Chapter 2
Herbal Nanocarriers for Cancer Therapy

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Contents

Abstract Cancer is a group of around 100 diseases that has been tormenting mankind since ancient time. Due to cancer, estimated 8.2 million people died globally in 2012, and the toll is expected to reach 13 million in 2030. Despite the improvement of conventional therapeutic modalities, the outcome of cancer patients has not improved significantly. So, alternative therapeutic modalities and new effective anticancer drugs are highly sought for. Different parts of plants and their extracts have been used to cure many diseases and relive from physical agony since ancient

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times. In the traditional system of medicine, herbal products have been used for treating different types of diseases and alignments globally. Active compounds from herbal medicine, such as curcumin, are found to be effective against cancer. Despite their excellent therapeutic ability, the potential of these herbal compounds or phytochemicals is limited due to their low water solubility and poor bioavailability.

Advances in nanomedicines are revolutionizing the healthcare sector. Significant progresses have been made in development of nanocarriers in recent decades. Therapeutic efficacies of conventional drugs are reported to enhance by many folds using these novel nanocarriers through the intervention of nanotechnology. Application of nanotechnology may be effective in overcoming limitations of herbal drugs such as low water solubility, poor bioavailability, toxicity, and poor therapeutic efficacy of the drugs. It greatly helps in achieving higher efficiency of the drugs compared to its molecular form. Development of herbal-based nanocarriers like polymeric nanoparticles, dendrimers, liposomes, and micelles is reported to be more effective in treatment and managements of cancer. Loading of herbal compounds within these nanodrug delivery systems changes their pharmacokinetics profile and increases their bioavailability and therapeutic efficacy.

In this review, a comprehensive effort has been made on discovery of herbal drugs, herbal nanocarriers, and their application for cancer therapy. The coverage of this review will also extend to its current status and future prospects with elaborative and graphical examples.

Keywords Cancer · Chemotherapy · Herbal compounds · Nanocarriers · Nanomedicine

2.1 Introduction

2.1.1 Cancer Overview

Cancer represents a diverse group of life-threatening diseases that causes abnormal and uncontrolled growth of malignant cells. These malignant cells are highly unorganized, irregular in shape and size, and capable of invading neighboring healthy tissues and organs. The characteristics of cancer cells are: ability of tissue invasion and metastasis, sustain angiogenesis, self-sufficiency in growth signals, limitless replicative potential, evasion of apoptosis, and insensitivity to anti-growth signals (Hanahan and Weinberg 2000; Gogoi et al. 2016). Cancer has been affecting mankind since ancient times. There are more than 100 types of cancers reported till date, and their subtypes are found within specific organs (Gogoi et al. 2016). With time, the tumor cells disintegrate from the primary tumor and migrate through the blood vessels and lymphatic streams to form their colonies at different sites of the patient's body. This process is called metastasis and it leads to the death of the host.

The exact causes and the ways of initiation and spreading of cancer are still not well understood, but both external factors (e.g., tobacco smoking, infections, exposure to retroviruses, chemicals, and radiations) and internal factors (e.g., inherited

metabolism mutations, hormones, and immune conditions) are believed to be the reasons for cancer formation and growth (Feng and Chien 2003). These factors may act together or in sequential manners to initiate and promote cancer. Till date, no complete curing procedure for cancer is available, only remission or palliation is possible with the current treatment procedures. A cancer is said to be in remission state when all clinical evidence of cancer has been disappeared and the microscopic foci of cancer cells may still remain (Feng and Chien 2003).

2.1.2 Limitation of Conventional Therapeutic Modalities

The most common and effective cancer treatment modalities are surgery, radiotherapy, chemotherapy, hormone therapy, and immunotherapy. All these modalities have their own advantages as well as disadvantages and usually combination of two or more modalities gives the best result (Feng and Chien 2003). Surgery is one of major treatment procedures for treating tumor; but, erroneous or inadequately margined resection of tumor cells may lead to faster metastasis (Feng and Chien 2003; Gogoi et al. 2017). Moreover, tumors at metastasis cannot be treated with either surgery or radiotherapy. Radiotherapy is not selective to cancer cells, and it kills both malignant and healthy cells. Success of chemotherapeutic agents in treating cancer is limited by their severe side effects and development of multidrug resistance by the cancer cells. A schematic representation of how chemotherapy kills cancer cells is shown in Fig. 2.1. Chemotherapeutic drugs which are effective against rapidly dividing cells cannot kill large portion of dormant tumor cells. Thus the chemotherapy is compromised (Gogoi et al. 2017; Paszek et al. 2005; Tannock 2001). Hormone therapy is applicable to only hormone-sensitive cancers like breast cancer, prostate cancer, ovarian cancer, etc. Hormone therapy inhibits the growth of cancer cell by blocking the action of hormones such as estrogen receptor-α responsible for the tumor growth (Hayashi and Kimura 2015). But, almost all patients with metastatic breast and prostate cancer that initially respond to hormone therapy develop resistance to hormone therapy, and it leads to progression of the disease (Abraham and Staffurth 2016). Despite having number of therapeutic options, cancer is posing as a big menace to mankind. In 2008, 7.6 million people died of cancer, and toll is

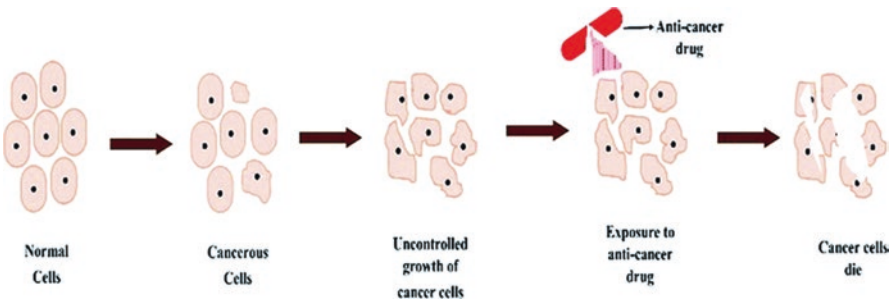


Fig. 2.1 Outline of chemotherapy (Subramanian et al. 2016)

expected to reach 13.2 million by 2030 (Global cancer facts and figures, 2015, 2nd ed.). So, search for new effective and developed therapy is still going on.

2.1.3 Importance of Nanomedicine

Application of nanotechnology especially nanomedicines opens up a window of opportunities to enhance the efficacy of anticancer drugs. According to the National Institute of Health, nanomedicine is referred as application of nanotechnology for treatment diagnosis, monitoring, and control of biological systems. Research into nanodrug delivery systems and diagnostic agents come within the preview of nanomedicine (Moghimi et al. 2005). The size of nanocarriers is generally in the range of 1 to 100 nm (Subramanian et al. 2016). But, for the purposes of this chapter, we are considering all the drug delivery systems below size 1000 nm as "nanodrug delivery systems" or "nanocarriers." Nowadays a lot of herbal nanocarrier-based nanomedicines are being investigated globally and showing promising results for the holistic treatment of cancer disease. Herbal compound-loaded nanocarriers can overcome the problems like aqueous solubility and permeability through biological membrane due to their size and modified surface properties as faced by herbal bioactive compounds. Encapsulation of herbal drugs in nanocarriers improves the pharmacological activity and biodistribution of drugs, ensures their solubility and stability, and helps in maintaining sustained delivery (Jain et al. 2011). Moreover, application of nanodrug delivery systems may help in (i) achieving enhanced and targeted delivery of phytochemicals; (ii) crossing the tight epithelial and endothelial barriers and delivering large molecules to intracellular sites of action; and (iii) co-delivering of two or more phytomedicines or therapeutic modalities for combined therapy and imaging the site of drug action (Lambert 2010; Liong et al. 2008; Gunasekaran et al. 2014). Targeted delivery herbal bioactive molecules to the tumor site(s) reduces the side effects caused by off targeted delivery and increases the therapeutic efficacy of the nanoformulations.

Herein, we are reviewing the different types of herb-based nanocomposite existing in the literatures along with illustrative figures and explanation, which have been specially applied for the cancer treatment. The current development and future prospects in this direction have also been discussed.

2.2 Bioactive Herbal Compounds: History and Discovery Strategies

Historically, plants and their products have been playing an important role in curing many diseases and reliving from different physical agonies. Plants are important sources of traditional medicines (Bhattacharjya and Borah 2008; Newman et al. 2000; Buss et al. 2003). Herbal medicines were reported to use in different

civilizations around the world since ancient times. In Mesopotamia, approximately 1000 plant-derived substances were reported to use as medicine in around 2600 BCE. Egyptians had been using herbal medicines since 2900 BCE; but, the *Ebers Papyrus* only properly reported use of over 700 drugs of mostly plant origin in 1550 BCE. The Indian Ayurvedic system is dated prior to 1000 BCE. Charaka Samhita and Sushruta Samhita documented use of 341 and 516 drugs, respectively (Kapoor 1990; Dev 1999).The Chinese materia medica also documented use of large number of herbal medicine for treating different diseases. The Greco–Roman knowledge on their traditional herbal medicine was dated back to the first century AD, and large amount of this knowledge bases were preserved by the Arabs during the dark and middle ages during the fifth to twelfth centuries (Cragg and Newman 2013). Much later, numbers of German books on herbal medicines were compiled during the period of the fourteenth to seventeenth century (Atanasov et al. 2015).

During all those periods, herbal medicines were used to treat different diseases or alignments without the in-depth knowledge of pharmacological activity or active components of the herbs (Atanasov et al. 2015). But, rational clinical investigation on medicinal herbs was laid down in the eighteenth century, when Anton von Störck had studied the properties of poisonous herbs like aconite and colchicum and William Withering had studied foxglove for the treatment of edema (Sneader 2005).

At the beginning of the nineteenth century, rational drug discovery from plants started when the German apothecary assistant Friedrich Sertürner had successfully isolated analgesic and sleep-inducing agent from opium named morphium (morphine). Later numbers of papers were published based on this discovery. This led to successful isolation and study of numerous natural drugs from herbs and followed by chemical synthesis of these drugs (Kaiser 2008). As per the world health organization (WHO) report, 80% of rural people of world's population especially in developing countries depend on the herbal medicine (World Health Organization Guideline 2001). Till today, substantial portion of therapeutic agents are comprised of natural products and their derivatives; e.g., 61% of anticancer compounds and 49% anti-infectives approved during the period of 1981 to 2010 are derived from nature (Newman and Cragg 2012). However, the pharmaceutical companies have been avoiding investigation on natural product discovery processes since 1990, due to difficulties in supply, screening, characterization, and increase in rate of rediscovering the known compounds (Li and Vederas 2009). Still, research on fast, inexpensive next-generation genome sequence technology and the discovery of natural product is flourishing at academic level (Luo et al. 2014).

The natural product discovery processes are broadly classified into two categories, namely, top-down and bottom-up approaches (Fig. 2.2). In top-down approaches, system level information are utilized to generate the new natural products without having prior knowledge of genes and enzymes involved in the biosynthesis. These approaches don't require complicated genome sequencing and sophisticated genetic manipulation.

In these approaches, biological samples are collected from diverse environments either for extraction or laboratory cultivation. The extracts are then screened for a desired bioactivity, and the "hits" are isolated for structural characterization. New

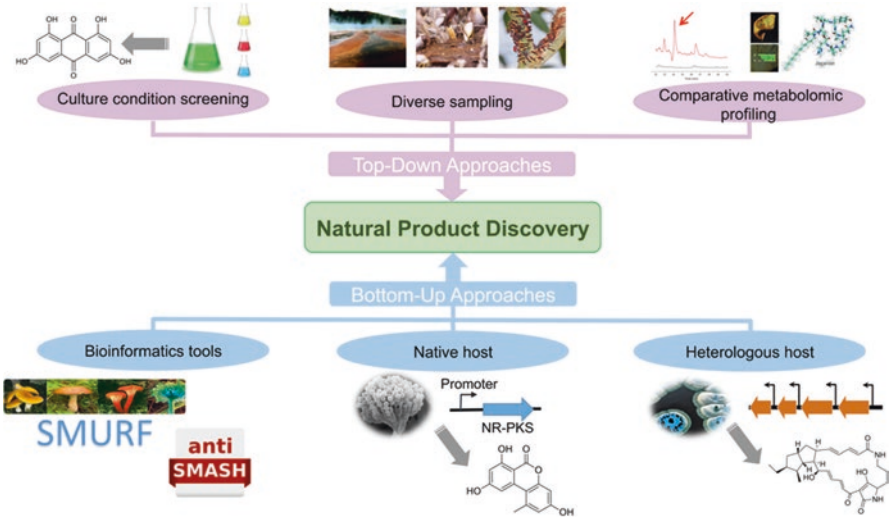


Fig. 2.2 Overview of the recent strategies applied for the discovery of natural products (Luo et al. 2014)

innovation in sampling and screening has mitigated the risk of rediscovering new chemical entities and allowing this approach to remain a viable means of natural product discovery (Luo et al. 2014). On the other hand, in the bottom-up approaches, the gene cluster of interest is identified, manipulated using transcription and translation processes, and then the corresponding natural product is synthesized (Luo et al. 2014). Plant-derived natural products are generally nontoxic to the normal cells and well tolerated by our body (Singh et al. 2016).

The plant-derived marketed anticancer compounds can be divided into four important classes, the vinca alkaloids (vinblastine, vincristine, and vindesine), the epipodophyllotoxins (etoposide and teniposide), the taxanes (paclitaxel and docetaxel), and the camptothecin derivatives (camptothecin and irinotecan) (Desai et al. 2008). Apart from these, the plants have tremendous potential to provide newer drugs, and search for new medicinal plants with potential anticancer compounds is going on.

Vinca alkaloids are herbal compounds extracted from Madagascar periwinkle plant, *Catharanthus roseus G. Don*., and they have the potential to treat diabetes and cancer (Moudi et al. 2013). Vinca alkaloids inhibit microtubule assembly and hence disrupt the cellular division process of tumor cells (Duflos et al. 2002). Moreover, disruption of microtubules function affects the cellular functions like intracellular organelle transport, cell migration, cell signaling, and mitosis (Perez 2009). Herbal compounds derived from vinca alkaloid are used to treat breast cancer, Hodgkin's lymphoma and Kaposi's sarcoma, severe lymphoblastic leukemia, non-Hodgkin leukemia, William's tumor, and non-small cell lung cancer (Safarzadeh et al. 2014).

Epipodophyllotoxins or podophyllotoxins are extracted from the root of the Indian podophyllum plant (*Podophyllum peltatum*). Etoposide and teniposide are

two active and semisynthetic compounds belonging to this family. These compounds arrest the proliferation of tumor cells by inhibiting topoisomerase II, which causes breakdown of DNA double strands (Damayanthi and Lown 1998; Safarzadeh et al. 2014).

Taxanes such as paclitaxel, docetaxel, and other taxane homologs are considered as the most effective antitumor agents and effective against wide range of cancers such as breast, ovary, lung, and other metastatic cancers. Paclitaxel is derived from Pacific yew bark (*Taxus brevifolia*). These taxanes inhibit the polymerization of microtubules and thereby prevent proliferation of tumor cells (Hagiwara and Sunada 2004).

Camptothecins are natural cytotoxic drugs isolated from *Camptotheca accuminata* of the Nyssaceae family. These are strong inhibitor of nucleic acid in mammalian cells and induce strand breaks in chromosomal DNA topoisomerase I (Hsiang et al. 1985).

Apart from these four groups of drugs, a large number of herbal drugs have been tried/investigated for their anticancer properties. These drugs from herbs or spices reveal their anticancer properties either by direct cytotoxic effects or modulating the immune system (Kitagishi et al. 2012). There are at least 2,50,000 species of plants out of which more than 1000 plants have been found to possess significant anticancer properties (Mukherjee et al. 2001). Active phytochemicals and their derivatives are found in leaf, root, flower, stem, and bark, and they perform number of pharmacological activities in human body (Singh et al. 2016). The search of novel bioactive compounds from natural sources continues with botanists, marine biologists, and microbiologists teaming up with chemists, pharmacologists, toxicologists, and clinicians. A comprehensive list of phytochemicals investigated for treatment of different cancers is shown in Table 2.1.

2.2.1 Structures of Important Herbal Compounds

Though a large number of plant-derived chemicals are investigated for their anticancer activity, only a few chemical entities were able to get approved for clinical applications due to stringent evaluation processes of pharmaceutical agents. The plant-derived anticancer agents approved for therapeutic use in the last 30 years (1984–2014) are summarized in Table 2.2.

2.3 Cancer Targeting Strategies and Herbal Nanostructures

Despite discovery of large numbers of plant-derived drugs, success in treating solid tumor is limited due to the severe side effects of chemotherapeutic agents and the development of multidrug resistance. Moreover, highly acidic and oxygen-deprived hypoxic environments within the tumor mass reduce the effectiveness of drugs that

Table 2.1 Phytochemicals found to be effective in different types of cancers (Singh et al. 2016)

Phytochemical(s)	Cancer models suppressed	References
Alexin B, Emodin (*Aloe vera*)	Leukemia, stomach cancer, neuroectodermal tumors	Elshamy et al. (2010)
Allylmercaptocysteine, allicin (*Allium sativum*)	Colon cancer, bladder carcinoma	Ranjani and Ayya (2012)
Amooranin (*Aphanamixis polystachya*)	Breast, cervical, and pancreatic cancer	Chan et al. (2011)
Andrographolide (*Andrographis paniculata*)	Cancers of the breast, ovary, stomach, prostate, and kidney, nasopharynx malignant melanoma, leukemia	Geethangili et al. (2008)
Ashwagandhanolide (*Withania somnifera*)	Cancers of the breast, stomach, colon, lung, and central nervous system	Yadav et al. (2010)
Bavachinin, corylfolinin, psoralen (*Psoralea corylifolia*)	Cancers of the lung and liver, osteosarcoma, malignant ascites, fibrosarcoma, and leukemia	Wang et al. (2011b)
Berberine, cannabisin-G (*Berberis vulgaris*)	Cancers of the breast, prostate, liver, and leukemia	Elisa et al. (2015)
Betulinic acid (*Betula utilis*)	Melanomas	Król et al. (2015)
Boswellic acid (*Boswellia serrata*)	Prostate cancer	Garg and Deep (2015)
Costunolide, Cynaropicrine, Mokkolactone (*Saussurea lappa*)	Intestinal cancer, malignant lymphoma, and leukemia	Lin et al. (2015)
Curcumin (*Curcuma longa*)	Cancers of the breast, lung, esophagus, liver, colon, prostate, skin, and stomach	Perrone et al. (2015)
Daidzein and genistein (*Glycine max*)	Cancers of the breast, uterus, cervix, lung, stomach, colon, pancreas, liver, kidney, urinary bladder, prostate, testis, oral cavity, larynx, and thyroid	Li et al. (2012)
Damnacanthal (*Morinda citrifolia*)	Lung cancer, sarcomas	Aziz et al. (2014)
β-Dimethyl acryl shikonin, arnebin (*Arnebia nobilis*)	Rat walker carcinosarcoma	Thangapazham et al. (2016)
Emblicanin A & B (*Emblica officinalis*)	Cancers of breast, uterus, pancreas, stomach, liver, and malignant ascites	Dasaroju and Gottumukkala (2014)
Eugenol, orientin, vicenin (*Ocimum sanctum*)	Cancers of the breast and liver and fibrosarcoma	Preethi and Padma (2016)
Galangin, pinocembrine, acetoxychavicol acetate (*Alpinia galangal*)	Cancers of lung, breast, digestive systems, and prostate and leukemia	Sulaiman (2016)
Gingerol (*Zingiber officinale*)	Cancers of ovary, cervix, colon, rectum, liver, urinary bladder, oral cavity, neuroblastoma, and leukemia	Rastogi et al. (2015)
Ginkgetin, ginkgolide A & B (*Ginkgo biloba*)	Glioblastoma multiforme, ovary, colon, hepatocarcinoma, prostate, and liver	Xiong et al. (2016)

(continued)

Table 2.1 (continued)

Phytochemical(s)	Cancer models suppressed	References
Glycyrrhizin (*Glycyrrhiza glabra*)	Lung cancer, fibrosarcomas	Huang et al. (2014)
Gossypol (*Gossypium hirsutum*)	Cancers of the breast, esophagus, stomach, liver, colon, pancreas, adrenal gland, prostate, and urinary bladder, malignant lymphoma and myeloma, brain tumor, and leukemia	Zhan et al. (2009)
Kaempferol galactoside (*Bauhinia variegata*)	Cancers of the breast, lung, liver, oral cavity, and larynx and malignant ascites	Tu et al. (2016)
Licochalcone A, licoagrochalcone (*Glycyrrhiza glabra*)	Cancers of the prostate, breast, lung, stomach, colon, liver, and kidney and leukemia	Zhang et al. (2016)
Lupeol (*Aegle marmelos*)	Breast cancer, lymphoma, melanoma, and leukemia	Wal et al. (2015)
Nimbolide (*Azadirachta indica*)	Colon cancer, lymphoma, melanoma, leukemia, and prostate cancer	Wang et al. (2016)
Panaxadiol, panaxatriol (*Panax ginseng*)	Cancers of the breast, ovary, lung, prostate, and colon, renal cell carcinoma, leukemia, malignant lymphoma, and melanoma	Du et al. (2013)
Plumbagin (*Plumbago zeylanica*)	Cancers of the breast and liver, fibrosarcoma, leukemia, and malignant ascites	Yan et al. (2015)
Podophyllin and podophyllotoxin (*Podophyllum hexandrum*)	Cancers of the breast, ovary, lung, liver, urinary bladder, testis, and brain, neuroblastoma, and Hodgkin's disease	Liu et al. (2015)
Psoralidin (*Psoralea corylifolia*)	Stomach and prostate cancer	Pahari et al. (2016)
Sesquiterpenes and diterpenes (*Tinospora cordifolia*)	Lung, cervix, throat, and malignant ascites	Gach et al. (2015)
6-Shogaol (*Zingiber officinale*)	Ovary cancer	Ghasemzadeh et al. (2015)
Skimmianine (*Aegle marmelos*)	Liver tumors	Mukhija et al. (2015)
Solamargine, solasonine (*Solanum nigrum*)	Cancers of the breast, liver, lung, and skin	Al Sinani et al. (2016)
Thymoquinone (*Nigella sativa*)	Cancers of the colon, breast, prostate, pancreas, and uterus, malignant lymphoma, ascites, melanoma, and leukemia	Fakhoury et al. (2016)
Ursolic acid and oleanolic acid (*Prunella vulgaris*)	Cancers of the breast, cervix, lung, oral cavity, esophagus, stomach, colon, and thyroid, malignant lymphoma, intracranial tumors, and leukemia	Wozniak et al. (2015)

(continued)

Table 2.1 (continued)

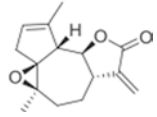
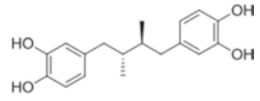
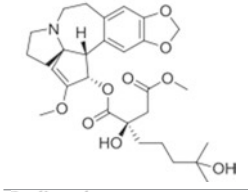
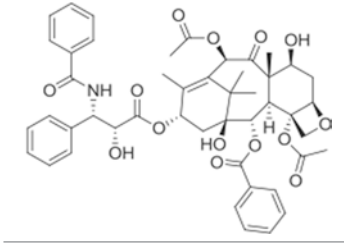
Phytochemical(s)	Cancer models suppressed	References
Ursolic acid (*Oldenlandia diffusa*)	Cancers of the lung, ovary, uterus, stomach, liver, colon, rectum, and brain, lymphosarcoma, and leukemia	Al Sinani et al. (2016) and Wozniak et al. (2015)
Vinblastine, vincristine (*Catharanthus roseus*)	Cancers of the breast, ovary, cervix, lung, colon, rectum, and testis, neuroblastoma, leukemia, rhabdomyosarcoma, malignant lymphoma, and Hodgkin's disease	Keglevich et al. (2012)
Viscumin, digallic acid (*Viscum album*)	Cancers of the breast, cervix, ovary, lung, stomach, colon, rectum, kidney, urinary bladder, and testis, fibrosarcoma, melanoma	Bhouri et al. (2012)
Withaferin A, D (*Withania somnifera*)	Cancers of the breast, cervix, prostate, colon, nasopharynx, and larynx and malignant melanoma	Lee and Choi (2016)

are basic in nature and/or utilize oxygen-free radicals for anticancer action (Kellen 1993). In solid tumor, a substantial portion of tumor cells present in dormant state, and they do not divide in the early stage of tumor formation (Rockwell and Hughes 1994). Therefore, chemotherapeutic agents effective against rapidly dividing cells could not kill them (Slingerland and Tannock 1998; Gogoi et al. 2017). Under this circumstances, the intervention of nanotechnology into the herbal drugs start playing an enhancing factor of its therapeutic efficacy towards the targeted diseases. Herbal drug-loaded nanoformulations can be prepared using methods such as high pressure homogenization, complex coacervation, co-precipitation, salting out, nanoprecipitation or solvent displacement, solvent emulsification–diffusion, supercritical fluid method and self-assembly method, etc. (Gunasekaran et al. 2014). Some of the common herbal nanodrug delivery systems are liposomes, emulsions, solid lipid nanoparticles, micelles, polymeric nanoparticles, dendrimers, carbon nanotube, inorganic nanoparticles (silica, ZnO), etc. These nanoparticles deliver drug to the cancer site(s) by two strategies, i.e., active and passive targeting.

2.3.1 Active Targeting

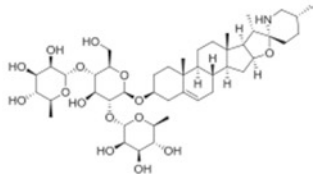
In active targeting, nanocarriers are channeled to tumor sites with the help of targeting ligands specific against receptors overexpressed on tumor cells or tumor vasculature, which are not expressed by normal cells. In this process, chemotherapeutic agent-loaded nanocarriers are conjugated with targeting ligands or moieties such as folic acid, monoclonal antibody, integrin, etc. which can target (i) receptors preferentially expressed on endothelial cells of tumor blood vessels (e.g., integrin-α_v β_3 and negatively charged phospholipids) (Li et al. 2004; Nisato et al. 2003); (ii) receptors overexpressed on tumor cells, e.g., HER2 and folate receptor (Chen et al. 2008; Pradhan et al. 2010); and (iii) lineage-specific targets that are expressed at the same

Table 2.2 Plant-derived anticancer agents approved for therapeutic use in the last 30 years (1984–2014) (Atanasov et al. 2015; Newman and Cragg 2012)

Generic name and chemical structures	Plant species (literature reference)	Trade name (year of introduction)	Indication (mechanism of action)
Arglabin 	*Artemisia glabella* Kar. et Kir. replaced by *Artemisia obtusiloba* var. *glabraLedeb.* (Adekenov et al. 1982)	Arglabin (1999)	Cancer chemotherapy (farnesyl transferase inhibition)
Masoprocol 	*Larrea tridentata* (Sessé & Moc. ex DC.) Coville (Luo et al. 1998)	Actinex (1992)	Cancer chemotherapy (lipoxygenase inhibitor)
Omacetaxine mepesuccinate (Homoharringtonine) 	*Cephalotaxus harringtonia* (Knight ex Forbes) K. Koch (Powell et al. 1974)	Synribo (2012)	Oncology (protein translation inhibitor)
Paclitaxel 	*Taxus brevifolia Nutt.* (Wani et al. 1971)	Taxol (1993), Abraxane (2005) and Nanoxel (2007)	Cancer chemotherapy (mitotic inhibitor)

(continued)

Table 2.2 (continued)

Generic name and chemical structures	Plant species (literature reference)	Trade name (year of introduction)	Indication (mechanism of action)
Solamargine 	*Solanum* spp. (Hsu and Tien 1974; Liljegren 1971)	Curaderm (1989)	Cancer chemotherapy (apoptosis triggering)

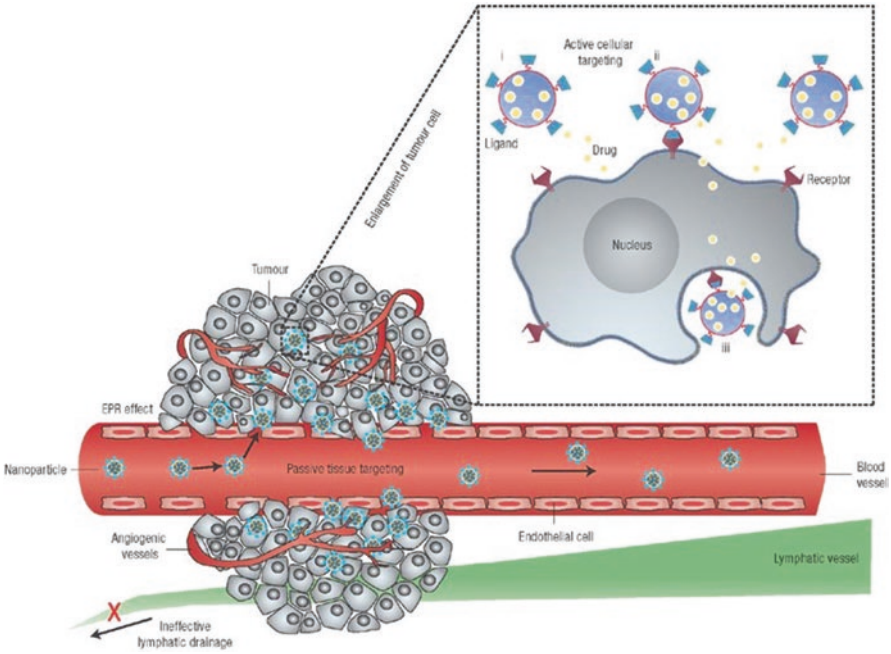


Fig. 2.3 Schematic representation of different mechanisms through which nanocarriers can deliver drugs at tumor sites. Polymeric nanoparticles are shown as representative nanocarriers (circles). Passive tissue targeting is achieved by extravasation of nanoparticles through enhanced permeability and retention (EPR) effect. Active cellular targeting (inset) can be achieved by functionalizing the surface of nanoparticles with ligands/moieties specific to the receptors/biomolecules expressed on the surface of the cancer cells (Peer et al. 2007)

level on both tumor and normal cells (e.g., CD19) (Cheng and Allen 2008) and kill tumor cells. These targeting ligands or moieties tagged effectively internalized by the tumor cells through receptor-mediated endocytosis. For effective deployment of active targeting strategy, the following issues need to be addressed: (i) liposome prepared for active targeting extravasated and bound to the first line of targeted tumor cells in the interstitial compartment and reported to obstruct the way for more liposomes to accumulate (Barenholz 2001), (ii) immunoliposomes prepared for active targeting were found to be cleared rapidly (Koning et al. 2002), and (iii) nanocarriers prepared for active targeting were reported to internalize via endocytosis process and end up with degradation in endosomes/lysosomes. Moreover, drug loading methods need to be devised properly so that the encapsulated drug does not form aggregate and degrade instantly for effective cancer treatment (Barenholz 2001). A schematic representation of active and passive targeting strategies of nanocarriers is demonstrated in Fig. 2.3.

2.3.2 *Passive Targeting: Enhanced Permeability and Retention (EPR) Effect*

In passive targeting process, nanocarriers/molecules are guided into the tumor interstitium or tissue through leaky tumor vasculature with the help of molecular movement within fluids (i.e., convection) or passive diffusion (Haley and Frenkel 2008). Conventional force mostly transports the larger molecules, whereas diffusion helps in transportation of low molecular weight compounds. It is well-known that tumor vasculatures are highly chaotic and complex structures, and they have the ability of extensive angiogenesis or forming hyperbranched defective vasculatures, impaired lymphatic drainage systems, and ability to generate number of vasculature permeability factors such as bradykinin, nitric oxide (NO) (Maeda et al. 1988; Matsumura et al. 1988; Maeda et al. 1994), and peroxynitrite ($ONOO^-$) (Maeda et al. 2000); and hence, tumor vasculatures are highly porous. The pore size in the tumor vasculature is in the range of 100–780 nm (Yuan et al. 1995) which is much larger than normal tissue junctions, i.e., less than 6 nm (Drummond et al. 1999). So, nanocarriers circulating in the blood selectively enter into the interstitial spaces of tumor tissues and get accumulated there due to impaired lymphatic drainage system. This effect is called enhanced permeability and retention (EPR) effect. But, the pore size of endothelium tissues of kidney glomerulus is in the range of 40–60 nm size; sinusoidal endothelium of liver and spleen have pores of size up to 150 nm (Seymour 1992). Nanocarriers like liposomes can avoid accumulation in the kidney due to their bigger size, but macrophages present in the liver and spleen can remove them from blood circulation. PEG coating onto surface of nanocarriers prevents their clearance by macrophages due to steric hindrance offered by PEG coating, increases their blood circulation time, and hence helps in selective accumulation of the nanocarriers in tumor through passive diffusion (Andresen et al. 2005).

A large numbers of nanocarriers have been investigated for treatment of cancer exploiting the active and passive targeting strategies. Surface functionalization of nanoparticles using PEG or similar molecules has been reported to improve the bioavailability of drugs at tumor sites in different preclinical animal models. However, clinical translation of the nanocarriers from bench to bedside is a huge challenge due to stochastic nature of ligand–receptor interactions and difficulties in controlling release of drug at diseased sites (Gogoi et al. 2017). In order to improve the therapeutic index of drugs, drug release at tumor sites is essential as it prevents their rapid metabolization and clearance from the patient's body. Drug release from nanocarriers can be triggered using either exogenous stimuli such as temperature, ultrasound, light, and electric fields or endogenous stimuli like change in pH, enzyme, redox potential, etc.

2.3.3 Herbal Nanostructures for Cancer Treatment

A large number of nanocarriers with herbal compounds have been investigated for treatment of various types of cancer. These nanocarriers target cancer cells either by active targeting or passive targeting strategy. A lot of herbal compounds are poorly soluble in aqueous solubility and resulting in poor bioavailability following oral administration (Bansal et al. 2011). Delivery of these poorly aqueous soluble drugs through nanocarriers reduces their systemic toxicity, improves pharmacokinetic properties, enhances their delivery at tumor sites, and hence improves the therapeutic indices of the drugs (Aqil et al. 2013).The following section discusses the application of herbal nanocarriers in treatment of cancer.

Liposomes and Other Lipid Carriers

Liposomes

Liposomes are spherical vesicles made up of phospholipids which have a hydrophilic head and a hydrophobic tail. These phospholipids self-assemble under given conditions to form a bilayered structure called liposome. These liposomes have the ability to carry both hydrophobic and hydrophilic payload together. They have the advantages of high biocompatibility, biodegradability, ease of preparation, chemical versatility, and the ability to modulate the pharmacokinetic properties by changing the chemical composition and the components of the bilayers (Terreno et al. 2008). Dhule et al. (2014) investigated the combined antitumor effect of curcumin and C6 ceramide (C6) against osteosarcoma (OS) cell lines. They prepared three liposomal formulations, i.e., curcumin liposomes, C6 liposomes, and C6-curcumin liposomes. Curcumin in combination with C6 was found to be effective against MG-63 and KHOS OS cell lines, in comparison with curcumin liposomes alone. The therapeutic efficacy of the preparations was tested in vivo using a human osteosarcoma xenograft assay. PEGylated and folate tagged liposomes prepared for targeted delivery of curcumin and C6 significantly reduce the tumor volume in vivo. Recently, Gogoi et al. (2017) investigated the therapeutic efficacy of paclitaxel-loaded magnetic liposomes in vitro and in vivo under self-controlled hyperthermic condition. Results showed that the combined thermochemotherapy was effective in treating cancer in comparison to the drug and heat alone. Similar results were demonstrated by Gharib et al. (2015) who treated breast cancer using artemisinin and transferrin-loaded magnetic liposomes under AC magnetic field. In another study, berberine derivatives and doxorubicin-loaded long-circulating liposomes were studied for their ability to target mitochondria of drug-resistant cancer cells. Results demonstrated the superiority of these liposomes over regular doxorubicin-loaded liposomes and free doxorubicin (Tuo et al. 2016).

Solid Lipid Nanoparticles (SLNs)

Solid lipid nanoparticles have generated tremendous attention in last few decades due to their good release profile and targeted drug delivery with excellent physical

stability. Good deals of studies on SLNs have been done for improvising the delivery of phytochemicals with anticancer properties in recent decades. Phytochemicals like berberine (Xue et al. 2015), resveratrol (Teskac and Kristl 2010), and paclitaxel (Pooja et al. 2016) were encapsulated in SLNs and studied their therapeutic properties. Teskac and Kristl (2010) demonstrated that encapsulation of resveratrol within SLNs enhances the bioavailability of drug and hence increases the therapeutic efficacy of the drug.

Micelles

Polymeric micelles have been drawing attention due to their ability of site-specific delivery of therapeutic agents, reducing off-target toxicity, and improving pharmacokinetics (Biswas et al. 2016). Tea epigallocatechin gallate and Herceptin loaded polymeric micelles were reported to use for cancer therapy. These nanomicelles demonstrated better tumor selectivity and growth reduction, as well as longer blood half-life, than free Herceptin (Chung et al. 2014). Micelles have been used for delivery of poorly water-soluble anticancer agent quercetin. Tan et al. (2012) reported development of quercetin-loaded micelles for treatment of lung cancer. Nanomicelles made from the diblock copolymer and polyethylene glycol (PEG)-derivatized phosphatidylethanolamine (PE) were found to enhance peroral anticancer activity and no apparent toxicity to the intestinal epithelium.

Polymeric Nanoparticles

Polymeric nanoparticles are drawing huge attention in cancer drug delivery due to their stability, ease of conjugating functional moieties, and ease of surface modification. Yallapu et al. (2012b) developed curcumin-loaded cellulose nanoparticles for targeting prostate cancer. They investigated and compared cellular uptake and cytotoxicity of these curcumin-loaded cellulose nanoparticles with β-cyclodextrin (CD), hydroxypropyl methylcellulose (cellulose), poly(lactic-co-glycolic acid) (PLGA), magnetic nanoparticles (MNP), and dendrimer-based curcumin nanoformulations in prostate cancer cells. Results demonstrated the superiority of curcumin-loaded cellulose nanoparticles in comparison to the other nanoformulations in inducing apoptosis in cancer cells. Recently, paclitaxel-loaded polymeric nanoparticles combined with chronomodulated chemotherapy were evaluated in lung cancer both in vitro and in vivo. Results suggested that these paclitaxel-loaded nanoparticles exhibit greater anti-tumor activity against A549 cells, in comparison with paclitaxel. The anti-tumor effect at 15 h after light onset (HALO) administration was reported to be the best in all groups (Hu et al. 2017). Curcumin-loaded PLGA nanoparticles were reported to enhance the aqueous solubility of curcumin and increase the antitumor potential of curcumin (Nair et al. 2012).

Nanoemulsions

Nanoemulsions are colloidal nanoparticles known for their stability and high loading efficiency. These carriers are solid spheres, and their surface is amorphous and lipophilic with a negative charge. Recently, a good deal of works has been done on herbal agent-loaded nanoemulsions for cancer therapy. Anuchapreeda et al. (2012) studied therapeutic efficacy of curcumin-loaded nanoemulsion in number of different cancer cell lines. Results showed high encapsulation of curcumin, physical stability of these nanocarriers, and their preserved toxicity. In another study, Pool et al. (2013) studied the feasibility of encapsulating hydrophobic quercetin in nanoemulsion. In a recent study, camptothecin-loaded polymer stabilized nanoemulsion was investigated for the in vitro cytotoxicity as well as their potential to target breast cancer in vivo. Results showed the possibility of targeting breast cancer using these nanocarriers (Sugumaran et al. 2017) (Fig. 2.4).

Nanocapsules

Nanocapsules consist of a liquid/solid core in which the drug is placed into a cavity, which is surrounded by a distinctive polymer membrane made up of natural or synthetic polymers. They have been drawing huge attention due to the protective coating which can be tuned to achieve sustain and controlled release of active ingredients (Kothamasu et al. 2012). Artemisinin crystals were encapsulated using nanocapsules composed of chitosan, gelatin, and alginate. This investigation showed the

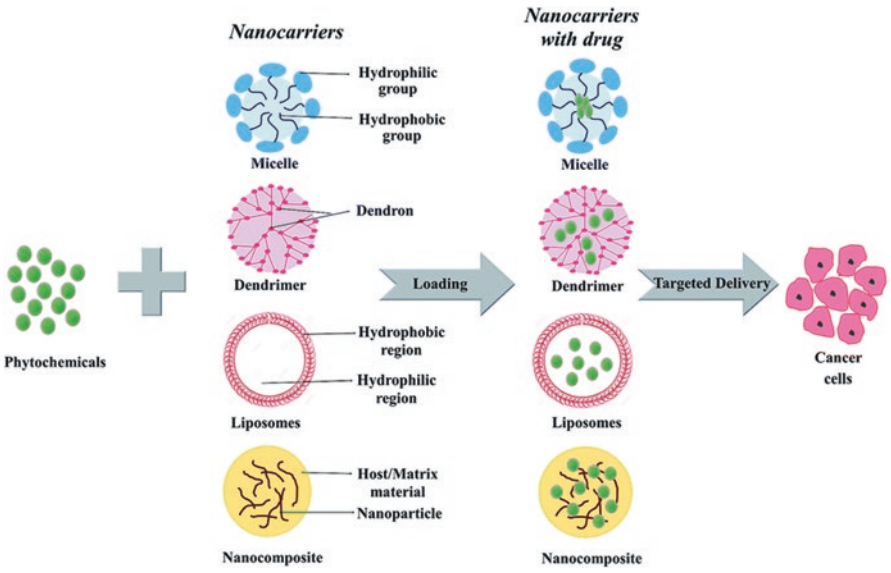


Fig. 2.4 Phytochemical loaded different types of nanocarriers (Subramanian et al. 2016)

possibility of achieving prolonged drug release through self-assembly of polyelectrolytes on natural drug crystals (Chen et al. 2009). In another study, anticancer drug quercetin was encapsulated in nanocapsules prepared for passive and active targeting to tumors. The investigators prepared nanocapsules from folic acid conjugated to poly(lactide-co-glycolide) (PLGA) polymer to facilitate active targeting to cancer cells and PEGylated PLGA for passive targeting. Comparative in vitro studies on the cytotoxicity and cellular uptake of the different formulations were carried out using MTT assay and confocal laser scanning microscopy, respectively. Results confirmed the selective uptake and cytotoxicity of the folic acid targeted nanocapsules to the folate enriched cancer cells in a folate-dependent manner. Finally, in vivo experiments were done to evaluate the passive tumor accumulation and the active targeting of the nanocapsules to folate-expressing cells in HeLa or IGROV-1 tumor-bearing mice. The developed nanocapsules provide a system for targeted delivery of a range of hydrophobic anticancer drugs in vivo (El-Gogary et al. 2014). Recently, Boissenot et al. (2016) developed a paclitaxel-loaded nanocapsule formulation composed of poly(lactide-co-glycolide)-polyethylene glycol shell and perfluorooctyl bromide (PFOB) core for cancer theranostic application. PFOB was used as imaging agent. This nanocapsule formulation was tested in vitro and in vivo. Results demonstrated that the formulation could be applied as a cancer theranostic agent.

Dendrimers

Dendrimers are hyperbranched polymeric architectures widely investigated these days due to their versatility in drug delivery and high functionality. These nanostructured macromolecules have the abilities to entrap and/or conjugate the high molecular weight hydrophilic/hydrophobic entities by host–guest interactions and covalent bonding (prodrug approach), respectively. Moreover, due to high ratio of surface groups to molecular volume, they are extensively studied for gene delivery (Madaan et al. 2014). Fox et al. (2009) prepared a PEGylated poly(l-lysine) (PLL) dendrimer formulation by covalently binding polymer conjugates of camptothecin to improve solubility, increase blood circulation time, enhance tumor uptake, and hence significantly improve efficacy of the drug. The reported formulation was found to be effective in treating HT-29 tumor-bearing mice. Therapeutic efficacy of hydrophilic paclitaxel-conjugated polyamidoamine (PAMAM) dendrimers was studied cancer cells. Combination of ensemble and single microtubule imaging techniques were used to determine the mechanism of action of these dendrimers in vitro. Results provided mechanistic insights into the cytotoxicity of paclitaxel-conjugated PAMAM dendrimers and uncovered unexpected risks of using such conjugates therapeutically (Cline et al. 2013). Anticancer agent berberine (BBR) was attempted to deliver using G4-PAMAM dendrimers by conjugation (BPC) as well as encapsulation (BPE) approach. The entrapment efficiency in BPE was found to be 29.9%, whereas the percentage conjugation in BPC was found to be 37.49% indicating high drug payload in conjugation. In vitro results showed significantly higher anticancer activity for the PAMAM-BBR ($p < 0.01$) against MCF-7 and

MDA-MB-468 breast cancer cells. In vivo results showed that the formulation was safer and biocompatible with very least but insignificant ($p > 0.05$) effects. The study demonstrated that conjugated formulation (BPC) was found to be more prominent than the encapsulated one (BPE) (Gupta et al. 2017).

Inorganic Nanoparticles

Inorganic nanoparticles including gold, oxides of iron, zinc, silicon, etc. were extensively investigated in both preclinical and clinical setting for delivering different anticancer phytochemicals. Poorly water-soluble curcumin was encapsulated in PMMA-PEG/ZnO bionanocomposite, and therapeutic potential and cellular uptake were studied in gastric cancer cell line (Dhivya et al. 2017). Results showed that curcumin-loaded PMMA-PEG/ZnO can induce the apoptosis of cancer cells through a cell cycle-mediated apoptosis corridor. In another study, cellular uptake and phototoxic potential of curcumin organically modified silica nanoparticle complexes and free curcumin were reported to investigate in multicellular spheroids of human oral cancer cells. Results showed accumulation of nanoformulated curcumin was higher in cancer cells, and hence cell death in the spheroids was more following irradiation of blue light in comparison to free curcumin. Results suggested that nanoformulated curcumin was able to improve the phototoxic effects of curcumin in spheroids in comparison to free curcumin (Singh et al. 2015). In another study, Janus magnetic mesoporous silica (Fe_3O_4-$mSiO_2$) nanoparticles consisting of a Fe_3O_4 head for magnetic targeting and a mesoporous SiO_2 body was reported to develop for berberine delivery. This pH responsive nanoformulation was designed for magnetic targeting of berberine to hepatocellular carcinoma. Results suggested that Janus nanocarriers driven by the magnetic field might be use for effective and safe delivery of berberine to against hepatocellular carcinoma (Wang et al. 2016).

Apart from these studies, a host of nanoparticles with different shape, size, architecture, materials, and inherent properties were studied for improvising delivery of anticancer agent in recent decades. These studies were tried to summarize with the help of Table 2.3.

In recent years a wide range of herbal compound-loaded nanocarriers with heterogeneous structures are developed and investigated their efficacy in various cancer cell lines. These nanocarriers are internalized by the cancer cells via phagocytosis or endocytosis processes depending upon their size, shape, and surface treatment (Zhang et al. 2015). These bioactive natural compounds inhibit the growth of cancer cells by inducing apoptosis or programmed cell death. Initifvtion of cell death indicated by the significant changes in DNA structure (Wei et al. 2009); ROS generation (Wei et al. 2009; Das et al. 2013); cytochrome C release (Guo et al. 2010; Mulik et al. 2010); activation of caspases 3/7 (Zheng et al. 2011; Guo et al. 2010; Zhang et al. 2013a); cell cycle arrest (Kumar et al. 2014); activation of NF-κB (Bisht et al. 2007); and downregulation of MMP, BaX, Cyclin D, and VEGF (Subramanian et al. 2016) along with visible morphological changes (Merlina et al. 2012). The different targets of bioactive compounds inside the cancer cell are demonstrated in Fig. 2.5.

Table 2.3 Nanoparticles used to deliver different phytochemicals with anticancer property and the statuses of these studies were summarized

Sl. no.	Nanocarriers	Drug	Status	References
1.	Magnetic liposomes	Paclitaxel	In vitro	Gogoi et al. (2014) and Kulshrestha et al. (2012)
2.	Magnetic liposomes	Paclitaxel	In vitro and in vivo	Gogoi et al. (2017)
3.	Solid lipid nanoparticles	Paclitaxel	In vivo	Banerjee et al. (2016)
4.	Polymeric micelles	Paclitaxel	Phase II, clinical trial	Saif et al. (2010)
5.	Nanohydrogel	Paclitaxel and cisplatin	In vivo	Wu et al. (2014)
6.	Nanoemusion	Paclitaxel	In vitro and in vivo	Kim and Park (2017)
7.	Polymeric nanoparticles	Paclitaxel	In vitro and in vivo	Hu et al. (2017)
8.	Dendrimers	Paclitaxel	In vitro	Cline et al. (2013)
9	Nanocapsules	Paclitaxel	In vitro and in vivo	Boissenot et al. (2016)
10.	Solid lipid nanoparticles	Paclitaxel	In vivo	Pooja et al. (2016)
11.	Liposomes	Curcumin	In vitro and in vivo	Chen et al. (2012)
12.	Polymeric nanoparticles	Curcumin	In vitro	Yallapu et al. (2012b)
13.	Silica nanoparticles	Curcumin	In vitro	Singh et al. (2015)
14.	ZnO nanoparticles	Curcumin	In vitro	Dhivya et al. (2017)
15.	Nanoemulsion	Curcumin	In vitro	Anuchapreeda et al. (2012)
16.	Nanohydrogel	Curcumin	In vitro	Teong et al. (2015)
17.	Magnetic nanoparticles	Curcumin	In vitro	Yallapu et al. (2012a)
18.	Phytosome	Curcumin	In vivo	Maiti et al. (2007)
19.	Nanospheres	Curcumin	In vitro	Mukerjee and Vishwanatha (2009)
20.	Polymeric nanoparticles	Curcumin	In vitro	Bisht et al. (2007)
21.	Polymeric nanoparticles	Curcumin	In vitro	Punfa et al. (2012)

(continued)

Table 2.3 (continued)

Sl. no.	Nanocarriers	Drug	Status	References
22.	Polymeric nanoparticles	Curcumin	In vitro	Nair et al. (2012)
23.	Protein nanoparticles	Curcumin	In vivo	Kim et al. (2011)
24.	Lipid carriers	Curcumin and genistein	In vitro	Aditya et al. (2013)
25.	Nanocapsule	Artemisinin	In vitro	Chen et al. (2009)
26.	Magnetic liposomes	Artemisinin	In vitro and in vivo	Gharib et al. (2015)
27.	Lipid nanoparticles	Artemisinin derivatives	In vitro	Zhang et al. (2013b)
28.	Solid lipid nanoparticles	Artemisinin derivatives artemisone	In vitro	Dwivedi et al. (2015)
29.	Polymeric magnetic nanoparticles	Artemisinin	In vitro	Natesan et al. (2017)
30.	Solid lipid nanoparticles	Berberine	In vivo	Xue et al. (2015)
31.	Liposomes	Berberine derivatives and doxorubicin	In vitro and in vivo	Tuo et al. (2016)
32.	Hybrid nanoparticle	Berberine	In vitro and in vivo	Yu et al. (2017)
33.	Dendrimer	Berberine	Ex vivo and in vivo	Gupta et al. (2017)
34.	Magnetic mesoporous silica nanoparticles	Berberine	In vitro	Wang et al. (2017)
35.	Polymeric nanoparticles	Camptothecin	In vitro and in vivo	Min et al. (2008)
36.	Magnetic cyclodextrin nanovehicles	Camptothecin	In vitro	Rajan et al. (2017)
37.	Polymeric nanoparticles	Camptothecin	In vivo	Householder et al. (2015)
38.	Dendrimer	Camptothecin	In vivo	Fox et al. (2009)
39.	Mesoporous silica nanoparticles	Camptothecin	In vivo	Lu et al. (2010)
40.	Nanoemulsion	Camptothecin	In vitro and in vivo	Sugumaran et al. (2017)
41.	Polymer nanoparticles	Epigallocatechin gallate	In vitro	Rocha et al. (2011)
42.	Polymeric nanoparticles	Epigallocatechin-3-gallate	In vitro and in vivo	Siddiqui et al. (2009)
43.	Polymeric nanoparticles	Epigallocatechin 3-gallate	In vitro	Sanna et al. (2011)
44.	Polymeric nanoparticles	Green tea	In vivo	Khan et al. (2013)
		Polyphenol EGCG		
45.	Micelle	Green tea catechin derivatives and protein drugs	In vitro and in vivo	Chung et al. (2014)

(continued)

Table 2.3 (continued)

Sl. no.	Nanocarriers	Drug	Status	References
46.	Liposomes	Epigallocatechin-3-gallate	In vitro	de Pace et al. (2013)
47.	Polymeric nanoparticles	Root extract of *Phytolacca decandra* Phytolaccaceae	In vitro and in vivo	Das et al. (2012)
48.	Polymeric NP	Ethanolic extract of *Polygala senega* Polygalaceae	In vitro	Paul et al. (2011)
49.	Liposomes	Vincristine, vinblastine and vinorelbine	In vitro and in vivo	Zhigaltsev et al. (2005)
50.	Liposomes	Vincristine	In vivo	Tokudome et al. (1996)
51.	Nanoemulsion	Quercetin	In vitro	Pool et al. (2013)
52.	Polymeric nanocapsules	Quercetin	In vitro and in vivo	El-Gogary et al. (2014)
53.	Liposomes	Quercetin	In vitro	Wang et al. (2012)
54.	Micelle	Quercetin	In vitro and in vivo	Tan et al. (2012)
55.	Liposomes	Resveratrol	In vitro and in vivo	Wang et al. (2011a)
56.	Polymeric nanoparticles	Resveratrol	In vitro and in vivo	Karthikeyan et al. (2013)
57.	Polymeric nanoparticles	Resveratrol	In vitro	Karthikeyan et al. (2015)
58.	Protein nanoparticles	Resveratrol	In vivo	Guo et al. (2010)
59.	Clay nanotube	Resveratrol	In vitro	Vergaro (2012)
60.	Polymer nanoparticles	Resveratrol	In vitro	Sanna et al. (2013)
61.	Liposomes, polymeric lipid-core nanocapsules and nanospheres and solid lipid Nanoparticles	E-resveratrol	Ex vivo	Detoni et al. (2012)
63.	Solid lipid nanoparticles	Resveratrol	In vitro	Teskac and Kristl (2010)
64.	Liposomes	Oleanolic acid	In vitro and in vivo	Tang et al. (2013)
65.	Solid lipid nanoparticles	Baicalein	In vivo	Tsai et al. (2012)
66.	Self-assembled polymer nanoparticles	Baicalein	In vitro and in vivo	Wang et al. (2015)
67.	Liposomes	Baicalein	In vitro and in vivo	Li et al. (2016a)

(continued)

Table 2.3 (continued)

Sl. no.	Nanocarriers	Drug	Status	References
68.	Magnetic nanoparticles	Baicalein	In vitro	Kavithaa et al. (2017)
69.	Liposomes	Combretastatin A4	In vitro	Nallamothu et al. (2006)
70.	Magnetic polymer nanoparticles	Noscapine	Synthesis and characterization	Abdalla et al. (2010)
71.	Human serum albumin nanoparticles	Noscapine	In vitro	Sebak et al. (2010)
72.	Polymeric nanoparticles	Noscapine	In vitro	Madan et al. (2011)
73.	Liposomes	Betulinic acid	In vitro and in vivo	Mullauera et al. (2011)
74.	Polymeric nanoparticles	Betulinic acid	In vitro and in vivo	Das et al. (2016)
75.	Polymeric nanoparticles	Curcumin and 5-fluorouracil	In vitro	Anitha et al. (2014)
76.	Liposomes	Paclitaxel/ epigallocatechin gallate	In vitro	Ramadass et al. (2015)
77.	Nanoemulsion	Paclitaxel and curcumin	In vitro	Ganta and Amiji (2009)
78.	Liposomes	Curcumin and resveratrol	In vivo	Narayanan et al. (2009)
79.	Mesoporous silica nanoparticles	Combretastatin A4 and doxorubicin	In vitro and in vivo	Li et al. (2016b)
80.	Nano cell	Combretastatin A4 and doxorubicin	In vitro and in vivo	Sengupta et al. (2005)
81.	Liposomes	Combretastatin A4 and doxorubicin	In vitro and in vivo	Mitrus et al. (2009)
82.	Nanocapsule	Combretastatin A4 and paclitaxel	In vitro	Wang and Ho (2010)
83.	Self-assembled polymeric nanoparticles	Betulinic acid and hydroxycamptothecin	In vitro and in vivo	Dai et al. (2015)

2.4 Challenges and Future Prospects

Though a large number of nanomedicines are investigated for treatment of different types of cancers, only few nanoformulations reached the market today. A nanocarrier formulation has to go through a host of evaluation processes before it reaches the market. Though most of the nanocarriers are developed based on EPR effect, the EPR effect is unlikely to be present and equal in all the tumors nor the sole driver for efficacy of nanocarriers. Moreover, the pathological heterogeneity among different types of tumors and within the same type of tumor possesses a big challenge in the nanomedicine development process (Hare et al. 2017).The success rate of nanomedicine can be improved by adopting a specific decision-making framework, such

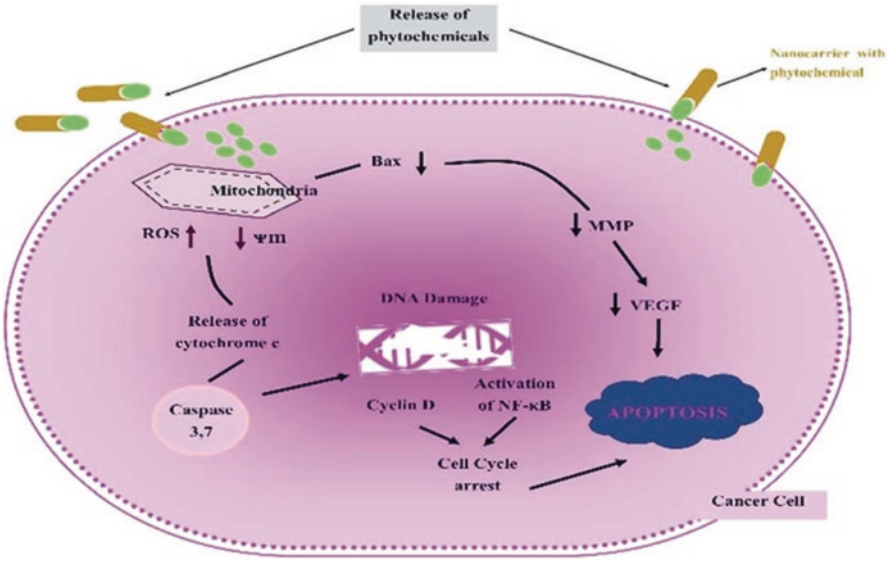


Fig. 2.5 Molecular targets of herbal compounds loaded nanocarriers against cancer cell (Subramanian et al. 2016)

as AstraZeneca's 5Rs principle: right target/efficacy, right tissue/exposure, right safety, right patient, and right commercial potential. The following points need to be addressed for development of cost-effective superior therapies for the patients, i.e., (i) should have a clear cut understanding about the heterogeneity of clinical cancers and the biological factors influencing the behavior of nanomedicines in patients' tumors; (ii) transition from formulation-driven research to disease-driven development; (iii) adaptation of more relevant animal models and testing protocols; and (iv) preselection of the patients most likely to respond to nanomedicine therapies.

Nanocarriers offer novel efficient strategies to treat cancer; nanotoxicity is a major area of concern as potentially high reactivity arising from the large surface-to-volume ratio of nanoparticles compared to bulk systems. Besides these, biodegradability of nanoparticles, side effects from by-products and bioaccumulation, and change in physicochemical characteristics of material at nanoscale are few apprehensions related to the nanomedicine. Moreover, distribution of nanocarriers in the body following systemic administration; development of mathematical and computer models to predict risk and benefits of nanoparticles; safe processes of nanoparticle manufacturing; and disposal and detrimental effects of nanoparticles to environment are few issues related to the nanomedicine to be addressed. Limited work has been done in scaling up laboratory or pilot technologies of nanodrug delivery for commercialization due to high cost of materials and challenges associated to maintain size and composition of nanomaterials at large scale.

2.5 Conclusions

Cancer has been tormenting the mankind from ancient times. Despite improvement in different therapeutic modalities, the number of deaths due to cancer is on rise. Therefore, a large number of herbs and their parts or extracts have been used to treat cancer. Nowadays, bioactive compounds from herbs have been extracted for effective treatment of different types of cancer. Due to the side effects of conventional therapies, herbal compounds or their derivatives have been loaded in different nanocarriers and investigated. Herbal compound-loaded nanocarriers have been able to effectively deliver drugs to the tumor site(s), reduce the side effects associated with the therapy, and kill the tumor cells more effectively. These nanocarriers can target tumor either by passive targeting or active targeting strategy. Though a host of nanocarriers have been investigated for cancer therapy, due to stringent preclinical evaluation and regulatory processes, only few nanoformulations have reached the market. The success rate of the nanocarriers in reaching market can be improved by adapting efficient decision-making strategies like AstraZeneca's 5Rs framework, implementing new validation method and preselection of patients, etc. Moreover, issues like nanotoxicity, prior prediction of nanoparticles distribution in the body, and risk–benefit analysis are to be addressed.

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