duct occlusion, at least in the short term following biliary endoprosthesis insertion, according to a placebo-controlled trial involving patients with incurable pancreatic cancer.[95]

Table 5.Herbal formulations based on microsphere drug delivery systems.

Sr.no	Plant/constituent used	Derived from plant	Biological activity	Application of technology	Ref.
1	The camptothecin	The stem and bark of *Camptotheca acuminata*	anti-tumor	Lowering the dose	[96]
2	Quercetin	oranges, apples, and onions	anti-tumor	Enhanced Permeation	[97]
3	Ginsenosides	*Panax* (ginseng) genus)	anti-inflammatory, anti-oxidant, and anti-cancer	Enhancement of Solubility and Stability	[98]

Ethosomes:

Transfersomes are employed to transfer pharmaceuticals to the upper layers of skin, whereas ethosomes are noninvasive delivery vehicles that allow drugs to reach the deep layers of skin and/or the systemic circulation. It is possible to adjust the size of Ethosomes vesicles from tens of nanometers to microns.[99] Phospholipids, ethanol, and water combine to form ethosomes, which are new types of lipid carriers.The capacity to capture both hydrophilic and hydrophobic molecules, as well as their increased malleability and stability, make these vesicular structures the second generation of liposomes.Their cost-effectiveness and convenience of implementation are appealing attributes.[100] Since its launch in 2000, ethosome technology has been commercialized; it is a rapidly developing field. Based on ethosomal technology, a number of commercial goods have been created. These include the hair growth promoter Nanominox® from Sirene of Germany; the topical anti-cellulite cream Noicellex® from Novel Therapeutic Technologies of Israel; the skin genuity® for cellulite treatment from Physonics, Nottingham, UK; and Supravir® cream, for the treatment of the herpes virus, from Trima of Israel; Cellutight EF®, a topical cream for cellulite, from Hampden Health of the USA; Decrin® cream, an anti-aging cream, from Genome Cosmetics, Pennsylvania, U.S.[101] Because they combine the qualities of their organic components (phospholipids and ethanol 20–45%) to overcome low skin permeability and achieve therapeutic efficacy while limiting undesirable effects, ethersomes are a form of nanocarrier utilized for topical and transdermal applications.[102]

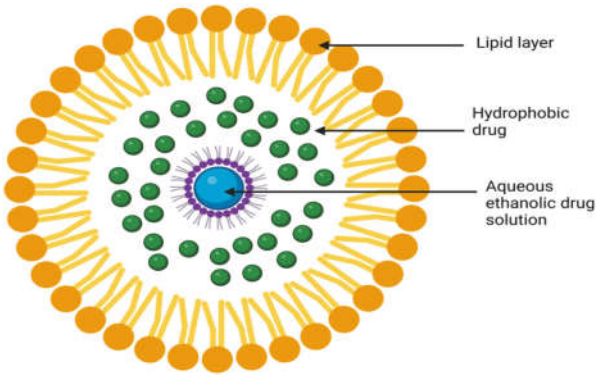

Figure 7.The basic structure of ethosome.

Table 6. Herbal formulations based on ethosomal drug delivery systems**.**

Sr.no	Plant used/ constituents	Derived from plants	Biological activity	Application of technology	Ref
1	Matrine	Flavescens Sophora	anti-cancer and anti-inflammatory.	Enhanced penetration and increased effectiveness	103
2	*Sophora alopencerides*	*Sophora alopencerides*	Enhanced penetration and increased effectiveness.	Improvement of penetration	104
3	Podophyllotoxin	Podophyllum hexandrum	Purgative, antiviral, anticancer, and anti-rheumatoid.	increased effectiveness of trapping	105

The polar portion of the lipid molecules interacts with alcohol through a mechanism that lowers the melting point of the lipids in the corneal layer. Alcohol fluidizes lipids, allowing ethosomes to pass through the stratum corneum and into the skin's deeper layers.[106] Preliminary and in vitro tests suggest that most vesicular medications approved for the treatment of skin cancer are safe and pose little harm to the body as a whole. It has been found that using ethosomes to treat skin cancer has significant advantages. Ethosomes can increase the effectiveness of anticancer activity while reducing the harmful side effects of chemotherapy.[107]

However, complement activation-related pseudo allergy (CARPA) has been reported in relation to lipid nanoparticle use. Since the complementing system is triggered by first exposure to fatty additions, faux allergy occurs in the absence of prior sensitization. There is currently limited information available on the topical application of vesicular drug delivery systems in the clinical-trial phases, despite a considerable number of in vivo and preclinical studies supporting their therapeutic applicability in the management of skin cancer. When compared to systemic delivery, topical therapy may lessen local drug concentration and side effects in dermatological conditions such skin cancer. However, the skin's stratum corneum acts as an effective barrier, and how important a given molecule is in proportion to a chemical property's molecular size affects how effective the barrier is.[108]

Advantages of ethosomes:

- Delivery of a range of medications.
- Skin penetration improvement.
- Medication delivery in a semisolid state.

Challenges toward Drug Delivery Systems in Anticancer Therapy:

The difficulties with anticancer nanomedicines and recommendations for solutions are covered in a number of papers.[109] The implementation of AstraZeneca's 5R principle—the right target, right patient, right tissue, right safety, and right commercial potential—is one tactic used by companies to address the translational dilemma.[110] By concentrating more on tumor biology and selecting the appropriate patients, Hare et al. highlight the necessity of employing more therapeutically relevant models for evaluating nanomedicines. Many nanomedicines fail clinical trials, even when they show excellent efficacy in preclinical models.[111] For ethical concerns, most authorized nanodrugs in clinical studies were compared with regular chemotherapy or combinations rather than free drugs.[112]

However, the creation of nanoformulations seeks to lessen the toxicity and improve the therapeutic efficacy of anticancer medications. By maximizing the pharmacokinetic characteristics of anticancer drugs and taking advantage of the increased permeability and retention (EPR) effect, nanoformulations may increase the therapeutic efficacy of these drugs.[113] and focused therapeutic methodology.[114] The negative effects are lessened by NDDs since they often have a lengthy systemic circulation and accumulate less in normal organ tissue than in tumor tissue. Apart from attenuating side effects, which are inherent to free anticancer drugs, nanomedicines may also result in off-target consequences.[115]

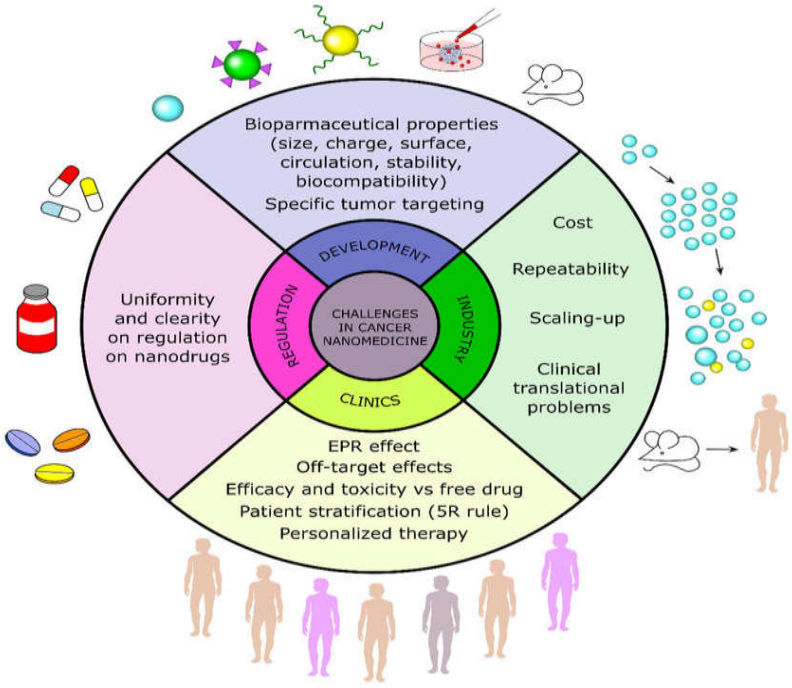

Figure 8. The main challenges toward drug delivery systems in anticancer therapy.

Nanomedicine-based approaches for improved delivery of phyto-therapeutics for cancer therapy:

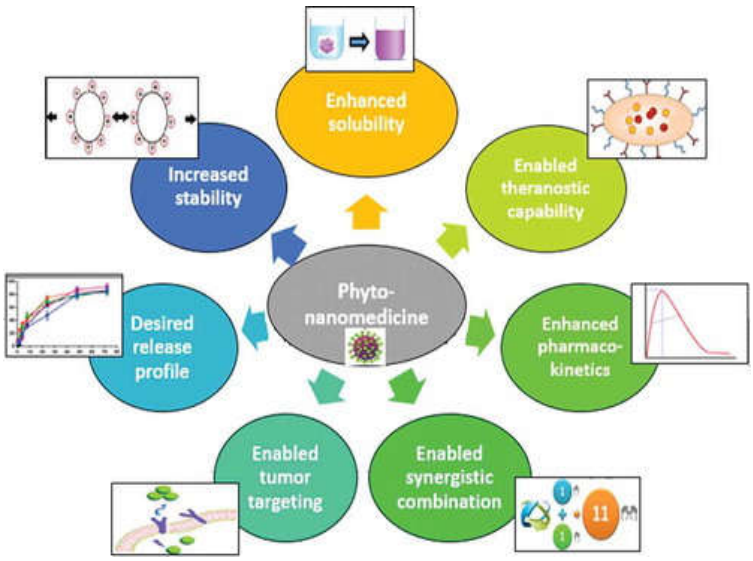

Figure 9.A schematic illustration showing the significance of phyto-medicinal nanocarriers.

Improved solubility

The majority of physiologically active polyphenolic phytoconstituents have low oral bioavailability and poor water solubility, which results in poor systemic absorption.Because they are not soluble, the delivery method is further restricted as intravenous injection is not possible.Diosmin (DSN), a strong herbal medication with chemo-preventive effects, is poorly soluble in water and most organic solvents, which prompted scientists to use nano-encapsulation to overcome this obstacle. For instance, DSN was effectively added to a pH-modulated nanoprecipitation technique-created nano matrix made of the hydrophobic protein gliadin for use in oral treatment of hepatocellular cancer.[116] Creating "nanocrystals" out of water-insoluble herbal medications using nanosuspension is one of the most effective ways to make them more soluble. After being formulated into a lyophilized tablet, the poorly soluble herbal medication Silymarin (SLM) nanosuspension's saturation solubility improved to 4616.1 mg, compared to only 1324.3 mg for pure SLM. Additionally, the pill represented as T90's disintegration rate increased to 44.2 minutes.[117]

Sustained release

Creating pharmaceuticals with high water solubility is a significant difficulty due to their rapid clearance and limited bioavailability. Furthermore, because the drug is released into the systemic circulation too soon after reaching its target, the rapid drug release results in a multitude of side effects following administration.[118] The isoquinoline alkaloid berberine (BRB) has a rapid initial release in aqueous conditions and a comparatively high water solubility. Two methods were used by to extend its release [119] comprising sodium deoxycholate (SDC) hydrophobic ion pairing to promote its entrapment into the hydrophobic core of the

amphiphilic case in micelles. Furthermore, before spray-drying the nanoparticles into a stable dry micellar powder, they were chemically crosslinked using genipin, a crosslinker with far lower cytotoxicity. The continuous release of BRB and improved tumor targeting efficiency were both made possible by the micelles. While free BRB showed a nearly 100% quick release after only one hour, the burst release of 45–55.5% of BRB was released after twenty-four hours due to the genipin-crosslinked micelles.[120]

Improved pharmacokinetics

Several pharmacokinetic benefits, including better biodistribution, greater metabolic stability, increased membrane permeability, improved bioavailability, and prolonged duration of action, are provided by drug encapsulation in nanoparticle form.Quercetin, a flavonoid found in herbs, was effectively encapsulated into phytosomes by complexing with phosphatidylcholine through both hydrophobic and hydrogen bonding interactions.[121] When quercetin was made into phytosomes instead of free, unformulated quercetin at the same dose, the pharmacokinetic analysis revealed a substantial improvement in quercetin absorption. The quercetin phytosomes' computed Cmax and AUC were, respectively, 20 and 18 times greater than those of free quercetin.Another study found that encapsulating resveratrol in zein nanocapsules significantly increased its oral bioavailability and pharmacokinetics.[122]

Enhanced tumor targeting

In addition to improving drug selectivity to target cells and selective cytotoxicity to avoid side effects on normal cells, active targeting nanoparticles also improve the anticancer efficacy of the medication and its accumulation in cancer cells, and they are useful in controlling drug release.[123] The mice treated with GA/LF-nanocapsules showed a significant reduction in Ki-67 expression (20%) when compared to 93.76%) in diethyl nitrosamide-induced HCC-untreated mice models. This indicates a decreased proliferation of tumor cells, resulting in a decrease of >93% in the number of liver tumor nodules. This further supports the enhanced tumor-targeting effect. Furthermore, as seen by a marked improvement in the level of the liver enzymes ALT and AST, the improved liver tumor-targeting reduced adverse effects and boosted safety.[124]

Increased stability

Many pharmacologically active herbal medications have weak chemical stability, which makes clinical translation difficult.Consequently, numerous methods, such as nano-encapsulation, were tried to increase their stability, shield those delicate molecules from untimely degradation, and ultimately increase their bioavailability. Epigallocatechin-3-gallate (EGCG) is an example of a sensitive herbal; its applications are limited due to its sensitivity to pH, temperature, and oxygen.It was discovered that adding EGCG to solid lipid nanoparticles (SLNs) improved their durability in both intestinal and gastric environments, resulting in a delayed release of roughly 21.8% of the medication at the conclusion of the incubation period in SIF (pH = 6.8, containing pancreatin) at 37°C.[125]

Enhanced localized drug delivery

As an encouraging alternative to systemic therapy for lung malignancies, inhalational chemotherapy is available. By using this method, the harmful systemic side effects of intravenous injection and the delivery of high dosages of chemotherapy are avoided. On the

other hand, rapid NP exhalation reduces their lung deposition.[126] Therefore, microencapsulated nanoparticles(nanocomposites) provide multiple advantages of enabling efficient aerosolization, deposition deeply in the lung, and excellent tumor cells targeting.Ellagic acid (EA), a natural medication, was combined with doxorubicin to create a lactoferrin-chondroitin nanocomplex through electrostatic complexation.[127]

Conclusion:

Nanoparticles have emerged as a promising approach in cancer treatment due to their unique properties, including enhanced drug delivery, targeted therapy, and the ability to overcome biological barriers. Their small size allows for improved penetration into tumors, while their surface modifications can facilitate targeted delivery to cancer cells, reducing damage to healthy tissues and minimizing side effects.

In conclusion, the use of nanoparticles in cancer therapy holds significant potential for improving treatment efficacy and patient outcomes. Ongoing research is critical to optimize their design, ensure safety, and understand their long-term effects. As the field advances, nanoparticles could play a transformative role in personalized medicine and more effective cancer treatments.

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