Chapter 6
Nanotechnology in Delivery and Targeting of Phytochemicals

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Contents

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Abstract Recently dietary and plant-derived phytochemicals are rising into limelight as many people developed a propensity towards opting nature-dependent healthy lifestyle. Scientific advancements highlight the effectiveness of phytochemicals in the treatment of many diseases and for various lifestyle benefits. Traditionally used in medicines, food supplements, and cosmeceutical products, phytochemical compounds are now conjoined with modern science to produce significant health benefits to humans as they possess fiddling risks compared to synthetic chemical entities. Phytochemicals are implemented in different forms and for different purposes such as phyto-, aroma-, and gemmotherapy for their potential health benefits. But the formulation of these phytochemicals for various applications is a major concern primarily owing to their low bioavailability, solubility, and the need to be taken in combination or as whole food. Hence, efficient delivery systems such as nano-engineered formulations are imperative to potentially yield the complete benefits from these phytochemicals. Besides enhancing the solubility and stability of phytochemicals, the nano-delivery systems can also prolong their average blood circulation time. Consequently, the high differential uptake efficiency, enhanced permeation, and retention characteristics in target tissues could prevent phytochemicals from premature interaction with the biological environment, thus resulting in decreased toxicity and favorable dose optimization possibilities. These advanced delivery systems also aid in the targeted delivery approaches. This chapter depicts the major natural products employed for the human benefits, their limitations, and nanotechnological solutions to triumph these limitations.

Keywords Nanomaterials · Phytochemicals · Supplements · Formulations · Bioavailability · Delivery · Inflammation · Cancer · Additive agents · Cosmeceuticals

6.1 Introduction

Phytochemicals are compounds which are derived from the plants and are generally non-nutritive to them. But these phytochemicals provide typical flavor and color to the fruits, vegetables, nuts, spices, grains, beverages, and other dietary plant-derived products (Chuan et al. 2017; Upadhyay and Dixit 2015). Despite providing color, odor, and flavor, they mainly protect the plants from diseases and environmental hazards such as pollution, stress, drought, UV exposure, and pathogenic attacks

(Saxena et al. n.d.). Traditional knowledge and current screening studies confirm similar protective effects in humans under diverse conditions and thus created a huge possibility for significant pharmaceutical applications that could benefit mankind in a more efficacious way than other synthetic medicines.

Phyto-applications have its own advantages like the existence of vast biodiversity of phyto-remediation system, easy availability, and cost and preference among population. Although many phytochemicals show significant promises in nutrient supplementation and in therapy, their hydrophobic nature, poor stability, poor absorption and bioavailability, rapid metabolism, elimination, and low target specificity make them difficult while administering at the therapeutic doses, an issue which can be possibly overcome using nanotechnology (Aqil et al. 2013).

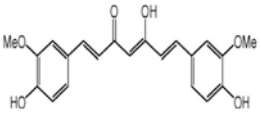
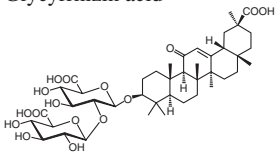
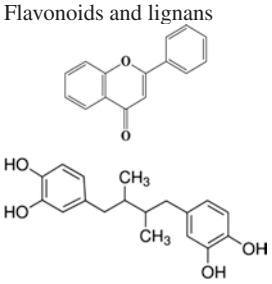
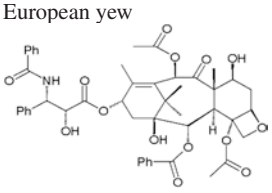
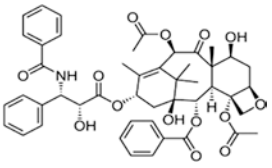
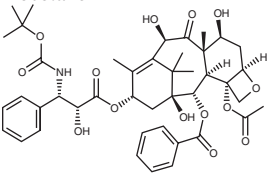
Several phytochemicals have been well recognized for their role as (a) antioxidants (e.g., allyl sulfides from onions, leeks, and garlic, carotenoids from fruits and carrots, flavonoids of fruits and vegetables, polyphenols from tea and grapes), (b) hormones (e.g., isoflavones of soy), (c) enzyme regulatory agents (protease inhibitors from soy and bean, indoles found in cabbages), (d) DNA replication modulators (saponins found in beans, capsaicin from hot peppers), and (e) antibacterial agents (proanthocyanidins from cranberries). These properties provide diverse opportunities in therapeutic, nutraceutical, industrial, and cosmetic applications.

In case of therapeutic application against cancer, phytochemicals can be potentially used to stimulate the weaker immune system; prevent carcinogenic activation; behave as anti-inflammatory, antioxidative principles; induce mutated cells to commit apoptosis; and regulate the hormonal and cellular mitogenic controls. Thus phytochemicals like carotenoids (such as beta-carotene, lycopene, lutein, zeaxanthin), flavonoids (such as anthocyanins and quercetin), indoles and glucosinolates (sulforaphane), inositol (phytic acid), isoflavones (daidzein and genistein), isothiocyanates, polyphenols (such as ellagic acid and resveratrol), and terpenes (such as perillyl alcohol, limonene, carnosol) are attracting serious scientific attention for use in cancer therapy nowadays (Hosseini 2015).

However with the shortage of available lead pharmacological compounds, along with the onset of side effects and resistance to the existing drug molecules, more extensive research is carried out for the implication of phytochemicals in the health industry. Globally, the development of potent plant-based drugs is given more importance hoping to find cures for disorders such as liver damage or pancreatitis for which there are hardly any reliable drugs for treatment (Leema and Tamizhselvi 2018).Thousands of phytochemicals have already been screened, and few potent ones were studied in detail for their favorable pharmacokinetic and pharmacodynamic properties (Table 6.1).

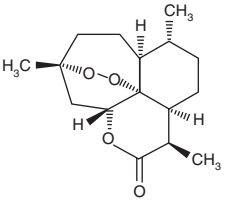
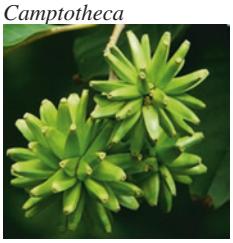
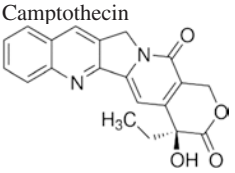
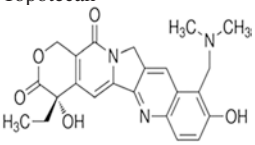
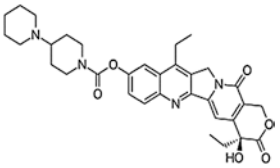
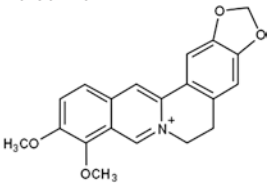
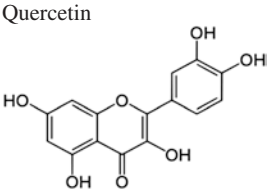
Interestingly several phytochemicals were also reported to have deleterious side effects which prevents them from regular applications. For instance, soybean-based trypsin inhibitors compromise the trypsin function which in turn leads to the release of cholecystokinin and excessive trypsin synthesis by pancreases, amylase inhibitors producing unwanted hypoglycemic effects, saponins interacting with cholesterol in the erythrocyte membrane and lysing the erythrocytes, association of dietary phytoestrogens with infertility and liver disease, and lignans having estrogenic and

Table 6.1 Partial list of active phytochemical molecules used in therapy and biological applications and their source of origin (Conte et al. 2017)

Sources	Active ingredients	Biological activity
Turmeric 	Curcuminoids 	Anticancer and antioxidant
Glycyrrhiza 	Glycyrrhizin acid 	Anti-inflammatory and antihypertensive
Psoralea corylifolia 	Flavonoids and lignans 	Hepatoprotective and antioxidant effects
Pacific yew tree bark 	Taxel 	Anticancer
European yew 	Paclitaxel 	
	Docetaxel 	

(continued)

Table 6.1 (continued)

Sources	Active ingredients	Biological activity
Artemisia annua 	Artemisinin 	Anticancer
Camptotheca 	Camptothecin  Topotecan  Irinotecan 	Anticancer
Berberis 	Berberine 	Anticancer
Broccoli 	Quercetin 	Antioxidant and anti-inflammatory properties

(continued)

Table 6.1 (continued)

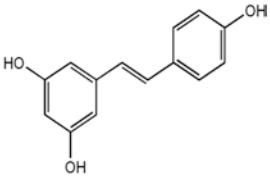
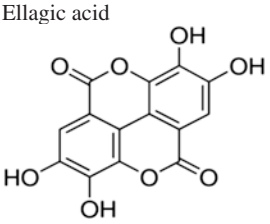
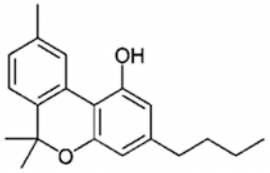
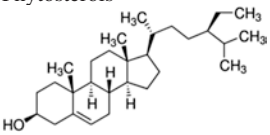
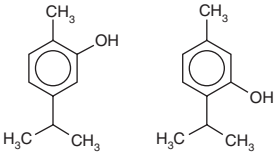
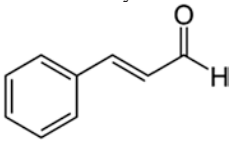
Sources	Active ingredients	Biological activity
Red grapes 	Resveratrol 	Anti-inflammatory properties
Pomegranate 	Ellagic acid 	Anti-inflammatory properties
Cannabis 	Phyto**cannabinoids: cannabin** 	Anti-inflammatory properties
Avocado 	Phytosterols 	Anti-inflammatory, anticancerous, and anti-atherogenic activities
Oregano  Cinnamon 	Carvacrol and thymol  Cinnamaldehyde 	Anti-inflammatory, antioxidant, and antimicrobial activity Anti-inflammatory properties

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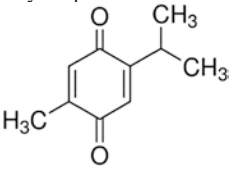
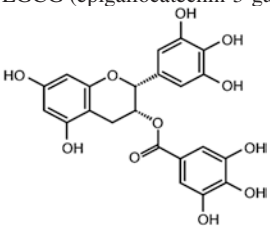
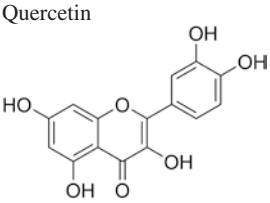
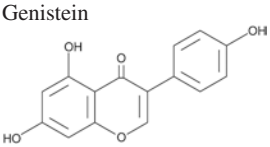
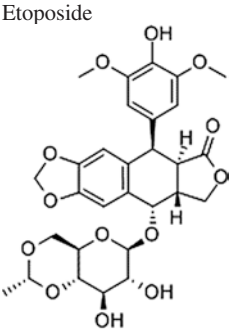
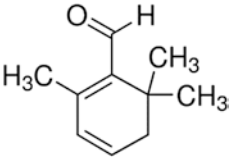
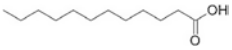
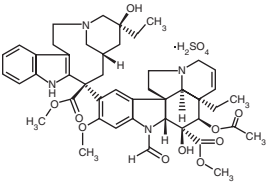
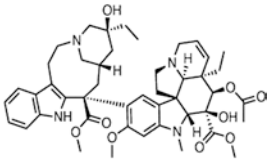
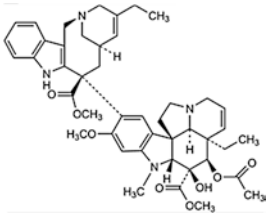
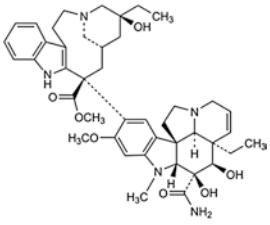
Table 6.1 (continued)

Sources	Active ingredients	Biological activity
Nigella sativa (black seed) 	Thymoquinone 	Antimicrobial, anti-inflammatory, antioxidant, anti-diabetic, anticancer, hepatoprotective, and renal protective activities
Green tea 	EGCG (epigallocatechin-3-gallate) 	Anticancer activity
Apple 	Quercetin 	Anticancer activity
Soybean 	Genistein 	Anticancer activity
Himalayan mayapple 	Etoposide 	Anticancer activity
Saffron 	Safranal 	Increased moisturizing effect and anti-UV activity

(continued)

Table 6.1 (continued)

Sources	Active ingredients	Biological activity
Coconut oil 	Lauric acid 	Antimicrobial activity
Catharanthus roseus 	Vincristine  Vinblastine  Vinorelbine  Vindesine 	Hypoglycemic and cytotoxic anticancer effects

antifertility effects. Likewise sugar-binding lectins and hemagglutinin may bind and agglutinate red blood cells (Hagerman et al. 1997).

Though they possess some threats, manipulating and modifying phytochemicals can be done to elicit more benefits and undermine harmful effects. Also, the reluctance among individuals to use phytocompounds is primarily because of treatment time, effectiveness, and nature of application. Thus, there is need for this type of therapy to be updated for the modern trends using technological advancements like nanotechnology. Nanotechnology has the potential in resolving the difficulties associated with phytochemicals with respect to access and delivery, overcoming the complexities of natural product chemistry, and quickening the inherent slow phase of action associated with working of natural products.

6.2 Nanotechnological Applications in Phytochemical Delivery

Although phytotherapy is followed for thousands of years, the mechanism-based phyto-applications are very limited today except with few serendipity-based drugs. In this regard, study on nanoparticles for targeted delivery or enhancing the efficacy of phytochemicals has gained much more importance. Nanotechnology is the emerging science that deals with particles in the range of 10 to 200 nm which serves as the effective vehicle for the drug delivery systems (Xie et al. 2016).

Existing phytochemical formulations face major issues mainly due to their unfavorable pharmacokinetic and pharmacodynamic properties. However when they are doped with nanoparticles, not only the solubility of the drug increases but also the efficiency of phytochemical is enhanced (Siddiqui et al. 2014). There are changes in biodistribution patterns of phytochemicals which, by interfering the therapeutic index of the phytochemicals, greatly enhance the drug efficacy and reduce the toxicity to the normal tissues (Fig. 6.1). The therapeutic index is the ratio of amount causing effective therapeutic activity to the amount causing toxic effect (Granja et al. 2016; Thangapazham et al. 2008).

The phytochemical agents could be loaded into nanomaterials or nanocarriers through encapsulation, conjugation, or adsorption to improve their therapeutic index and pharmacokinetic profiles (Brigger et al. 2002). These formulations enhance their absorption, stability, bioavailability, and prolonged systemic circulation and protect them from enzymatic degradation. Therefore, sustained and controlled release with increased uptake efficiency can be achieved. As a matter of fact, by conjugating through target-specific ligands, potential targeting of cancer cells could be achieved (Fig. 6.2). Already few nanotechnological formulations are approved as cancer therapeutic products in recent times (Siddiqui et al. 2014; Granja et al. 2016; Singh et al. 2014; Creixell and Peppas 2012).

Also it has to be noted that nanotechnologically modified phytochemicals themselves may exhibit some adverse pharmacokinetic profiles and exert negative

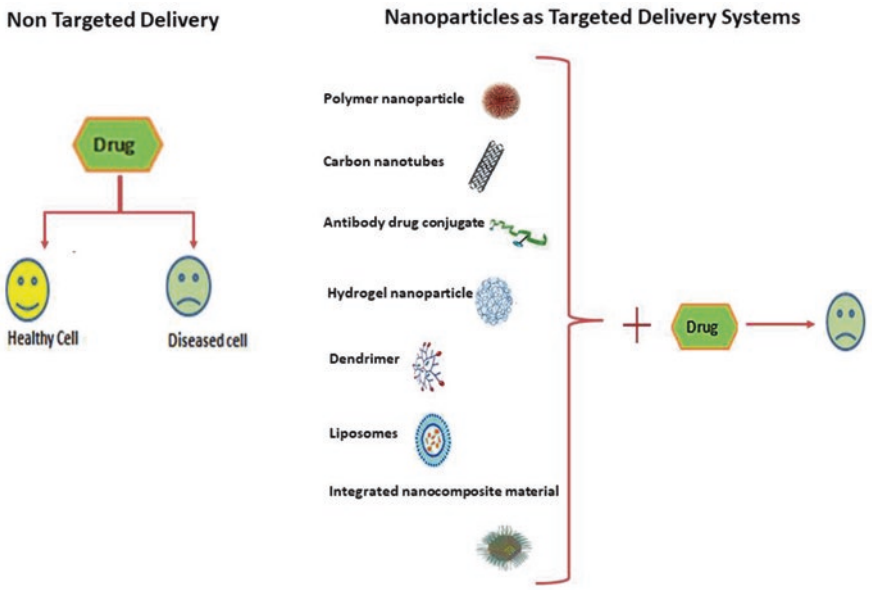


Fig. 6.1 Enhancement of phytochemical delivery using nanocarriers. Compared to the free, conventional form of delivery, nanocarrier-mediated delivery systems enrich the phytochemicals at the target site enhancing the kinetics and dynamics of the drug

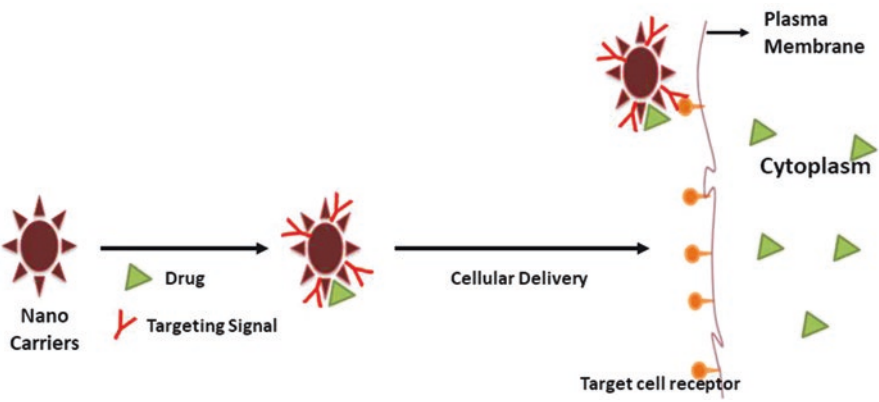


Fig. 6.2 Nanoparticles as targeted drug delivery systems. Drug-loaded, ligand-guided nanocarrier interacts precisely with the target cell receptors/surface molecules, providing specificity for therapy

influence on the therapeutic index or toxicity. However in these cases also, surface modifications of nanocarriers can avoid such toxicity issues and enhance cellular phytochemical delivery through changing biophysical interactions between nanocarriers and cell membrane (Alkilany and Murphy 2010).

Table 6.2 Nano-based applications and the food additive compounds commonly applied in the food industry

Purpose	Example
For improving the food qualities to (1) enhance dispersibility in food products; (2) improve food tastes; (3) enable hygienic food storage, (4) reduce the use of fat, salt, sugar, and preservatives; and (5) improveme the uptake and bioavailability of nutrients and supplements	**Food additives:** synthetic form of the tomato carotenoid lycopene, benzoic acid, citric acid, ascorbic acid, and supplements such as vitamins A and E, isoflavones, ß-carotene, lutein, omega-3 fatty acids, coenzyme-Q10
	Inorganic nanomaterials: transition metals and metal oxides (e.g., silver, iron, titanium dioxide), alkaline earth metals (e.g., calcium, magnesium), and non-metals (e.g., selenium, silicates)

The nanoparticles are made of variety of materials, and the individual composition depends on the purpose and characteristics such as the ability for eventual degradation. Based on the type of material used, nanoparticles can be classified into synthetic biocompatible polymeric nanoparticles and natural degradable biopolymers. Examples for synthetic polymers include poly(lactic-co-glycolic acid) (PLGA) and polylactic acid (PLA) nanoparticles. On the other hand, gelatin-, albumin-, cellulose-, or chitosan-based nanoparticles come under natural, degradable biopolymers (Brigger et al. 2002). So far a variety of nano-applications have been studied, and some proposed nanotechnologically modified phyto-additives and supplements are listed in Table 6.2.

Likewise the few modified phytochemicals available in market as reviewed recently (Bradley et al. 2011; Mamillapalli et al. 2016; Safhi et al. 2016) are:

1. Nanoparticles of *Cuscuta chinensis*: flavonoids and lignans are applied for their hepatoprotective and antioxidative role in the form of oral nano-suspension.
2. Artemisinin nanocapsule: artemisinin molecules are used for anticancer applications using self-assembled nanocapsulation procedure.
3. *Radix salvia miltiorrhiza* nanocapsule: used against heart disorders which applies spray-drying technique for synthesizing the phyto-nanocapsules.
4. Taxel-loaded nanoparticles: anticancer drug paclitaxel is loaded in nanoparticles for enhanced and sustained availability.
5. Berberine-loaded nanoparticles: berberine-loaded nanoparticles are prepared through ionic gelation method for sustained anticancer activities.
6. Nano-herbal cosmetic formulations: St. herb Nano Breast Cream and red blood cell Life Science's "Nanoceuticals Citrus Mint Shampoo" and conditioner.

Various nanostructured herbal formulations have been made as the combinational therapy. As reviewed earlier (Gopi and Amalraj 2016), curcumin, for instance, can be applied in different nano-combinational formulations. Curcumin–diclofenac diethylamine nanocarrier and curcumin–celecoxib-loaded nanoparticles for anti-inflammatory and antioxidative activities, curcumin–hydroxypropyl methylcellulose (HPMC) and polyvinylpyrrolidone (PVP)-loaded nanoparticles for antimalarial

activity, and curcumin–temozolomide-loaded magnetic nanoparticles for antitumor activity are some selected curcumin-based combinational nano-approaches.

In food industries various nutraceuticals are formulated as nanoforms for making the functional food components. Potential phyto-applications in this regard include nanoformulations of hydrophobins and vitamin D_3, folic acid–whey protein and starch, DL-α-tocopheryl acetate and β-carotene, vitamin D_3 entrapped whey protein and calcium, folic acid and calcium, carotenoids and lipids, long chain fatty acids and CoQ10, omega-3-fatty acids and oil soluble vitamins, clove oil and Eugenol, dextran and isoflavone genistein (Gopi and Amalraj 2016).

6.2.1 Advantages of Nanotechnology-Based Interventions

The major benefits of nanotechnological applications during phytotherapy include reducing the toxicity, enhancing the drug release, improving the solubility cum bioavailability, and eventually providing better formulation opportunities and efficacy for drugs (Alkilany and Murphy 2010; Fukumori and Ichikawa n.d.).

Interestingly the enhanced permeability and retention (EPR) effect is the key mechanism for targeting tumors specifically by nanovehicles. The prolonged circulatory presence of drug provides the adequate time required for delivery via the EPR effect (Brigger et al. 2002; Acharya and Sahoo 2011). In order to achieve the target-specific drug delivery in the solid tumors, the structural and architecture abnormalities in the circulatory and lymphatic vasculature of the tumor are exploited in this EPR approach (Maeda et al. 2000). Nevertheless, here the size of the nanoparticle needs to be customized for efficient targeted drug delivery, as anticancer drugs nanoformulated for intravenous administration could possibly escape the renal clearance. Also fine-tuning the physiological characteristics and functionalization through surface modifications and drug conjugations make them resistant to macrophage-based removal. These measures thus reduce the dose requirement through improved stability and circulation time. Moreover, the enhanced permeability and retention (EPR) effect allows the macromolecular compound and its nanocarriers to escape and leak favorably into the neighboring tumor tissue (Torchilin 2011). Further the defective lymphatic drainage in the tumors leads to drug enrichment in the cancer cell surroundings, whereas in normal tissues, this effect cannot be seen (Fig. 6.3) (Yin et al. 2014). The size of the nanoparticles and its biocompatibility are the most crucial parameters for the EPR effect. The minimum molecular size of 40 kDa for macromolecules and particle size of 5 nm for nanocarriers usually have the active EPR effect (Gopi and Amalraj 2016; Hu and Huang 2013). Thus nanotechnology-derived EPR advantage provides the crucial support while designing the phytochemical-based clinical applications.

Though phytochemicals are easily extracted using methanol, chloroform, and acetone, there are no suitable delivery systems available for effective delivery. Also for effective phytochemical activity, in most of the cases, they have to be given in very high dosages. However dose minimization is preferred for patient compliance

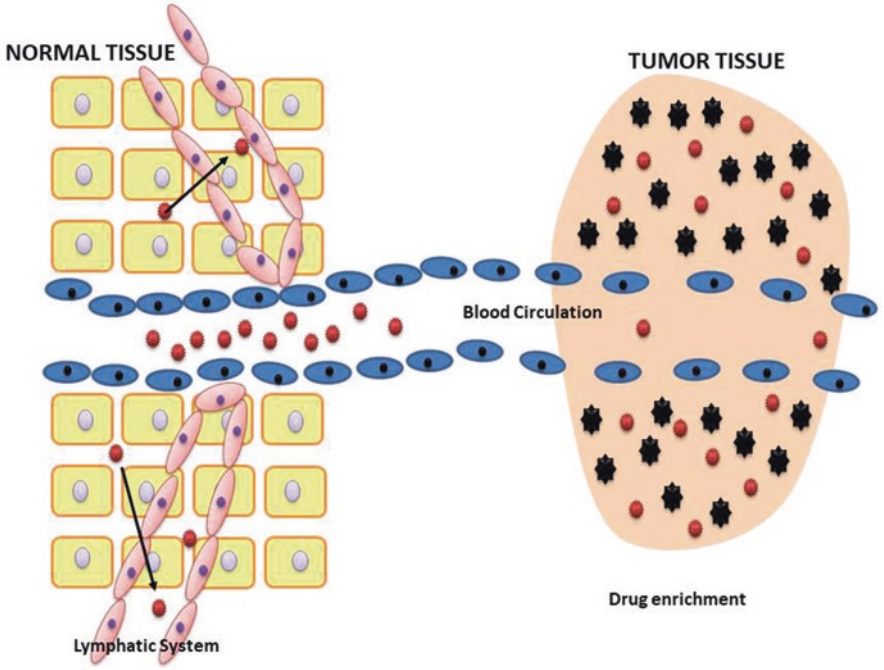


Fig. 6.3 Enhanced permeability and retention (EPR) effect in nanocarrier-mediated drug formulations. Improved stability, circulation time, defective lymphatic drainage, and leaky vasculature of the tumor provide the targeted drug delivery at the tumor sites (Yin et al. 2014)

which can be easily favored through nanoformulations (Ansari et al. 2012). Thus herbal compounds and phytochemicals are the right candidates to be delivered through nano-delivery system (Amol and Pratibha 2014; Ajazuddin and Saraf 2010). Mainly available current phyto-based therapeutic formulations do not have target specificity. However when nano-delivery systems are considered in such cases, they significantly enhance the delivery of phytocompounds at targeted site.

6.3 Nano-delivery Platforms for Phytochemicals

The phytochemicals are vast and diverse in nature, and their customization with respect to various physical and chemical properties is crucial to ensure efficient delivery into the desired system. The major limitations associated with the phytochemicals and herbal medicinal combinations are poor solubility in aqueous media, poor bioavailability, poor stability, and toxicity (Ansari et al. 2012). Using nanoencapsulation and nanoformulation techniques, particles can be designed to have different shapes, sizes, and compositions. These nanoformulations can be functionalized

and modified to have the unique physicochemical properties, thereby improving the delivery characteristics of bioactive molecule.

Both organic biocompatible and biodegradable nanoparticles such as nanoliposomes, nanoemulsions, lipid nanocarriers, phytosomes, micelles, and poly(lactic-co-glycolic acid) (PLGA) nanoparticles and inorganic nanoparticles, e.g., gold, silver, zinc, copper oxide, aluminum oxide, iron oxide, ceramics, and carbon nanoparticles are used in phytochemical studies (Sarker and Nahar 2017). Some prominent forms of nano-delivery approaches attempted recently for phytochemical delivery are discussed below (Fig. 6.4).

6.3.1 *Liposomes*

Liposomes are nanocarriers of size 20 to 1200 nm diameter and have an aqueous core internally and phospholipid bilayer on the external surface. Liposomes are highly advantageous because of their optimization capabilities by altering the surface charge and functionality in addition to the targeted delivery option of anticancer drugs to tumor tissues (Hofheinz et al. 2005).

Already targeted delivery of curcumin is attempted through cyclodextrin-encapsulated curcumin-loaded liposomes (Dhule et al. 2012). Similarly Marqibo®,

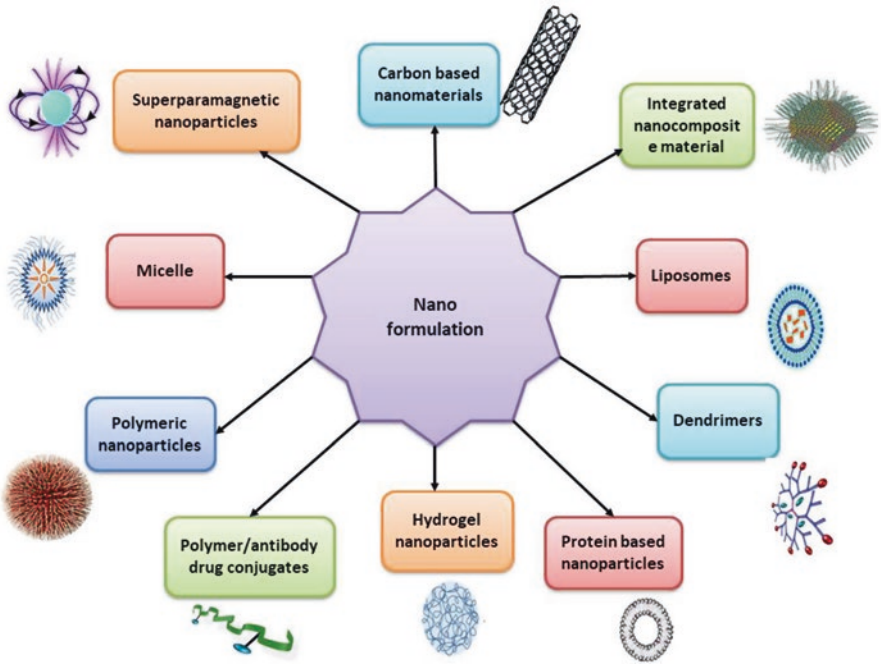


Fig. 6.4 Diagrammatic representation of different drug delivery platforms

a liposomal formulation of vincristine made of sphingomyelin and cholesterol (Silverman and Deitcher 2013; Chang and Yeh 2012), has already been approved by the Food and Drug Administration (FDA), whereas Lipusu®, a liposomal formulation of paclitaxel, has been approved by the Food and Drug Administration in China (Xu et al. 2013; Ye et al. 2013). It is proven that a novel liposomal formulation of doxorubicin has reduced the undesirable delivery of doxorubicin at off-target heart or renal system, increasing the concentration only in the tumor tissues due to EPR effect (Creixell and Peppas 2012; Muggia et al. 1997; Gabizon and Martin 1997).

Likewise, berberine-loaded liposomes are developed as the controlled delivery platform for prolonging the drug release (Sailor et al. 2015; Ai et al. 2014). Also to synergize the therapeutic potential, 5-fluorouracil and resveratrol were incorporated and positively tested using PEGylated liposome (Mohan et al. 2014).

6.3.2 Micelle

Micelles range from 10 to 400 nm in size and are basically smaller in size in comparison with other nanocarriers. Micelles are one of the popular drug delivery carriers for phytochemicals.

Interestingly thymoquinone-based nanoparticles were tested against breast cancer cell growth for their antioxidant and anticancer activities (Ganea et al. 2010). In a targeted approach, the folate-conjugated doxorubicin-loaded micelles were internalized by the cancer cells using receptor-mediated endocytosis (Yang et al. 2010). Similarly copolymeric, biodegradable, and biocompatible encapsulated paclitaxel were specifically targeted using this approach (Liu et al. 2011a; Bamrungsap et al. 2012).

6.3.3 Nanocrystals or Nanoparticles

Nanocrystallite particles ranging from 10 to 100 nm in size with drugs embedded on to the surface are used to deliver less water-soluble drugs with poor dissolution rate. After formulation the surface area of the drug increases and results in enhanced solubility and improved dissolution rate. As a consequence, plasma concentration of the drug is maximized, thus leading to dose minimization of loaded chemicals (Domínguez-Villegas et al. 2014). On the other hand, drug itself can be reduced in size and formulated as nanosized drug which has the ability to act as self-carrier. After nanosizing, these drugs can be administered in different routes for use as oral, nasal, and injectable formulations (Ajazuddin and Saraf 2010; Ramalingam et al. 2016). This formulation could specifically aid in delivering the polyphenols and other phytochemicals, as they suffer from low stability and unfavorable pharmacokinetics. Using this approach, green tea polyphenols are encapsulated in

chitosan-based delivery system, improving the stability of tea polyphenols and preventing their oxidative loss or degradation in the gastrointestinal tract (Liang et al. 2017).

6.3.4 *Polymeric Nanoparticles*

Polymeric nanoparticles are colloidal in nature with the size ranging from 10 to 100 nm. They are formulated as spheres, branched structures, or core–shell structures using natural collagen, albumin, alginate, gelatin, and chitosan molecules. Also it can be fabricated using synthetic yet biodegradable polymers like poly lactide-poly glycolides, poly caprolactones, and poly acrylates (Bhatia 2016). It was reported that the biodegradable polymeric formulation containing *Syzygium cumini* was found to retain the antioxidant activity of plant extract in rat model study (Bitencourt et al. 2016). Similarly green-synthesized AgNPs using extracts of *Vitex negundo* L. retained cell viability inhibition in human colon cancer cell lines (Prabhu et al. 2013). Moreover it is possible to make "smart polymers" which are sensitive to stimuli and can alter its physiochemical properties in response to the surrounding environment. The triggering responses include physical stimuli (temperature, ultrasound, light, electricity, and mechanical stress), chemical niche (pH and ionic strength), or biological signals (enzymes and biomolecules) (Fig. 6.5). Also, it is

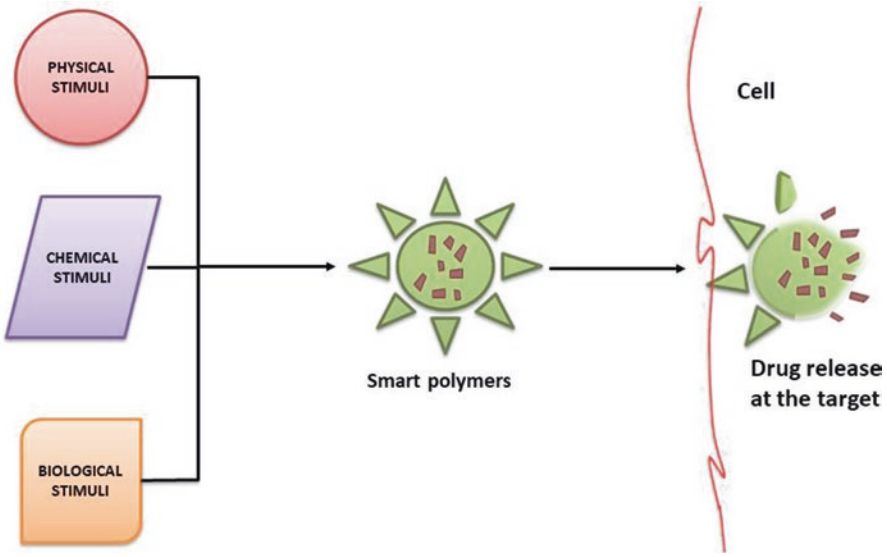


Fig. 6.5 Stimulus-sensitive delivery: various environmental stimuli at the diseased or induced site can alter the chemical properties of nanocarriers, thus releasing the cargo drug in response to the environmental stimuli

possible to tune up drug release in response to the stimulus within a narrow range, thus resulting in more accurate and programmable drug delivery. Currently linear polymers made using covalent chemistry, polymeric micelles from amphiphilic block copolymers, and hydrogels of water-filled depot for hydrophilic drug encapsulation are more common (Kale and Torchilin 2007; Fleige et al. 2012).

6.3.5 Prodrugs

The prodrugs are the polymeric nanocarriers having covalent conjugation of the drug with the linear arm of the polymers. Conjugation of drug with macromolecular polymeric compounds gives more blood circulation time. In addition to peptides or protein drugs, many anticancer drugs of small molecular size are also PEGylated for improved pharmacokinetics. For example, PEG–camptothecin also known as PROTHECAN® entered into clinical trials for the cancer therapy (Joralemon et al. 2010). Table 6.3 lists out the free and various nanoformulations of camptothecin and its derivatives from *Camptotheca* species which are in different process of clinical development (Lerchen 2002). Similarly in CRLX101, camptothecin molecules are conjugated to cyclodextrin–poly(ethylene glycol) copolymers (Fig. 6.6) (Ganesan and Choi 2016; Moody et al. 2015). With this approach there are some limitations like increase in production cost, requirement of additional purification steps, and regulatory issues with approval agencies (Lerchen et al. 2001). Thus there are only a limited numbers of drugs and polymers which have been used to develop polymer–drug conjugates (Table 6.4).

Table 6.3 List of free and various formulations of camptothecin which are in different processes of clinical development (Lerchen 2002)

Drug Name	Delivery System	Source	Status
Irinotecan HCI (CPT-11)	Water soluble	Pharmacia/Aventis	Launched
Topotecan HCI	Water soluble	GlaxoSmithKline	Launched
Rubitecan (9-NC)	Lipophilic	Supergen	Phase III
Exatecan mesylate (DX·8951-f)	Water soluble	Daiichi	Phase III
Lurtotecan (OSI-211)	Liposomal formulation	OSI Pharm.	Phase II
CKD-602	Water soluble	Chong Kun Dang	Phase II
Diflomotecan (BN80915)	Homocamptothecin	Beaufour lpsen	Phase II
Afeletecan HCI (Bay38-3441)	Water-soluble prodrug	Bayer	Phase II
PROTHECAN®	PEG conjugate	Enzon	Phase II
BNP-1350 (karenitecin)	Lipophilic	BioNumeric	Phase I
Gimatecan (ST-1481)	Lipophilic	Sigma Tau	Phase I
DE-310	Polymeric conjugate	Daiichi	Phase I
Camptothecin polyglutamate	Polymeric conjugate	Cell therapeutics	Phase I

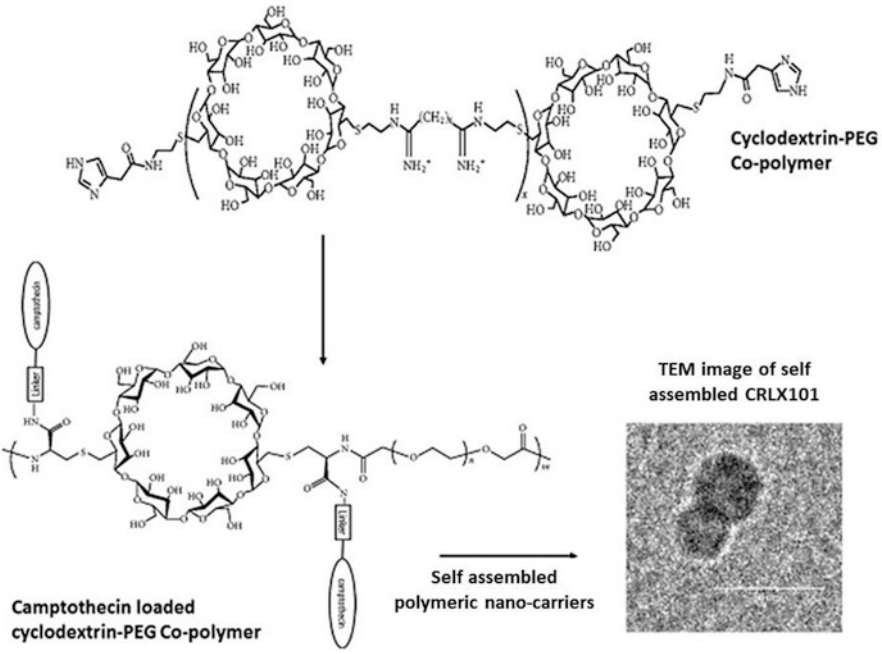


Fig. 6.6 Schematic diagram of CRLX101, a copolymeric nanoparticle formulation, where the phyto-derivative cancer drug camptothecin is conjugated to the linear, cyclodextrin–poly(ethylene glycol) (CD-PEG) (Ganesan and Choi 2016; Moody et al. 2015)

Table 6.4 Commonly used polymers and the corresponding drugs for nano-conjugate preparations

Polymer drug conjugates	**Drug**
	Doxorubicin
	Camptothecin
	PTX
	Platinate
	Polymer
	N-[2-hydroxylpropyl]methacrylamide [HPMA] copolymer
	Poly-L-glutamic acid [PGA]
	PEG
	Dextran

6.3.6 Hydrogel Nanoparticles

Hydrogels are cross-linked networks of hydrophilic polymers that can absorb and retain more water and at the same time maintain the distinct three-dimensional structural network (Bhatia 2016).

Hydrogels are mainly useful for the slow release of drug molecules into the biological system. It was demonstrated that the implantation of hydrogel nanoparticle caused high drug concentration and retention of the drug at the target tissue.

Furthermore the hydrogel could be combined with the magnetic nanoparticles to develop a hybrid hydrogel, which can be transported to the target site by applying magnetic field externally (Bamrungsap et al. 2012; Bhatia 2016; Hamidi et al. 2008). Although nanoparticulate, hydrogel-based drug delivery systems are not commercially applied, owing to their highly biocompatible and efficient drug-loading properties, they have high possibility to be further developed for drug delivery systems in the future.

6.3.7 Dendrimers

Dendrimers are the uniformly branched, macromolecular structures synthesized in a stepwise manner so that they are developed into the size of 1–10 nm particles. This treelike structure is distinct from other linear polymers that the molecular weight and the chemical composition can be precisely controlled. The dendrimers possess internal cavity-like structures where the drugs are encapsulated and which helps for slower, controlled release from the inner core. The dendrimers also allow the embedding of the drugs onto the outer surface using covalent or ionic interactions (Bhatia 2016; Avti and Kakkar 2013).

Dendrimers are synthesized using divergent or convergent techniques. The divergent technique allows synthesis of the inner core, and it is further built into other layers. In the convergent approach, the dendrimer synthesis starts from the outer periphery and ends in the inner core. Dendrimers are good anticancer drug delivery system due to their increased drug solubility, permeability, and intracellular targeted drug delivery (Fig. 6.7) (Fleige et al. 2012; Joralemon et al. 2010; Hamidi et al.

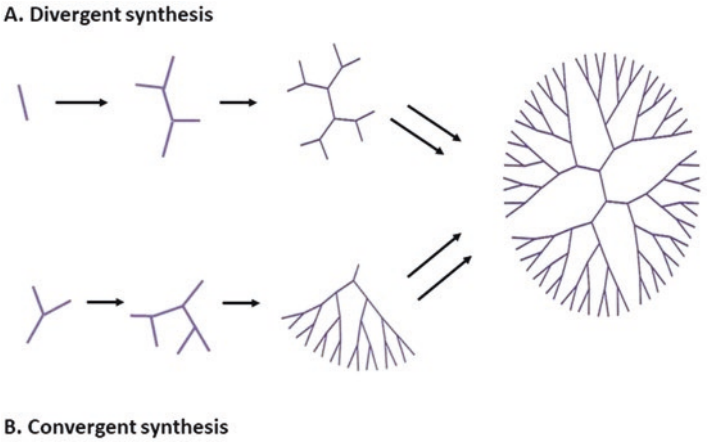


Fig. 6.7 Divergent synthesis (A), where the nanomaterial develops from inner core to other layers, though in convergent approaches (B), the development starts from periphery to inner core for the synthesis of dendrimer as explained thematically in the review (Fleige et al. 2012; Joralemon et al. 2010; Hamidi et al. 2008)

2008) . It was reported that the bioavailability of quercetin could be improved by incorporating it in polyamidoamine (PAMAM) dendrimers (Madaan et al. 2016).

6.3.8 Inorganic Platforms

The gold (Au) nanoparticles are emerging as a more promising drug delivery system due to their advantages like low toxicity from their inertness, ease to synthesize, increased surface area, and tuneable stability. Gold (Au) nanoparticles can be synthesized using biological method via bioreduction of *Piper guineense* aqueous leaf extract, and the drug formulation has highest release efficiency when compared to the drug-alone application (Shittu et al. 2017). It is possible to target the gold nanoparticles into the tumor and destroy the tumor by hyperthermic reactions. Also the gold nanoparticles can be monitored by contrast-based imaging during theragnostic applications. Still the key issue that needs to be addressed with gold nanoparticles is the engineering of the particle surface for optimized properties, such as bioavailability, biocompatibility, and non-immunogenicity (Kuo et al. 2010).

6.3.9 Superparamagnetic Nanoparticles

Recently magnetic nanoparticles are designed with the motive of drug carriers for targeted delivery. Magnetic nanoparticles are embedded in polyelectrolyte capsules and delivered for sustained release of drugs by applying external magnetic field. For example, iron (II) oxide particles are used to deliver microcapsulated drugs by applying magnetic field (Lu et al. 2002). Also after internalization, the magnetic nanoparticles can be induced to produce heat and cause hyperthermic effect. For example, a grafted thermosensitive polymeric system was developed using poly(*N*-isopropylacrylamide)-based hydrogels in which FePt nanoparticles were embedded. Using these nanoparticles, sustained release of loaded drug was attained by increasing the temperature based on the magnetic thermal heating event (Bamrungsap et al. 2012; Pankhurst et al. 2009). Magnetic nanoparticles also could influence the microcapsule permeability by oscillation using external magnetic fields. The major benefits of the magnetic nanoparticles in comparison to conventional cancer treatments are its less invasive nature, accessibility even of hidden tumor, and the reduced side effects.

6.3.10 Carbon-Based Nanomaterials

Recently, carbon-based nanomaterials are gaining popularity in drug delivery since it has the advantage of surface functionalization for grafting of nucleic acids, peptides, and proteins. However the major limitation of the carbon-based

nanocarriers is their cytotoxicity. There are varieties of carbon-based nanomaterials available, such as carbon nanotubes (CNTs), fullerenes, and nanodiamonds. Among these carbon-based nanocarriers, carbon nanotubes are shown to inhibit cell proliferation and cause apoptosis in cells. Also, the toxicity is high in carbon nanotubes because of the presence of the functional groups such as carbonyl, carboxyl, or hydroxyl groups on the surface of the carbon nanotubes (Kang et al. 2007; Liu et al. 2011b).

Betulinic acid (3β-hydroxyl-lup-20(29)-en-28-oic acid) of birch tree effectively induces caspase activation, mitochondrial membrane alterations, activation of reactive oxygen species (ROS), and DNA fragmentation and hence triggers the death of cancer cells. Carbon nanotubes (CNTs) are widely explored to deliver betulinic acid, and a poorly water-soluble drug was formulated using oxidized carbon nanotubes with diameter of 20–30 nm and length of 0.5–2.0 μm by chemical vapor deposition process. Studies confirmed that the CNT-formulated betulinic acid has increased efficiency than the free drug when studied using human lung cancer cells (A549) and human liver cancer cells (HepG2) (Tan 2014).

6.3.11 Integrated Nanocomposite Materials

Combining different nanocarriers helps in improvement of already existing nano-drug delivery platforms. Liposomes when combined with polymeric nanoparticles tend to have the benefits of both the systems. Also, liposomes can be frequently coated with PEG in order to prolong the in vivo plasma circulation time (Gabizon and Martin 1997; Yu et al. 2008; Allen and Cullis 2013). Similarly, liposomes formulated with dendrimers have slow and sustained drug-releasing abilities with improved drug loading capacity. "LipoMag" is the formulation where the inner core is made of magnetic nanocrystal coated with oleic acid, and the outer shell is made of cationic lipid molecules (Fig. 6.8) (Pankhurst et al. 2009; Xie et al. 2010; Namiki et al. 2009).

The bio-efficacy of phytochemicals, especially polyphenols, is improved by edible nanoencapsulation vehicles (ENVs). Efficacy enhancement is through

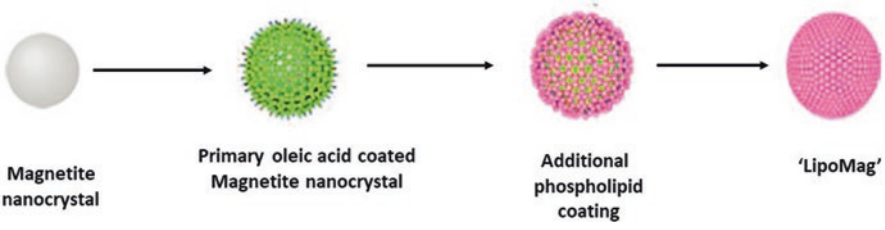


Fig. 6.8 "LipoMag" formulation of oleic acid-coated magnetic nanocrystal core and a cationic lipid shell. These nanoparticles could be magnetically guided to deliver at the specific targeted sites (Pankhurst et al. 2009; Xie et al. 2010; Namiki et al. 2009).

influencing phytochemical dispersion and gastrointestinal stability, rate of release, transportation efficiency across the endothelial layer, systemic circulation and biodistribution, and regulation by gut microflora. Furthermore, the rational design of the size, surface property, matrix materials, and compartment structure of ENVs also influence the bio-efficacy of the ENVs (Xiao et al. 2017).

6.3.12 Traditional and Green Synthesis of Nanoparticles

The production of nanoparticles basically involves two major approaches, namely, the top-down technique and the bottom-up approach of the components. The top-down techniques comprise milling, grinding, and applying laser to shred and break the larger particles into smaller-sized nanoparticles. The bottom-up technique allows the creation and engineering of nanoparticles based on an atom scale arrangement controlled by thermodynamic regulations (Manickam et al. 2017). With the aim of sustainable, pollution-free, nano-chemical synthetic approaches, the development of efficient green chemistry methods has drawn the interest of many researchers in recent years. Basically the aim of green biosynthesis of nanoparticles is to have cost-effective and environmentally friendly alternative approaches compared to the chemical and physical methods. Among the green alternatives, plants and phytoextracts are considered to be the best candidates of choice for the biosynthesis of nanoparticles. The advantages of using plant and plant extracts for the synthesis of nanoparticles include cost-efficiency, prolonged stability, and faster and large-scale synthesis (Sharma et al. 2009).

6.4 Nano-phytochemical Applications Against Inflammation

Inflammation is the process which characterizes the physiological reaction of the body to tissue damage (e.g., stress, irritants, and radiations), infections (microbial and viral), or genetic changes. It is a defensive response which involves immune cells, blood vessel, and different types of mediators (Surh 2003). Many biological processes associated during the inflammatory events include local vasodilatation, increased capillary permeability, accumulation of fluid and blood proteins into the interstitial spaces, recruitment of neutrophils out of the capillaries, and release of inflammatory mediators (Tabas and Glass 2013; Baum and Arpey 2005; Gurtner et al. 2008; Karin and Clevers 2016).

But if the tissue injury is not fixed during the acute inflammatory phase and prolonged, it leads to chronic inflammation which causes various immunopathological changes in the biological system (Baum and Arpey 2005; Hench 2005; Ryan and Majno 1977; Golia et al. 2014). Many diseases and their pathological progression are associated with inflammation which includes diabetes, cancer, cardiovascular disease, neurodegenerative diseases, obesity, asthma, and inflammatory disease like

acute pancreatitis and arthritis (Ryan and Majno 1977; Golia et al. 2014; Montecucco et al. 2017; Amor et al. 2014; Velusamy and Tamizhselvi 2018; Chen et al. 2016; Perretti et al. 2017; Lambrecht and Hammad 2015; Zhong et al. 2017; Crusz and Balkwill 2015; Bhatia et al. 2005).

Many synthetic compounds currently used against these disorders are associated with side effects like liver failure, skin problems, asthma, headache, nausea, ulcer, and gastric problems. To overcome these side effects, the focus is turned on towards a range of natural phytoconstituents including phenolics, alkaloids, and terpenoids for the regulation of inflammatory processes (García-Lafuente et al. 2009). Partial list of some phytochemicals used for anti-inflammatory approaches and the formulations used for effective delivery as reviewed in recently are listed below (Table 6.5) (Conte et al. 2017).

The ability of phytochemicals in inhibiting iNOS activity, reducing iNOS expression, or regulating cyclooxygenase-2 (COX-2) function has been proven in various studies. Also, phytochemicals suppress Akt, protein kinase-C, and mitogen-activated protein kinase (MAPK) signaling pathways by modifying the DNA-binding abilities of transcription factors such as nuclear factor kappa-B (NF-κB) (Fig. 6.9) (Montecucco et al. 2017). During the allergic reactions, by inhibiting the release of histamine, phytochemicals can be used as anti-inflammatory drugs.

In spite of the high potential of raw plant extracts for controlling inflammations, poor solubility, poor stability, short biological half-life, and rapid elimination hamper their clinical use. Likewise, absorption is adversely affected by the massive molecular size and altered pharmacokinetics due to high acidic gastric pH (Milbury et al. 2010).

To overcome these ill effects, nanosized carriers are applied while delivering the anti-inflammatory phytochemicals to the respective delivery site. Various phytochemical-conjugated nanotechnological formulations are applied in enhancing the anti-inflammatory properties and some of which are discussed here.

6.4.1 Polyphenolic Compounds

Polyphenols are most active towards chronic disease by boosting the response of the immune system. Polyphenolic compounds are prominently involved in anti-inflammatory activity. These anti-inflammatory principles are structurally arising due to their primary aromatic ring, oxidation status, and associated functional groups and functionally because of their potent-free radical scavenging properties and interactive abilities with proteins, enzymes, and membrane receptors activity (González et al. 2011). Hence the polyphenolic quercetin, resveratrol, and tannins are acknowledged as painkillers (Etheridge et al. 2013). However, clinical applications of polyphenolic compounds are limited due to both intrinsic (chemical structure, molecular weight, and low hydrosolubility) and extrinsic issues (poor stability in the gastrointestinal environment). Polyphenolic compounds were able to maintain the structural and functional integrity when delivered through the nano-delivery systems (Li et al. 2009).

Table 6.5 Some of the common phytochemicals used for anti-inflammatory, anticancerous, and other therapeutic approaches as reviewed in (Conte et al. 2017)

Phytocompounds	Reported mode of delivery system
Quercetin (polyphenol)	Solid lipid nanoparticles made up of soya lecithin, Tween 80, and PEG
	Poly(lactic-co-glycolic acid) (PLGA) nanoparticles loaded with quercetin
	Quercetin-loaded Eudragit-polyvinyl alcohol nanoparticles
	Lipid-coated nanocapsules
	Quercetin-loaded poly(lactic-co-glycolic acid) (PLGA) NC
Resveratrol (polyphenol)	Encapsulated in PLGA nanoparticles
	Resveratrol in Eudragit RL 100 nanoparticles
	Carboxymethyl chitosan nanoparticles
	Loaded in solid lipid nanoparticles with controlled releasing profile
	Resveratrol loaded in solid lipid nanoparticles
	Cyclodextrin-based nano-sponges
Ellagic acid (phenolic class of tannins)	Ellagic acid loaded in PLGA nanoparticles
	Poly(lactic-co-glycolic acid) (PLGA)–polycaprolactone (PCL) nanoparticles
Curcumin (polyphenol)	Encapsulated in hydrogel-/glass-based nanoparticles
	Oil in water nanoemulsion containing curcumin in oil phase
	Encapsulation of curcumin in liposomes (lipid nanoparticles)
D-9-Tetrahydrocannabinol (phyto-cannabinoid)	Encapsulated in nanostructured lipid carriers
	Loaded in lipid nanoparticles containing lecithin
	Poly(lactic-co-glycolic acid) (PLGA) nanoparticles containing surface-modifying agents such as chitosan, Eudragit RS, lecithin, and vitamin E
	Cannabidiol-loaded PCL particles
	D9-THC-loaded poly(lactic-co-glycolic acid) (PLGA) nanoparticles
Phytosterol	Nanodispersion produced by emulsification–evaporation using hexane
	Phytosterols colloidal particles using anti-solvent precipitation
	Nanodispersion obtained by suspensions of submicron particles of phytosterol
Oregano and cassia essential oil	Encapsulated in corn zein nanocapsules via phase separation techniques
Thymol and carvacrol essential oil	Nanoencapsulation in corn zein nanoparticles via liquid–liquid dispersion method
Thymol and cinnamaldehyde essential oil	Inclusion in cyclodextrin
Lippia sidoides essential oil (50%–70% thymol)	Encapsulated aliginate/cashew gum (biopolymer blend) nanoparticles via spray-drying
Cumin and basil essential oil	Polyamide capsules, release cargo oil under UV-light radiation

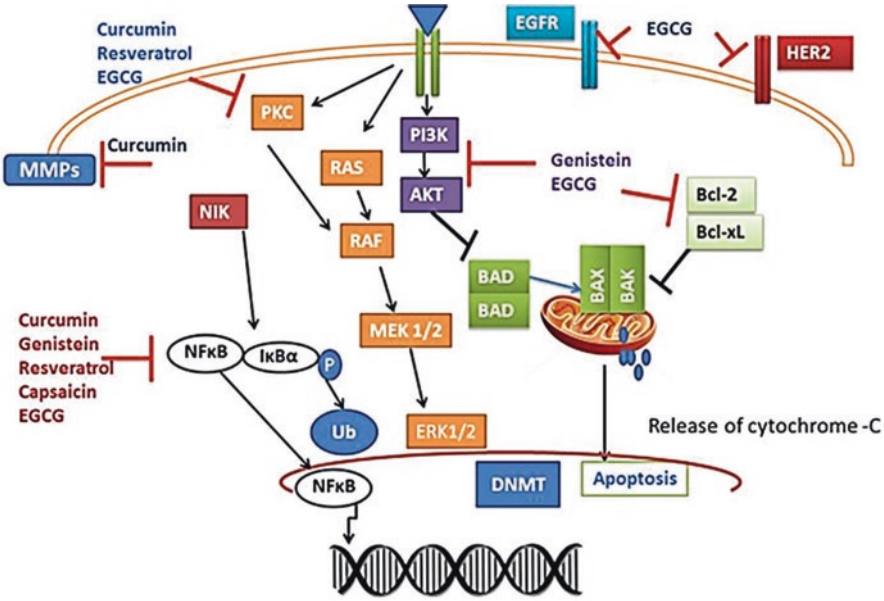


Fig. 6.9 Many phytochemicals target various mitogenic signaling pathways like Akt, protein kinase C (PKC), mitogen-activated protein kinases (MAPKs), MMPs, transcription factors like nuclear factor kappa B (NF-κB) (Montecucco et al. 2017)

6.4.2 Quercetin

Quercetin is semi-lipophilic flavonol present in the plant of tomatoes, leafy green vegetables, and berries. For encapsulation-based delivery of quercetin, solid lipid nanoparticles made of soya lecithin, Tween-80, and polyethylene glycol (PEG) were used, and here 91% encapsulation effectiveness was achieved. Using this approach, there was a 5.7-fold enhancement in the absorption of poorly water-soluble quercetin during the oral delivery (Barras et al. 2009).

Quercetin formulated using lipid-coated nanocapsular approach enhanced the solubility by hundred times compared with the free form of quercetin. Also here the stability was improved by more than 10 weeks without any drastic degradation (Wu et al. 2008). Activity-wise, enhanced antioxidant properties like DPPH scavenging, superoxide anion scavenging, and anti-lipid peroxidation were strengthened, and more efficiency was reached with quercetin-loaded nanoparticles than pure quercetin. Release of quercetin from carriers was increased by 74-fold than the free form, when nanoprecipitation was used with Eudragit E® and polyvinyl alcohol (PVA) during synthesis of quercetin-loaded nanoparticles.

Poly(lactic-co-glycolic acid) (PLGA)-based nanofabrication has been developed for encapsulation and controlled release of phytocompounds. Pool et al. synthesized quercetin-loaded poly(lactic-co-glycolic acid) (PLGA) nanocapsules aimed at preventing oxidative stress in human body against peroxyl radical-induced lipid peroxidation,

thus ensuring more potent applications in anti-inflammatory therapy (Chakraborty et al. 2012; Pool et al. 2012). Even in a rat model, the effectiveness of orally administered quercetin–PLGA nanoparticles was confirmed (Singh and Pai 2014a).

6.4.3 Tannins

Ellagitannins (ETs) and ellagic acid (EA) belong to the family of bioactive polyphenolic class of tannins (Heber 2011) and are abundantly present in pomegranates (Sonaje et al. 2007). To enhance the bioavailability, ellagic acid was loaded with poly(lactide-co-glycolide) (PLGA) and polycaprolactone (PCL) using PEG 400 with DMAB or PVA as the stabilizers. Significantly enhanced intestinal uptake of DMAB-stabilized nanoparticles was observed than carboxymethyl cellulose suspension or when compared with the PVA-stabilized ellagitannins in rats. Evidentially from biochemical and histopathological studies of kidney, it was shown that ellagic acid nanoparticles were capable to check the induced nephrotoxicity in rat models (Chainani-Wu 2003).

6.4.4 Curcuminoids

Curcuminoids are chemicals present in turmeric and show therapeutic potential against different pathological conditions. This group includes mainly curcumin (diferuloyl methane), demethoxycurcumin, and bisdemethoxycurcumin. Curcumin was shown to have anti-inflammatory actions by inhibiting the key molecules mediating inflammation (Zhang et al. 2016). Different attempts were made to increase the efficacy of these molecules. For example, topical application of curcumin captured in hydrogel-/glass-based nanoparticles protects the chondroprotective activity of curcumin and increases its bioavailability in osteoarthritic mouse model (Li et al. 2005). Also liposomes are used as nano-vectors for encapsulating and release of curcumins, and Takahashi et al. developed encapsulation of curcumin in liposomes by using commercially accessible lecithin (Takahashi et al. 2009). These nano-delivery procedures demonstrated that encapsulation enhances the bioavailability and increases the pharmacokinetics of drug.

6.4.5 Phytocannabinoids

Cannabis, commonly known as marijuana, is a product of the *Cannabis sativa* plant, and the active compounds are collectively referred to as *phytocannabinoids*, and to date around 70 phytocannabinoids are reported (Hill et al. 2012). Cannabinoids are anti-inflammatory in nature and mediate their effects through different mechanisms

which include induction of apoptosis, inhibition of cell proliferation, suppression of *cytokine* production, and induction of T-regulatory cells (Nagarkatti et al. 2009).

Cannabinoids in different experimental models such as multiple sclerosis, rheumatoid arthritis, colitis, and hepatitis have reported to guard the host from the pathogenesis through stimulation of multiple anti-inflammatory pathways (Henson 2003; George et al. 2008; Esposito et al. 2016).

To avoid any potential psychotropic drug exploitation and precisely to target the active principle, encapsulated phytocannabinoids have been prepared using nanolipid carriers by ultrasonication. Similarly, a lipid nanoparticle-based cannabinoid formulation was developed against chronic pain (Durán-Lobato et al. 2016).

Also the surface-modified poly(lactic-co-glycolic acid) nanoparticle (PLGANP) was developed using modifying agents like chitosan, Eudragit RS, lecithin, and vitamin E to increase the release rates of the particles (Martín-Banderas et al. 2015). Hernán Pérez de la Ossa et al. used oil in water emulsion–solvent method to prepare suitable dosage form of cannabidiol-loaded PCL particles (Hernan Perez De La Ossa et al. 2012).

From multiple studies it is clear that these nanocarriers maintained the original physicochemical properties and long-term stability and improved the pharmacokinetics of these phytochemicals.

6.4.6 Phytosterols

Phytosterols, the natural components of human diets which involve plant sterols and stanols, and phytosteroids are found mostly in vegetable oils, cereals, fruits, and vegetables.

Experimental (Medeiros et al. 2007; Vitor et al. 2009; Holanda Pinto et al. 2008; De Jong et al. 2008) and clinical (Hallikainen et al. 2008; Aldini et al. 2014) studies have confirmed the anti-inflammatory properties of plant sterols in addition to anticancerous and anti-atherogenic activities (Hu et al. 2017). Recently phytosterol supplementation has shown no significant effect on growth but could extraordinarily decrease diarrhea rate and develop resistance and anti-inflammatory action in animal models like weaned piglets (Leong et al. 2011).

Conversely the absorption rate of phytosterols is less than 2%, and to increase the phytosterol pharmacokinetics, the formulation and characterization of phytosterol nanodispersions are done by using emulsification–evaporation process. These formulations with food application are highly water soluble and characterized by significantly enhanced absorption (Rossi et al. 2010).

Similarly, stable colloidal dispersions having hydroxyl groups on the particle surface and non-ionic stabilizer-based sterically stable formulations were prepared. Turk et al. used the technique which involves a rapid expansion of a supercritical solution using four different surfactants to produce stable suspensions of submicron particles of phytosterol. Most cases bimodal particle size of about 500 nm were obtained and long-term stability was observed (Mancini et al. 2014; Türk and Lietzow 2004).

6.4.7 *Essential Oils*

Essential oils (EOs) are hydrophobic liquid rich with volatile aroma compounds, extracted from aromatic plants as secondary metabolite, and have a significant role in the traditional pharmacopeia. Due to its biological activity and medicinal properties, essential oils are used for antimicrobial, anti-inflammatory, and other pharmaceutical applications (Ajazuddin and Saraf 2010; Elshafie et al. 2015). Additionally essential oils have been applied in various industries while preparing perfumery, cosmetics, feed, food, and beverage-based products. With essential oils, encapsulation techniques are applied for upgrading the bioavailability, pharmacological activities, solubility, targeted delivery, and reduction by biodegradation (Parris et al. 2008). Recently 100% pure essential oil of oregano, red thyme, and cassia have been encapsulated through phase separation into zein nanospheres (Parris et al. 2008; Wu et al. 2012). Similarly, liquid–liquid dispersion method used to encapsulate thymol and carvacrol in the nanoparticles of zein was applied which has improved antioxidant as well as antimicrobial activity (Pinho et al. 2014; Zhou et al. 2018).

Like zein, cyclodextrins have also been used to improve the solubilization and stabilization of natural active product. Cyclodextrin formulations are used to load molecules which are less polar than water (Pinho et al. 2014; Loftsson and Brewster 1996). Alternatively alginate/cashew gum nanoparticles were developed into a biopolymer blend for encapsulation of essential oil using spray-drying method (Fleige et al. 2012; de Oliveira and Paula 2014).

Recent innovative approaches include controlled and triggered release of phyto-compounds using stimuli-responsive materials during the encapsulation methods. In this regard, Bizzarro et al. prepared cumin and basil oil-loaded polyamide capsules, which have the capability of delivering their cargo oil under UV-light irradiation (Bizzarro et al. 2016).

Though many phyto-modifications were proposed using nano-approaches for anti-inflammatory functions, currently they are only in laboratory level for developmental purpose and not been entered into any clinical applications.

6.5 Anticancerous Approaches Using Phyto-nanotechnology

Evidences from the in vitro, in vivo, clinical trial data reveal that the plant-based diet can help to fight many chronic disorders including cancer. Phytochemical compounds control cancer by regulating the crucial pathogenic transformation process like mediating apoptotic cell death, inhibiting angiogenesis, blocking metastasis, and others (Fig. 6.10). Recently, a lot has been studied about the potential role of medicinal plants in anticancer therapy, and it is proven that phytochemical agents are associated with better efficacy and lesser side effects. Evidentially, around 47% of FDA-approved anticancer drugs are derived from plants (Carter et al. 2003). Phytochemicals could be used as a single chemotherapeutic agent or in

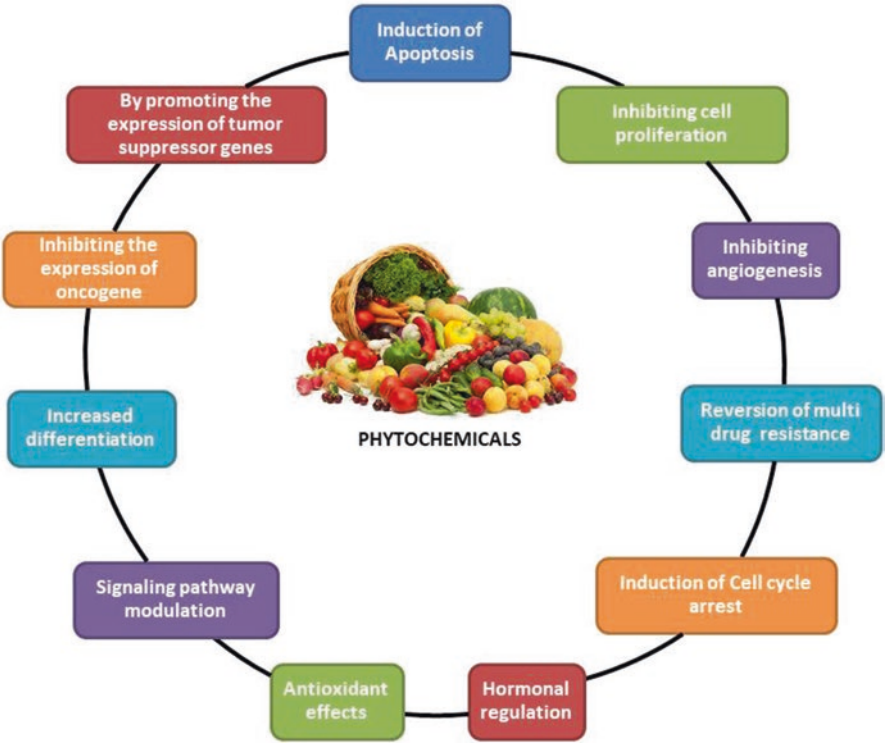


Fig. 6.10 Phytochemical compounds control cancer by regulating the crucial pathogenic events. Phytochemicals combat cancer by the inducing apoptosis, by inhibiting cell proliferation, by cell cycle arrest, by modulating many signaling pathways, by hormonal regulation, by diverting the neoplastic cells for differentiation, by interfering with the expression of oncogenes, by overexpressing tumor suppressor genes, by reverting the drug resistance, by inhibiting angiogenesis and metastasis, and by exerting its antioxidant effects

combination as adjuvants with standard chemotherapeutic drugs to increase their effectiveness while decreasing their side effects.

Some of the promising phytochemicals or its derivatives already marketed for cancer treatment include paclitaxel, vinblastine, and topotecan, and the nanotechnological approaches in formulation and enhancing their efficiency are discussed below.

6.5.1 Nanotechnological Approaches in FDA-Approved Phyto-derivatives for Cancer Therapy

Paclitaxel

Paclitaxel (PX) is a mitotic inhibitor isolated from the bark of Pacific yew (*Taxus brevifolia*). It is considered to be one of the important and most effective chemotherapeutic drugs ever developed, and it exerts its cytotoxic effects against a

broad range of cancers such as lung, ovarian, and breast cancers. It belongs to the class of plant alkaloids. The underlying mechanism of action of paclitaxel for attaining its cytotoxicity is by promoting and stabilizing microtubules and inhibiting late G2 or M phases of cell cycle. It is highly hydrophobic, and due to this reason it is formulated in a mixture of Cremophor EL and dehydrated ethanol (50:50, v/v), a combination known as Taxol. Due to the presence of surfactants like Cremophor EL® (BASF Corp.) for paclitaxel, and Tween-80® (ICI Americas, Inc.) for docetaxel, Taxol has severe side effects. Therefore, there was an ultimate need for the development of alternative Taxol formulations (Lines and Studies 2015). Researchers developed nano-particular albumin-bound paclitaxel (Abraxane®) which has been approved by the FDA and marketed by Celgene for the treatment of metastatic breast cancer and non-small-cell lung cancer (NSCLC).

Abraxane® nanoparticles are 130 nm in diameter and are made of human serum albumin. The albumin-based nanoparticle is formulated to bind to the drug paclitaxel non-covalently and is reversible. This formulation also increases the drug-carrying capacity of the nanocarrier as it can carry about extra 10% of the drug paclitaxel (Green et al. 2006; Miele et al. 2009).

In addition, there are plenty of novel paclitaxel nanoparticle formulations which are in different stages of clinical trials. For instance, paclitaxel-loaded PLA–PEG nanoparticles were synthesized and characterized for their cytotoxic activity on breast (MCF7, MDA-MB-231, and BT-474) and ovarian cancer cell (SK-OV-3) lines, which showed sustainable nontoxic drug-releasing properties. Further in tumor xenograft models, distribution of these nanoparticles was visualized for efficient delivery (Hou et al. 2015). Paclitaxel-loaded poly(lactic-co-glycolic acid) (PLGA) particles were tested for the viability of human hepatocellular carcinoma (HepG2) cells, and this nanoparticle formulation effectively inhibited the proliferation and induces the apoptosis in HepG2 cells. Using this cost-effective nanoformulation approach, sustained release of paclitaxel was achieved (Moudi et al. 2017).

Vinca Alkaloids

Vinca alkaloids are a subset of drugs obtained from the Madagascar periwinkle plant (*Catharanthus roseus*) which are antimitotic and anti-microtubule targeting alkaloids. They possess hypoglycemic as well as cytotoxic effects. Four major vinca alkaloids are in clinical use for cancer: vinblastine, vinorelbine, vincristine, and vindesine. These vinca alkaloids halt the division of cells and cause cell death. During cell division, they bind to the tubulin molecules and disrupt its microtubule function and directly cause metaphase arrest (Lee et al. 2015). Tubulin protein normally works in cells to create “spindle fibers” (also called as microtubules). These microtubules provide cells with both the structure and flexibility they need to divide and replicate. Without microtubules, cells cannot divide. Vinca alkaloids are highly neurotoxic. Moreover vinca alkaloids are susceptible to multidrug resistance in the earlier phase of treatment which limits severely the clinical usage of vinca

alkaloids. To minimize these problems and enhance the therapeutic efficiency of vinca alkaloids, many researchers have developed nanotechnological strategies such as using liposome-entrapped drugs, chemical or peptide-modified drugs, polymeric packaging drugs, and chemotherapy drug combinations. Because of the resistance developed from decreased uptake and increased drug efflux, Wang et.al encapsulated vincristine into folic acid-conjugated PEGylated liposomes to improve the anti-tumor efficacy on multidrug resistant cancers (Wang et al. 2012). These nanoparticles inhibited tumor growth effectively both in vitro on KBv200 cells and on in vivo KBv200 xenograft models.

Etoposide

Etoposide (ETP) belongs to a class of plant alkaloids. It is a semisynthetic derivative of podophyllotoxin, an inhibitor of topoisomerase II, which interfere with structural arrangement of DNA which is necessary during replication.

Etoposide has a significant activity against malignant lymphoma, small-cell lung cancer, stomach cancer, and ovarian cancer. However, because of its low solubility, the short biological half-life (1.5 h), poor bioavailability, and severe side effects (cardiotoxicity and myelosuppression), etoposide (ETP) has limited clinical applications. To overcome these problems, there is a need for finding the new systems of efficient and targeted drug delivery which could deliver anticancer agents precisely to the target cancerous cells. Henceforth etoposide-loaded nanostructured lipid carriers (ETP-NLCs) were synthesized and evaluated for their antitumor activity in vitro and in vivo. ETP-NLCs significantly enhanced the cytotoxic effects in vitro and in vivo antitumor effect against SGC7901 cells and gastric cancer animal model compared to the free drug (Zhang et al. 2017).

Folate (FA)-decorated and etoposide-loaded NLCs (FA-ETP-NLCs) were prepared and analyzed for anticancerous activities both in vitro and in vivo. In vitro cytotoxic effects were on three cell lines CT26, SGC7901, and NCI-H209, and nanostructured carriers were found to increase cytotoxicity compared to the EPT solution form. The in vivo studies on BALB/c nude mice for gastric cancer models illustrated that FA-ETP-NLCs had the best biodistribution in tumor tissue and the highest antitumor activity than free form (Pimple and Manjappa 2012).

For testing the synergistic effect of etoposide and quercetin on lung cancer cell lines, PLGA nanoparticles separately loaded with etoposide (ETP) and quercetin dihydrate (QDN) were designed by using solvent diffusion (nanoprecipitation) technique. In the encapsulated form, the drug-loaded PLGA nanoparticles showed sustained release of drugs as compared to faster clearance of free form. The in vitro cytotoxicity assays on A549 (human lung adenocarcinoma epithelial cell line) revealed significant increase in cytotoxicity with nanoparticle formulations than the free drug form. The comparison was also made with respect to cytotoxic activity of individual drug against combination drugs in the form of free drugs as well as nanoparticles. The combination treatment in the form of nanoparticles is found to produce significant cytotoxic effects (Ma and Mumper 2013).

6.5.2 Other Phytochemicals in Cancer Therapy

In addition to the approved and marketed phyto-derivatives, other promising phytochemicals and their nanotechnical formulations were reported for cancer therapies, and some of which are discussed below.

Resveratrol

Resveratrol (3,5,4′-trihydroxy-*trans*-stilbene) is a phytoalexin produced in plants in response to injury or upon pathogen attack like fungus and bacteria. It is abundantly found in many plant species like the skin of grapes, berries, etc. It is considered to be a major active polyphenol of red wine and exerts numerous health benefits including improved metabolism, cardiac protection, and cancer chemoprevention (Lee et al. 2012; Karthikeyan et al. 2013).

Many in vitro and in vivo studies explained the promising anticancer properties of resveratrol, even though it has many drawbacks when considered for clinical applications. For instance, its bioavailability is highly limited because of various reasons including poor stability, lesser absorption, poor water solubility, and shorter biological half-life. Thus it is very difficult to maintain the therapeutically relevant doses in the bloodstream (Karthikeyan et al. 2013; Singh et al. 2016). To address these limitations, researchers found a way to increase its anticancer properties by developing many biocompatible nanoparticles.

Resveratrol-loaded gelatin nanoparticles were studied for their anticancer properties on lung cancer cell line, NCI-H460, and showed promising anticancer effects than free resveratrol. This increase in anticancer activity is due to enhanced reactive oxygen species and by increase in DNA damage. Also the bioavailability of resveratrol was increased when it is loaded into the gelatin nanoparticles than when applied in its free form (Karthikeyan et al. 2013).

Bu et al. (2013) developed trans-resveratrol-loaded chitosan nanoparticles which are conjugated with two ligands biotin and avidin on the surface. This approach is to target the resveratrol selectively to the hepatic carcinoma, instead of directing towards whole liver. The biotin-bound polymers tend to accumulate in malignant tissue than normal tissues, and avidin-bound polymers are rapidly eliminated from blood circulation and accumulate in the liver. In this study they have concluded that the resveratrol bioavailability dramatically increased when it is loaded into the biotin-coated chitosan nanoparticles (B-CS-NP) and avidin–biotin-coated chitosan nanoparticles (A-B-CS-NP). They have also succeeded in increasing accumulation of trans-resveratrol-loaded chitosan nanoparticles in liver by conjugating either biotin or avidin. In another study resveratrol-loaded poly(ethylene glycol)–poly(lactic-co-glycolic acid) polymeric nanoparticles are studied for their cytotoxic and metabolic effects on CT26 cancer cells by comparing to that of the free compound. Increasing the stability and circulation time of resveratrol (RSV) by loading into nanoparticles allows significant metabolic and antitumor effects in

tumors of live mice models. Convincingly the results provide an encouraging outlook on the potential of PEG–PLA polymeric nanoparticles as an effective method to deliver resveratrol in vivo for cancer therapy (Bu et al. 2013).

With respect to nanocapsules, Carletto et al. (Carletto et al. 2016) has developed resveratrol-loaded nanocapsules with high drug-loading efficiencies and high in vitro cytotoxicity in B16F10 skin cancer cells. In in vivo studies, these nanocapsules loaded with resveratrol significantly reduced the tumor size of B16F10-bearing tumor mice models (Carletto et al. 2016).

In addition to its application in cancer therapy, resveratrol is having anti-inflammatory activities during human applications, and efforts are on to enhance its efficacy through nano-modification procedures during nutrient supplementation for various other disorders. Thus resveratrol turned more efficient when encapsulated as nanoparticulate form than the free one. Orally administered PLGA nanoparticles of resveratrol with particle size of about 170 nm have been reported to be more efficient by 78% than the free form. Furthermore, it was demonstrated that there is significant increase in rate and extent of oral bioavailability of Eudragit-RL-100 formulated trans-resveratrol. It was proven that biodistribution of it in liver and spleen has been significantly affected by Eudragit RL 100 composition (Singh and Pai 2014b). Also carboxymethyl chitosan-encapsulated resveratrol enhanced the solubility and thus enhanced the antioxidative property of resveratrol (Zu et al. 2014).

In an in vitro approach, nanosomes like spherical cyclodextrin have been reported to enhance the solubility and stability of resveratrol with better encapsulation efficiency, however without compromising the biological activity of pure form (Ansari et al. 2011). Similarly Pandita et al. prepared resveratrol-loaded solid lipid nanoparticles with drug integration efficiency of 89%, having improved plasma availability compared to the freely delivered drug (Pandita et al. 2014).

Thymoquinone

Thymoquinone (TQ) (2-methyl-5-isopropyl-1,4-benzoquinone) is a phytochemical compound and is a major active component present in the plant *Nigella sativa* (black seed) with long history of traditional medical applications. The thymoquinone is said to have many therapeutic properties including antimicrobial, anti-inflammatory, antioxidant, antidiabetic, anticancer, hepatoprotective, and renal protective activities. Although it possesses many health benefits, it has major limitations in its clinical properties due to its poor solubility. Its hydrophobic nature causes decreased bioavailability and reduces its formulation characteristics and poor membrane penetration capabilities. The lack of bioavailability and unfavorable pharmacokinetic parameters prevented the use of thymoquinone in clinical settings. To improve the bioavailability and cytotoxicity, thymoquinone-loaded nanostructured lipid carrier (TQ-NLC) was developed and tested using breast cancer cells (MDA-MB-231 and MCF-7) and cervical cancer cell lines (HeLa and SiHa). The TQ-NLC has shown high cytotoxic effects in MDA-MB-231 cells compared to the other cell lines (Fakhoury et al. 2016).

In another study, thymoquinone nanoparticles (TQ-NP) were formulated in poly(styrene-b-ethylene oxide) (PS-PEO) for theranostic approach, i.e., simultaneous imaging and cytotoxicity induction in breast cancer cell lines (MDA-MB-231, MCF-7). By comparing with non-tumorigenic cell line MCF-10A, the authors confirmed the stability, increased cellular uptake, and improved entry into nucleus, and as a consequence cytotoxic potential of thymoquinone was greatly enhanced in cancer cells (Soni et al. 2015).

In a synergistic approach, polymeric biodegradable poly(lactic-co-glycolic acid) (PLGA) nanoparticles encapsulated with thymoquinone and paclitaxel have shown to exert enhanced anticancer potential than the free drugs on MCF-7 breast cancer cells (Ng et al. 2015). In an in vivo setup, thymoquinone encapsulated in biodegradable polymeric nanoparticles was studied for any improvement in bioavailability. When tested on colorectal tumors of murine model, this nanoformulation of thymoquinone showed significant increase in the therapeutic activity by decreasing the tumor volumes and increasing the survival rate of the cancerous animals (Odeh et al. 2017).

Delivery of drug molecules using liposomes is considered to be a promising strategy to increase the therapeutic efficiency of targeted compound and to reduce the drastic side effects exerted by them. Liposomes loaded with thymoquinone were developed to increase the solubility of thymoquinone while reducing its side effects and to check their anticancer potential on breast cancer cells (Odeh et al. 2017).

Curcumin

Curcumin is a potential dietary component of turmeric (*Curcuma longa*), which belongs to the family Zingiberaceae. It is a natural phenolic compound which is responsible for the yellow color of the turmeric. Chemically it is referred to as diarylheptanoid belonging to the group of curcuminoids. Studies have indicated that curcumin shows potential anticancer effects by killing cancer cells and preventing the cells from growing. It has the best anticancer effects on breast cancer, bowel cancer, stomach cancer, cervical cancer, liver cancer, colon cancer, skin cancer cells, etc.

Curcumin is a hydrophobic polyphenol with very low toxicity even at very high doses. Though curcumin is considered to have potential anticancer activities, its low bioavailability makes its less useful for its therapeutic applications. Subsequently, different nanotechnological measures were attempted to enhance the bioavailability and some of which are discussed here. For instance, the curcumin-loaded poly(lactic-co-glycolic) nanoparticles (PLGA-CUR-NPs) were shown to have effective therapeutic potential on prostate cancer cells by inhibiting the cell proliferation in androgen-dependent and androgen-independent prostate cancer cell lines. The inhibitory role is achieved in both in vitro and in vivo models by inhibiting cell proliferation, inducing apoptosis, by interfering β-catenin, AKT, and STAT3 signaling pathways. Moreover the PLGA-CUR-NPs show to downregulate the oncogenic miRNA *miR21* and upregulate the beneficial *miR-205* (Saeed et al. 2017).

In a recent study, PLGA (poly(lactic-co-glycolic acid)) nanospheres encapsulated with curcumin (NCur) were tested on PC3 prostate cancer cell lines for their cytotoxic effects. In these cells, NCur has shown increased cell death, which is mediated mechanistically by both apoptosis and autophagy compared to the free curcumin (Wang 2017).

Nanostructured lipid carriers (NLCs) are the second-generation solid lipid nanoparticles.

These nanocarriers possess many important properties which make them as a preferred drug carrier. It is considered to increase the stability and improve the releasing properties of the loaded drug. NLC can be administrated through oral, pulmonary, intravenous, and percutaneous routes. NLC loaded with curcumin was studied in vitro for their anticancer properties on A549 lung cancer cell lines, and its pharmacokinetic effects were studied in rat models injected with curcumin-loaded NLCs (Cur-NLCs). This study has revealed that the intraperitoneally injected Cur-NLC showed very good in vivo tissue distribution characteristics of curcumin. Evidently the in vitro results proved the promising antiproliferative effect of Cur-NLC on A549 cell line by inhibiting the cell proliferation and directing the cells to apoptosis. Like in vivo results, with in vitro model also, the cellular uptake of curcumin has increased significantly when delivered through NLC than free curcumin (Yin et al. 2013).

In a study using different types of curcumin-loaded nanoparticles, which when tested against the lung cancer cells, it was proven to have potent anticancer activities. Three types of curcumin-loaded nanoparticles (mPEG4k PCL20k, mPEG2k PCL4k, mPEG10k PCL30k) were prepared as amphilic methoxypoly(ethylene glycol) (mPEG)–polycaprolactone (PCL) copolymers and were tested on A549 lung cancer cell lines for their anticancer potentials. Among them, mPEG10k PCL30k has shown highest drug-loading efficiency and sustained release pattern. The curcumin-loaded nanoparticles have exerted their anticancer activity through apoptosis, which is better when compared to the free form of curcumin (Li et al. 2005).

Epigallocatechin-3-gallate

EGCG (epigallocatechin-3-gallate) is a biologically active and most abundant catechin found in green tea (*Camellia sinensis*). Its chemotherapeutic role was studied extensively using in vitro and in vivo studies. It exerts its anticancer activity by inhibiting the proliferation of cancer cells, inducing apoptosis through Bcl-2 and BCl-xL proteins, by inhibiting epidermal growth factor receptor (EGFR) (Masuda et al. 2003) and human epidermal growth factor receptor-2 (HER2) (Fang et al. 2003), by blocking the DNA methyltransferase to interfere at DNA hyper methylation (Li et al. 2013), by regulating cell cycle, and by suppressing the angiogenesis by downregulating VEGF through HIF-1α (Hsieh et al. 2011) (Fig. 6.11). Intake of high amounts of green tea polyphenols can exert toxic effects against cancer cells. Despite its potential anticancerous properties, its use is still limited due to its excessive toxicity, less bioavailability, and ineffective systemic

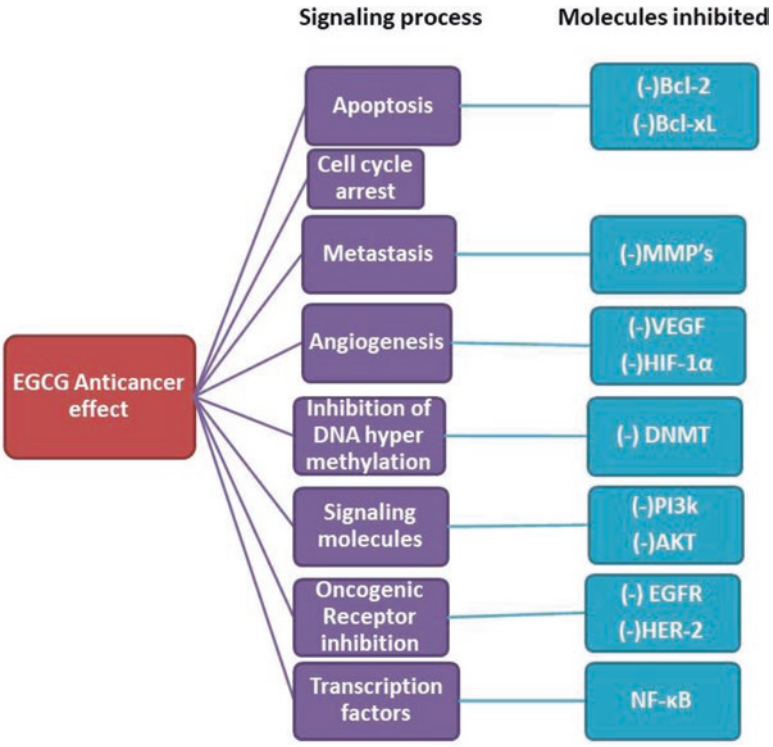


Fig. 6.11 Chemotherapeutic principle of epigallocatechin-3-gallate (EGCG) is mediated through negative interference of various molecules in different cell signaling processes. EGCG exerts its anticancer activity by inducing apoptosis by inhibiting survival-related genes like *BCL2* and *BCl XL*, by inhibiting the activation of receptors like epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor-2 (HER2), by blocking the DNA methyltransferase (DNMT) to inhibit the DNA hypermethylation, by regulating cell cycle, and by suppressing the angiogenesis by downregulating VEGF through HIF-1α, and it prevents metastasis by inhibiting matrix metalloproteinases (MMPS), by inhibiting signaling molecules like PI3K and AKT, and by preventing nuclear translocation of transcription factor NF-κB

delivery. To improve its pharmacokinetic, pharmacodynamics properties and deliver as the optimized therapeutic agent, nanotechnological aspects can be implemented.

Gold nanoparticles (AuNPs) are gaining more interest as they offer many advantages. They are very much biocompatible and nontoxic, and these nanoparticles possess unique optical and biochemical properties. Hence gold nanoparticles are not only used for drug delivery, but it exerts its applications in diagnosis also. In a study using gold nanoparticles, EGCG was conjugated to the surface of the gold nanoparticles (EGCG-pNG) and tested for its anticancer potential on bladder cancer. It was found to kill effectively the bladder cancer cells (MBT-2) by intrinsic pathway of apoptosis, however without showing any toxic effects to the normal cells. Compared to free EGCG, it also effectively reduced the tumor size in C3H/HeN mice cancer model induced by MBT-2 cells (Hsieh et al. 2011).

Also EGCG nanocarriers were developed using chitosan specifically for the oral administration. *This nano-EGCG when checked using melanoma cell-based xenograft model was found to have many advantages than the native EGCG.* In vitro *studies of EGCG on Mel 928 cells showed the cytotoxic effects even at eight fold lower doses than the native EGCG by inducing apoptosis and cell cycle inhibition. In* in vivo *setup also, it inhibited the growth of Mel 928 tumor xenograft implanted in nude mice* even at tenfold lower dose than the native agent. It was reported that nano-EGCG inhibited the expression of proliferative marker proteins like PCNA and ki-67 (Siddiqui et al. 2014).

Quercetin

Quercetin (3,3′,4′,5,7-pentahydroxyflavone) is a polyphenol which is present excessively in fruits, seeds, vegetables, tea, coffee, bracken fern, and natural dyes. It is considered to have very strong antioxidative and anti-inflammatory properties. However quercetin is highly hydrophobic, and delivery is limited by its poor percutaneous permeation and skin deposition. Quercetin significantly inhibits the growth of cancerous cells like leukemia and breast, hepatic, ovarian, colorectal, gastric, and endometrial cancers. Several studies have shown that quercetin controls the growth of cancer cells by inducing apoptosis, regulating specific signaling pathways, decreasing oncogene expression, and inhibiting angiogenesis (Kumar et al. 2014). Though discussed in the previous section with respect to enhancing the anti-inflammatory roles, various attempts were also made using nanoformulation procedures for enhancing the pharmacological applications of quercetin against cancer.

Magnetic Fe_3O_4 nanoparticles were conjugated with quercetin was tested for their in vitro anticancer properties on MCF-7 breast cancer cell line. A simple precipitation method was used to conjugate quercetin on the surface of dextran-coated Fe_3O_4 via carboxylic/amine group using nanoprecipitation method. The cytotoxicity of quercetin-conjugated Fe_3O_4 nanoparticles increased significantly in comparison with pure quercetin, and this was supposedly due to the increased bioavailability of the compound (Guan et al. 2016).

In a study, quercetin-loaded poly(lactic-*co*-glycolic acid)-d-α-tocopheryl polyethylene glycol succinate nanoparticles (QPTN) were prepared for targeted treatment of liver cancer. These nanoparticles were prepared by ultrasonic emulsification–solvent evaporation technique, and for these study three different nanoformulations, QT-loaded PLGA-TPGS NPs (QPTN), QT-loaded PLGA NPs (QPN), and QT/coumarin-6-loaded PLGA-TPGS NPs (QCPTN) were prepared. In vitro studies on HepG2 and HCa-F/T cells showed efficient uptake and internalization of the fluorescently labeled QPTN nanoparticles. In case of cell viability studies, QPTN showed higher cytotoxicity than QPN. They both induced apoptosis in liver cancer cells in a dose-dependent manner. However in the in vivo studies, QCPTN nanoparticles were highly targeted towards liver than QPN (Sarkar et al. 2016).

Hence these nanoformulations can be effectively used both for diagnosis and treatment.

Folic acid (FA) armed mesoporous silica nanoparticles (MSN-FA-Q) loaded with quercetin nanoparticles were tested on breast cancer cells (MDA-MB-231 and MCF-7) for their anticancer properties. In this nanoformulation, the bioavailability of quercetin was increased by reducing its hydrophobicity. These nanoparticles caused apoptosis by increasing BAX proteins and downregulating phospho-AKT. Additionally these nanoparticles restricted the migration of breast cancer cells (Tian et al. 2013). Thus nanoformulative measures provide us the opportunity in unraveling and utilizing the complete antioxidative and anti-inflammatory and anticancerous properties of quercetin.

Genistein

Genistein is a major isoflavone constitute present in soybean and considered to be a most important phytochemical in cancer therapy. It is a natural angiogenesis inhibitor and also a phytoestrogen as its structure is similar to the 17β-estradiol. The anticancer properties of genistein were demonstrated in many in vitro and in vivo studies. It shows its anticancer effect in different cancer cell types including breast, prostate, colon, gastric, non-small-cell lung cancers, as well as in leukemia. Many recent reports demonstrated that genistein could act as potent agent which can be used as chemopreventive agent either individually or in combination with conventional cancer drugs. Interestingly in Asian populations, the lower incidence of breast and prostate cancer is due to the regular dietary intake of soy products which is rich in genistein. Genistein is poorly soluble in water which limits its clinical applications, and so the nano-technical modifications were proposed. In this regard, genistein-loaded biodegradable TPGS-b-PCL (d-α-tocopheryl polyethylene glycol 1000 succinate-b-poly(ε-caprolactone-ran-glycolide)) nanoparticles were tested on cervical cancer cells. Genistein-loaded TPGS-b-PCL NPs were more effective in suppressing cancer in both in vitro and in vivo than the native form of genistein. These nanoparticles increased the bioavailability of genistein and helped in increasing its therapeutic potential (Yang et al. 2015).

6.6 Nano-cosmeceuticals

In addition to their pharmaceutical and nutritive applications, the bioactive components derived from the plant and plant extracts have increased beautifying cosmetic effect in human beings. The cosmeceutical industry is a rapidly blooming industry which has been using several phytochemicals as active component since ancient times. Phytochemicals are applied to treat variety of skin and other diseases including aging, hair loss, inflammation, psoriasis, and protection from ultraviolet (UV) radiations (Kapoor 2005).

Variety of plant-derived compounds used in synthesis of beauty and healthcare products includes catechins, epicatechins, gallic acids, quercetin, ascorbic acids, curcumin, luteolin, alpha- and beta-carotene, complex polysaccharides, and hydroxyl benzoic, cinnamic, and other fatty acids (Ganesan and Choi 2016).

Still there are significant challenges with respect to particle size and solubility resulting in low-quality cosmeceuticals, reduced skin penetration, and prolonged non-beneficial effects. These challenges lead to the quest for finding more novel and efficient technologies to synthesize more enhanced cosmetics and associated products. Nanotechnological applications attempt to solve the abovementioned challenges like enhancing the efficiency of the phyto-derived cosmeceutical products. In order to increase the activity of the nano-cosmeceutical products, different nano-delivery systems and methods are attempted (Hu and Huang 2013). These include nanoemulsions, dendrimers, hydrogels, and lipid nanoparticles (Bhatia 2016). Some of the phyto-derived cosmeceutical products and the application of nanotechnology as reviewed in (Ganesan and Choi 2016) are listed in Table 6.6.

Evidentially the use of nano-based phytochemicals is eventually increasing in sunscreens and other skin protectants. At present, a variety of natural and synthetic cosmetics having nanoformulations are marketed with multiple effects like skin

Table 6.6 Nanotechnology in phyto-derived cosmeceutical products (Ganesan and Choi 2016)

Phytocompounds	Nano-delivery methods	Size (nm)	Applications
Rice bran oil	Nanoemulsion	69	Moisturizer Antiaging Skin care
Rice bran and raspberry seed oil	Lipid nanocarriers		Sunscreens
Lavender extracts	Polymeric poly(lactic-co-glycolic)acid [PLGA] nanoparticle	301–303	Antiaging, antioxidant
Rosemary extracts	Solid lipid nanocarriers Nanostructured lipid carriers	57 68	Antioxidant(skin) Antioxidant
Aloe vera extract	Nano-liposome	200	Skin care
Safflower extracts	Nanostructured lipid carriers	100	Hair care
Lutein	Nanostructured lipid carriers and nanoemulsion	150–350	Skin care
Quercetin	Nanostructured lipid carriers	215	Skin care
Ganoderma triterpenoids	Nanostructured lipid carriers gel	179	Skin enhancement
Hinokitiol	Poly(epsilon-caprolacton) nanocapsules	223	Hair care
Hinokital	Bilayer vesicles		Hair growth
Curcumin	Nanoencapsulation	190 and 276	Skin care
Tocopherol	Nanostructured lipid carriers and nanoemulsion	67 and 576	Skin care
Resveratrol	Solid lipid nanocarriers versus nanostructured lipid carriers	287.2 and 110.5	Skin care

whitening, UV protectant, and moisturizing capabilities. Recently, polymeric nanoparticles of sizes 70 nm, 156 nm, and 202 nm were tested to build a nanoemulsion system of flavanones obtained from *Eysenhardtia platycarpa* leaves to increase the efficiency of antiaging activity (Domínguez-Villegas et al. 2014). Besides, co-encapsulating the phytochemicals such as curcumin and resveratrol showed high antioxidant and antiaging activity due to the enhanced delivery measures (Ramalingam and Ko 2016; Siddiqui et al. 2015).

6.6.1 Moisturizers and Skin Enhancers

The skin at adverse conditions loses its moisture content leading to dryness and skin damage. The moisturizer on the other hand forms a thin layer or film on the outer surface of skin in order to retain the skin moisture content and acts as a protectant. Plant-derived natural compounds are gaining more significance in cosmetic products and formulations since they have the ability to protect the skin from both endogenous and exogenous damaging agents. The nanocarriers like emulsions, liposomes, and solid lipid carriers are used in moisturizing formulations with phyto-bioactive compounds to restore skin hydration and increase the efficiency of the beauty products (Mota et al. 2017). Moreover the solid lipid nanoparticle carriers with reduced viscosity and greasiness provide more efficient moisturizing and skin hydrating effects (Wissing and Müller 2003) (Fig. 6.12).

Plant-based moisturizing nano-delivery systems are now in the early stages of its development. One such product is safranal, a terpenic phytochemical obtained from saffron, constructed using solid lipid nanoparticles of 100 nm diameter. It provides an increased moisturizing effect and anti-UV activity (Golmohammadzadeh et al. 2011). Similar to safranal, the nanoemulsions from rice bran oil is also developed to subsidize the effect of many skin diseases like psoriasis and dermatitis (Bernardi et al. 2011; Rigo et al. 2014; Wu et al. 2013). Besides these products, the nanoemulsions from the extract of *Opuntia ficus-indica* (*L.*) and variety of vegetable oils are developed with varying particle size to study their potential moisturizing effect (Ostrosky et al. 2015; Klang et al. 2010).

6.6.2 Skin Cleansing Agents

Skin cleanser is an important skin care product in maintaining the skin health. Skin cleansing plays an active role in reduction of skin odor by directly eliminating the bacteria inhabiting the outer surface of the skin. Phytochemical ingredient found in the cleansing formula helps in opening of pores and oil content of the skin promoting the cleansing activity.

Further, the usage of phytochemicals in treatment of skin problems like acne is very well studied. In case of lauric acid, when constructed as nanosized liposomes

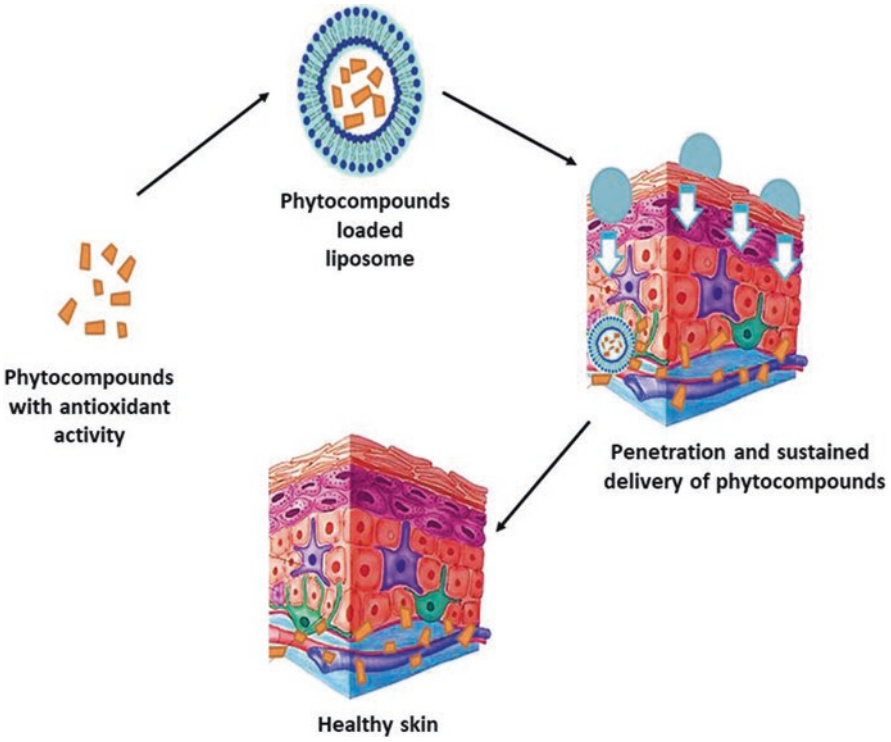


Fig. 6.12 Liposomes and other lipid carriers loaded with the phyto-active compounds are used to restore skin hydration, enhance the moisturizing effect, and increase the efficiency of the beauty products (Wang 2017; Yin et al. 2013)

of 113 nm showed increase in the antimicrobial activity against the acne (Ganesan and Choi 2016; Garg 2016). Recently niosomes are discussed for their applications as drug carriers in cosmeceuticals. Niosomes are nanocarriers formed by association of non-ionic surfactants and cholesterol as bilayer in an aqueous phase (Fig. 6.13). Non-ionic surfactants possess no charged groups in the hydrophilic heads which renders them non-immunogenic and readily biodegradable (Hamishehkar et al. 2013). They also have a prolonged shelf life and high stability and show good target specificity. Also lauric acid and curcumin, when combined and rendered using niosomes, enhance the antimicrobial activity to prevent the skin infections from acne (Amol and Pratibha 2014).

6.6.3 Sun Protective Agents

Sunscreens and protective agents are available commercially as lotions and vanishing creams that contain compounds protecting against harmful radiation from the sun. Sunscreens block the penetration of UV and other harmful irradiations, thus

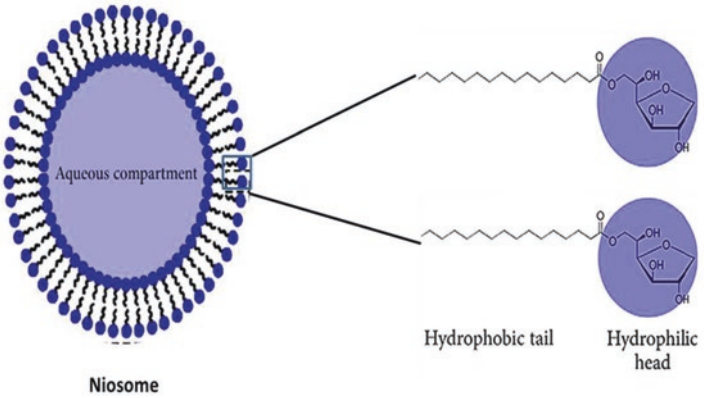


Fig. 6.13 Nano-phyto-carriers like niosomes are made of non-ionic surfactants and cholesterol as bilayer in an aqueous phase. They are non-immunogenic, are readily biodegradable, prolong the shelf life, have high stability, and show very good specificity (Amol and Pratibha 2014; Hamishehkar et al. 2013)

preventing from irritation and other skin problems. However, the plant bioactive compound-based sunscreens are more advantageous over the conventional synthetic ones. Synthetic sunscreens form a chalky layer and create greasiness over the skin and are also toxic. Some of these disadvantages are avoided with natural sun protectants containing phyto-based active ingredients. Bulla et al. have recently studied the use of plant-based bioactive compounds in sunscreens using the extracts of *Schinus terebinthifolius Raddi* and Brazilian *Lippia* species and showed that they have enhanced antioxidant and photo-protective activities (Bulla et al. 2015; Vivina et al. 2007).

Although phyto-based natural active ingredients in sunscreens show enhanced photo-protective effects, the use of nano-delivery systems in creams and lotions play an active role in providing stability and skin protective effects. Recently, safranal in the nano-range of 103 to 233 nm built with solid lipid nanoparticles increased the sun protective activity (Antunes et al. 2017; Khameneh et al. n.d.). Similarly, rice bran oil, pomegranate seed oil, and raspberry oil with lipid nanocarrier enhance the sunscreen activities with higher antioxidant and UV protection (Badea et al. 2015).

6.7 Conclusion

Today we are innovating ourselves into personalized diets and therapy using informatics and artificial intelligence (AI)-based approaches to solve food and pharma problems. Traditionally plant and plant-derived compounds are used for food supplementation and cosmeceutical and medical applications. Taking the cue from conventional knowledge of nontoxic nature and cost-effectiveness of phyto-materials,

and with the deliberations of issues such as high cost, time taken for new drug development, and high drug attrition rate associated with synthetic drug discovery process, herbal or natural sources for the development of lead compound are evolving to be the global trend in the pharmaceutical industry (Pan et al. 2013).

However in most of the cases, phytochemicals work effectively only when delivered in a mixed combination. Therefore by applying the formulative nanotechnological knowledge in surface science, organic chemistry, molecular biology, delivery, and molecular engineering, the scope of phytochemical applications can be inflated. Using nanotechnology, it is possible to increase the solubility and stability of phytochemicals, enhance their absorption, enhance permeation and retention in target tissues, increase bioavailability, protect them from premature degradation in the body, exhibit high differential uptake efficiency in the target cells, and prolong their circulation time (Sarker and Nahar 2017). Nanotechnology provides us with the fertile ground for future research, development, and application with respect to sustainable use of plant materials, biomass waste, and by-products (Griffin et al. 2017).

Nanotechnology has already made a huge impact in the field of synthetic drug delivery and is now influencing the phytochemical research and drug delivery process. Enhanced bioavailability and net effectiveness of phytomolecules including quercetin, genistein, naringin, sinomenine, piperine, glycyrrhizin, and nitrile glycoside have been demonstrated using various nanotechnological formulations. Currently approved nanomaterials in pharma industry are based on relatively simple and established nanoparticles like PEGlyated liposomes. However the future prospects for nanotechnology are claimed to be with actively targeting the delivery chemicals, multifunctional materials, and more complicated materials.

It has to be noted that observed properties of nanomaterials differ entirely from those of their constituent atoms and molecules and from those of the bulk material. Nano-engineered substances can have substantially altered bioavailability and thus come with new safety issues from their non-engineered counterparts. Human use of existing nano-enabled phytocompounds has not yet been thoroughly investigated, and further research is needed with regard to safety and effectiveness. Specifically knowledge on conjugated phytochemicals, the unique nanoformulation-specific signaling pathways, toxicological profile, and the complete disposal machineries are deficient. There exist a hiatus in information about safety, effectiveness, environmental impact, and regulatory status of the developed nano-products mainly because of weak, insufficient regulatory mechanisms.

Regarding the toxicological and regulatory side, there exists a huge void in the dosing, reproducible toxicological evaluation, and standardized reporting of newly engineered nano-products. As there is nanomaterial originated interference in colorimetric cytotoxicity assays, standardization has to be performed using nanoparticle noninterfering techniques like flow cytometry (Kumar et al. 2015).

In case of safety-related screening studies, it is perfunctory to obtain knowledge mainly from in vitro⁄ex vivo systems which usually is incomplete for nanoformulations, and therefore obtaining knowledge on systemic toxicity using in vivo models should be given priority. Other than the beneficial effects, the

clearance system from body after the indented action and environmental impact have to be analyzed in detail. These testing and approval have to be coordinated among different institutions, regulatory agencies, and approval committees, so that fast decision can be reached during discovery and developmental cycle.

Moreover a repository of toxicological data can be established where toxicity response of available novel delivery systems can be listed. This database can be predictively used during new product development using the clues of past success and failures. Also big data or informatics-based predictive platforms have to be established exclusively for the nano-conjugated lead phytocompounds. This could save the time, and also the prediction-derived alternative strategies could be implemented at the designing stage itself. Naturally existing nano-mechanisms could be closely evaluated for designing safe nanoformulation-based products.

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