Chapter 6
Applications of Nano-based Novel Drug Delivery Systems in Herbal Medicine-Mediated Cancer Therapy

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Abstract Nanotechnology is a fast-growing field with numerous applications in the field of medical science. One such application comprises nanoparticle biosynthesis from plant extracts and their compounds with their potential applications in cancer therapy. These plant-based nanoparticles have been observed to be effective against various types of cancerous cells both *in vitro* and animal models. Another application of nanotechnology is the herbal therapeutics comprising the use of novel nano-based drug delivery systems in the treatment of cancer. These novel drug delivery systems aid in increasing the therapeutic value and bioavailability of the herbal medicine. The application of nanoherbal formulations as novel drug delivery systems (NDDS) is more valuable as compared to other therapies. These novel drug delivery systems include phytosomes, liposomes, microsphere, nanocapsules, ethosomes, transfersomes, nanoemulsions, and polymeric nanoparticles. The effectiveness of these different plant-based nanodrug delivery systems has been studied against various cancer types. These alternative drug delivery systems help in increasing the efficiency of a drug delivery and safeguard the drug from metabolic processes alongside its sustained delivery, proper distribution, and protection from physical and chemical deterioration. In addition, they reduce the possible side effects of the drugs. In spite of the advancements, cancer endures to be a predominant and fatal disease. This has led to the increased use of nano-based anticancer drugs and their delivery systems, also known as nanotherapies against tumors due to their ability of site-specific targeting and multifunctionality. In this chapter, recent advancements in application of plant-based nanomaterials in cancer therapy and impending strategies are discussed.

Keywords Drug delivery systems · Ethosomes · Nanocapsules · Nanoemulsions · Nanotechnology

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6.1 Introduction

Cancer is characterized by a condition when there is an uncontrolled growth of cells, having the capacity to invade and spread to distant body parts. The World Health Organization (WHO) has reported that among the main determinants of morbidity and mortality throughout the world, cancer is a major cause and it is projected to increase by 70% in the next two decades. The worldwide deaths estimated due to cancer till 2012 are 8.2 million with lung cancer topping the list, followed by liver, stomach, colorectal, and breast cancers (WHO 2015). Natural products from plant resources are being used in the treatment of different disorders in Egypt, China, India, and Greece from ancient times, and numerous drugs have been developed from medicinal plants (Arumugam et al. 2016; Swamy et al. 2016, 2017; Swamy and Sinniah 2016; Mohanty et al. 2017). The first documented proofs on the uses of medicinal plants date back to 2600 BC. Researchers throughout the world are focusing on use of herbal medicines to modulate immune system against cancer. Thorough understanding of the synergistic interactions of different constituents of herbs possessing anticancer activity and novel formulations can be useful to kill the cancerous cells without any other cellular toxicity. The very first phytochemicals that are being used clinically include vinca alkaloids, vinblastine, and vincristine from the Madagascar periwinkle, *Catharanthus roseus* (Apocynaceae). The isolation and identification of paclitaxel from the bark of Pacific yew, *Taxus brevifolia* Nutt. (Taxaceae), also represent the successful application of a natural product in the field of drug discovery. Epipodophyllotoxin, an isomer of podophyllotoxin, has been isolated and is reported to have antitumor activity. Etoposide and teniposide are another two semisynthetic derivatives of epipodophyllotoxin which are being utilized in the treatment of lymphomas and bronchial and testicular cancers. *Bleekeri avitensis* A.C. Sm., a medicinal plant of Fijian origin, is being used in France for treatment of breast cancer (Cragg and Newman 2005). Similarly *Allium sativum* consists of more than 100 biologically active secondary metabolites including alliinase, alliin, S-allyl cysteine (SAC), allicin, diallyl trisulfide (DATS), diallyl disulfide (DADS), and methyl allyl trisulfide. *Aloe vera* contains aloe emodin, a compound reported to activate the macrophages against cancer. Silvestrol isolated from the fruits of *Aglaia silvestris* (M. Roemer) Merrill. (Meliaceae) is reported to exhibit cytotoxicity against lung and breast cancer cell lines (Cragg and Newman 2005). Acetogenins isolated from *Annona* species possess significant anticancer activity against leukemia and sarcoma. *Arctium lappa* consists of various potent anticancer agents and is being used in the treatment of malignant melanoma, lymphoma, and cancers of the breast, pancreas, esophagus, ovary, bile duct bladder, and bone (Shabani 2016).

Different alkaloids and flavonoids isolated from numerous medicinal plants exhibit cytotoxic efficacy against different types of cancerous cells both *in vitro* and *in vivo* (Mohanty et al. 2014, 2017; Swamy and Sinniah 2015). One of the modes of

action of these compounds includes inhibiting cancerous cell growth. Nanotechnology has helped in the development of new dosage forms in medicine. Till now, researchers have majorly concentrated on the use of metallic nanoparticles due to their rapid actions. Metallic nanoparticles possess unique physical and chemical properties due to their size leading to diverse biomedical applications. Silver, gold, iron oxide, zinc oxide, aluminum oxide, and copper oxide are some of the major metallic nanoparticles synthesized (Rudramurthy et al. 2016; Kanagesan et al. 2016a, b).

AgNPs synthesized using *Premna serratifolia* leaves exhibited noteworthy anticancer activity in carbon tetrachloride (CCl_4)-induced liver cancer in a study performed on Swiss albino (BALB/c) mice. In another study by Sre et al. (2015), the cytotoxic activity of biologically synthesized AgNPs using *Erythrina indica* on MCF-7 (breast cancer) cells and HepG2 (hepatocellular carcinoma) cells was reported. The *in vivo* and *in vitro* cytotoxic effects of AuNPs have also been stated in numerous studies, exhibiting the anticancer properties of AuNPs by the induction of oxidative stress. AuNPs synthesized using *Gymnema sylvestre* leaf extracts have also been investigated for their anticancer activity against hepatocellular carcinoma (HepG2) cell lines at concentrations of 250 μg/ml (Rao et al. 2016). Iron oxide nanoparticles have been observed for their antitumor activity both directly and indirectly via nontoxic wavelength radiation, which gets readily absorbed by toxic stimuli of reactive oxygen species production. The synthesis of iron oxide (Fe_3O_4) nanoparticles from seaweed (*Sargassum muticum*) has also been stated recently. Titanium oxide is another inorganic nanoparticle which can be surface-modified for inhibition of tumor cell growth. The advancements in nanotechnological approaches have the capability to deliver a solution to limitations faced by other dosage forms. It can be surface-engineered to inhibit tumor growth. The innovative nanotechnological approaches may provide a solution to limitations faced by many of phytochemical, physicochemical, and pharmacokinetic properties (Rao et al. 2016). This chapter discusses on the role of nano-based formulations and their applications in the field of herbal medicine and applications of nanotechnology in designing novel drug delivery systems containing bioactive compounds from the plant origin.

6.2 Hallmarks of Cancer

Cancer reconceptualization has come due to research advancements that have been made in the past decades at the molecular, cellular, and biochemical levels. Some of the specific traits which are acquired by the cancer cells result in the complexity of treating this disease. These features include self-reliance in growth signals, antigrowth signal insensitivity, unlimited replication capacity, persistent angiogenesis, avoidance to apoptosis, invasion, and metastatic potential (Fig. 6.1). These characters are shared by almost all types of cancer (Flavahan et al. 2017). Several growth

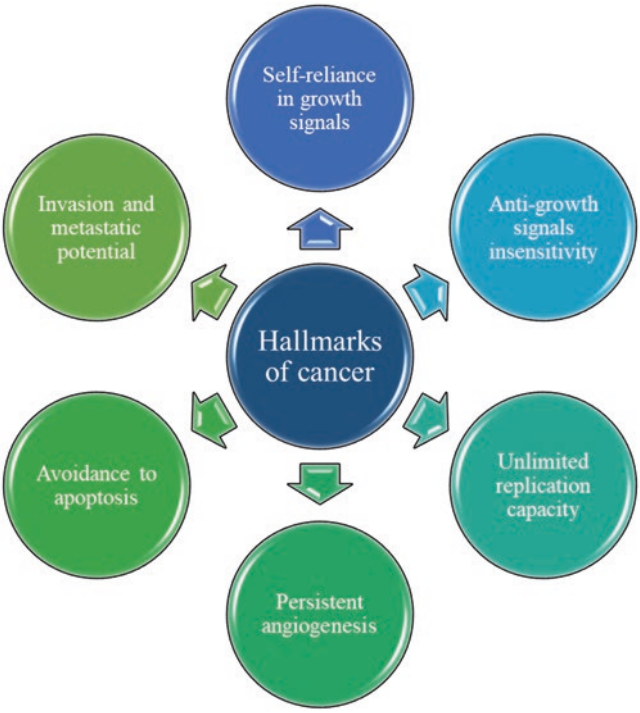

Fig. 6.1 Diagrammatic representation of various cancer hallmarks

and anti-growth signals regulate the cell cycle carefully in normal cells. Cancer cells disrupt these regulatory mechanisms and impart their own proliferative signals. Growth factors are supplied to the cancer cells via either growth factor ligands produced by themselves or by stimulation of the normal tumor-associated stromal cells which supply growth factors necessary for the cancer cells in return (Bhowmick et al. 2004). The cancer cells have the property to evade the growth suppressors in order to have prolonged growth-promoting factors. Various tumor suppressor genes have been investigated and certified, out of which two proteins, namely, RB (retinoblastoma-associated) and TP53 (tumor protein p53), play crucial roles in cell senescence and apoptosis. The cellular signals from varied extracellular ligands incorporated by RB protein decides the fate of a cell, i.e., whether a cell should proceed in the cell cycle or not (Burkhart and Sage 2008; Hanahan and Weinberg 2011; Flavahan et al. 2017). TP53 gene can stop the cell cycle in the presence of abnormal signals until the reappearance of normal conditions or otherwise in conditions of a permanent damage to DNA and apoptosis induction (Evan and Littlewood 1998; Xia et al. 2017).

Cancer cells have the ability to escape the natural cell barrier to cancer growth, i.e., apoptosis. Different members of Bcl-2 family molecules regulate apoptosis.

Cancer cells have different mechanisms to avoid apoptosis including damage to TP53 function, enhancement in anti-apoptotic factor expression, and decreased expression of pro-apoptotic factors (Adams and Cory 2007; Dzutsev et al. 2017). Due to senescence and crisis phase, normal cells undergo a limited number of cell cycle, but these obstacles can be bypassed by cancer cells resulting in the immortalization and infinite potential of replication. At the end of the chromosomes, telomeres are present that prevent the end-to-end fusion of normal cell DNA which can frighten the cell viability. The length of telomeric DNA is also regulated, but in the cancer cells, telomerase (a DNA polymerase enzyme) responsible for addition of the telomere at the DNA ends and prevents the telomere erosion (Dagg et al. 2017).

Cancer cells are capable of developing new blood vessels by activating an "angiogenic switch." Pro- and anti-angiogenic members regulate this process (Folkman and Shing 1992). Angiogenesis can be inhibited by TSP-1 (thrombospondin-1), endostatin, and angiostatin; these are natural barriers. Tumor progression in mice has been seen after deleting the genes encoding these inhibitors (Nyberg et al. 2005). Tumor cells invade and metastasize by establishing the communication between tumor cells, tumor microenvironment, and stromal cells (Ost et al. 2015). Cancer cells also require the nutrients for growth. Recent discoveries have investigated that the cancer cells also have the capability to reprogram the cell's metabolism in order to get the fuel (van der Heiden and De Berardinis 2017). Potential of cancer cells to evade the immune system has also been reported (Flavahan et al. 2017). These features provide the basic stage for most of the cancer research advancement and are helpful in revealing the cancer concepts.

The worldwide load of cancer augmented to approximately 14 million new cases per year in 2012, which is further expected to increase at a rate of 22 million annually in the next two decades. It is also projected that cancer deaths are going to increase from 8.2 to 13 million annually. Worldwide, most common types of cancers diagnosed in 2012 were lung (1.8 million cases, 13.0% of the total), breast (1.7 million, 11.9%), and large bowel (1.4 million, 9.7%). The cancers most commonly responsible for deaths include lung (1.6 million, 19.4% of the total), liver (0.8 million, 9.1%), and stomach (0.7 million, 8.8%) (GLOBOCAN 2012). In this regard, phytomedicines have been playing as important source of pharmacologically active compounds since ancient times, and their usage has increased owing to their therapeutic activity and lower effects as compared to other drugs. Nanotechnology can be employed to improve targeted delivery of drugs, delivery of poorly water-soluble herbal drugs, co-delivery of two or more drugs, release of large herbal molecules, and observation of sites of drug delivery by incorporating herbal drugs with imaging modalities (Liong et al. 2008; Lambert 2010; Gunasekaran et al. 2014). Researchers in the fields of herbal medicine and nanomedicine have observed that therapeutic nanoparticles (NPs) are more effective drug delivery system as compared to traditional drug delivery systems.

6.3 Role of Plant-Based Remedies and Herbal Medicine in Cancer Treatment

Herbal products, specifically medicinal plants, are being utilized in the treatment of various diseases since thousands of years. Terrestrial plants are being employed as medicines in India, China, Egypt, and Greece from thousands of years, and a large number of modern chemo drugs against cancers have been discovered and synthesized from them. The first compounds/agents taken into clinical use for different types of cancer treatment including lymphomas, leukemia, lung and breast cancers, advanced testicular cancer, etc. include vinca alkaloids (vinblastine and vincristine) isolated from *C. roseus* which ascertained a new era for utilization of plant materials as anticancer drugs. The revelation of the compound paclitaxel isolated from barks of the Pacific yew, *T. brevifolia* (Taxaceae), also narrates a success story in natural product drug discovery (Cragg and Newman 2005; Stathis et al. 2017). *Taxus baccata* is also reported for its utilization in the Indian system Ayurvedic medicine for treatment of cancer. Paclitaxel is expressively active against advanced breast and small and non-small cell lung cancer. Irinotecan and topotecan are two semisynthetic derivatives synthesized from camptothecin, which are being used in the treatment of ovarian and small cell lung cancer and colorectal cancer, respectively (Bhokare et al. 2016; Stathis et al. 2017). Epipodophyllotoxin, an isomer of podophyllotoxin, is isolated as an antitumor compound from the roots of *Podophyllum peltatum* and *P. emodi* (Berberidaceae). Etoposide and teniposide, two semisynthetic derivatives of epipodophyllotoxin, are being utilized in the treatment of bronchial and testicular cancers and lymphomas (Shabani 2016). Homoharringtonine, isolated from the Chinese tree *Cephalotaxus harringtonia* (Cephalotaxaceae), is also a plant-derived agent take into clinical use (Itokaw and Wang 2005). Combretastatins, isolated from the bark of *Combretum caffrum* (Combretaceae), is active against leukemia and colon and lung cancers (Ohsumi et al. 1998; Sherbet 2017).

6.4 Nanotechnology and Nanomedicine

Technology at the nanoscale is playing a crucial role to unfold solutions for many biological problems that were rigid a few years ago. In recent times, silicon chip technology has helped to manipulate the atoms and molecules resulting in revolution in the field of life sciences. Nanotechnology and nanomedicine are regarded as two complementary disciplines, targeting for betterment of life. Applications of nanotechnology in medicine consist of both materials and devices, which can be designed to interact with living systems at molecular scale with high specificity. This eventually results in their potential applications in targeted cellular- and tissue-specific uses and thus helps in acquiring higher therapeutic efficacy (Gunasekaran et al. 2014; Gortzi et al. 2008). Hence, in the existing situation, nanotechnology is

beneficial in solving problems in different fields of medical science (Bhati-Kushwaha and Malik 2017). Different types of nanomaterials used in therapeutic applications are explained below.

6.4.1 Polymer Nanoparticles

Polymer nanoparticles are colloidal and solid particles having their size in the range of 10–1000 nm. These are also called as nanocapsules and nanospheres. Polymeric nanoparticles are synthesized by using preformed polymers or by polymerization of monomer units. For this purpose, different methods like salting out, solvent evaporation, supercritical fluid evaporation, rapid expansion of supercritical solution, and dialysis are being employed (Ma et al. 2017). The selection of preparation method is done on the basis of numerous factors including the area of application, type of polymeric system, size obligation, etc. The polymeric nanoparticles, prepared by these techniques, have been observed for their efficient therapeutic activities.

Lectins are known to bind carbohydrate moieties. This lectin-carbohydrate interaction is highly specific and can be utilized in development of NPs directed to certain lectins (De Mejia and Prisecaru 2005; Sharon 2007). Various lectins have been observed to exhibit anticancer activities *in vitro*, *in vivo*, and also in human case studies and are being used as therapeutic agents, for inhibition of tumor growth (Parveen and Sahoo 2008). Likewise, Tsutsui et al. (2007) developed a drug delivery system capable of targeting brain tumors using bionanocapsules (BNCs). In their study, they substituted the pre-S1 peptide with the antibody affinity motif of protein A and prepared hybrid BNCs conjugated with antihuman EGFR antibody recognizing EGFRVIII. The results exhibited that the hybrid BNCs were efficiently delivered to glioma cells and not to the normal glial cells. PLG [Poly(lactide-co-glycolide)] and its monomers have been found to have potential in wide applications for encapsulation and delivery of various anticancer drugs. In another study, Zhang and Feng (2006) analyzed the drug encapsulation efficiency, *in vitro* drug release, cellular uptake, and cytotoxicity of TX-loaded poly(lactide)-tocopheryl PEG succinate NPs. The drug encapsulation efficiency and *in vitro* drug release profile of this drug were analyzed using HPLC and the cancer cell lines HT-29 and Caco-2 (Zhang and Feng 2006; Xiong et al. 2017).

6.4.2 Metallic Nanoparticles

Metallic nanoparticles are nanosized metals with size ranging from 1 to 100 nm. There are numerous liquid phase approaches for synthesis of metallic nanoparticles, including chemical reduction, reverse micelle and sol gel, etc. Novel metallic nanoparticles having spherical shape and size were synthesized by different chemical reduction methods (Schwarz et al. 2004; Wang et al. 2008). MNPs have a wide

range of applications owing to distinctive features including large surface area and process a large number of low coordination sites and electronic structure between molecular and metallic states. MNPs are being used in drug delivery, magnetic separation of labeled cells and other biological entities, and also as agents for contrast enhancement in magnetic resonance imaging.

Gold-silver (Au-Ag) nanorods conjugated with molecular aptamers were shown to need up to six times lower laser power irradiation to induce cell death compared to Au nanoshells or Au nanorods. These aptamer Scg8-AuAg nanorod conjugates exhibited exceptional hyperthermia efficiency and selectivity toward CEM cells, larger than the affinity of aptamer probes alone. Bimetallic Au-Ag nanostructures having dendrite morphology have been examined to destroy A549 lung cancer cells. The photothermal activity of these dendrites needed lower NP concentrations and laser power for efficient damage to the cancer cells. AuNPs have been reported for their application as vehicles for the delivery of different anticancer agents, including paclitaxel. The hydrophobic drug administration necessitates molecular encapsulation, and the efficiency of nanosized particles in evading the reticuloendothelial system is well studied (Conde et al. 2012; Hnawate and Deore 2017).

6.4.3 Magnetic Nanoparticles

Magnetic nanoparticles have been produced with numerous different phases and compositions including both pure metals and metal alloys (Schwarz et al. 2004). A number of methods have been reported including sonochemistry, coprecipitation, solvothermal, combustion synthesis, colloidal method, hydrothermal method, thermal decomposition, and microemulsion methods (Iwaki et al. 2003). The key applications of magnetic NPs are in the field of bioseparation processes, in which conjugation of the target biomolecules with magnetic nanoparticles, functionalized with specific receptors, produces complexes and hence can be easily separated using applied magnetic field, thus providing a suitable and time-saving method for bioseparation (Kharisov et al. 2014).

6.4.4 Nanomedicine in Therapeutics

During the past decades, much consideration has been paid to the enhancement of new novel drug delivery systems (NDDS) for herbal medicines. Plant-based unique drug delivery system has advantages over traditional drug delivery systems for delivery of herbal drug at optimal rate and targeted drug delivery, thus minimizing toxicity and enhancing bioavailability of the drug. In these drug delivery systems, the dissemination control of drug is attained by loading the drug in a carrier (Biju

et al. 2006). Herbal compounds have become more popular with time due to their extensive applications in the treatment of a variety of diseases with lower toxicity and enhanced therapeutic effects (Atmakuri and Dathi 2010). But herbal medicines possess some short comings including, instability at acidic pH and metabolism occurring in lever resulting in lower levels of drug in blood. These constrains can be overcome by utilization of nano based novel drug delivery systems (Uhumwangho and Okor 2005). Amalgamation of novel drug delivery technology with herbal compounds reduces the drug deterioration rates, metabolism, and also side effects due to drug accumulation. Numerous NDDS including microspheres, liposomes, and phytosomes are being studied for the delivery of herbal drugs. Combination of herbal compounds in these delivery systems also assists in the upsurge in solubility, improved stability, reduced toxicity, greater biological activity, enhanced distribution, sustained drug delivery, and also guarding from degradation in metabolic processes. One such example is the use of liposomes in delivery of anticancer compounds by increasing the drug concentration in tumor-affected area and lowering the drug exposure in normal cells and tissues, hence checking toxicity effects (Yadav et al. 2011).

Nanotechnology has a wide range of applications in the development of new drug delivery systems which can overcome the drawbacks of conventional drug delivery systems including immediate requirement for drugs with improved therapeutic efficacy against CSCs (cancer stem cells). Nanoparticle (NP)-based carriers (nanocarriers) including micelles, liposomes, polymeric nanoparticles, dendrimers, etc. are being preferred as drug delivery systems. Though various anticancer agents have been identified, most of these have limitations when rendered to clinical studies such as off-target effects, low pharmacokinetics, a hydrophobic nature, inconsistent stability, and lower distribution of the drug. Nanotechnology can help to overcome these limitations. In the past years, researchers have concentrated on developing a single nanoformulation capable to carry dual drugs (one specific against CSCs and a second against bulk tumor cells) for their delivery to the target site through active or passive targeting (Singh et al. 2017).

6.5 Novel Drug Delivery Systems for Herbal Drugs

Before entering in the blood stream, the phytoconstituents of the herbal drugs face highly acidic pH of the stomach, and some of them also get metabolized in the liver, due to which the optimum quantity of the biologically active compounds does not reach the blood leading to lower or negligible therapeutic effects of the drug. Use of nanocarriers with herbal drugs carry optimal quantity of the drug to the action site, detouring barriers including acidic pH and metabolism in the liver, and upsurge the sustained drug circulation in the blood (Kuntal et al. 2005). Some of the types of novel herbal drug delivery systems are discussed below.

6.5.1 Phytosome

Phytosomes are phospholipid-based NDDS, which have been observed to be favorable for herbal drug delivery. Mixing the phytoconstituents at specific molar ratios with phosphatidylcholine leads to synthesis of phytosomes. It is the phytolipid-based drug delivery system which bridges the conventional and novel delivery systems. The word phytosome narrates to phyto (plant), whereas some represents cell-like. Phytosomes are unconventional types of herbal preparations with better absorption characteristics, as compared to conventional herbal compounds. Phytosomes also exhibit better therapeutic and pharmacokinetic profiles as compared to conventional extracts obtained from medicinal plants. Phytosomes can be synthesized by mixing the polyphenolic phytoconstituents at specific ratios with phosphatidylcholine. The phytosomal analysis has been focused on *Silybum marianum*, which consists of liver-protective flavonoids. The fruit of the *S. marianum* plant (family, Asteraceae) consists of flavonoids exhibiting hepatoprotective activities (Atmakuri and Dathi 2010). The phytosome plays a role in protecting phytoconstituents from degradation in digestive systems and gut microorganisms by synthesizing little compartment capable of being transferred to the lipid-friendly surroundings of the enterocyte cell membranes and then entering the blood stream (Sharma 2014).

Phytosomes can be identified as complex between a natural product and natural phospholipids. This complex can be prepared by reactions of stoichiometric quantities of substrate and phospholipids in a suitable solvent. It has been observed that the phospholipid substrate interaction can be attributed to the formation of hydrogen bonds between the polar head of phospholipids and the polar functional groups present on substrate using spectroscopic techniques. In aqueous environments, phytosomes acquire micellar liposomal-like structures. In phytosomes the active compound is attached to the polar head of phospholipids, thus becoming an integral part of the membrane (Kumar et al. 2017).

6.5.2 Liposomes

Liposomes are regarded as concentric and bilayered compartments where the aqueous phase is surrounded by a lipid bilayer membrane majorly consisting natural or/and synthetic phospholipids. The liposomes are sphere-shaped particles which encapsulate the drugs in the interior. Liposomes are synthesized using phospholipids, having hydrophilic polar head and hydrophobic tail (Ju Qun and Guo 2007). The polar end comprises of phosphoric atom bound to a hydrophilic molecule. Liposomes have the capability to encapsulate both hydrophilic and lipophilic compounds. Liposome exhibits properties which make them capable to augment the bioavailability, bio-distribution, ingredient solubility, altered pharmacokinetics, and both *in vitro* and *in vivo* stability. Liposome-based NDDS can increase the therapeutic efficacy of herbal compounds (Saraf 2010).

Paulis et al. (2012) observed that liposomes having size of 100 nm were capable to move out of the vasculature (extravasation) slowly and were slower to go to the tissue and release the active constituents over a period of time resulting in controlled and sustained release of the drug and also helped in maintaining the higher drug concentrations over a longer period of time being suitable in treatment of myocardial infarction and also to enhance the cardioprotection in a rat model of ischemia/reperfusion (IR) injury. The lipophilic interior of the liposome helps in the inclusion of drugs having lipophilic nature. Liposomes also help in improving the bioavailability of the drug as compared to conventional drug delivery systems (Geldenhuys et al. 2017).

6.5.3 Nanoparticles

Nanoparticles are nanosized structures comprising of semisynthetic or polymers. Recently, nanoparticles for herbal compounds have engrossed much consideration. Nanoparticles represent colloidal systems having particles of size distribution from 10 to 1000 nm. It is regarded as an efficient system as the compound is encapsulated in the nanoparticle and gets delivered at site of action easily. The nanospheres are spherical particulates with solid core having dimensions in nanosize. Nanospheres consist of herbal compounds implanted in the matrix or engrossed onto the surface, whereas nanocapsules exhibit vesicular system, where the herbal drug is encompassed inside (Vyas and Khar 2002). The nanoparticulate system is advantageous due to its increased solubility as compared to traditional drug delivery systems. Microencapsulation of herbal drugs in nanoparticles is an efficient way employed for the protection of drug or food ingredients from degradation, premature interaction, and volatile losses. The advantages of the nanoparticle include improvement in absorption of the herbal compounds, reduction in dosage formulation, and increase in solubility (Prabhu et al. 2010).

The nanoparticles can be classified into two categories, viz., hard and soft, dependent on their physicochemical characteristics and the method by which the drug is loaded into the nanoparticles. Hard NPs can be classified as materials on which the drug can be loaded only on the surface through passive adsorption or covalent attachment. Examples of hard nanoparticles include quantum dots, silver (Ag) NPs, gold (Au) NPs, and metal oxide NPs. Soft nanoparticles are the materials in which the drug can be loaded into the central core. The examples of soft NPs include liposomes, micelles, and polymeric NPs such as poly(D,L lactic-co-glycolic acid) (PLGA) (Sangtani et al. 2017).

6.5.4 Emulsions

Emulsions are biphasic systems where one phase is dispersed into the other as minute droplets with diameter ranging between 0.1 and 100 μm. In emulsion-based drug delivery system, the drug is distributed properly due to lymph affinity.

Microemulsions can be defined as solutions consisting of nanosized droplets of an insoluble liquid disseminated in an aqueous buffer where the droplets are covered with a surfactant for reducing the surface tension among both the phases. Emulsions result in targeted sustained release and also enhance the permeability of drugs into the mucous and skin (Cui et al. 2009).

Microemulsions have vast range of applications both in drug targeting and controlled release of the drug (Garg and Goyal 2012). The major problem faced in the delivery of oil-soluble drugs through oral route is its low aqueous solubility. Microemulsions exhibit imitable capability to evade problems related to solubility (Goyal et al. 2013). Microemulsions can encapsulate the drugs having variable solubility due to the presence of polar, nonpolar, and interfacial domains present in them. Microemulsions safeguard the amalgamated drugs from both oxidative and enzymatic degradation. Microemulsion formulations consisting of cyclosporin A, ritonavir, and saquinavir are available commercially (Fricker et al. 2010). Microemulsions help in reducing drug dosage and also enhance the bioavailability (Goyal et al. 2014). Betamethasone dipropionate exhibits antiproliferative, immunomodulatory, and anti-inflammatory activity (Kaur et al. 2016a, b). The addition of corticosteroids and keratolytic agents in microemulsions results in an improved and sustained corticosteroid delivery rate, resulting in superior antipsoriatic activity. Use of hydrogels as immunotherapeutic agents has abundant potential for refining the efficacy of vaccines and immunotherapeutics in disease treatment (Kaur et al. 2016a, b).

6.5.5 Microsphere

Microspheres consist of fine particles, having diameters ranging between few micrometers. Microspheres are also regarded as microparticles. Microspheres can be prepared using numerous synthetic and natural materials. Microspheres can be either biodegradable or non-biodegradable. Examples of biodegradable microspheres include altered starch microspheres, albumin microspheres, gelatin microspheres, polypropylene dextran microspheres, and polylactic acid microspheres. Solid and hollow microspheres have large variations in their densities and hence different applications (Scarfato et al. 2008). The polymers utilized in synthesis of microspheres can be either biodegradable or non-biodegradable. Different polymers are being used in fabrication of these carriers, including gelatin, albumin, polypropylene, modified starch, polylactic acid, dextran, polylactide, etc. (Burgess and Hickey 2009). The drug release in this type of delivery system is regulated by the dissolution and degradation of encapsulating matrix.

Numerous methods, including evaporation and ionic cross-linking techniques, are being used (Das and Senapati 2008) in preparation of mucoadhesive, buoyant microspheres. These microparticle systems have advantages as compared to other delivery systems as they can be ingested or injected and help in sustained release

action and site-specific delivery. Gastroretentive floating microspheres of silymarin have been studied for sustained drug delivery (Garg and Gupta 2010). Microspheres containing turmeric oleoresin have been prepared using a spray-drying technique. The stable emulsion safeguarded the resin from degradation by different conditions and chemical agent, and it also enhanced the therapeutic effect of the drug (Kshirsagar et al. 2009). Targeted delivery of rutin (Xiao et al. 2008) from formulated microspheres (rutin alginate-chitosan) was observed through its targeting on cardiovascular and cerebrovascular regions. Oxidized cellulose microspheres incorporated with camptothecin (Chao et al. 2010) were synthesized by a spray-drying process and have been effectively utilized to enhance the solubility and cytotoxicity of camptothecin.

6.5.6 Ethosome

Ethosomes are phospholipid-based pliable nanovesicles with higher content of ethanol (20–45%). Ethanol is observed to be an effectual permeation enhancer. Ethosomes are prepared as unique lipid carriers comprising of phospholipids, ethanol, and water. Ethosomes enable the herbal drugs to reach deeper skin layers and/or systemic circulation. Owing to higher amounts of ethanol, the lipid membrane is packed less compactly as compared to conventional vesicles, with comparable stability (Touitou and Godin 2000). Transdermal drug delivery systems assist the movement of therapeutic drugs through the skin and into the general circulation for systemic effects (Shaik et al. 2011). It is observed that herbal drugs can be employed with superior efficacy by incorporating them into transdermal drug patches alongside penetration enhancers such as terpenes (Rathva et al. 2012). The commonly available transdermal drug delivery patches are the nicotine patches to help people quit smoking (Jatav et al. 2011).

6.5.7 Solid Lipid Nanoparticles

Solid lipid nanoparticles were first developed in the 1990s. These are specifically used in the delivery of lipophilic herbal drugs. Solid lipid nanoparticles can be prepared by various methods such as homogenization and warm microemulsion. The typical size of solid lipid nanoparticles lies between 50 and 1000 nm. Solid lipid nanoparticles comprise lipid matrix, which solidifies at room and body temperatures (Pople and Singh 2006). The main advantages of solid lipid nanoparticles (SLNs) as compared to conventional drugs include exceptional physical stability and protection of assimilated drugs from deterioration (Kakkar et al. 2010). Various types of nanodrug delivery systems that have been synthesized for delivering plant-based anticancer drugs are tabulated in the Table 6.1.

Table 6.1 Different types of nanodrug delivery systems synthesized for delivering plant-based anticancer compounds

Drug carrier	Active ingredients	Biological activity	References
Phytosome	Quercetin	Quercetin is a dietary flavonol which shows poor absorption after oral administration. To increase its bioavailabilty, quercetin-loaded phytosome nanoparticles (QP) have been prepared, and its encapsulation efficiency was found to increase. Treatment of ovariectomized model with QP has shown increased level of serum calcium and glutathione as well as improved lipid profile. Therefore, QP emerged as a promising therapy for hormonal replacement	El-Fattah et al. (2017)
	Silybin	In this study, the effect of silybin on the accumulation and metabolism of lipid and oxidative stress was examined on liver steatotic cells by incubating it with phytosome and silybin complex with vitamin E. And, it has been shown that fat accumulation as well as oxidative imbalance was decreased	Vecchione et al. (2016)
	Naringenin	Complex of naringenin-phospholipid has been investigated for its antioxidant activity in carbon tetrachloride-induced rats. After performing the liver function test, naringenin-phospholipid complex was found to have better antioxidant capacity than free form of naringenin; it also enhanced the antioxidant activity of biomolecules for liver protection	Semalty et al. (2010)
Liposome	*Myrtus communis*	In this study, antibacterial activity of *Myrtus communis* has been investigated against several bacterial strains as food preservatives	Bouyahya et al. (2016)
	Diospyrin	Diospyrin is a plant product, i.e., bisnaphthoquinonoid. It shows antitumor activity *in vivo* and cancer cell lines of human *in vitro*. But due to some toxicity, it was encapsulated in lysosome to reduce the toxicity	Hazra et al. (2005)

(continued)

Table 6.1 (continued)

Drug carrier	Active ingredients	Biological activity	References
Nanoparticles	Berberine	Berberine is a plant alkaloid that reduces the *H. pylori* proliferation. This study has developed a unique nanoparticle berberine carrier with a heparin shell for localization of berberine at the infection site of *H. pylori*, and it has been observed that the *in vitro* drug carrier method controlled the berberine release, which interacted to intercellular space at the infection site precisely	Chang et al. (2011)
	Piperine	In this study, the piperine liposome complex formulation has been prepared and investigated by spectroscopic methods, and the formulation was found to be stable for 3 weeks after storing it at 4 °C	Pentak (2016)
	Ginseng	Ginseng, a phytochemical-mediated synthesis of gold nanoparticles have exhibited shieling effect from aggregation alongside leading to the nontoxic nature of ginseng-AuNP conjugates analyzed against normal cervical cell lines	Leonard et al. (2011)
Emulsions	Docetaxel	Microemulsions containing docetaxel as bioactive constituent were prepared, and the increased bioavailability of the drug was observed. Also the increased solubility of the hydrophobic drug was observed	Cui et al. (2009)
Microspheres	Quercetin	The study focused on development of a delivery system which can exhibit controlled release of the drug in treatment of rheumatoid arthritis along with increased biocompatibility of the delivery system	Natrajan et al. (2010)
	Zedoary oil	Zedoary turmeric oil (ZTO) shows broad pharmacological action spectrum including antitumor, antibacterial activity, etc. The ZTO-microsphere formulation increases the bioavailability of drugs in comparison to conventional methods	Ghule et al. (2016)
Ethosomes	Matrine	Ethosome-matrine complex has been found to increase per cutaneous permeation, and it also helps in the improvement of anti-inflammatory effect	Bhokare et al. (2016)

6.6 Advantages of Plant-Based Nanodrug Delivery Systems

Nanosized delivery systems have numerous advantages when compared to conventional drug delivery systems (Kuntal et al. 2005). Some of them are given below:

(1) Capable to deliver high drug concentrations to infected sites due to their distinctive size and high loading capacities.
(2) Deliver the drug in the smaller particle size thus increasing the surface area of the drugs resulting in better dissolution in the blood.
(3) The drug persists at active sites for longer periods, resulting in enhanced permeation and retention effect, which include greater permeation through barriers due to smaller size and better retention owing to poor lymphatic drainage in tumor-affected tissues.
(4) Novel drug delivery systems exhibit passive targeting to the site of action without the need of any particular ligand moiety.
(5) Use of novel drug delivery systems results in lowering of the side effects.
(6) Decrease in the dose of the drug formulation.

6.7 Conclusions and Future Prospects

Herbal medicine is accepted throughout the world as an alternative system of medicine. Yet, the available drug delivery systems for herbal compounds are traditional and outdated. A widespread research is happening in the field of NDDS for herbal medicine. Though, research in the mentioned fields is still at the initial stages. Numerous plant constituents including tannins, flavonoids, terpenoids, etc. exhibited improved therapeutic efficacies after incorporation into NDDS as compared to conventional plant extracts. Henceforth, great potential is available in the development of NDDS. Nanomaterials in drug delivery systems have been incorporated into formulations having specific characteristics both *in vivo* and *in vitro*. Small number of clinical studies have exhibited greater efficacy in animal models, but translation of these results into clinical success is very limited. Successful conversion needs to reconsider the role of nanomaterials in drug delivery, their limitations, and facing inconvenient facts. Nano-based drug delivery systems for herbal drugs exhibit potential to augment the biological activity. Though, noteworthy challenges persist for execution of clinically sustainable therapies. Trials of novel approaches to regulate nanomaterial- biological system interactions signify recent challenges in rendering these technologies into therapies. The challenges in the development of nano-based drug delivery systems include the feasibility of scale-up and the possibility of attaining multifunctional systems to accomplish numerous biological and therapeutic requirements. For the mentioned approach to be fruitful, fine-tuning of the procedures to increase the usefulness of the nanoparticle in novel drug delivery systems is required. Herbal remedies are thriving resources for valuable compounds including antioxidants and other phytoconstituents. This type of two-way approach

among the traditional herbal remedies and novel approaches of contemporary drug delivery system such as nanotechnology has established the therapies to the pharmaceutical sciences in the near future that will augment human health. It is estimated that the effective significance of the natural products and herbal remedies being combined with the nanocarriers will improve the importance of existing drug delivery systems.

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