Recent advances in lipid-engineered multifunctional nanophytomedicines for cancer targeting

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Highlights:

- Phytoconstituents are new emerging therapeutics against cancer.
- These molecules can be combined with existing therapeutics for better outcome.
- Lipidic vesicles are compatible carriers and mimic the biological membrane.
- Nanoengineering in lipidic carriers enhances its efficacy.

Abstract

Cancer is a leading cause of death in many countries around the world. However, the efficacy of current treatments available for variety of cancers is considered to be suboptimal due to the pathophysiological challenges associated with the disease which limits the efficacy of the anticancer drugs. Moreover, the vulnerability towards off-target effects and high toxicity also limits the use of drugs for the treatment of cancers. Besides, the biopharmaceutical challenges like poor water solubility and permeability of the drugs, along with the absence of active targeting capability further decreases the utility of drugs in cancer therapy. As a result of these deficiencies, the current therapeutic strategies face noncompliance to patients for providing meaningful benefits after administration. With the advancements in nanotechnology, there has been a paradigm shift in the modalities for cancer treatment with the help of phytomedicine-based nanosized drug delivery systems coupled with variegated surface-engineering strategies for targeted drug delivery. Among these delivery systems, lipid-based nanoparticles are considered as one of the highly biocompatible, efficient and effective systems extensively explored for anticancer drug delivery. These include diverse range of systems including liposomes, nanoemulsions, solid lipid nanoparticles, nanostructured lipidic carriers and supramolecular carriers, which alters pharmacokinetic and biodistribution of the drugs for active targeting to the desired site of action by overcoming the biopharmaceutical challenges associated with anticancer drug delivery. The present review endeavours to provide a comprehensive account on the recent advances in the application of lipid-based nanostructured systems for improving the pharmacotherapeutic performance of phytomedicines for cancer targeting application.

Keywords: Phytomedicines; Nanotechnology; Lipids; Cancer targeting; Surface engineering; Pharmacotherapeutics

1. Introduction

Hippocrates explain cancer as finger like projections which mind the crab shape[1,2]. Cancer is characterized by abnormal growth of cell with potential to invade other areas or distant part of body[3–5]. Different terms are used for explaining the cancers and malignant cells, with all depend on its origin whether it is sarcoma (like fat, bones, muscles, cartilages, and blood vessels), carcinoma (like skin or any internal tissue), leukemia (like bone marrow) or lymphoma (like immune system). As per WHO cancer report of 2018, it is second leading cause of death globally, which accounts 9.6 million deaths [6,7]. Cancer cells have six prominent features: (i) self-sufficient signals; (ii) no sensitivity to anti-growth signals; (iii) apoptosis invasion; (iv) limited repetition in potential; (v) sustaining of angiogenesis; (vi) metastasis of tissue and its invasion[8]. Most common cancer includes lung, colorectal, prostate, liver, stomach and head-neck carcinomas. Symptoms and signs of cancer specifically depend on its size, type, location, extent to the tissues and organs. There are more than 100 types of cancers which exist till date. In humans, general signs and symptoms due to presence of cancer cells are incomprehensible events of pain, night sweats, fever, weight loss, unusual bowel movements, prominent events of cough, lumps[9,10].

Almost 30% of deaths arising due to cancer can be thwarted by slight modification or avoidance of risk factors. Various approaches employed for cancer treatment are hormone-based therapy, surgical interventions, chemotherapy, photodynamic therapy, immunotherapy, radiation therapy and genetic therapy[11–13].Treatment choice depends on the stage and type of tumour and organ affected. For example, in case of non metastatic cancer, major goal is to eradicate tumour from regional lymph nodes and prevention of metastasis stage. Eradication of cancer can be achieved by surgical removal of cancer site and near by lymph nodes along with systemic administration of anti cancer moieties (preoperative or postoperative). In case of

metastatic cancer, major goal is prolongation of life and decrease of morbidity. Presently, metastatic cancer remains incurable and systemic therapy is done to prolong the prognosis of disease.As per the WHO guidelines in which new treatment options were adopted with an initiative for cancer treatment especially in low- and middle-income nations[14,15]. Treatment of cancer is highly herculean task due to various unwanted events like aggression in proliferation of tumour and its spreading to multiple organs, therapeutic resistance, heterogenous in metastasis, barriers in drug permeation. Most commonly approach practiced in case of cancer therapy is chemotherapy but it imparts acute as well as chronic side effects to patients and thus overall hinders the quality of life[16]. Recent cancer treatment patterns have been changed with targeting to oncogenes and immune oncology-based cancerous ailments [17]. However, still there are miles of way existing for overcoming the challenges pertaining to cancer therapy. Sequence-based analysis for pre-screening of molecules in clinical research is advantageous but it restricts the clinical application owingto large volume of genomic data [18]. Also, precision-based oncology treatment is limited due to the heterogeneity as well as resistance acquired by cancer cells, while immune check-point inhibitors does not aid in success to cancer treatment because of lack of suitable validation process for markers.

2. Biopharmaceutical challenges for phytomedicines-based drug therapy

From ancient times, phytomedicinesare used as the crucial source for drugs. Till date almost 50% of drugs are obtained from natural sources[19,20]. Most of the patients develop their interest towards the phytomedicine because of theirlow cost, better efficacy and verylimited side-effects[21]. However, phytomedicines have also reported to have compromised *in vivo* activity owing to more than one reasons like poor water solubility, lack of appropriate molecular sizing and compromised systemic availability[22]. Most of the phytoconstituents are secondary metabolites and generally isolated from the plant materials. Amount of secondary metabolites in plants is very low and their amount varies on various factors like species of plant

material, anatomical part (like seeds, leaf, flower, roots), storage of material, geographical horizon, harvest time [23,24]. Another challenge exists is phytoconstituents screening for medicinal property by high-throughput screening but the crude extracts contain the mixture of compounds. However,the active constituents identified in crude extracts provide pseudo positive results in high-throughput screening. Additionally, proper identification and isolation of phytoconstituents in active form requires lots of time and involves cost economy [25–27]. Many phytoconstituents and their extracts exhibit biological instability in structure, premature loss in drug due to rapid clearance and frequent biotransformation, gastric or enzymatic degradation.

For overcoming these biopharmaceutical issues, nanotechnology is an emerging area which paved its way couple of decades back. Nanotechnology has revolutionized the pharmaceutical and medical field for addressing the unmet needs. Nano-based herbal development provides an add on advantage in enhancing solubility, bioavailability, reducing toxicity, pharmacological activity enhancement, stability increment, sustaining the release profile, physical and chemical stability for achieving desired safety and efficacy. Furthermore, nanotechnology accomplishes the need for: (a) more accumulation at targeted site; (b) targeting of phytoconstituents specific to the cell; (c) enhancing large molecule delivery; (d) combinational delivery of two or more phytoconstituents[28,29].

3. Lipid-based nanostructured drug delivery systems

Advancement in the field of science have discovered many novels and fulfilled the demand of healthcare facilities to great extent. Drug designing have paved the way for discovery of new anti-cancer molecules, but limited in clinical setup due to their compromised biopharmaceutical properties[30]. Till date micro or nano based phytoconstituents are not available in market. Most of the newly identified and isolated phytoconstituents suffers from poor solubility and bioavailability. Nano-based approaches are the need of the hour for

effective delivery of bioactive. Lipid-based nanocarriers are growing at fast pace and have gained significant interest in herbal drug delivery foraddressing the challenges. Various categories of lipid-based nanocarriers include liposomes, niosomes, emulsions, solid lipid nanoparticles, nanostructured lipid carriers, lipid nanocapsules[31,32]. Self-assembled lipidic carriers are thermodynamically stable along with platform available for stimuli-responsive carriers that provide tailored release profiles at the desired site.Phytoconstituents can be encapsulated in nanocarriers are considered as safe and effective and can easily sort-out the biopharmaceutical issues. **Figure 1** highlights the mechanistic insight into the application of lipid-based herbal systems for targeting cancer. Also, **Table 1** summarizes the recent advances in the nanovesicular systems for delivery of phytomedicines for cancer treatment.

3.1 Liposomal therapeutics

Liposomes derived their nomenclature from Greek word: “lipo” means fat and “soma” means body. The spherical shaped nanoscopic vesicles can be formulated using phospholipids, cholesterol, and resembles like lipidic bilayer membranes. Indeed, the developed nanocarriers have the ability of enhancing biopharmaceutical properties like pharmacokinetics and therapeutics of entrapped molecules[33,34]. Incorporation of phytoconstituents in the bilayer vesicles potentiates the efficacy and safety, therebyreducingthe side-effects. Some of the liposomal systems are available in the marketare based on phytoconstituents like curcumin, berberine, quercetin, resveratrol[35] and many more. Encapsulation of phytoconstituents in lipid layers enhances numerous physiological properties. Lopes and co-workers formulated pH sensitive liposomes of ursolic acid and evaluated in MDA-MB-231 breast cancer cell line. Nano-sized liposomes depicted higher anti-cancer activities in comparison to free ursolic acid[36]. Similarly, Wang and co-workers prepared PEGylated Resveratrol conjugated liposomes with and without glycine for anti-cancer. Results reported show higher drug entrapment efficiency for glycine conjugated system (84.50%) in comparison to non-glycine

conjugated system (12.50%)[37]. Girish et. al., prepared berberine loaded liposomes where release of berberine from liposomes was compared with free berberine for 24 h. From liposomal loaded berberine, it was observed that 70% of content was released within 10 h in comparison to free berberine that was released in 24 h[38]. Odeh and co-workers formulated thymoquinone loaded liposome and evaluation on MCF-7 cells and fibroblast cells. Cell line studies revealedthat liposome loaded with thymoquinone suppresses MCF-7 cell proliferation[39]. Saengkrit and co-workers developed cationic liposome using dimethyl dioctadecyl ammonium bromide (DDAB) as phospholipid and encapsulatedcurcumin. Thecurcumin loaded liposomes evaluated for cytotoxicity studies on HeLA and SiHa cell lines showed efficient anti-cancer and apoptotic effects[40]. Liposomal curcumin formulation inhibits the proliferation, induction of apoptosis by nuclear transcription factor (NF-ƘB) in pancreatic cancer cell line[41]. Curcumin (CUR) liposome decorated with 2-hydroxypropyl-γ-cyclodextrin demonstrated anticancer activity breast and osteo carcinoma[42]. Curcumin liposomes were also found to be very promising formulation for dermal applicability for enhanced anti-melanoma activity. Mahmud and co-workers reported that PEGylated liposomes with low ratio of curcumin to lipid have higher plasma stability and enhanced bioavailability as seen in adenocarcinoma-based cell lines[43]. PEGylation of paclitaxel loaded liposomes demonstrate higher anticancer and lower toxicity in comparison to plain paclitaxel. Furthermore, use of phosphatidylserine-based lipid aids in higher entrapment of paclitaxel. Paclitaxel entrapped in liposomes were effective against lung carcinoma[44]. Semi purified extract of Job's tear obtained from *Coixlacrymajobi* in liposomes have enhancement in anticancer potential towards colon cancer and stability[45]. *Colchicum autumnale* synthesise natural toxin as colchicine which loaded in liposome demonstrated higher depolarization of microtubules at lower concentration in comparison to plain colchicine [46].

Niosomes are the vesicular system with main composition of nonionic surfactant and cholesterol. These vesicular systems act as reservoir for lipophilic and amphiphilic bioactive agents. The advantages of these vesicular based drug delivery systemis protection of entrapped bioactives from the harsh condition and enhance the overall therapeutic efficiency. Niosomes can be tailored depending on the type of surfactant and controls the physicochemical properties of novel vesicles. Niosomes loaded with curcumin inhibit the ovarian cancer cell growth. Surface modification of niosomes by induction of cationic charge provides more targeting. Inhalable CUR loaded cationic niosomes demonstrates enhanced apoptosis and antitumour potential in lung carcinoma cell lines[47]. Doxorubicin and curcumin were co-administered in PEGylated niosomes by surface coating with cell penetrating peptide (i.e., tLyp-1) and tumour homing peptide shows enhanced potential against human mesenchymal cells and U87 human glioblastoma cells [48]. Niosome-loaded with lycopene demonstrated higher antiproliferative activity with enhanced stability to thermal and photo-degradation.

3.2 Lipidic nanoemulsions

Nanoemulsions preparation for phytoconstituents leads to optically transparent, stable, soluble formulation and prevention against sedimentation as well as creaming for biological active constituents[49]. Nanoemulsion is better option as drug delivery system for phytoconstituents delivery. Nanoemulsion-based delivery systems have both aqueous and lipid phases and it can solubilizes vast majority of hydrophilic as well as lipophilic molecules [50]. Curcumin is reported to have physicochemical and biopharmaceutical issues thus limiting its functional as well as biological activities. For enhancing its bio accessibility, nanoemulsion is the best approach. In similar fashion quercetin and resveratrol were also formulated in nanoemulsion for enhancing the plasma stability and further increment in uptake for anti-cancer effects[51,52]. Above stated nanoemulsion formulation demonstrated predicted enhanced anti-cancer activities in pre-clinical investigation only.

3.3 Solid lipid nanoparticles (SLNs)

SLNs are versatile nanocarriers for drug delivery that overcomes the disadvantages arises due to liposomes and polymeric nanoparticles[53]. SLNs are formulated of solid-lipid composites like monoglycerides, diglycerides, fatty acids, phospholipids and many more. SLNs provide physicochemical and extended compatibility, reduced levels of toxicity, biocompatible and biodegradable properties. SLNs solid-lipid core provide protection of inner encapsulated agents from chemical environment. SLNs have an advantage of encapsulating both lipophilic and hydrophilic anticancer agents[54]. Hu and co-workers loadedCucurbitacin B in SLNs for hepatic carcinoma treatment. Cellular uptake studies of formulated SLNs in human hepatic carcinoma Hep-G2 cell line shows higher uptake near to ~2-fold times when compared with free Cucurbitacin B. *In vivo* studies of Cucurbitacin B loaded SLNs depicted ~3.5-foldsimprovement in plasma area under curve as compared to free Cucurbitacin B[55]. Similarly, Zhu and co-workers synthesised podophyllotoxin-loaded SLNs. *In vitro* anticancer activity of podophyllotoxin loaded SLNs was compared with free podophyllotoxin on 293T human embryonic kidney cells and HeLa human cervical cells. Studies reported enhanced anticancer activity for SLNs when compared with free drug [56]. In similar fashion, PEGylated noscapine loaded SLNs were formulated and *in vitro* anticancer activity evaluation of SLNs showed2-folds reduced inhibitory concentration as compared to free noscapine in U87 glioblastoma cells. *In vivo* pharmacokinetic study of SLNs showed 11-folds higher plasma half-life in comparison to free noscapine[57]. Wang and co-workers formulated berberine loaded SLNs and activity was observed on MCF-7, HepG2 and A549 cells. As per cell line studies, sustained release of berberine was observed[58]. Emodin-loaded SLNs were formulated and higher cytotoxicity was observed on HepG2 and MCF-7 cells when compared with free emodin[59].

3.4 Nanostructured lipidic carriers (NLCs)

NLCs are considered as second generation SLNs with compositions of lipid-lipid, solid-lipid, lipid mixture.Advantage with NLCs is that it does not contain surfactants for carrying the phytochemical constituent load. Another advantage is its administration via various routes with sustained and tailored release from these carriers for cancer therapeutics[60,61]. NLCs conjugation with PEG escapes reticuloendothelial system (RES) capturing that provides additional advantage than conventional NLCs. NLCs accumulate passively in tumour microenvironment and traversing in leaky vasculatures due to enhanced permeability and retention (EPR). Modifications of NLCs can be possible with low molecular weight ligands and antibodies for active targeting applications. Lin and coworkers formulated curcumin loaded NLCs by folic acid (NLCs-CUR-FA) decoration for breast cancer targeting. NLCs loaded with curcumin provide initially burst release followed by sustain release for 60 h. *In vitro* MCF-7 breast cancer cell line studies revealed enhanced IC_{50} values for NLCs-CUR-FA in comparison to CUR-NLCs and free CUR, i.e., 3.50- and 10.40-times, respectively[62]. Jyoti and coworkers developed 9-bromo noscapine NLCs for lung carcinoma treatment. *In vivo* pharmacokinetic studies exhibited enhanced elimination half-life of 9-bromo noscapine NLCs up to1.75-foldsas compared to free 9-bromo noscapine [63]. In similar trends, thymoquinone encapsulation was done with NLCs and evaluated for MDAMB-231 anti-proliferative activity in SiHa and HeLa cervical cancer cell. *In vitro* cell line studies predicted promising inhibitory concentration in dose dependent fashion. Thymoquinone loaded NLCs depicted cell cycle-based apoptosis when compared with free thymoquinone [64]. Zhang and co-workers fabricates isoliquiritigenin loaded NLCs for hepatocellular carcinoma treatment. Higher anti-tumour activity of NLCs encapsulated isoliquiritigenin was observed in comparison to free isoliquiritigenin[65]. Carbone and co-workers formulated ferulic acid loaded NLCs for glioblastoma. *In vitro* studies on glioblastoma cell lines exhibits sustained anticancer activity for ferulic acid loaded NLCs when compared to free ferulic acid[66]. Rahman and co-workers

developed Zerumbone (natural based terpenoid against lung, skin, cervical and breast cancer) loaded NLCs for lymphoblastic leukemia. IC_{50} value of Zerumbone loaded NLCs was found to be 3.50 mg/mL after 72 h of treatment[67].

3.5 Lipid-polymer nanohybrid carriers

First ever nanohybrid carriers were reported in 1984 with formation of polymeric self-assemblies for solubilizing drug and enhancing their anticancer activity. Nanohybrid carriers include lipid-based and polymer-based carrierswith size in nano range and possess ability to deliver anticancer moieties at malignant sites through active and passive targeting mechanisms [68,69]. Advantage with this system is providing specific targeting to tumour cells; deep penetration inside physiological barriers; sustaining the drug release at site; reduction in dose and cytotoxicity to normal cells[70]. The promising biomedical applications of nanohybrid carriers arise due to its smaller sizes which enables more accumulation of these particles in the tumours. Conjugation with lipids enhances the lipophilicity and alteration of physical chemical properties of phytomolecules and phytoconstituents[71]. These chemical modifications results in bioavailability enhancement of phytoconstituent as well as targeting to tumour cells[72,73]. Fucoidan-oleic acid nano assemblies were prepared by incorporating paclitaxel and curcumin for cancer therapy. Tailored release profile of curcumin and paclitaxel was observed at pH 4.5 and 7.5, respectively[74]. Siddiqui and coworkers prepared epigallocatechin gallate (EGCG)encapsulated PLA-PEG nanoparticles with 10-folds enhancement in angiogenesis and proapoptotic activity observed through *in vitro* and *in vivo* cancer models[75]. Chung et al. prepared micellar nanocomplex of EGCG oligocomplexed with Herceptin followed by complexation of PEGylation demonstrated better tumour selection, reduction in growth and enhancing the biological half-life of herceptin in murine model[76]. Bisht and coworkers fabricated nanohybrids of curcumin by forming micellar aggregates of N-isopropylacrylamide (NIPAAM), with poly(ethyleneglycol)monoacrylate (PEG-A) and N-vinyl-2-pyrrolidone

(VP). These nanohybrids were evaluated under *in vitro* conditions on human pancreatic cell lines showed clonogenicity and cellular viability[77].

4. Key challenges and critical considerationsin the design and development of phytomedicine-based lipidic nanotherapeuticsystems

As per the literature reports, most of the phytomedicines derived from secondary metabolitesexhibit limited bioavailability. Recent COVID-19 crisis has diverged the pharmaceutical industry interest towards the designing and development of herbal-based drug delivery systemsas new treatment strategies [78,79]. Past studies like development of nanoparticles for *Cuscuta chinensis*,a Chinese traditional herbal medicine with pharmacological activity of rejuvenating the liver and kidney with biopharmaceutical limitation of poor aqueous solubility have been developed[80]. Various phytomedicine based drugs have been encumbered in the polymeric nanoparticles for enhancing the biopharmaceutical properties of them. The examples of curcuminoids and cucurbitacin, where both anticancer agents from herbal origin when delivered in polylactic acid nanoparticles showed significant improvement in solubility and anticancer activity [81,82].Various Chinese formularies have also reported working on the nanophytomedicines for overcoming the biopharmaceutical challenges of the well-known herbal moieties. Apart from the polymeric nanoparticles, other nanotechnology driven drug delivery systems were also developed like nanostructured lipidic carriers, solid lipid nanoparticles, dendrimers, polymeric micelles, liposomes, nanoemulsion, and many more, for the anticancer delivery via oral route. Apart from this, oral route has been blessed with various advantages like self-administration by patients, ease of administration and no monitoring required for chemotherapeutic and area of interest for the formulation scientist in the oncology area[83,84].

Recent paradigms in nano-based drug delivery systems for the herbal or plant-based bioactives can be boon for enhancing their therapeutic potential to overcome the constraints arising from the plant based bioactive. However, the question that haunts the biologists, pharmacist,

physiologist is the therapeutic establishment of nanophytomedicine for catering the clinical requirements especially in this area[85,86]. Literature reported by various researchers related to this area highlights the issues of these nanocarriers interaction with biological systems and associated challenges for clinical development in this area. Other challenges related to this area are scale up of theseadvanced nanoengineered phytomedicine to market and prosperous multifunctional for accomplishment of therapeutic and biological necessities[87].

Major goal behind designing nanophytomedicineincludes enhancement of pharmacokinetic parameters by modifying or tailoring the release behaviour from the novel system at the targetsite for enhancing the bioavailability and decreasingthe side-effects associated with conventional dosage forms. There are lot of research works being carried out across the globe for the development of nanophytomedicines with both preclinical and clinical studies[88]. The only challenge faced is the development of the apt dosage form which caters the delivery of bioactives at site of action.

Herbal medicines are used worldwide as a complementary approach along with synthetic drugs for the management of cancer [29]. The key challenges associated with phytomedicines include identification, and evaluation of safety and efficacy through pharmacological activity. As reported in literature,the nano-based phytomedicineshave shown promising results under *in vitro* and *in vivo* studies. Reasons for failure of reproducibility of these nanophytomedicine is due to their poor biopharmaceutical properties like poor aqueous solubility, inappropriate molecular size might leadsto low bioavailability and biodistribution potential.Otherhurdles associated with herbal-based nanomedicine are identification of chemical markers for specific bioactive for which development of analytical method is required.

5. Surface engineering strategies for nanolipidic systems

Surface modification of nanocarriers is possible by coating of surface with mucoadhesive surfactants, polymers, stabilizers, ligands, etc for impart various characteristics like

mucoadhesion, stability, protein adsorption, zeta potential distribution and site-specific targeting of the nano-engineered particles. Surface modification also plays an important role in the cellular uptake of nanocarriers. **Figure 2** provides the overview of the strategies used for surface modification of the nanocarriers for active targeting applications in cancer treatment. The permeation and membrane passage can be enhanced by surface modulation. Tailoring the transit time of lipidic nanoparticles will overcome the issue of poor aqueous solubility by enhancing the dissolution transit time of herbal based bioactives in the intestine[89,90]. Another advantage of surface modification is improvement of targetability and biocompatibility. Chitosan decorated lipidic carriers can be used as better carriers for delivery of herbal bioactives through mucosal routes and enhanced intestinal transit time. Advantage of chitosan coating provides more mucosal adherence to orally delivered phytoactives with more diffusion in the intestine[91]. Chitosan decoration over quercetin loaded SLNs provide less cellular uptake on CaCO-2 cell line in comparison to undecorated SLNs[92]. Asiatic acid loaded SLNs were formulated using glyceryl monostearate as lipid and Poloxamer 188 as surfactant for surface modification by solvent injection method. Optimization of formulation was done using Box-Behnken design. Particle size of prepared SLNs was <250 nm and found to be spherical under microscopy. SLNs were found to be stable for 1 month at 4°C and stable at acidic pH of 1.2. *In vitro* cellular studies predicted promising antiglioma activity[93,94]. Various transfection based surface coating can be done over the lipidic carriers for drug targeting and rapid uptake by cells. Some researchers reported surface modification with peptide to facilitate internalization of peptide decorated lipidic carriers. These surface fabricated ligands on lipidic carriers can be used to target the receptors which are overexpressed on the cellular surface of cancer cells and improvement of the binding with the cells thus paving the way for selective targeting. Polyethylene glycol coating on lipidic carriers avoid reticuloendothelial system uptake and prolongs the circulation time in plasma. PEGylation also

provide hydrophilicity to the lipidic carriers thus aids in easy permeation of the nano-carriers[95].

6. Effective tumour targeting by phytomedicines-loaded lipidic nanoparticles and mechanistic insights

Amphiphilic nature of lipidic carriers enables the assemblage of single or combination of bilayer concentric structures which are well dispersed in water. Lipidic carriers provide an excellent alternative for various biopharmaceutical issues like insolubility, shortened half-life, toxicity and many more. Vesicular systems provideexcellententrapment for water insoluble drugs and enhance the solubility[96]. Furthermore, vesicular systems tend to delay the metabolism of drugs and protectthemfrom certain enzymes ultimately paving the way for sustaining the release of bioactive in the physiological system. Lipidic vesicular systems provide protection of entrapped bioactive from the body tissues and selectively uptaken by the cancer cells. Both hydrophobic and hydrophilic phytoconstituents can be loaded in lipidic vesicular systems. Hydrophobic constituents entrap inside the bilayer of liposome and hydrophilic constituents are entrapped on the bilayer interface[97]. As per the literature reports, various researchers have reported promising anticancer activity of the phytoconstituents delivered through vesicular carriers. Various researchers prepared new generation liposomes by conjugating them with phytochemical constituents. Polar head of lipids were conjugated with herbal bioactives which enhances the pharmacodynamic and pharmacokinetic properties of phytoconstituents. The collective term coined for these next generation nanocages are "Phytosomes"[98].

Literature reports have indicated that biocompatible polymers have paved much attention in the area of clinical trials for targeting phytomedicine with anticancer activities in a suitable carrier system. Polymeric nanocarriers have predicted promising potential for phytomedicine delivery. USFDA has approved various biopolymers for biomedical applications. PLGA is one of the most acceptable polymers due to its promising biocompatibility nature. Curcumin loaded

in PLGA significantly inhibits proliferation in various cell lines like PC3, DU145, LNCaP, A2780CP, MDA-MB231, A549,and also in various cancer induced murine models. Conjugation of PLGA nanoparticles with receptors (like antibody, epidermal factors, peptides), PEGylation, binding with ligands (like 1,2-distearoylglycerol-3-phospho-ethanolamine) helps in providing more specificity for targeting to cancer cells [99]. PLGA loadedsilymarin nanoparticles inhibited cancer proliferation by induction of apoptosis[100]. Furthermore, grape seed extract loaded in PLGA nanoparticles provided enhancement in apoptotic index in comparison to free extract[101].

Chitosan is a positively charged polymer with chains of D-glucosamine and N-acetyl glucosamine conjugated via β-(1,4)-glycosidic bonds and has shown immense ability for various drug delivery applications. Numerous properties of chitosan like biocompatibility, biodegradability and adjuvant pharmacological properties (like anticancer, antifungal, antimicrobial) make it for designing more suitable nanocarriers [102]. Chitosan is used as a suitable material for synthesis of nanocarriers for the delivery of anticancer bioactives such as quercetin, resveratrol[103], epigallocatechin-3 gallate (EGG), curcumin. PLGA and chitosan-based nanoparticles showed exceptional promise in enhancing the stability and solubility propertiesof resveratrol [104]. Further, casinophosphopeptideconjugation on chitosan for EGG-loaded nanoparticles showed enhanced antioxidant activity[105]. Metallic nanoparticles were also studied for prominent anticancer activities. In a report, EGG surface adsorbed on the gold nanoparticles showed significant reduction in the bladder tumour size in a murine model[106]. Furthermore, EGG conjugation with gold nanoparticles have shown promising potential against murine B16F10 melanoma cells[107].

It has been observed that the most important perspective of cancer therapy is specific targeting of the drug molecules to the cancer cells followed by their destruction without affecting non cancerouscells[108]. Longer circulation profile of the nanotherapeutics in plasma with escape

from RES uptake have shown great promise in cancer [109]. For passivedrugtargeting to cancer cells, EPR effect is very useful when particle size>100 nm isaccessible to the cancer cells[110]. Besides, the approach of masking of the nanoparticles with stealth bioprotective coating has also shown great success in RES escape regardless of the size. Hydrophilic coating also helps in passive targeting of the nanoparticles which repels plasma proteins and inhibit RES uptake. Enhanced circulation time masked nanoparticles helps in attaining maximal accumulation in the tumour bearing organs. PEGylation is considered as a linker with ligand property which reduce the stereo inhibition between ligand and receptor[111]. Generally, plasma proteins with size >10 nm can't pass the filtration barriers (exception to kidney defects and nephritis). For designing the nanosystem with effective targeting ability, the sound knowledge on pathophysiological perspectives of cancer should be considered. Targeted nanocarriers face many checkpoints prior to entry into the cancer system. The key barriers include muscular and endothelial, along with high cellular density and interstitial fluid pressure in tumour microenvironment. For overcoming these barriers new and alternative approaches are under development like targeting with endothelial system, thus aids in better permeation in vasculature and circumnavigate high density cellular matrix and interstitial fluid volume. These approaches starve the cancerous cells from oxygen and essential nutrients required for their survival. These targeted nano systems enable to release the contents deep inside the tumour environment. For an effective chemotherapy, there is need to develop a combinational approach of targeted ligand and vesicular-based carrier systems for each tumour.

7. Clinical trials, regulatory status and commercial landscape

Luteolin (a flavonoid 3',4',5,7-tetrahydroxyflavone) nanoformulation is under Phase I trial for lip and oral cavity cancer. Initial *in vitro* studies were done on squamous cell carcinoma cell lines (TSCC, OSCC, HNSCC) which reveal promising results by targeting Caspase 3 gene expression and induces apoptosis[112,113].Polyglutamate (a biodegradable polymer)

conjugated with paclitaxel to form paclitaxel-poliglumex complex demonstrated more survival rate in females in comparison to males. This gender-based response was in correlation with cathepsin B activity and estrogen levels. Cathepsin B activity is closely in relation to taxol release from the novel conjugated system. Thus, it was summarized as both estradiol levels as well as Cathepsin activity are potential biomarkers for prediction of effective treatment[114]. The best example known till date is Liposomal doxorubicin and is regarded as reference standard for clinical practice. PEGylation of liposomal Doxorubicin (Doxil® by Johnson and Johnson; Lipo-Dox® by Taiwan Liposome) had been approved for metastatic breast cancer (MBC), multiple myeloma, ovarian cancer, Karposi's sarcoma with more effectiveness and reduced cardiotoxicity. Myocet® is another doxorubicin-loaded liposomal product in combination with cyclophosphamide approved by European Union (EU) and Health Canada against MBC treatment. These novel systems provide more accumulation at tumour site by EPR effect due to the presence of leaky vasculature[115]. Myocet reported very less cutaneous reactions like skin related side effects, low cardio toxicity and hemato toxicity. Other liposomal formulation Galen (Daunorubicin), DepoCyt (Cytarabine), Marqibo (Vincristine sulfate) had been approved for lymphomatous meningitis, Karposi's sarcoma, children osteosarcoma, acute lymphoblastic leukemia with certain restrictions[115]. All the above-mentioned liposomal formulations were not found very highly effective in comparison to conventional dosage forms. This could leads to the failure of these systems to release drug near tumour site. After the failure of these trials, cationic liposomes were developed for better anticancer drug delivery. The cationic surface charge initiates binding with the endothelial cells which are negatively charged for the enhanced therapeutic activity. However, this remains a myth that such formulations can be a potential candidature for the clinical phases.

There has been a paradigm shift in the drug targeting approaches to the tumour cells using receptor-based endocytosis mechanism. The clinical trials have shown that immunoliposomes

of doxorubicin surface modified with antigen fragments of cetuximab with specific binding ability to EGFR[116]. However, such formulation was failed in clinical trial phase I without any promising results. Thermal sensitive liposomal formulation of doxorubicin was developed under the commercial name Thermo Dox®. This is the most advanced system developed using lysolipid thermally sensitive liposome (LTSL) which undergoes structural transformation at 40° to 45° C. Such formulation system showed 25-times higher delivery of doxorubicin as comparison to that of the intravenous administration of conventional doxorubicin and 5-times higher efficacy in comparison to the liposomal doxorubicin at the tumour site. Furthermore, Thermo Dox® acts on tumour biology by two ways: first way is that liposomes have more permeability in leaky vasculatures and second way is heating provides more permeation to the site of tumour. Phase III clinical trials have indicated the efficacy of Thermo Dox® in primary liver cancer with an average of 2 year enhancement in life expectancy. Similar clinical trials were performed for breast cancer up toPhase II trials, in combination with radiation ablation against the liver neoplasms and hepatocellular carcinoma in Phase III[117–119].

Development of polymeric conjugates for delivery of anticancer drugsto the target site is also considered as a very effective alternative. Irinotecan, a semisynthetic derivative of camptothecin, conjugated with PEG (Etirinotecan pegol) showed four times higher plasma half-life in preclinical studiesand excellent tolerability and pharmacokinetic profile in phase III clinical trials [120]. Micelles are another group of novel formulations which provide hydrophilic coating or shells because of their amphiphilic and self assembling properties. Hybrid-nanosystem prepared is polymeric micelles that have advantages like small size, better hydrophobic drug payload and increase in blood circulation time or retention time. Genexol containing Cremophor EL entrapping paclitaxel in a micellar system showed enhanced performance against breast cancer and colon cancer in South Korea[121]. Livatag (Doxorubicin) and Paclical (PTX) polymeric micelles prepared using polyalkylcyanoacrylate

are approved for ovarian and hepatocellular carcinoma by FDA and EU[122]. Abraxane contains albumin nanoparticles of PTX was first approved in 2005 by FDA against MBC. Advantage for Abraxane over other PTX based nanosystem is the use of solvents like Cremophor EL that have some persistence for polyneuropathy. Therapy of Abraxane was also extended for other tumours like pancreatic, colon, head and neck cancer[123]. **Figure 3** provides instance of various nanophytomedicines under clinical trials, while **Table 2** summarizes clinical trials in relation to nanophytomedicine-based therapeutics for diverse cancer treatment.

8. Opportunities in lipidic nanotherapeuticsystems for cancer treatment

8.1 Nanolipid bubbles (NLB)

NLBs are stabilized nano-sized lipid bubbles with outer covering of lipid and internal void structure. Recently, such carriers have attracted wider attraction in drug delivery imaging using the ultrasound guided targeting approach. NLBs have advantage of ease of penetration in tumour region with high drug loading capacity and drug stability. Till date, NLBs are explored for molecular imaging as well as drug and gene delivery applications. For instance, application in prostate cancer imaging where PSMA over expression helps in binding A10-3.2 aptamer into the NLBs [124]. NLBs also provide synergism in the thermal ablation therapy for breast cancer treatment using microbubbles or liquid perfluorocarbon droplets. Apart from NLBs, lipidic nanocapsules (LNCs) are vesicular systems filled with core containing active constituents are embedded in the reservoir coated with a polymeric layer. LNC enables intratumoural distribution, tailored drug release profile and protection of the drugs from premature degradation. LNCs loaded with hypericin prevents genesis of aggregation in aqueous media thus improves aqueous solubility and production of singlet oxygen species using photodynamic therapy in cancer. *In vitro* cell line studies have shown significant reduction in the cell viability in HeLa cells[125].

8.2 Nanosponges (NS)

These are novel hyper-cross linked polymer constituted of cyclodextrins. These are colloidal particles in nano range and can encapsulate a large number ofdrug molecules. These porous and small sized structures have effortless binding with lipophilic drugs for better solubility and bioavailability. NS can be explored for tailoring the release and encapsulate both hydrophobic as well as hydrophilic drugs, biosensors, delivery of protein and genes, photothermal application[126–128].

8.3 Tocosomes

Tocosomes are another class of novel delivery system. The preparation of tocosomes is done using two derivates of vitamin E (i.e., di-α-tocopheryl phosphate and α-tocopheryl phosphate)and encapsulating with phospholipids or lipids like stearyl amine, phosphatidylcholine and phospholipon (both 100 H and 90 H). These tocosomes have higher encapsulation efficiency, narrow distribution of size, high stability even for more than 2 years[129].

8.4 Smart delivery systems

Nanocarrier based drug delivery systems release drug by trigger from the specific physiological systems at targeted site and exact time are explained as smart system. Structural composition of delivery system changes on application of internal or external stimulation and final releasing an encapsulated drugs[130]. These structural changes are in conformational with the tumour physiological microenvironment. pH sensitive nanosystems with encapsulation of basic or acidic drugs triggers the release of protons from tumour microenvironment. pH of tumour microenvironment is from 6.5 to 6.8, while endosome or lysosomes have acidic characteristics with pH ranging from 4.0 to 6.3. Temperature or thermo sensitive nanosystems tend to change their structural conformation or release the drug pay load when delivered in elevated temperature physiological environment. These nanosystems fabrication can be done via

biosensitive extracellular vesicles like glucuronidases, proteases, and carboxylesterases. In similar fashion light, ultrasound, magnetic based smart nanosystems are involved for encapsulation of herbal drugs as green cargos for diffusion. External application for triggering the release was done for these smart systems. Furthermore, smart conjugated systems were also under development in which cleavage of these bonds were done by enzymatic action before the drug diffusion will take place.

Another system which has paved the way for recent application in cancer therapeutics is "Theranostics". These systems are dual carriers with application of drug delivery and diagnosis both. These advanced systems are used for selective targeting to the diseased organ or tissue and to curb the menace of disease by upsurging the therapeutic or diagnostic selectivity. These theranostics makes the treatment shorten, safe and effective. Recently nanomedicines emphasized its concerns to provide specific therapy and diagnosis. Another advancement includes tagging nanocarriers with dyes of contrast agents for fluorescent, magnetic, optical imaging provides better theranostic ability[131].

9 Future prospects and conclusions

Nanophytomedicines have proven to be highly effective in augmenting the biological performance and reducing the side-effects of conventional anticancer therapy. There is a general notion for nano-based therapeutic system is high cost over the conventional drug carriers. However, nano-based therapeutics hasbenefitsof reducing the dose and maximizingefficacy. Various factors contributing the success of nanophytomedicinesinclude regulatory approval process across the globe, geographical barriers and commercialisation opportunities. More efforts need to be given on screening the materials used for the development of carriers along with control of the chemistry and manufacturing process to produce the nanomedicines with high quality and efficacy.

Conflict of Interest

The authors declare no conflict of interest among themselves.

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Table 1: Summarized studies of Nano phytoconstituent done for Cancer

Phytoconstituent	Nanocarrier	Type of Cancer	Studies done on
Curcumin	Nanodisk using apolipoprotein scaffold	Hepatic	*In vitro*: Jeko and HepG2 cells
	Methyl and ethyl cellulose nanospheres	Breast and Hepatic	*In vitro*: HepG2 and MCF7 cells
	MethoxyPEG-palmitate amphiphilic micelles	Cervical	*In vitro*: Hela cells
	Human serum based albumin nanoparticles	Colon	*In vitro*: HCT116 cells
	Fibrinogen	Breast	*In vitro*: PC3 and MCF7 cells
	PLGA nanospheres		*In vitro*: PC3, LNCaP and DU145 cells
	PLGAsulfosuccinimidyl nanoparticles		*In vitro*: MDA-MB-3 cells
	PEG-5000-PLGA nanoparticles	Breast, colon, leukemia, oesophageal	*In vitro*: MDAMB-231, Jurkat, KBM-5, DU145, HCT116, and SEG-1 cells
	PLGA nanoparticles	Hepatocellular	*In vivo*: N-Nitrosodiethylamineinduced hepatic carcinoma in rats
	PLGA nanoparticles (PVA stabilised)	Ovarian and Breast	*In vitro*: MDA-MB-3 and A2780CP cisplatin resistant cells
	Co-administered with Doxorubicin PLGA nanoparticles	Myelogenous leukemia	*In vitro*: K-562 cells
	Chitosan-dextran sulfate nanoparticles	Breast	*In vitro*: PC3 and MCF7 cells
	Chitosan nanoparticles		*In vitro*: MCF7 cells
	Tricomposite: Chitosan, alginate, pluronic nanoparticles	Cervical	*In vitro*: HeLa cells
	Chitosan/PCL nanoparticles		
	Chitosan coated PBCA nanoparticles	Hepatocellular	*In vitro and In vivo*: HepG2, Huh7 and Bel7402 and xenografted murine model
	Co-administered with Doxorubicin PBCA nanoparticles	Breast	*In vitro*: MCF7 cells
	N-isopropylacrylamide, N-vinyl-2-pyrrolidinone, and PEG acrylate micelles	Pancreatic	*In vitro*: BxPC3, AsPC1, MiaPaca, XPA-1, XPA-2, PL-11, PL-12, PL-18, PK-9, and

			Panc 2.03 cells
	Chitosan-g-poly (N-isopropylacrylamide) and chitosan-g-poly (N-vinylcaprolactam) nanoparticles	Breast	*In vitro*: MCF 7, PC3, KB cells
	β-cyclodextrinnanosponges	Prostate	*In vitro*: C4-2 and DU145 cells
	2-hydroxypropyl-γ-cyclodextrin decorated liposomes	Breast	*In vitro*: MCF 7 and KHOS cells
	Hybrid nanogels: polystyrene inner shell and PEG outer shell with bimetallic Ag/Au nanoparticle core	Melanoma	*In vitro*: B16F10cells
	Nanogels: chitin	Melanoma	*In vitro*: A375 cells
	Chitosan-cholesterol micelles	Breast	*In vitro*: MCF 7 cells
	Chitosan nanoparticles	Oral	*In vitro*: SCC 9 cells
	Co-administered with Chrysin PLGA nanoparticles	Colorectal	*In vitro*: Caco-2 cells
	Co-administered with metformin PLGA nanoparticles	Breast	*In vitro*: T47D cells
	Co-administered with docetaxel PLGA nanoparticles	Breast and Prostate	*In vitro*: MCF 7 and DU145 cells
	Co-administered with Paclitaxel PLGA nanoparticles	Ovarian	*In vitro*: A2780 cells
	Co-administered with 5-fluorouracil PLGA nanoparticles	Breast	*In vitro*: MCF cells
	Co-administered with aspirin PLGA nanoparticles	Ovarian	*In vitro*: SKOV3 cells
Epigallocatechin gallate	PCL-Carbon nanotube based nanofibers	Hepatocellular	*In vitro*: A549 and HepG2 cells
	Co-administered with Caffeic acid based PCL nanofibers	Adenocarcinoma	*In vitro*: MKN-28 cells

	Polysaccharide nanoaprticles: (maltodextrin-gum arabic matrix)	Prostate	*In vitro*: DU145 cells
	Gold nanoparticles	Bladder	*In vivo*: MBT-2 murine bladder tumour
	Caseinophosphopeptides and chitosan	Gastric carcinoma	*In vitro*: Caco-2 cells
	PLA–PEG	Breast	*In vitro*: PC 3 cells
	PCL–PLGA–PEG	Prostate	*In vitro*: PSMA-expressing LNCaPcells
	Gelatinnanoparticles	Breast	*In vitro*: MDA-MB-3 cells
	Folate-targeted BSAnanoparticles		*In vitro*: PC 3 cells
Resveratrol	Resveratrol-methoxyPEG-PCL nanoparticles	Glioblastoma	*In vitro*: C6 cells
	DQA–PEG2000–DSPE–liposomes	Hepatocellular	*In vitro*: A549 cells
	Tranferosomes: surfactant polysorbate 80, sodium cholate, and sodium deossicholate	Skin	*In vivo*: Murine model
	BSA nanoparticles	Ovarian	*In vivo*: SKOV3implanted in nude mice
Silymarin	PLGA nanoparticles	Breast	*In vitro*: PC-3 cells
Saponin	Nanosaponin cross linked with sodium tripolyphosphate		*In vitro*: L929 and PC3 cells
Grape seed extract	PLGA nanoparticles		*In vitro*: MCF 7 cells

PLGA- Poly(lactic-co-glycolic) acid, PEG-polyethylene glycol, PVA- Polyvinyl alcohol, PCL- Poly(ε-caprolactone), PBCA- Polybutylcyanoacrylate, DQA- Dequlinium, DSPE-Distearoylphosphatidylethanolamine, BSA-Bovine serum albumin

Table 2: Phytomedicine-based nanotherapy approved for clinical studies

Nanocarriers	Phytoconstituents	Product name	Intended for
Liposomes	Doxorubicin	Doxil	Karposi's sarcoma, Ovarian cancer, Multiple myeloma
		Caelyx	Karposi's sarcoma, multiple myeloma, breast andovarian cancer
		Lipo-Dox	Karposi's sarcoma, breast and ovarian cancer
		Myocet	Breast cancer (Co-administration with cyclophosphamide)
	Daunorubicin	DaunoXome	Karposi's sarcoma
	Vincristine	Marqibo	Acute lumphocyticleukemia
	Irinotecan	MM-398 (PEP02)	Pancreatic cancer
Smart thermo sensitive based nanosystems	Doxorubicin	ThermoDox	Hepatocellular carcinoma
Drug-conjugates	Irinotecan	NKTR-102/Etirinotecan pegol	Breast cancer
	Paclitaxel	Paclitaxel poliglumex (PPX)	Non small cell lung cancer
Micelles		Genexol-PM	Breast cancer
		Paclical	Ovarian cancer
	Doxorubicin	Livatag	Hepatocellular carcinoma
Albumin-bound nanoparticles	Paclitaxel	Abraxane	Breast cancer, Pancreatic cancer, Non small cell lung cancer

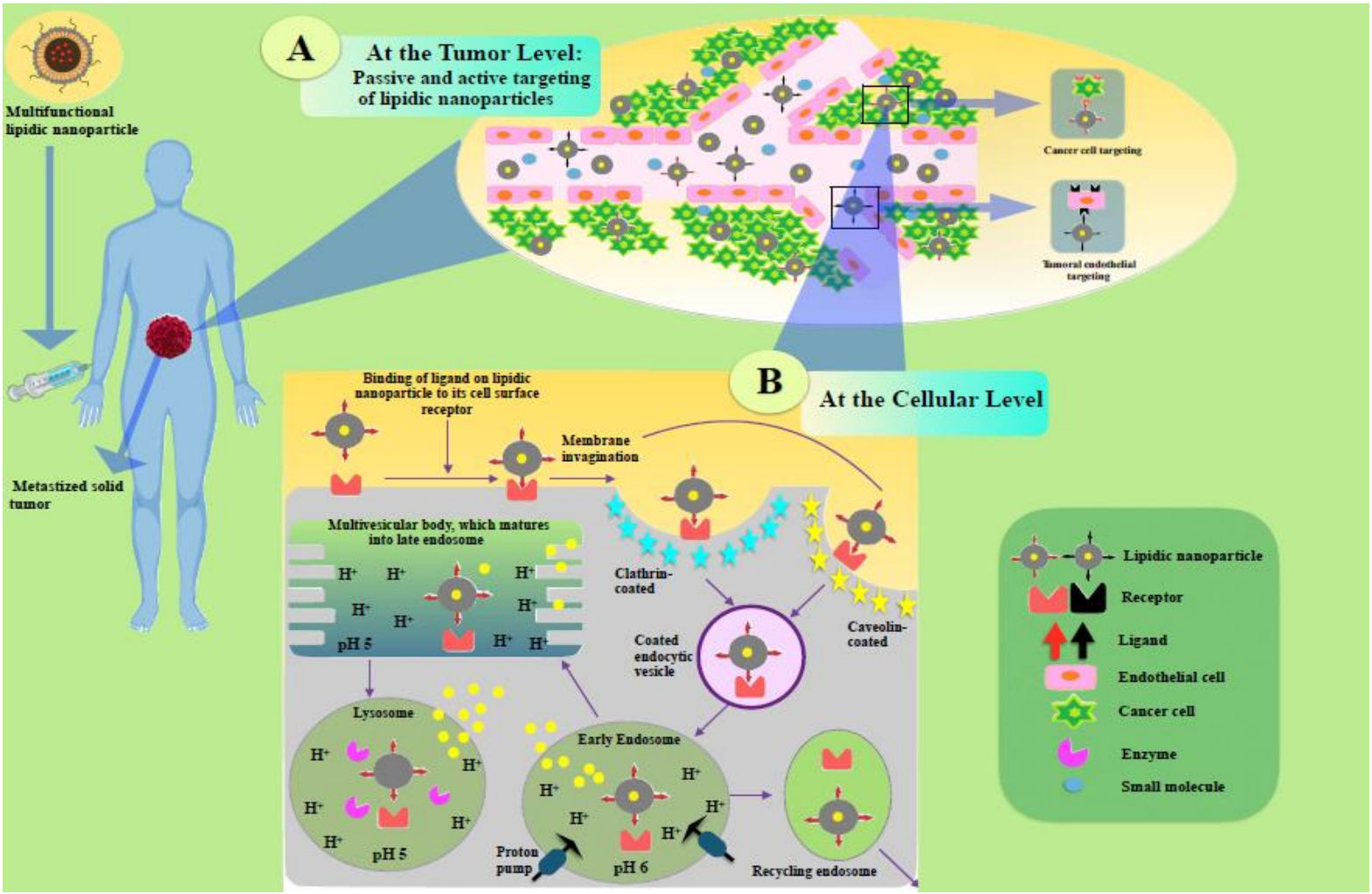

Figure 1:Mechanistic insight on lipidic nanoparticles for tumour targeting application and cascade of physiological events at molecular level;[A]*(i)Passive targeting of lipidic nanoparticles and(ii)Active targeting of nanoparticles to cancer tumours,* (B) *Uptake of lipidic nanoparticles via receptor-mediated endocytosis*

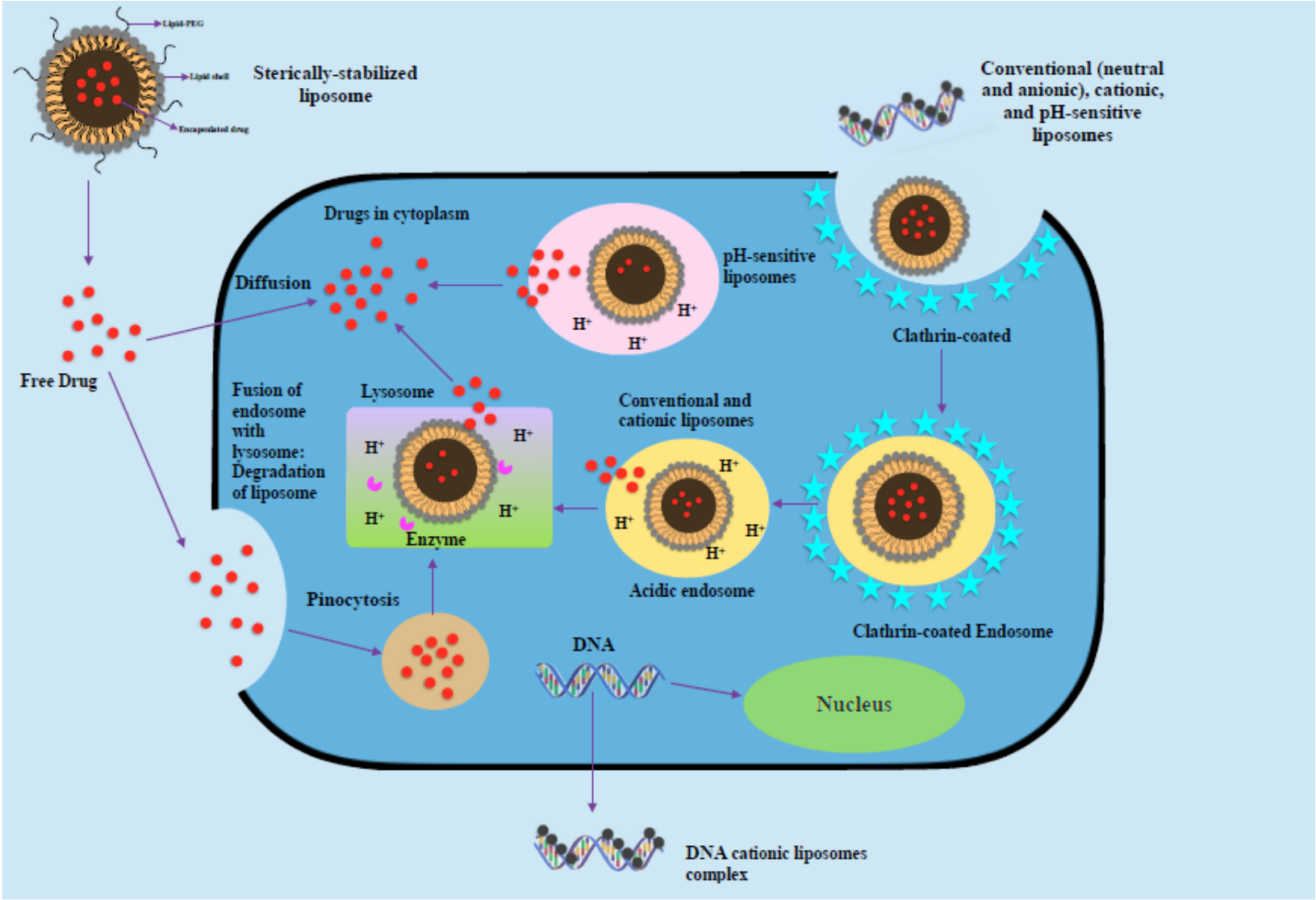

Figure 2: Cellular uptake pathways of different types of multifunctional lipidic carriers

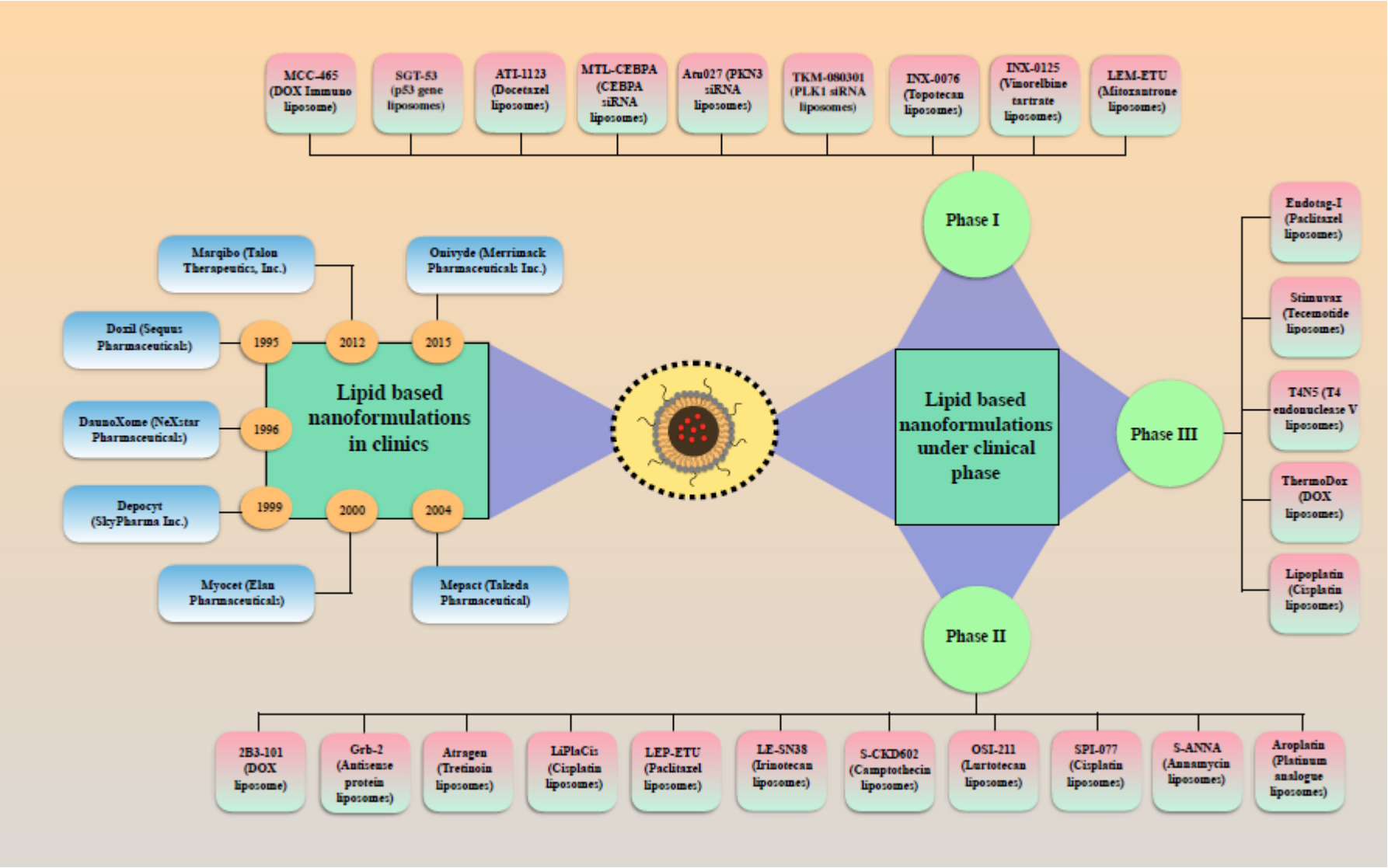

Figure 3:Overview of the lipid-based nanoformulations of chemotherapeutic agents in clinics and under clinical trials (Phase I, II, III)