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Recent trends in nano-based drug delivery systems for efficient delivery of phytochemicals in chemotherapy

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The advent of nanotechnology has revolutionized various scientific inventions, out of which the debut of nanomedicine is outstanding. Especially, research has embarked on nano-drug delivery for treating cancer. Natural compounds present in plants, namely phytochemicals, have been extensively exploited for their anticancer properties. Despite their excellent anticancer abilities, phytochemicals are limited by their low water solubility and poor bioavailability. However, the field of nanotechnology has overcome these limitations. This review focusses on various methods of nano-drug delivery of phytochemicals against the killer disease, cancer. Common carriers that were employed ranged from micelles, with a polymeric base, to dendrimers, liposomes and nanoparticles. The phytochemicals were found to become more soluble when delivered by the nanocarriers and exhibited a remarkable effect on the cancer cells, compared to their free form. More interestingly, the half-maximal dose of the phytochemical was reduced significantly when it was delivered by the nanocarrier. On the whole, this review encourages the idea of "cancer-nanotechnology" after in-depth clinical studies on these phytochemical-loaded nanocarriers. Moreover, it will epitomize the nanocarriers as a crusader in improving cancer chemotherapy by reducing undesired effects and will invigorate site-specific drug delivery.

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1. Introduction

Nature is able to help the technically evolving world with respect to several newly arising diseases. Naturally available plant-derived products have been used to prevent as well as treat various diseases for many centuries by mankind.[1] The curative properties of these plant products are believed to be linked to the natural compounds present in them. These compounds are known as phytochemicals, or plant-derived chemicals. These are chemical compounds produced by the plants that give color or other organoleptic properties to them.[2] Contemporary researchers have shown that these natural compounds can protect against many diseases.

Several population studies have shown that there are a few-phytochemicals from fruits, vegetables and whole grains that are active against cardiovascular disease, diabetes and neurodegeneration. Apart from this, there is much literature evidence to show the various health benefits of phytochemicals present in plants.[3–5] Among these, the potential ability of natural compounds against the killer disease, cancer, is significant. Regardless of these biological benefits possessed by the bioactive plant components, their usage in the medicinal field has a long way to go.[6] Some of the factors that influence this are low water solubility, poor bioavailability and the requirement for high doses. Furthermore, many investigations have shown that these issues can be easily overcome by the nano-based delivery of these phytochemicals. Nano-based formulations have been found to improve solubility, bioavailability, and specific targeting, while reducing the doses and achieving steady-state therapeutic levels in cancer treatment.[7]

In general, all the biological processes that happen inside the body, including the origin and prognosis of cancer, are said to occur at the nano-level.[8] Due to this, the application of nanotechnology in the field of medicine has flourished. Nanotechnology is one of the advanced multidisciplinary technologies that typically involves nano-level (10^{-9} m) investigation.[9] Cancer is a major threat to mankind and is claimed to be the second leading cause of death worldwide. According to a survey, about 595 690 Americans are expected to die of cancer and 1 685 210 new cancer cases are expected to be diagnosed in the US during the year 2016.[10] The available treatments for cancer

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vary from chemotherapy to targeted radiotherapy. Regardless of these different treatment procedures, there is no single medical procedure to treat cancer. Hence, the continuing threat of cancer deaths motivates scientists to steadily concentrate on the field of oncology. One such more advanced mode of treatment is cancer-nanotechnology, which combines nanomedicine and cancer.[11]

The application of nanotechnology in the field of oncology offers different approaches to making significant advances in both cancer diagnosis and treatment. These renewed approaches mainly deal with nanoparticles that are designed to specifically target and treat cancer by increasing the solubility and bioavailability of encapsulated drugs.[12] Although there is a large number of studies to show the anticancer properties of phytochemicals, this review mainly deals with the nanotechnology-based drug delivery of several naturally available chemical compounds in the treatment of various types of cancer. Before leading into this, a brief introduction to chemotherapy is provided.

2. Chemotherapy

Chemotherapy is a common choice of treatment adopted by cancer patients around the globe. It mainly utilizes one or more chemical substances known as anticancer drugs or chemotherapeutic drugs.[13] These chemical substances are found to have anti-cancer properties, along with the ability to destroy cells that divide rapidly, one of the major properties of cancer cells. This treatment is adopted before, after or during other types of treatment procedures, such as radiotherapy, surgery and targeted radiotherapy.[14] The effectiveness of chemotherapy is entirely dependent on the type as well as the stage of the cancer. The efficacy is fair and curative for cancers like leukemia, while the treatment is unsuccessful in the case of brain tumors or non-melanoma skin cancers. Nevertheless, the effectiveness of the treatment can be measured only after 2 or 3 cycles of chemotherapy.[15]

Some of the commercially available chemotherapeutic drugs include 5-fluorouracil, doxorubicin, paclitaxel, oxaliplatin, cisplatin, and epirubicin. All these chemotherapeutic drugs affect the cancer cells and induce apoptosis.[16] Apoptosis is a programmed cell death in multicellular organisms involving a series of biochemical changes as well as morphological changes, finally leading to the death of the cell.[17] A schematic representation of the action of anti-cancer drugs on cancer cells is given in Fig. 1. Chemotherapeutic drugs are generally consumed orally. However, not all drugs can be orally administered and hence some are injected subcutaneously, intra-muscularly or intravenously. Another major complexity of chemotherapy is the dosage at which the chemotherapeutic drugs can be administered. The dose is prescribed depending upon the weight and height of a person and also based on the type of drug.[18] This is mainly because, if the dosage is low, then the treatment becomes ineffective, whereas if the dosage is high, the chemotherapeutic drugs cause side effects.

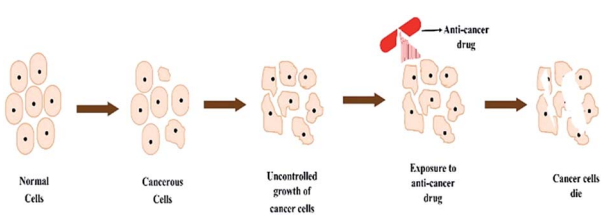


Fig. 1 Outline of chemotherapy.

Adverse effects or side-effects of chemotherapy are a foremost concern of physicians and cancer patients around the globe. A wide range of side-effects are exhibited, depending on the type of medication used. As chemotherapeutic drugs affect fast-growing cells, other growing cells, such as hair cells, blood cells, bone marrow cells and the cells lining the mouth, stomach, and intestines, are also affected. Due to this, pregnant women are advised to undergo abortion before chemotherapy.[19] Besides this, chemotherapy leads to immunosuppression, infertility, myelosuppression, gastrointestinal distress, typhlitis, anemia, fatigue, peripheral neuropathy, nausea and vomiting.[20] All these undesirable effects of chemotherapeutic drugs trigger research to search for a harmless substance with significant anticancer properties for cancer treatment. In addition to new anticancer drugs, there is also much research on administration methods that can individually target cancer cells.

3. Phytochemicals

The word phyto means "plants" in Greek and phytochemicals are naturally occurring plant-derived compounds. They are the secondary metabolites or the bioactive compounds of plants. These compounds are produced by plants as a protection against different environmental stresses, which include insects, bacteria, fungi and weather changes.[21] Nevertheless, the occurrence of phytochemicals cannot be confined, as it is spread throughout the range of flora and fauna found in nature. A plant contains a variety of phytochemicals and the same phytochemical is present in more than one plant.[22] The chemical formulae and the sources of the various phytochemicals enlisted in this review are listed in Table 1. In the case of eugenol, the main source is clove, while it is also found in wormwood, cinnamon, vanilla, celery, and basil.[23] Clove also contains acetyl eugenol, beta-caryophyllene, vanillin, crategolic acid, bicornin, gallotannic acid, methyl salicylate, eugenin, kaempferol, rhamnetin, eugenitin, oleanolic acid, stigmasterol, campesterol, and several sesquiterpenes.[24] In order to maintain a classification scheme, these plant-derived compounds have been classified into groups and subgroups based on their functional groups, structures and biosynthetic origins.[25] A summary of phytochemical classifications is given in Fig. 2.

Phytochemicals are more abundant in the fruit and vegetable extracts, chocolate, and tea, which are consumed in day-to-day life. These compounds are usually described as non-essential nutrients as they minimally contribute to the growth, development and well-being of the individual. They have long remained unnoticed by healthy eaters or dietitians due to the fact that they are not required to sustain life.

Table 1 Different types of phytochemicals and their sources

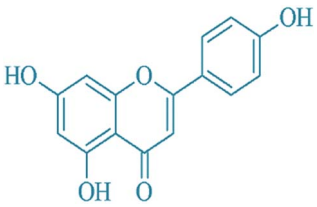
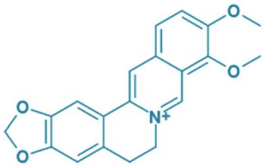
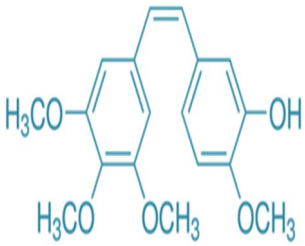
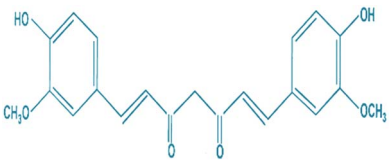
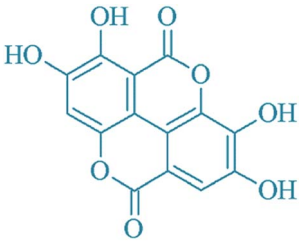
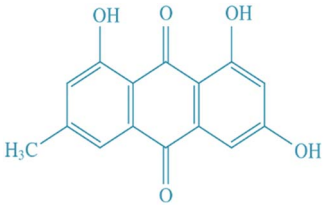
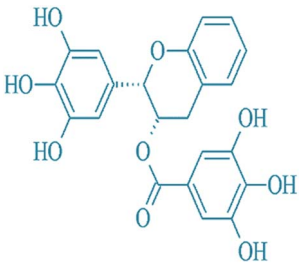
Phytochemical	Chemical structure	Major source
Apigenin		Parsley, celery, celeriac, chamomile tea
Berberine		Oregon grape, barberry, tree turmeric, goldenseal, yellow root, amur cork tree, Chinese goldthread, prickly poppy, Californian poppy
Combretastatin A-4		Eastern Cape South African bush-willow tree, Brazilian mofumbo
Curcumin		Turmeric
Ellagic acid		North American white oak, European red oak, medicinal mushroom *Phellinus linteus*
Emodin		Rhubarb, buckthorn, Japanese knotweed
Epigallocatechin gallate		White tea, green tea, black tea, apple skin, plums, onions, hazelnuts, pecans and carob powder

Table 1 (*Contd.*)

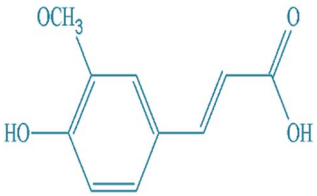
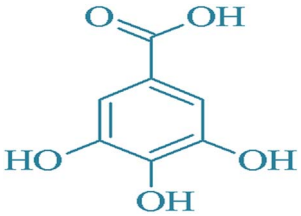
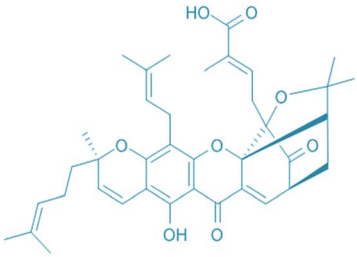
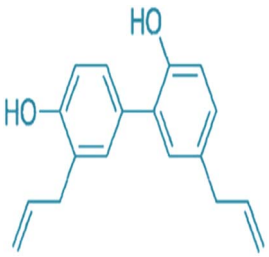
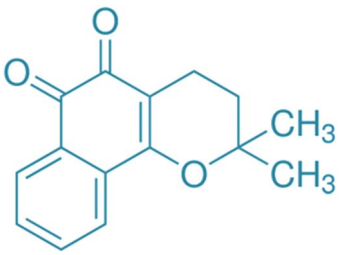
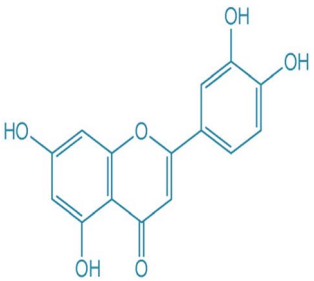
Phytochemical	Chemical structure	Major source
Ferulic acid		Coffee, apple, artichoke, peanut, orange, female ginseng, flaxseed
Gallic acid		Indian gooseberry, gallnut, witch hazel, raspberry, North American white oak, sundew, blackberry, hot chocolate, green tea
Gambogic acid		Brownish or orange resin of Indian gamboge tree
Honokiol		In the bark, seed cones, and leaves of trees belonging to the genus Magnolia
β-Lapachone		In leaves and barks of Chinese catalpa
Luteolin		Ragweed pollen, celery, broccoli, green pepper, parsley, thyme, chamomile tea, carrots, olive oil, peppermint, navel oranges

Table 1 (*Contd.*)

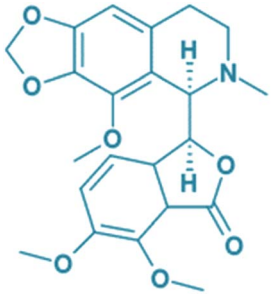
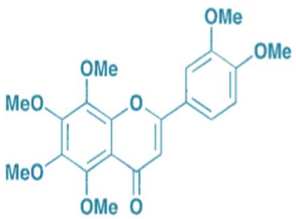
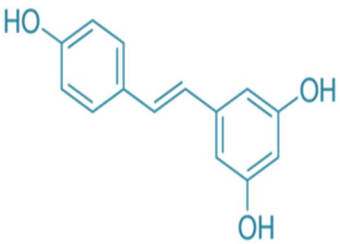
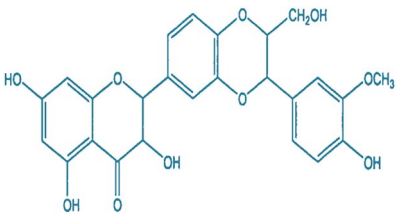
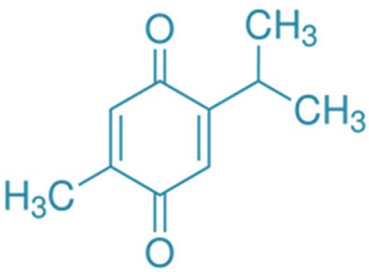
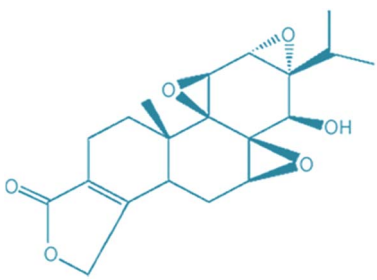
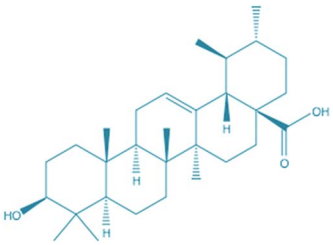
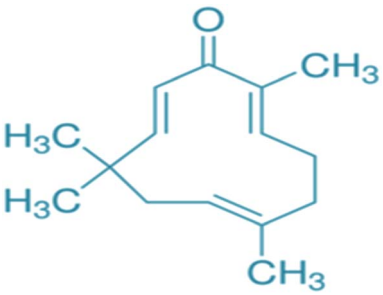
Phytochemical	Chemical structure	Major source
Noscapine		In all plants of the *poppy* family
Nobiletin		In the peels of citrus fruits
Resveratrol		In the skin of grapes, blueberries, raspberries, mulberries
Silibinin		Milk thistle seeds
Thymoquinone		In the plant *Nigella sativa* and wild bergamot
Triptolide		Thunder god vine

Table 1 (*Contd.*)

Phytochemical	Chemical structure	Major source
Ursolic acid		Apples, basil, cranberries, elder flower, peppermint, rosemary, lavender, oregano, thyme, hawthorn, prunes
Zerumbone		Ginger

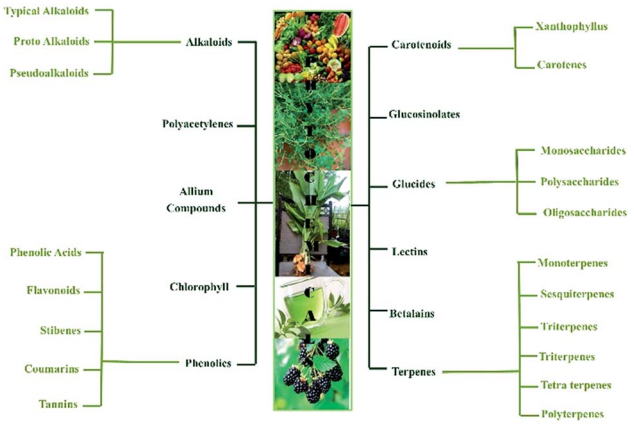


Fig. 2 Classification of phytochemicals.

However, much research has been focused on these plant-derived bioactive compounds and their biological benefits. Phytochemicals, when consumed along with the diet, have proven effective in fighting many chronic diseases, especially cardiovascular disorders and cancer.[26] Phytochemicals are found to be a great source of antioxidants. Most phytochemicals are found to excellently inhibit the proliferation of cells as well as angiogenesis, the two main trademark characteristics of cancer.[27] Investigations of the anti-carcinogenic effects of phytochemicals under laboratory conditions and in various animal models have been conducted. The results obtained showed an improvement in the excretion of carcinogens, inhibition of mitosis, subdual of inflammatory processes, such as cyclooxygenase-2 expression, and induction of apoptosis at different stages of cancer.[28] Phytochemicals are proven to fight against various types of cancers, such as lung cancer, prostate cancer, oral cancer, melanoma, leukemia, lymphoma, colon cancer and breast cancer.[29] Before embarking on various studies related to the anticancer properties of phytochemicals, understanding their bioavailability is more important.

4. Bioavailability of phytochemicals

Bioavailability is an important aspect of pharmacology. Bioavailability literally means the amount or fraction of the administrated drug that is absorbed into the systemic circulation. The bioavailability of a drug depends upon the method of administration and the receiving individual.[30] Technically, the bioavailability of a drug administered intravenously is one hundred percent, while the bioavailability of drugs administered non-intravenously is found to degenerate due to poor absorption. In the case of other dietary supplements or medicinal herbs, the bioavailability is much reduced when they are consumed orally.[31]

The bioavailability of the phytochemicals present in the food we consume is a critical factor that is extensively researched. Manach *et al.* found that the bioavailability of dietary polyphenols is influenced by the absorption in the gut, the microbiota metabolism, glucuronide excretion to the intestinal lumen, plasma kinetics, liver and gut metabolism, accumulation in tissues and bile, urinary excretion and a variety of metabolites in the bloodstream, bonding to albumin, cell assimilation and metabolism.[32] The plasma concentrations of the various phytochemicals were calculated to study their complex bioavailability. For example, catechins are absorbed rapidly and are supposed to be absorbed in the small intestine, yet are affected by dimerization. Compounds such as

epigallocatechin gallate and other catechin monomers are found to have similar properties. Meanwhile, the flavanones are slowly absorbed due to the attached disaccharides. The highest bioavailability was seen in the isoflavones subclass. In the case of aglycones and glucosides, the absorption was relaxed, suggesting absorption from the colon. Anthocyanins are quite rapidly absorbed, but their bioavailability seems to be the lowest of all flavonoids.[33] Similarly, proanthocyanidins and hydroxycinnamic acids, which are abundant in the human diet, were also not absorbed. The plasma concentrations of the isoflavones were found to be 5 μmol L^{-1}, whilst the plasma concentrations for proanthocyanidins did not exceed 1 μmol L^{-1}. The bioavailability of phytochemicals is also influenced by the esterification process.[34]

For the most part, the phytochemicals present in plant foods are poorly absorbed by human subjects, in which they are rapidly metabolized and excreted. This is one of the major issues to be faced before implementing these phytochemicals in the war against cancer.

However, drug delivery involving nanocarriers has proven to increase the bioavailability of these drugs. Manzoor *et al.* studied the bioavailability of doxorubicin when delivered with nano-liposomes. The bioavailability of doxorubicin was improved by thermally sensitive liposomes released inside the tumor vasculature. The maximum penetration of free doxorubicin was previously limited to 34 μm, while this study depicted a diffusion distance of about 78 μm in both sides of the capillary bed of the tumor.[35,36] Hence, the nano-drug delivery of phytochemicals is thought to increase the possibility of anticancer activity. The improved bioavailability during nanodrug delivery is related to the route by which the phytochemicals from food and the nanocarrier reach cancer cells. This is shown diagrammatically in Fig. 3. The anticancer effects of the nano-drug delivery of phytochemicals against various types of cancer is discussed in further chapters.

A particular study was carried out to overcome this limitation by Manzoor *et al.* The bioavailability of doxorubicin was improved by the release of thermally sensitive liposomes inside the tumor vasculature. The maximum penetration of doxorubicin was previously limited to 34 μm, while this study depicted a diffusion distance of about 78 μm in both sides of the capillary bed of the tumor.[25,26] Therefore, the nano-drug delivery of the phytochemicals is thought to increase the possibility of anticancer activity. The anticancer effect of the nano-drug delivery of phytochemicals against various types of cancer is discussed in further chapters.

5. Nano-drug delivery of phytochemicals against cancer

Despite the advanced treatment choices available for cancer patients, there is no particular method to cure cancer completely. This motivates scientists to continue their research on anticancer drugs and an effective way of administration. In addition to this, there is an enormous group of phytochemicals that have been proven to exhibit anticancer effects against different types of cancer. To enhance their minor backlogs, scientists employ the recently developed technique nanotechnology. This is a technology that manipulates matter with at least one dimension at the nanometer scale. The comprehensive nature of nanotechnology has allowed its application in a number of scientific fields, including organic chemistry, surface science, semiconductor physics, molecular biology, microfabrication, medicine, and biotechnology. In almost all cases, these applications involve the use of nanomaterials.[37] In particular, nanomaterials are used to build nano-systems that vary in size from 1–100 nm and are employed as transport modules to carry another substance or drug in nanomedicine. Such a nano-system may also be called a nanocarrier.[38] There are different kinds of nanocarriers that are used to deliver drugs to treat deadly diseases, such as cancer. The role of nanocarriers in cancer is inevitable as it plays a major part in both visualization and therapy. This is due to the fact that these nanocarriers can be easily fabricated to selectively target cancer cells from normal cells.[39] Some of the main nanocarriers used in cancer are micelles, liposomes, dendrimers, carbon nanotubes, nanoshells and nanocages. The major principles involved in the manufacturing of some nanocarriers are diagrammatically depicted in Fig. 4. As shown in the diagram, a micelle is an aggregate of molecules with an outer hydrophobic head region and a hydrophilic tail region in the micelle centre. A dendrimer

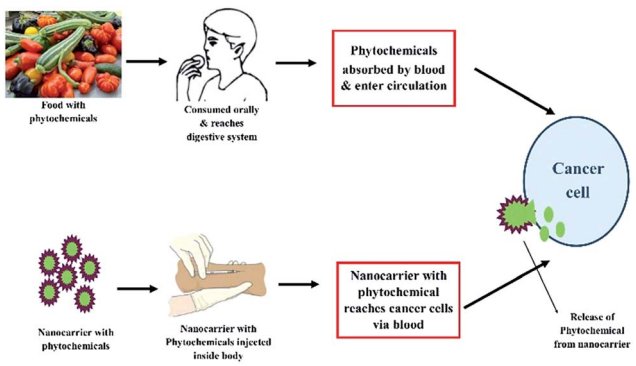


Fig. 3 Common routes of phytochemical administration from food and nano-carriers.

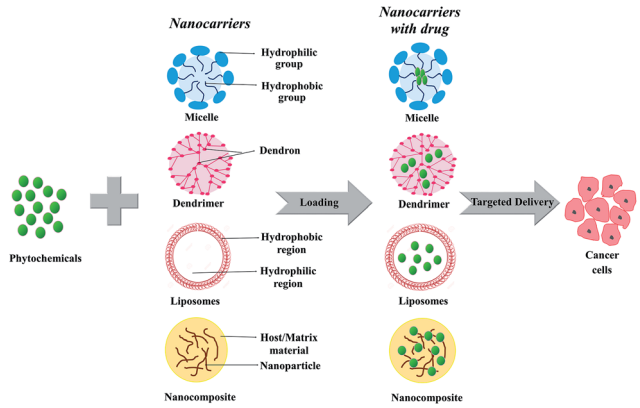


Fig. 4 Phytochemicals loaded to different types of nanocarriers.

is a highly branched, star-shaped macromolecule with nanometer-scale dimensions that is symmetric around the core.[40,41] Liposomes are similar to micelles; they are spherical vesicles in which hydrophilic and hydrophobic groups are arranged to form a lipid bilayer. A nanocomposite consists of multiphase materials with at least one of them being in a nano-dimension.[42,43]

All these nanocarriers allow the delivery of hydrophobic and hydrophilic drugs throughout the body. As most of the human body contains water, this ability of the nanocarrier contributes to the therapeutic efficiency, while another is the targeted delivery of the drug.[44] The drugs carried are harmful to the normal cells present in the human body. The nanocarriers carefully deliver the drugs to the specific site due to their site-specificity and smaller size. The four types of targeting characteristics of nanocarriers are passive, active, pH-sensitive and temperature-sensitive. The nanocarrier targets the delivery based on pH and temperature changes in cancer cells, and it may also be cloaked to match the circulation time by coating materials such as PEG. In the case of active targeting, the nanocarrier is provided with a cell-specific ligand.[45] The foremost application of these nanocarriers is focused on cancer chemotherapy. This may be because of the lower pH, the higher temperature, the hydrophobic nature of the anticancer drugs and the potential need for specific targeting ability.[46] Another major advantage of nanocarriers in cancer is the enhanced permeability and retention (EPR) effect. This involves the aggregation of macromolecules or nanoparticles in the extravasation in the tumor tissue during angiogenesis or the formation of new blood vessels. All the above factors make the application of nanotechnology in cancer beneficial.[47] However, the major literature on the nano-drug delivery of various phytochemicals against major cancers is enumerated in the following subdivisions.

5.1 Lung cancer

Lung cancer is also known as pulmonary carcinoma, and is characterized by uncontrolled cell growth in the lungs. It is one of the most common causes of cancer-related death in men and women. The major types of lung cancer include small-cell lung carcinoma, non-small-cell lung carcinoma and lung carcinoid tumor.[10,48] The small-molecule, polyphenol honokiol, was found to have a therapeutic effect against lung cancer. The honokiol was loaded to micelles based on poly(ε-caprolactone)–poly-(ethylene glycol)–poly(ε-caprolactone) copolymer (PCEC). The size of the obtained honokiol-loaded PCEC micelles was about 61 nm. However, the particle size decreased in correspondence to an increase in temperature, making it more suitable for drug delivery when injected *via* blood. Both the free honokiol and honokiol-loaded micelles had a dose-dependent anti-proliferative effect on A549 human lung adenocarcinoma cells and were comparable. The prepared micelles showed a typical two-phase-release profile under *in vitro* conditions.[49] Merlin *et al.* studied the anticancer effect of phenolic phytonutrient ferulic-acid-loaded poly-D,L-lactide-*co*-glycolide (PLGA) nanoparticles on non-small-cell lung carcinoma cell lines. The ferulic-acid-loaded PLGA nanoparticles were prepared by a double emulsion method and had a particle size of about 483 nm. The NCI-H460 cells were treated with ferulic acid alone as well as with the ferulic-acid-loaded PLGA nanoparticles. The results depicted an increased anticancer effect by the ferulic-acid-loaded nanoparticles. Furthermore, the nanoparticle-induced cytotoxicity involved an increase in the level of reactive oxygen species (ROS), DNA damage, altered mitochondrial transmembrane potential (MMP) and apoptotic morphological changes. These factors suggest that ferulic-acid-loaded PLGA nanoparticles are a suitable therapeutic tool against lung cancer.[50]

The novel anticancer drug, β-lapachone (β-lap), which is bioactivated by NAD(P)H:quinone oxidoreductase-1 (NQO1), an enzyme found specifically overexpressed in non-small-cell lung cancer (NSCLC), was delivered using nanoparticles. The β-lap was incorporated into poly(ethylene glycol)-*co*-poly(D,L-lactic acid) (PEG–PLA) polymer micelles using a film sonication procedure. The prepared micelles had core–shell architecture and were about 30 nm in size. The β-lap micelles were injected *via* the tail vein or caudal vein of mice with subcutaneous A549 lung tumors and the biodistribution was studied. The results showed a prolonged blood circulation and increased accumulation of β-lap. In addition, the *in vitro* administration of the micelles to LLC tumors led to DNA damage and PARP-1 hyperactivation.[51] The basic principal involved in the formation of polymeric micelles is illustrated in Fig. 5. Zhang *et al.* examined the combinational effect of β-lapachone and paclitaxel micelles against A549 non-small-cell lung cancer (NSCLC) cells. The co-encapsulation of β-lapachone and paclitaxel in the PEG–PLA micelles had an encapsulation efficiency of 100.7 ± 2.2% and a drug-loading efficiency of about 100.3 ± 3.0%. The combinational β-lapachone and paclitaxel micelle was found to have an improved effect compared to the β-lapachone micelle and paclitaxel micelle alone. The combinational micelle had a significant antiproliferative effect at an IC_{50} of 0.16 μM, while the individual IC_{50} s were 4.5 μM and 0.32 μM for the β-lapachone micelle and the paclitaxel micelle, respectively. Thus, the two compounds were supposed to exhibit a synergistic effect against lung cancer.[52]

The flavonoid, luteolin, was encapsulated into a nanocarrier and tested against H292 lung cancer cells. The nanocarrier had a polymeric base, made up of polylactic acid and polyethylene glycol (PLA–PEG). The nanoparticle formed had a mean size of

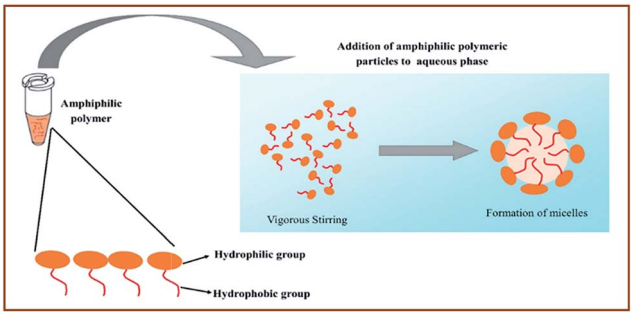


Fig. 5 Formation of polymeric micelles.

about 115 nm. The luteolin-loaded nanoparticle and free luteolin both showed antiproliferative activity against H292 cells. The IC_{50} of nano-luteolin was significantly less than that of free luteolin, showing that the nanosystem contributes to improved bioavailability. Similar results were observed in a colony formation assay.[53]

5.2 Breast cancer

Breast cancer is a malignant tumor that starts in the cells of the breast and occurs commonly in women. Women around the age of 40 to 70 years are more prone to breast cancer. It ranks as the second most common cause of death worldwide and, if left untreated, easily spreads to other parts of the body. The metastasis of breast cancer is found to cause lung cancer in many cases.[10,48] The diarylheptanoid compound, curcumin, was delivered using a biologically derived nanoparticle to MCF-7 and MDA-MB-453 breast cancer cell lines and its therapeutic effects were recorded. The nanoparticle was manufactured from covalently blended silk fibroin and chitosan (SFCS) polymers or silk fibrin polymer alone by the capillary-microdot technique. All the synthesized nanoparticles were less than 100 nm in size and were tested with breast cancer cell lines. Interestingly, the silk fibroin showed a higher uptake and efficacy than SFCS nanoparticles in both breast cancer cell lines. The cell viability of both the breast cancer cell lines was decreased more by the silk fibroin nanoparticles than by the SFCS nanoparticles.[54] Sebak *et al.* produced a nanoparticle from human serum albumin (HSA) for the targeted delivery of noscapine and enumerated its response with SK-BR-3 breast cancer cells. Noscapine is obtained from plants of the poppy family and is a benzylisoquinoline alkaloid. The pH-coacervation method was employed to form HAS nanoparticles and noscapine-loaded nanoparticles. The nanoparticle size ranged from 150–300 nm and had 85–96% drug-loading efficiency. About 10% of noscapine was released with the initial burst from the nanoparticle followed by a sustained drug release. The SK-BR-3 breast cancer cells were treated with the HAS nanoparticles as well as with the noscapine-loaded HAS nanoparticles. Both the drug-loaded and drug-free nanoparticles reduced the viability of the breast cancer cells, whilst the effect of noscapine-loaded nanoparticles was significantly higher.[55]

A pH-sensitive liposome was used to deliver ursolic acid, a triterpenoid compound, to MDA-MB-231 breast cancer cells. The pH-sensitive liposomes were prepared by the lipid hydration method. The liposomes had a mean diameter of 191.1 ± 6.4 nm and long-term stability. The liposomes were predominantly of a vesicle size less than 100 nm, promising good drug-loading efficiency. The MDA-MB cells were exposed to the pH-sensitive ursolic acid liposomes. The IC_{50} value of the ursolic acid liposomes was much lower than that of the free ursolic acid, indicating the improved anticancer activity of the nano-liposomes.[56] Odeh *et al.* prepared two different kinds of liposomes, thymoquinone-loaded liposomes (TQ-LP) and thymoquinone loaded in liposomes modified with Triton X-100 (XLP). Thymoquinone is an herbal-derived phytochemical that has excellent chemopreventive properties and is hydrophobic in nature. Both the nanoparticles had a diameter of about 100 nm, while the entrapment efficiency was more than 90% for TQ-LP and 49.6% for XLP. Their biological activity was studied using both MCF-7 cancer cells and fibroblast cells. However, the TQ-LP effectively suppressed the proliferation of MCF-7 cells and exerted very low toxicity on normal periodontal ligament fibroblasts.[57]

The inhibitory effect of silibinin and D-α-tocopheryl polyethylene glycol 1000 succinate (TPGS) on breast cancer cells was recorded. Silibinin-loaded lipid nanoparticles containing TPGS and phosphatidylcholine were designed and prepared by a thin-film hydration method. The nanoparticles had an average size of 45 nm and the encapsulation efficiency of silibinin in the nanoparticle was $98.63 \pm 0.30\%$. Cellular uptake studies showed that the drug content in MDA-MB-231 breast cancer cells after silibinin nanoparticle treatment for 24 h was about twice as much as that after free silibinin treatment. Corresponding results were observed for cell viability, invasion and migration assays. However, the silibinin-loaded nanoparticles strongly suppressed the invasive and migratory capabilities of MDA-MB-231 cells at a concentration of 20 $\mu g\ mL^{-1}$ through the downregulation of the MMP-9 and Snail pathways. Thus, it was concluded that the silibinin-loaded TPGS nanoparticles could be used as a novel therapeutic agent against breast cancer.[58] Sharma *et al.* used dendrimers to deliver the phenolic phytochemical, gallic acid, for inhibiting breast cancer cells. The dendrimers were made up of polyamidoamine (PAMAM) using Tomalia's divergent growth approach. The dendrimers provided a high degree of surface functionality and versatility for the gallic acid loaded onto them. The cytotoxicity of the gallic-acid-loaded PAMAM nanoparticles was found using MCF-7 human breast cancer cells. The MCF-7 cells were treated with the PAMAM dendrimer, gallic acid and the gallic-acid-loaded PAMAM nanoparticles. The IC_{50} values showed that the gallic-acid-loaded PAMAM nanoparticles had a synergistic antiproliferative effect on the growth of MCF-7 cells.[59]

5.3 Colorectal cancer

Cancer that occurs in the colon or rectum is termed as colorectal cancer. It ranks as the third most common type of cancer, as the American Cancer Society estimates 136 830 new cases and 50 310 deaths due to colorectal cancer in the United States for 2016. It is more susceptible to the foods we consume as the colonic epithelial cells come into direct contact with them.[10,48] Zheng *et al.* recorded the cytotoxicity of triptolide and triptolide-loaded polymeric micelles against HT-29 human adenocarcinoma cells. Triptolide is a diterpenoid tri-epoxide purified from the Chinese herb, *Tripterygium wilfordii*, which has anticancer properties but exhibits some other side effects. The triptolide-loaded polymeric micelles (TP-PM) were synthesized using methoxypoly(ethylene glycol)–poly lactic acid (MePEG–PLA) copolymer by a solvent evaporation method. Both the free triptolide and the TP-PM had a dose- and time-dependent effect on the HT-29 cells; however the inhibitory effects of TP-PM on the tumor cell growth were more significant for all incubation times and concentrations. In addition to this, the incubation of

HT-29 cells with triptolide and the TP-PM also resulted in an increase in the caspase 3/7 activity, indicating apoptosis, with the highest apoptosis index at 6.96 after 48 h incubation with 10 ng mL^{-1} TP-PM. Hence, the polymeric micelles served as an excellent carrier of TP and reduced its toxicity.[60] The small-molecule polyphenol compound, honokiol, was loaded into the self-assembled biodegradable star-shaped micelles and tested for chemotherapeutic effects. The biodegradable polymeric micelles were made up of monomethoxy poly(ethylene glycol) (MPEG) and poly(ε-caprolactone) (PCL) and loaded with the honokiol by a direct dissolution method assisted by ultrasonication. The average particle size of the obtained honokiol micelles was about 40 nm and these were used to treat CT26 murine colon carcinoma cells. The release rate of honokiol from the star-shaped polymeric micelles was slower. Nevertheless, they exhibited an antiproliferative effect against the CT26 cells in a dose-dependent fashion. Therefore, this star-shaped honokiol micelle may be used to design a new dosage form.[61]

Ravindran *et al.* studied the anti-proliferative properties of the bioactive phytochemical, *Nigella sativa* thymoquinone, loaded in poly(lactide-*co*-glycolide) (TQ-PLGA) nanoparticles using human colon cancer HCT116. The TQ-PLGA nanoparticles had an encapsulation efficiency around 94% and ranged between 150 and 200 nm in size. The TQ-PLGA nanoparticles had an effective anticancer effect against the HCT116 cells. Apart from this, the nanoparticles were active in inhibiting NF-kB activation and in suppressing the expression of cyclin D1, matrix metalloproteinase (MMP)-9, and vascular endothelial growth factor (VEGF) when compared to the free thymoquinone. On the whole, the results demonstrate that encapsulation of TQ into nanoparticles enhances its anti-proliferative effects.[62] Luteolin (Lu), is a flavonoid with anticancer activity but it is said to have poor water solubility. This was delivered by monomethoxy poly(ethylene glycol)–poly(ε-caprolactone) (MPEG–PCL) micelles under *in vivo* conditions to evaluate the biodistribution and to C-26 colon carcinoma cells to determine their anticancer properties. The MPEG–PCL micelles encapsulated Lu by a self-assembly method. Fabricated Lu/MPEG–PCL micelles were water-soluble with an approximate size of about 38.6 nm and an encapsulation efficiency of about 98.32%. The pharmacokinetics of free luteolin and Lu/MPEG–PCL micelles was studied in rats, suggesting that the bioavailable concentration of luteolin was more when the Lu/MPEG–PCL micelles were used. Furthermore, the Lu/MPEG–PCL micelles inhibited the growth of C-26 colon carcinoma cells at an IC_{50} of 12.62 ± 2.17 μg mL^{-1}. Hence, the study indicates that encapsulation of Lu into MPEG–PCL micelles created an aqueous formulation of Lu with a potential anticancer effect.[63]

Zhang *et al.* enlisted the effects of self-carried curcumin nanoparticles for *in vitro* and *in vivo* colon cancer therapy. The curcumin nanoparticles were prepared by the re-precipitation method and were then anchored to poly(maleic anhydride-*alt*-1-octadecene)–polyethylene glycol (C_{18}PMH–PEG) on the surface by ultrasonication to improve the biocompatibility of the nanoparticles. The nanoparticles had a loading efficiency of about 78.5%, an encapsulation efficiency of about 95.8% and displayed sustained release behaviour without any initial burst. The curcumin nanoparticles were tested for their anticancer properties with CT-26 colon cancer cells. The results showed that the curcumin nanoparticles produced an 8-fold decrease in the half-maximal inhibitory concentration (IC_{50}) values of the free curcumin (IC_{50} = 33.4 μM) compared to the curcumin nanoparticles (IC_{50} = 4.2 μM). Analogous results were seen in the *in vivo* testing. After administration of the curcumin and curcumin nanoparticles to CT-26 tumor-bearing nude mice, the tumor volumes were 87% and 32%, respectively. This shows that the curcumin nanoparticle has a greater effect than free curcumin on the tumor cells. However, the curcumin nanoparticles had no adverse effects or toxicity when investigated for *in vivo* systemic toxicity.[64]

5.4 Skin cancer

Skin cancer is the most common form of cancer, globally accounting for at least 40% of cases, and it is especially common among people with light skin. The most dangerous type of cancer occurs in the melanoma or the cells that contain melanocyte pigments. Exposure to the ultraviolet radiation emitted by the sun is said to be a major cause of cancer.[10,48] Das *et al.* extensively studied the effects of the flavone, apigenin, against melanoma when delivered using poly(lactic-*co*-glycolide) nanoparticles. These were prepared by the solvent displacement method. The prepared nanoparticles demonstrated a biphasic release profile, showing an initial burst followed by controlled release for 3 days. The anti-proliferative effect of the nanoparticles was examined with A375 skin melanoma and HaCaT keratinocytes. It was observed that the nanoparticle had a dose-dependent effect on the A375 cells, with an IC_{50} of 15 μM, where the apigenin alone had an IC_{50} of 25 μM. In contrast, there was no cytotoxic effect on the normal HaCaT cells. The nanoparticles induced the intercalation of double-stranded DNA (dsDNA), along with an increase in ROS accumulation and a reduction in the antioxidant enzyme activities, mediating apoptosis through mitochondrial dysfunction.[65] This was followed by a study on the anti-carcinogenic effect of apigenin-loaded poly(lactic-*co*-glycolide) nanoparticles against ultra-violet B (UVB) and benzo(*a*)pyrene (BaP)-induced skin tumor in mice. Along with the anti-carcinogenic effect, changes in the mitochondria were also studied after apigenin delivery. The apigenin-loaded nanoparticles showed better results against UVB–BaP-induced melanoma, which may be related to their smaller size and faster mobility. The nanoparticles decreased the tissue damage as well as the frequency of chromosomal aberrations. Apart from this, there was an increase in the ROS generation, mitochondrial matrix swelling and modulation of the apoptotic markers, such as Apaf-1, bax, bcl-2 and cyt c. Thus, the apigenin-loaded poly(lactic-*co*-glycolide) nanoparticles possess potential ability for therapeutic management of skin cancer.[66]

In yet another study, the dihydrostilbenoid, combretastatin A-4 was co-encapsulated with doxorubicin and tested for anticancer properties under both *in vitro* and *in vivo* conditions. The compounds were loaded onto the RGD-modified liposomes. The cellular uptake of doxorubicin by the integrin-

overexpressing B16 and B16F10 melanoma cells was improved by the disrupting agent, combretastatin A-4. Moreover, the co-encapsulated liposomes were more toxic towards the melanoma cells than the doxorubicin-loaded liposomes. Similarly, the combretastatin A-4 and doxorubicin-loaded liposomes exhibited the most pronounced tumor regression effect in male C57BL/6 mice inoculated with melanoma B16F10 cells. Thus, the combretastatin A-4 encapsulation improved the efficacy of the doxorubicin.[67] Siddiqui *et al.* recently studied the anti-proliferative and pro-apoptotic effects of epigallocatechin 3-gallate (EGCG) encapsulated in chitosan nanoparticles on human melanoma cell growth, under both *in vitro* and *in vivo* conditions. The EGCG was loaded onto nanoparticles made up of polylactic acid–polyethylene glycol in order to enhance its bioavailability to the melanoma cells. The Mel 928 cells were used to test the effects of EGCG-loaded nanoparticles and free EGCG. The results showed that there was about an 8-fold dose advantage of this nano-formulation over native EGCG in retarding the growth of melanoma cells. Furthermore, a growth of Mel 928 tumor xenograft in the mice model was observed when EGCG-loaded nanoparticles were given. This inhibition included cell cycle phase arrest and changes in the level of cyclins D1 and D3 protein expression.[68]

5.5 Ovarian cancer

Ovarian cancer occurs when there is an uncontrolled growth of cells in the ovary. Women who have ovulated more over their lifetime and those who have never had children are more vulnerable to ovarian cancer. According to the statistical reports, about 14 240 women will die from ovarian cancer in the US alone and death from ovarian cancer is more common in North America and Europe than in Africa and Asia.[10,48] The small-molecule polyphenol, honokiol, was loaded onto a nanoparticle and was delivered to ovarian cancer cells under laboratory conditions. The nanocarrier was manufactured with monomethoxy poly(ethylene glycol)–poly(lactic acid) (MPEG–PLA) by the ring opening polymerization method and then honokiol was loaded onto it by a solvent extraction method. The honokiol-loaded MPEG–PLA nanoparticles had a spherical appearance with a mean particle size of *ca.* 80 nm. The nanoparticles were found to release 53% of the drug within 24 h under laboratory conditions. Both the free honokiol and honokiol-loaded MPEG–PLA decreased the viability of A2780 human ovarian cancer cells with increasing concentration. However, the honokiol-loaded MPEG–PLA nanoparticles potentially inhibited the growth of A2780 cells at an IC_{50} was 8.45 μg mL^{-1}. This was greater than the effect of the free honokiol.[69] Yallapu *et al.* studied the improved therapeutic effects of curcumin loaded to poly(lactic-*co*-glycolide) (PLGA) nanoparticles and its anti-cancer effect against cisplatin-resistant A2780CP ovarian cancer cells. The fabricated nanoparticles were found have an average size of 560.4 nm and exhibited a sustained and controlled drug release of curcumin under *in vitro* conditions. The curcumin-loaded PLGA nanoparticles inhibited the growth of the A2780CP cells at an IC_{50} of about 13.9 μM, which was superior when compared to the effects of free curcumin. Similar results were seen in the examination of long-term effects and the curcumin-loaded PLGA nanoparticles reduced the number of cancer cells in the colony. These results suggest that the curcumin-loaded PLGA nanoparticles are an ideal therapeutic agent.[70]

The anticancer activity and molecular mechanism of resveratrol-bovine serum albumin nanoparticles (RES-BSANP) on subcutaneously implanted human primary ovarian carcinoma cells in nude mice was examined in recent years. A tumor was induced by injecting SKOV ovarian cancer cells into the nude mice, which were given 200, 100, and 50 mg kg^{-1} RES-BSANP or 0.5 mL RES once a week. Observation of the tumor progression showed that the RES-BSANP significantly retarded the growth of carcinomas in nude mice from the third week onwards, and the inhibition rate was markedly higher than in mice treated with RES. The RES-BSNAP was found to induce apoptosis by releasing cytochrome c and regulating caspase-3, 9, thereby indicating a mitochondrial apoptotic pathway.[71] The hydrophobic drug, curcumin, was encapsulated into a hydrophilic polymeric core and delivered to the SKOV-3 ovarian cancer cells. The hydrophilic polymeric core was made up of poly(2-hydroxyethyl methacrylate) [PHEMA] nanoparticles. After loading the curcumin, the nanoparticles had a size of about 300 nm. *In vitro* investigations showed that the curcumin-loaded nanoparticles showed better tumor cell regression activity than free curcumin. Furthermore, they also showed a notable decrease in the G0/G1 phase cells. These nanosystems that delivered curcumin showed excellent biocompatibility when studied with a zebrafish embryo model.[72]

5.6 Prostate cancer

The malignant growth of cells in the prostate gland of the male reproductive organ leads to prostate cancer. As the cancer develops in the glands, it is medically termed as adenocarcinoma. According to the American Cancer Society, about 180 890 new cases of prostate cancer are expected in 2016, which means that 1 in 7 American men will be diagnosed with prostate cancer.[10,48] The gallic acid ester derivative, epigallocatechin 3-gallate (EGCG) was delivered to prostate cancer cells by a biodegradable nanoparticle. Here, EGCG was combined with polylactic acid–polyethylene glycol polymeric profiles along with prostate-specific membrane antigen (PSMA)-targeting ligands. The pseudomimetic dipeptide, *N*-[*N*-[(*S*)-1,3-dicarboxypropyl]carbamoyl]-(*S*)-lysine (DCL) was the PSMA-targeting ligand. An anti-proliferative effect was exhibited by the targeted nanoparticles as well as the non-targeted nanoparticles on LNCaP androgen-sensitive human prostate adenocarcinoma cells. Both the nanoparticles were exposed to PCa prostate cancer cells. The growth inhibition exhibited by EGCG-loaded nanoparticles showed high efficacy and target specificity. Apart from this, the EGCG-loaded nanoparticles were found to be ineffective in inhibiting HUVEC proliferation. Thus the developed nanoparticles were proven to exhibit selective toxicity against prostate cancer.[73] Zu *et al.* evaluated the enhanced targeting ability of folate-mediated EGCG bovine serum albumin nanoparticles (FA-EGCG-BSANP) against PC-3 prostate cancer

cells. The nanoparticles were prepared by the desolvation method and possessed a mean particle size of about 200 nm with an entrapment efficiency of about 81.5%. The folate-mediated nanoparticles were found to exhibit concentration-dependent targeting to the PC-3 cells. The PC-3 cells' uptake of FA-EGCG-BSANP was 23.65 times that of the EGCG-BSANP. The folate present in the nanoparticles was found to improve the lethality toward PC-3 cells due to FA-EGCG-BSANP.[74]

In yet another experiment, the gallate, EGCG, was delivered to prostate cancer cells using a nanocarrier and its results were recorded. The nanocarrier was made up of polylactic acid–polyethylene glycol (PLA–PEG) and was tested under *in vivo* as well as *in vitro* conditions. The effect of nano-trapped EGCG was 10-fold higher than that of free EGCG against PCa prostate cancer cells. The IC_{50} was measured to be 3.74 μmol L^{-1} for the EGCG-loaded nanoparticles and there was a significant increase in pro-apoptotic Bax with a concomitant decrease in anti-apoptotic Bcl-2 in the PCa cells. The 22Rv1 cells were injected into the mice, which were then given EGCG-loaded nanoparticles as well as free EGCG. The outcome was similar to that under *in vitro* conditions and the tumor size was reduced significantly.[75]

Besides the gallate, the yellow polyphenol, curcumin, was also explored for its anticancer properties. Mukerjee *et al.* developed a curcumin-loaded nanoparticle and investigated its anticancer properties against the prostate cancer cell lines, LNCaP, PC3 and DU-145. Curcumin was loaded to poly(lactic-*co*-glycolic acid) (PLGA) nanospheres prepared by a solid/oil/water emulsion solvent evaporation method. The prepared nanospheres were found to have a mean size of about 45 nm with a biphasic drug release manner. The curcumin-loaded PLGA nanospheres were found to be more effective than the free curcumin. This was reflected in the half-maximal inhibitory value. The IC_{50} of curcumin-loaded PLGA nanospheres ranged from 20 μM–22.5 μM, while that of free curcumin ranged from 32 μM to 34 μM. Besides this, the curcumin-loaded PLGA nanospheres also strongly inhibited the NF-κB function when compared to free curcumin.[76] In yet another study, the anticancer effect of nanoemulsion containing both curcumin and resveratrol was done. Separate nanoemulsions containing liposomes loaded with curcumin and liposomes loaded with resveratrol were prepared and co-administered to the PTEN-CaP8 cancer cells and the PTEN knockout mice with prostate cancer. *In vitro* studies showed that the curcumin with resveratrol effectively inhibited cell growth and induced apoptosis. In addition to this, the combination also significantly repressed the expressions of p-Akt, AR, cyclin D1 and mTOR proteins in PTENCap8 cells with loss of PTEN. Similarly, the mice that were given the combination (25 mg kg^{-1}) had a more positive response than the mice administered with either lipo-curcumin or lipo-resveratrol (50 mg kg^{-1} each) for 7 weeks. A notable reduction in the prostate weight in the combination treatment group confirmed the decrease in the incidence of mouse prostatic intraepithelial neoplasia (mPIN) lesions. Apart from these, the availability of curcumin was improved during the co-administration of lipo-curcumin and lipo-resveratrol.[77] A diagrammatic representation of extraction as well as loading of curcumin is given in Fig. 6.

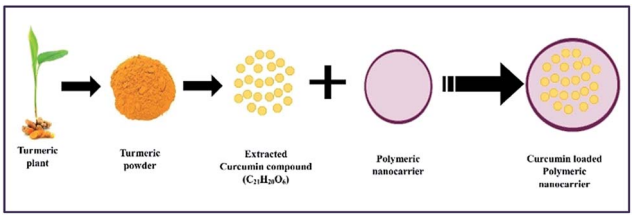


Fig. 6 Extraction and loading of curcumin.

5.7 Cervical cancer

Cervical cancer is a cancer arising from the cervix, a part of the uterus. In 90% of cases, cervical cancer is found to occur due to human papillomavirus (HPV) infection. It ranks as the fourth most common cause of death from cancer in women, globally. However, cervical pre-cancers are diagnosed far more often than invasive cervical cancer.[10,48] A fluorescence study of the curcumin–casein micelle complex and its application as a drug nanocarrier to cancer cells was done by Sahu *et al.* The curcumin was loaded to bovine casein micelles and the prepared micelles were less than 200 nm with a roughly spherical shape. These curcumin-micelles were formed due to hydrophobic interactions between the casein micelles and curcumin. HeLa cervical cancer cells were used to study the cellular uptake and toxicity of free curcumin and curcumin–casein micelles. The green fluorescence emitted after the treatment showed that the casein micelles had improved the uptake of the curcumin. The cellular uptake showed a concentration-dependent increase. Similar results were obtained from cytotoxicity studies and the IC_{50} of free curcumin and the CM-curcumin complex was 14.85 and 12.69 μM, respectively. This showed that the casein micelles proved to be a good drug carrier.[78] Das *et al.* loaded the yellow phytochemical, curcumin, to alginate–chitosan–pluronic composite nanoparticles to deliver it to HeLa cancer cells. The nanocomposite particles were created with the alginate, chitosan and pluronic using ionotropic pre-gelation and polycationic cross-linking. The pluronic was used to improve the solubility of curcumin, which was verified in the encapsulation efficiency studies. The nanoparticles had an average size of about 100 nm. The drug release from the nanoparticle occurred in a controlled manner and the cellular uptake was acceptable in the HeLa cells. Apart from this, the cell viability of HeLa cells was significantly decreased by the curcumin-loaded composite nanoparticles at a concentration of 500 μg mL^{-1}.[79]

5.8 Liver cancer

Liver cancer, often referred as hepatic cancer, is a cancer that originates in the liver. It is usually diagnosed accidentally and mostly occurs due to cirrhosis, which is due to due to either hepatitis B, hepatitis C, or alcohol. About 39 230 new cases are expected to be diagnosed by the American Cancer Society in 2016.[10,48] Lin *et al.* investigated the effect of berberine, a form of isoquinoline alkaloid, in the liposomal form against hepatoma. The berberine liposome was manufactured by the thin-film hydration/extrusion method and contained 5% mol polyethylene

glycol (PEG). The berberine liposomes had an encapsulation efficiency of 14% and were exposed to HepG2 liver hepatocellular carcinoma cells. The berberine liposomes exhibited 2.5 times more toxicity against the HepG2 cells than the berberine solution. The berberine liposome significantly inhibited the growth of HepG2 cells at 1.67 μg berberine per mL and induced apoptosis through the caspase/mitochondria-dependent pathway. Furthermore, the liposome was tested under *in vivo* conditions in nude mice bearing the HepG2 tumor. The results showed that the berberine liposomes effectively reduced the size and weight of tumors, causing a reduction in the rate of elimination of berberine in both plasma and tissues. Therefore, the work demonstrated that the liposome was a good carrier for the berberine.[80] On the other hand, the same phytochemical was delivered as a nanosuspension to the human hepatocytes, HepG2 and Huh7 cells. The nanosuspension consisted of the berberine phytochemical and D-α-tocopheryl polyethylene glycol 1000 succinate (TPGS) with an average size of 73.1 ± 3.7 nm. The nanosuspension had a significant effect on the growth of HepG2 and Huh7 cells at concentrations of 8.1 and 4.7 μg mL^{-1}. In contrast, the free berberine suppressed the growth of the hepatoma cells at 18.3 and 6.5 μg mL^{-1} (HepG2 and Huh7 cells, respectively). In the *in vivo* experiment with H22 solid tumor-bearing mice, the berberine nanosuspensions had an inhibition rate of 63.7%, while the free berberine had an inhibition rate of only 41.4%. Thus, the nanosuspension has improved the availability of the phytochemical to the cancer cells.[81]

Studies to were done record the effect of a xanthonoid, gambogic acid, loaded in lactoferrine nanoparticles, against cancer. Lactoferrine is a cationic iron-binding glycoprotein and gambogic acid-lactoferrin nanoparticles (GL-NPs) were produced by nanoparticle albumin-bound (NAB) technology. The GL-NPs had a mean size of about 150 nm and an encapsulation efficiency of 7.2%, and the *in situ* intestinal perfusion displayed a good absorption of the gambogic acid from the GL-NPs. The GL-NPs showed almost an identical antiproliferative effect in the HepG2 liver carcinoma cells to that of the arginine solution of gambogic acid. Apart from this, the GL-NPs exhibited a high inhibitory rate when orally administered to S180 tumor mice and controlled the tumor growth. This was about 1.39-fold higher than the effect of an arginine solution of gambogic acid. These studies have also paved a preliminary way for the study of lactoferrine as an oral drug delivery carrier.[82] Zhai *et al.* prepared apigenin-loaded polymeric micelles and tested their antiproliferative effect against HepG2 liver carcinoma cells. The polymeric micelles were composed of Pluronic P123 and Solutol HS 15 with an average diameter of 16.9 nm. They had an entrapment efficiency and drug loading of 96.36% and 1.32%, respectively. Around 84% of the apigenin was delivered by the polymeric micelles, displaying a sustained drug-release behaviour. The IC_{50} values on HepG2 cells for apigenin-loaded polymeric micelles and free apigenin solution were 5.57 μg mL^{-1} and 20.19 μg mL^{-1}, respectively. The growth of HepG2 cells was significantly reduced by the apigenin micelles at lower concentrations than the free apigenin, which may be related to its improved hydrophilic characteristics.[83]

The diarylheptanoid compound, curcumin, was conjugated to gum arabic and was used against hepatoma cell lines. Gum arabic is a polysaccharide substance, which is used to improve the solubility of curcumin. The self-assembled conjugates had a spherical structure and a mean size of 270 nm. When tested, the formed curcumin conjugate had improved the solubility and stability of curcumin at physiological pH. Apart from this, the curcumin conjugation retarded the growth of the HepG2 hepatocellular carcinoma cells. They also exhibited a higher targeting ability toward the cells due to the galactose groups present in gum arabic.[84] Beside the berberine nanosuspensions, resveratrol nanosuspensions were also prepared recently. The resveratrol nanosuspension contained resveratrol and poloxamer 188 and was manufactured using a high-pressure homogenization technique. The average size of the nanosuspension was 159 nm and it was evaluated for its effect on HepG2 cells, along with free resveratrol. The results of an MTT assay showed that the resveratrol inhibited the proliferation of HepG2 cells at an IC_{50} of 2.91 μg mL^{-1}. In contrast, the free resveratrol had a similar effect only at 7.13 μg mL^{-1}. Hence, these results suggest that the delivery of the resveratrol nanosuspension is a promising approach for treating tumors.[85]

5.9 Pancreatic cancer

Pancreatic cancer arises in cells in the pancreas, a glandular organ behind the stomach; therefore, it is mostly termed as pancreatic adenocarcinoma. It ranks as the seventh most common cause of death with about 40 560 deaths predicted in 2016 alone. It is usually due to usage of tobacco and obesity.[10,48] The polyphenol, curcumin, was explored for its anticancer properties against pancreatic cancer. Nanocurcumin or curcumin-encapsulated nanoparticles were synthesized using micellar aggregates of cross-linked and random copolymers of *N*-isopropylacrylamide (NIPAAM), with *N*-vinyl-2-pyrrolidone (VP) and poly(ethylene glycol)monoacrylate (PEG-A). The developed nanocurcumin was found to readily disperse in an aqueous medium, displaying its hydrophilic nature. The MiaPaca pancreatic cancer cell line was treated with curcumin and nanocurcumin. Both of these significantly suppressed the growth of pancreatic cancer cells at 10 and 15 μM, respectively. Furthermore, the nanocurcumin obstructed the activation of nuclear factor kappa B (NFκB) and downregulated the IL-6, IL-8, and TNFα cytokines, thereby inducing cellular apoptosis. Thus, it was found that the nanocurcumin possessed all the properties of curcumin with better solubility.[86] Wei *et al.* entrapped the phytochemical, curcumin, as an ester to cholesteryl-hyaluronic acid (CHA) nanogel and employed this in a targeted delivery to CD44-expressing drug-resistant MiaPaca cancer cells. The curcumin-conjugated nanoparticle was 20 nm in diameter with a spherical structure. Gastrointestinal stability studies showed that the curcumin-loaded nanoparticles were absorbed in the gastrointestinal tract and then entered the blood circulation. Thus, it was concluded that the oral administration of the nanoparticles with curcumin would lead to 2–5% loss. Apart from this, the nanoparticle induced apoptosis in cancer cells, suppressing the expression of NF-κB, TNF-α, and COX-2 cellular

targets in a similar way to free curcumin. Moreover, the curcumin-loaded nanoparticles suppressed the tumor growth by up to 13-fold in a 4T1 mice model injected with the MiaPaca cells. Hence, the nano-drug delivery of curcumin is found to be an ideal therapy for cancer.[87]

Kesharwani *et al.* produced parenterally administrable nanomicelles of 3,4-difluorobenzylidene curcumin (CDF) for treating pancreatic cancer. The 3,4-difluorobenzylidene curcumin is a non-toxic analogue to the curcumin known for its high anticancer activity, and it showed improved pancreas-specific accumulation *in vivo*, compared with curcumin. The nanomicelles were prepared by self-assembling the styrene–maleic acid copolymer (SMA) with CDF, using non-covalent hydrophobic interactions. These were found to have a sustained drug release behaviour when exposed to MiaPaCa-2 and AsPC-1 pancreatic cancer cell lines. The free CDF and the SMA–CDF nanomicelles showed toxicity against both the cell lines and the effect of the nano-micelles was superior to that of the free CDF. The IC_{50} was calculated as 230 ± 4.68 nM for MiaPaCa-2 cells and 710 ± 3.81 nM for AsPC-1 cells.[88] In addition to this, the same research group evaluated the response of CDF loaded to hyaluronic acid-conjugated polyamidoamine dendrimers given to CD44-overexpressing MiaPaCa-2 pancreatic cancer cells. The nanocarrier was made of poly(amidoamine) (PAMAM) and hyaluronic acid (HA) as a targeting ligand and then loaded with the CDF (HA–PAMAM–CDF). The whole dendrimer system had a particle size of 9.3 ± 1.5 nm. These displayed a dose-dependent cytotoxicity against MiaPaCa-2 and AsPC-1 human pancreatic cancer cells. The half-maximal value was found to have a 1.71-fold increase in the presence of the HA-ligand. However, the developed nanocarrier was found to be an excellent therapeutic device against CD44-overexpressing pancreatic cancer.[89]

5.10 Oral cancer

Any cancerous growth witnessed in the oral cavity is generally termed as oral cancer. Usually, it arises as a primary lesion in any of the tissues in the mouth, which gradually spreads. Oral cancer is twice as common in men as in women and the American Cancer Society estimated 9450 deaths due to this in 2016.[10,48] Dihydroartemisinin (DHA), the active metabolite of artemisinin, was loaded onto a co-polymeric micelle and delivered to oral cancer cells under laboratory conditions. The co-polymeric micelles were made up of methoxy poly(ethylene glycol)/poly(L-lactic acid) (mPEG) and loaded with the DHA using a modified solvent evaporation method. Physicochemical observations revealed that the nanoparticles were stable, spherical in shape and had a mean size of about 130 nm. The release of DHA from the co-polymeric micelles was pH-dependent and exhibited biphasic drug release behaviour, with an initial burst followed by a slightly faster drug release. An MTT assay showed that the DHA delivered from the micelle had a superior anticancer effect on KB human oral cancer cells as the IC_{50} was found to be 18.70 μM, while that for the free DHA was 24.55 μM. This showed that the nano-drug delivery improved the availability of the drug delivered. Besides, the DHA-micelle-treated cells showed some physical signs of apoptosis.[90] In recent years, the polyphenolic compound, ellagic acid, was encapsulated in chitosan nanoparticles and delivered to the KB human oral cancer cell line. The ellagic acid was entrapped in the chitosan nanoparticles using the ionic gelation method. The nanoparticles were found to have a spherical shape and an average size of about 176 nm. Furthermore, the drug encapsulation efficiency was around 94%, while the loading efficiency was 33%, and the nanoparticle was found to exhibit sustained drug release behaviour. The ellagic acid was found to have a better therapeutic competence against the KB cells when delivered using the chitosan nanoparticles. They exhibited a dose-dependent effect and had an IC_{50} value of 0.953 μg mL^{-1}, along with visible DNA fragmentation in the KB cells.[91]

5.11 Leukemia

Leukemia is the name given to a group of cancers that usually begin in the bone marrow and result in high numbers of abnormal white blood cells. It is common among children in developed countries and about 24 450 deaths were estimated by the American Cancer Society.[10,48] Anand *et al.* investigated the antiproliferative activity of curcumin-loaded PLGA nanoparticles under laboratory conditions as well as the improved bioavailability of this method by *in vivo* examination. The curcumin drug was loaded to a polymer-based nanoparticle made up of poly(lactide-*co*-glycolide) (PLGA) and a stabilizer, polyethylene glycol (PEG), with 97.5% encapsulation efficiency. KBM-5 human chronic myeloid leukemia cells were then exposed to the curcumin-loaded PLGA–PEG. It was found that the curcumin-loaded nanoparticles showed an improved cellular uptake, inhibition of TNF-induced NF-κB activation, suppression of NF-κB-regulated proteins involved in cell proliferation (cyclin D1), invasion (MMP-9), angiogenesis (VEGF) and induced apoptosis compared to free curcumin. In the case of the mice, 2.5 mg kg^{-1} of curcumin nanoparticles were injected intravenously. HPLC analysis showed that the curcumin nanoparticles were more bioavailable and had a longer half-life than free curcumin.[92] In another study, a co-formulation of doxorubicin and curcumin in poly-(D,L-lactide-*co*-glycolide) nanoparticles suppressed the development of multidrug resistance in K562 chronic myeloid leukemia cells. The doxorubicin and curcumin-loaded PLGA nanoparticles were prepared by the single emulsion solvent evaporation technique with an encapsulation efficiency of 46% and 86%, respectively. When used to treat K562 cells, the cellular uptake of dual drug-loaded NPs was nearly 8 times higher than the dual drug in solution. Apart from this, the nanoparticles exhibited significant growth inhibition at an IC_{50} value of 0.1 μg mL^{-1} when the nanoparticles were administered in equivalent concentrations, along with a gradual decrease in the expressions of MDR1 and BCL-2 at the mRNA level. Overall, this combinational strategy has more noteworthy promise than that of the drugs alone.[93]

Wang *et al.* studied the antileukemia mechanism of the multifunctional Chinese traditional medicine, emodin, when

conjugated to D-α-tocopheryl polyethylene glycol 1000 succinate (TPGS) to form liposomes. The liposomes had a high encapsulation efficiency of about 95.2% ± 3.0% and had a particle size of 121.1 ± 44.9 nm. The emodin-TPGS liposomes were found to have an increased cytotoxicity toward L1210 and K562 leukemia cell lines. This cytotoxicity included the regulation of protein levels of myeloid cell leukemia 1 (Mcl-1), B-cell lymphoma-2 (Bcl-2) and Bcl-2-associated X (Bax). A bio-distribution study showed that the emodin-TPGS liposomes improved the bioavailability of emodin by 1.7 times compared to the free emodin in lungs and kidney.[94] The antiproliferative activity of citrus polymethoxylated flavone nobiletin-loaded chitosan nanoparticles was recorded in parallel. The nobiletin-loaded chitosan nanoparticles were formed *via* Schiff-base formation and had a loading efficacy of 7.0%. An *in vitro* experiment was carried out using RAW264.7 Abelson murine leukemia virus-induced tumor cell lines and L-929 normal subcutaneous connective tissue at various time intervals. It was found that both the raw nobiletin as well as the nobiletin-loaded chitosan nanoparticles suppressed the growth of RAW264.7 cells, while they did not affect the growth of L-929. Moreover, the nobiletin-loaded chitosan nanoparticles showed considerable inhibition at an IC_{50} of 8 μg mL^{-1} toward cancerous cells, revealing their great potential for applications in cancer chemotherapy.[95]

Rahman *et al.* studied the antileukemic effect of a natural dietary lipophilic compound when loaded to nanostructured lipid carriers. The zerumbone-loaded nanostructured lipid carriers were formed by a high-pressure homogenization technique. The obtained ZER-NLC particles had an average size of 52.68 ± 0.1 nm and a drug-loading efficiency of about 7.92%. The drug release of zerumbone from ZER-NLC was about 46.7% over 48 hours. When used to treat Jurkat acute lymphoblastic leukemia cells, the ZER-NLC significantly inhibited their growth with an IC_{50} of 5.64 ± 0.38 μg mL^{-1}. Thus, the study suggests the ZER-NLC is a suitable sustained-release drug carrier system for the treatment of leukemia.[96]

5.12 Cancer in the nervous system

The occurrence of cancer in the nervous system is a very rare scenario and affects the nervous system; examples are brain cancer and sarcomas of the nerves.[48] The growth inhibition effect of resveratrol when delivered by a biodegradable nanoparticle was studied by Shao *et al.* A biodegradable nanoparticle was made up of mPEG–PCL and the resulting nanoparticle has a smooth spherical shape. The drug-loading efficiency was about 19%, while the encapsulation efficiency was 91% for the mPEG–PCL nanoparticles. These were tested against C6 glioma cells. A glioma is a tumor that starts from the brain or spine and from the glial cells. The resveratrol-loaded nanoparticles exhibited greater cytotoxicity than the free resveratrol. Furthermore, the amount of ROS generated by the C6 cells when exposed to the resveratrol-loaded nanoparticles was comparatively more. Hence, this study suggests that Res-loaded nanoparticles could be a potential chemotherapeutic formulation for malignant glioma therapy.[97] The curcumin phytochemical, which has the capacity to inhibit beta amyloid, is investigated for its ability to retard the growth of SH-SY5Y neuroblastoma cells. Neuroblastoma is an extracranial solid cancer growth composed of neuroblasts, most commonly in the adrenal gland. The curcumin was loaded to apolipoprotein E3-mediated poly(butyl) cyanoacrylate nanoparticles, which had a particle size of around 195 nm. Moreover, cell viability studies showed an enhanced therapeutic effect on neuroblastoma cells with a sustained drug-release effect. Similar to the anticancer activity of curcumin, the developed nanoparticles induced ROS generation and sub-G1 cell cycle phase arrest along with induction of caspase-3. Hence, they concluded that the curcumin-loaded nanoparticles induced apoptosis in SH-SY5Y cells.[98]

5.13 Other cancers

Sou *et al.* studied the cytotoxicity of self-organized assemblies of curcumin micelles against myeloma cells. Myeloma is a malignant tumor that occurs in the bone marrow cells, known as plasma cells. The lipophilic drug, curcumin, was loaded to the amphiphatic poly(oxyethylene) cholesteryl ether (PEG-Chol) to form micelles. The curcumin-loaded PEG-Chol nanoparticles possessed more cytotoxicity against the myeloma cells. The viability of the myeloma cells was significantly decreased by the curcumin-loaded PEG-Chol nanoparticles at 1 μM, while the free curcumin had a significant effect at 5 μM. Hence, the PEG-

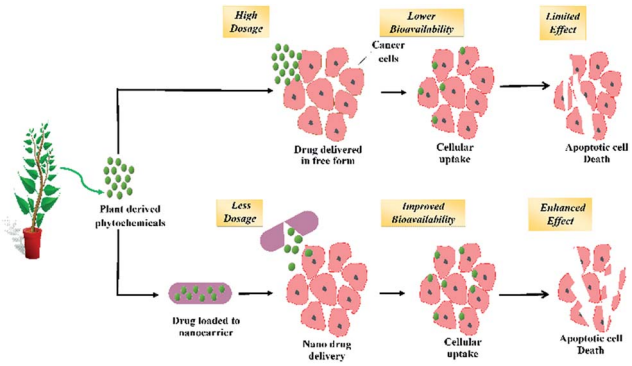


Fig. 7 Effect of phytochemicals against cancer cells.

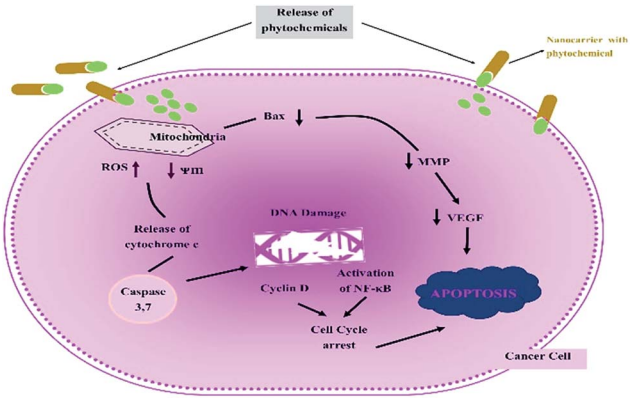


Fig. 8 Molecular targets of phytochemicals loaded inside nanocarriers against cancer cells.

Table 2 Summary of phytochemicals and their nanocarriers employed against various cancers

Type of cancer	Cell line tested	Phytochemical	Nanocarrier	Reference
Lung	A549 human lung adenocarcinomic cells	Honokiol	Poly(ε-caprolactone)-poly(ethylene glycol)–poly(ε-caprolactone) copolymer micelle	49
	NCI-H460 non-small-cell lung carcinoma cells	Ferulic acid	Poly-D,L-lactide-*co*-glycolide (PLGA) nanoparticles	50
	A549 human lung adenocarcinomic cells	β-Lapachone	Poly(ethylene glycol)-*co*-poly(D,L-lactic acid) (PEG–PLA) polymer micelles	51
	A549 human lung adenocarcinomic cells	β-Lapachone and paclitaxel	Poly(ethylene glycol)-*co*-poly(D,L-lactic acid) (PEG–PLA) polymer micelles	52
	H292 lung cancer cells	Luteolin	Polylactic acid and polyethylene glycol (PLA–PEG) nanoparticles	53
Breast	MCF-7 human breast adenocarcinoma cell line and MDA-MB-453	Curcumin	Silk fibroin and chitosan (SFCS) polymer nanoparticles	54
	SK-BR-3 human breast cancer cells	Noscapine	Human serum albumin (HSA) nanoparticles	55
	MDA-MB-231 breast cancer cells	Ursolic acid	pH-sensitive liposomes	56
	MCF-7 human breast adenocarcinoma cell line	Thymoquinone	Liposomes modified with Triton X-100 (XLP)	57
	MDA-MB-231 breast cancer cells	Silibinin	Lipid nanoparticles containing D-α-tocopheryl polyethylene glycol 1000 succinate (TPGS) and phosphatidylcholine	58
	MCF-7 human breast adenocarcinoma cell line	Gallic acid	PAMAM dendrimers	59
Colorectal	HT-29 human adenocarcinoma cells	Triptolide	MePEG–PLA copolymer micelles	60
	CT26 murine colon carcinoma cells	Honokiol	Monomethoxy poly(ethylene glycol) (MPEG) and poly(ε-caprolactone) (PCL) star-shaped micelles	61
	HCT-116 human colon cancer cells	Thymoquinone	Poly(lactide-*co*-glycolide) (PLGA) nanoparticles	62
	C-26 colon carcinoma cells	Luteolin	Monomethoxy poly(ethylene glycol)–poly(ε-caprolactone) (MPEG–PCL) micelles	63
	CT-26 colon cancer cells	Curcumin	Curcumin nanoparticles anchored with C_{18}PMH–PEG on the surface	64
Melanoma	A375 skin melanoma and HaCaT keratinocytes	Apigenin	Poly(lactic-*co*-glycolide) nanoparticles	65 and 66
	B16 and B16F10 melanoma cells	Combretastatin A-4 and doxorubicin	RGD (arginylglycylaspartic acid)-modified liposomes	67
	Mel 928 melanoma cells	Epigallocatechin 3-gallate (EGCG)	Polylactic acid–polyethylene glycol nanoparticles	68
Ovarian	A2780 human ovarian cancer cells	Honokiol	Monomethoxy poly(ethylene glycol)–poly(lactic acid) (MPEG–PLA) nanocarrier	69
	A2780CP ovarian cancer cells	Curcumin	Poly(lactic-*co*-glycolide) (PLGA) nanoparticles	70
	SKOV ovarian cancer cells	Resveratrol	Bovine serum albumin nanoparticles	71
	SKOV-3 ovarian cancer cells	Curcumin	Poly(2-hydroxyethyl methacrylate) [PHEMA] nanoparticles	72

Table 2 (*Contd.*)

Type of cancer	Cell line tested	Phytochemical	Nanocarrier	Reference
Prostate	LNCaP human prostate adenocarcinoma cells and PCa prostate cancer cells	Epigallocatechin 3-gallate (EGCG)	Polylactic acid–polyethylene glycol prostate-specific membrane antigen (PSMA) ligands	73
	PC-3 human prostate cancer cells		Bovine serum albumin nanoparticles	74
	PCa prostate cancer cells		Polylactic acid–polyethylene glycol (PLA–PEG) nanocarrier	75
	LNCaP human prostate adenocarcinoma cells, PC3 human prostate cancer cells and DU-145 PC3 human prostate cancer cells	Curcumin	Poly(lactic-*co*-glycolic acid) (PLGA) nanospheres	76
	PTEN-CaP8 Mouse prostate epithelium cancer cells	Curcumin and resveratrol	Curcumin and resveratrol nanoemulsions	77
Cervical	HeLa cervical cancer cells	Curcumin	Bovine casein micelles	78
			Alginate–chitosan–pluronic composite nanoparticles	79
Hepatoma	HepG2 hepatocellular carcinoma cells	Berberine	Berberine polyethylene glycol (PEG) liposome	80
		Berberine	Berberine and D-α-tocopheryl polyethylene glycol 1000 succinate (TPGS) nanosuspension	81
		Gambogic acid	Lactoferrine nanoparticles	82
		Apigenin	Pluronic P123 and solutol HS 15 polymeric micelles	83
		Curcumin	Gum arabic nanoparticles	84
		Resveratrol	Resveratrol and poloxamer 188 nanosuspension	85
Pancreatic	MiaPaca pancreatic cancer cell line	Curcumin	*N*-Isopropylacrylamide (NIPAAM), with *N*-vinyl-2-pyrrolidone (VP) and poly(ethylene glycol) monoacrylate (PEG-A)	86
			Cholesteryl-hyaluronic acid (CHA) nanogel	87
		Difluorobenzylidene curcumin (CDF)	Styrene–maleic acid copolymer (SMA) micelles	88
			Poly(amidoamine) (PAMAM) and hyaluronic acid nanocarrier	89
Oral	KB human oral cancer cells	Dihydroartemisinin	Methoxy poly(ethylene glycol)/poly(L-lactic acid) (mPEG) micelles	90
		Ellagic acid	Chitosan nanoparticles	91
Leukemia	KBM-5 myeloid leukemia cells	Curcumin	Poly(lactide-*co*-glycolide) (PLGA) and polyethylene glycol (PEG) nanoparticles	92
	K562 myeloid leukemia cells	Doxorubicin and curcumin	Poly-(D,L-lactide-*co*-glycolide) nanoparticles	93
	L1210 mouse lymphocytic leukemia cells and K562 myeloid leukemia cells	Emodin	D-α-Tocopheryl polyethylene glycol 1000 succinate (TPGS) liposomes	94
	RAW264.7 abelson murine leukemia virus-induced tumor cell lines	Nobiletin	Chitosan nanoparticles	95
	Jurkat acute lymphoblastic leukemia cells	Zerumbone	Nanostructured lipid carriers	96
Glioma	C6 glioma cells	Resveratrol	mPEG–PCL nanoparticles	97

Table 2 (*Contd.*)

Type of cancer	Cell line tested	Phytochemical	Nanocarrier	Reference
Neuroblastoma	SH-SY5Y neuroblastoma	Curcumin	Apolipoprotein E3 mediated poly(butyl) cyanoacrylate nanoparticles	98
Myeloma	Myeloma cells	Curcumin	Poly(oxyethylene) cholesteryl ether (PEG-Chol) micelles	99
Gastric	SGC7901 gastric cancer cells	Ursolic acid	Methoxy poly(ethylene glycol)–polycaprolactone (mPEG–PCL) nanocarrier	100

Chol nanosystem seems to act as a stable drug carrier for curcumin.[99] The hydrophobic ursolic acid is able to induce cell death when delivered to SGC7901 gastric cancer cells using nanoparticles. Gastric cancer develops from the cells present in the inner lining of the stomach and generally affects older people. Ursolic acid nanoparticles were prepared using methoxy poly(ethylene glycol)–polycaprolactone (mPEG–PCL) block copolymers as drug carriers by the nano-precipitation method. The produced nanoparticles are nearly spherical, have an average size of 144 nm and around 80% encapsulation efficiency. It was found that the free ursolic acid and ursolic acid-loaded nanoparticles had an effect on SGC7901 cells, whereas the nanocarrier alone did not produce any toxic effect. Moreover, the ursolic-acid-loaded nanoparticles had a stronger effect and elicited more cell death. Cell death involved the inhibition of COX-2 and activation of caspase-3. Therefore, the study offers an effective way to improve the anticancer efficiency of UA through a nano-drug delivery system.[100]

6. Conclusion

Nature has provided us with a vast variety of things and has become part of man's life. It has not only given us food to eat, water to drink, and fresh air to breath, but it has also provided some other supports that can save our lives. Phytochemicals are one such wonderful gift that helps to cure some threatening diseases. These phytochemicals have been continuously exploited by scientists for their medicinal properties, such as antibiotic, antioxidant, antifungal, and antiviral. One of the most prominent properties is the anticancer effect of these phytochemicals, as cancer is claimed to be the second leading cause of death worldwide.[10] A sustained search for a novel anticancer drug and a better method of administration has always existed. In this scenario, the advanced field of nanotechnology has elevated cancer therapy to a new level.

The nano-drug delivery of anticancer agents has interested many researchers in recent years. This is primarily due to their reliable and targeted delivery, increased drug efficiency, and improved cellular interaction, along with less toxicity to the surroundings. These advantages are the same for synthetic anticancer drugs and phytochemicals with an anticancer effect. Fascinatingly, the response elicited by the phytochemicals delivered using nanocarriers is similar to that of the same phytochemical in the free form. However, the half-maximal inhibitory concentration of the drug is reduced to a greater extent when nanotechnology is employed (Fig. 7). These natural compounds are found to suppress the growth of cancer cells by inducing programmed cell death, which is indicated by notable changes, such as DNA damage,[49] increased ROS generation,[49,65] release of cytochrome C,[71,98] activation of caspases 3/7,[60,71,100] cell cycle arrest,[72] activation of NF-κB[86,92] and downregulation of MMP, BaX, cyclin D and VEGF,[62,92,94] along with visible morphological apoptotic changes.[50] The different targets of phytochemicals loaded inside nanocarriers are given in Fig. 8.

The review summarized the nano-drug delivery of more than fifteen phytochemicals against various types of cancer. Among them, the yellow diarylheptanoid compound, curcumin, has been exploited against almost all types of cancer enlisted in the review. Phytochemicals such as apigenin, resveratrol, honokiol and epigallocatechin gallate (EGCG) are other commonly tested compounds. The phytochemicals are found to become more hydrophilic in nature when attached to a nanocarrier. From our studies, it is found that the most regularly preferred nanocarrier is a micelle with a polymeric base. A micelle is a nanostructure that has both a hydrophobic part and a hydrophilic part. The common polymeric bases employed for the micelles are poly(ethylene glycol) (PEG), polylactic-acid (PLA), poly-lactide-*co*-glycolide (PLGA), and methoxy poly(ethylene glycol) (mPEG), which are known for their good biocompatibility and biodegradable behaviour. Apart from the nano-micelles, dendrimers, liposomes, nanocomposites and nanoparticles act as nanocarriers for delivering drugs. The various phytochemical and their nanocarriers along with the cell line tested is given in Table 2.

The nano-drug delivery of phytochemicals has been extensively investigated in a large number of cell studies and a few animal studies. Preclinical testing with normal mice, nude mice and knockout mice bearing cancer cells has shown suppression of tumor growth. Besides these positive aspects, there is a lack of studies that deal with the toxicity and other adverse effects that are produced by the nanocarriers. Hence, more in-depth studies relating to the genotoxicity of the nanocarriers and other possible side effects should be initiated. Moreover, the phytochemicals are known to exhibit a synergistic effect against cancer cells. They have the ability to increase a particular property when used in combination. Previous studies have shown that phytochemicals when combined have improved cytotoxicity towards cancer cells.[101] It would be interesting to

investigate the outcome of these combinations with nano-drug delivery for cancer. In addition to this, clinical studies on nano-drug delivery as well as the mode of administration should be carried out to promote them in the field of medical oncology.

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