# Chapter 8
# Lipid-Based Nano-delivery of Phytobioactive Compounds in Anti-aging Medicine

**Oleh Lushchak, Roman Karpenko, Alina Zayahckivska, Alexander Koliada, and Alexander Vaiserman**

**Abstract** Aging population presents a major public health challenge across developed societies. Since phytobioactive compounds (PBCs) including resveratrol, quercetin, curcumin, catechin, and epigallocatechin-3-gallate have been repeatedly reported to demonstrate anti-aging properties, they are increasingly investigated for their anti-aging potential now. The therapeutic efficiency of orally administered PBCs is, however, largely limited by their poor stability, solubility in the gastrointestinal tract, and, subsequently, bioavailability. Apart from the use of polymeric nanoparticles in therapeutics delivery as depicted in Section II, biomaterials have been widely used as drug carriers. One of these biomaterials is lipids, which are a large and diverse group of naturally occurring organic compounds important to cell physiology. It has been reported that PBC-loaded lipid nanocomposites provide many benefits over their conventional formulations, including improved solubility and stability, prolonged half-life, enhanced epithelium permeability and bioavailability, and also improved tissue targeting and minimized side effects. This chapter will summarize recent advances in this research area.

**Keywords** Lipid · Anti-aging · Nanomaterials · Phytobioactive compounds · Healthspan

## 8.1 Introduction

The general trend of extended average life expectancy is observed in most developed countries. According to demographic projections made by WHO, the number of people older than 65 years will reach about 1.5 billion in 2050 that is almost

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three-fold more than in 2010 (World Health Organization (2012)). However, the general extension of the lifespan is not necessarily accompanied with traits related to **healthspan** (Hansen and Kennedy 2016). It means that we also have to pay attention to the quality of life together with its extension. Notably, some health benefits were already described for drugs which are able to extend the lifespan (Piskovatska et al. 2019a). Since aging is already defined as a major risk factor for many pathological conditions, fast gown fraction of elderly people is an important challenge for most modern societies. Aging affects the progression of cardiovascular and neurodegenerative diseases, osteoporosis, T2D, and varied cancer types to be faced as the significant problems for healthcare system (Beard and Bloom 2015). Every year, increasing amount of people define aging as diseases and thus it can be treated. However, successful treatment requires the discovery of anti-aging drugs with fewer side effects (Vaiserman et al. 2016), development of delivery systems to increase drug efficiency, and personalized multidrug treatments. Moreover, all the treatments are affected by factors contributing to the determination of life expectancy and development of pathologies. Parental programing of offspring traits (Vaiserman and Lushchak 2019), dietary interventions (Costa et al. 2019), nutrition (Lushchak et al. 2019), microbiome (Vaiserman et al. 2017), and lifestyle are among main factors affecting tightly linked aging and metabolism.

Many compounds or drugs were described to extend the lifespan and healthspan of model organisms (Piskovatska et al. 2019a). However, only resveratrol, rapamycin, aspirin, and metformin have extended the lifespan in worms, fruit fly, mice, and rats. Being effective in model organisms, metformin showed significant health outcomes in human being (Piskovatska et al. 2019b). Phytochemicals, a plant-derived natural compounds, are promising molecules for the development of novel drugs and dietary supplements for treating age-related pathologies. They are mostly secondary metabolites that protect plants from environmental stresses such as rush conditions, pollutants, and infections. Dietary supplementation with **phytobioactive compounds** (PBCs) such as resveratrol, quercetin, curcumin, epigallocatechin gallate, catechin, and sulforaphane have been extensively reported to cause beneficial effects with prolongevity properties (Corrêa et al. 2018; Santín Márquez et al. 2019). They have been shown to act as antioxidants (Franco et al. 2019), have anti-inflammation (Zhu et al. 2018), anti-tumor (Chikara et al. 2018), cardioprotective (Shah et al. 2019) and neuroprotective (Sarker and Franks 2018) properties, and other anti-aging activities in animal and human studies.

Being effective, anti-aging agents PBCs possess the properties that significantly limit their **bioavailability** due to low solubility, chemical instability, intrinsic dissolution rate, low absorption, scarce distribution, and poor accumulation in the human body (Khadka et al. 2014). This significantly limits their use via oral administration. However, specific formulations-based development of certain types of PBC-loaded nanoparticles (NPs) suitable for oral administration may increase the stability and solubility, prolong half-life, and improve cell and tissue permeability and bioavailability of compounds. Moreover, so-called nanoformulations of PBS may enhance tissue-specific delivery and decrease possible side effects (Date et al. 2016; Lin et al. 2017). In recent decade, these nanotechnological formulations have been increasingly

applied in treating chronic age-related pathologies such as cardiovascular diseases (Li et al. 2017), type 2 diabetes (Jeevanandam et al. 2015), obesity (Zhang et al. 2018), neurodegeneration (Silva Adaya et al. 2017), and cancer (Qiao et al. 2019). In this chapter, we will focus on the lipid-based nanoformulations, their applications with specific insight into NPs loaded with resveratrol, quercetin, curcumin, genistein, and epigallocatechin gallate.

## 8.2 Main Types of Lipid-Based Nano-delivery Systems and Possible Applications

The problems related to low bioavailability of PBCs can be partially solved by the use of lipid-based **nanocarriers** for the oral administration. Bioavailability might be further improved by surfactants and emulsifiers that are important counterparts of lipid NPs (Chakraborty et al. 2009). Most useful lipid-based **nano-delivery** systems are nanoemulsions, solid lipid NPs (SLNs), self-emulsifying drug delivery systems (SEDDSs), and nanostructured lipid carriers (NLCs) (Fig. 8.1) (Hsu et al. 2019). They carry bioactive compounds to increase their solubility and bioavailability. Lipid NPs have good solubility in **lipids**, and thus encapsulated active compounds possess improved pharmacokinetic properties, biocompatibility, and reduced toxicity (Dumont et al. 2018). These formulations are also easily absorbed

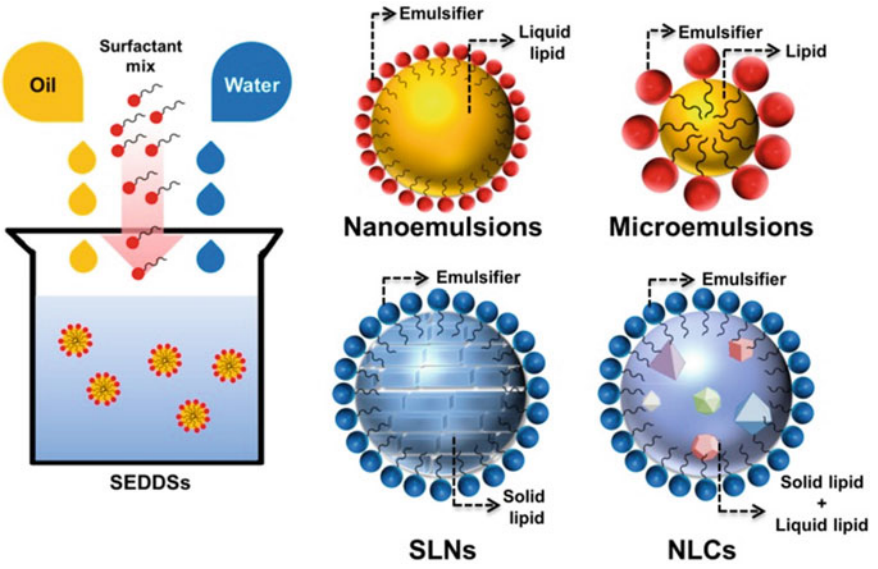


**Fig. 8.1** Structures of lipid-based NPs: self-emulsifying drug delivery systems (SEDDSs), nanoemulsions, microemulsions, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs). Reproduced from (Hsu et al. 2019) with permission from MDPI

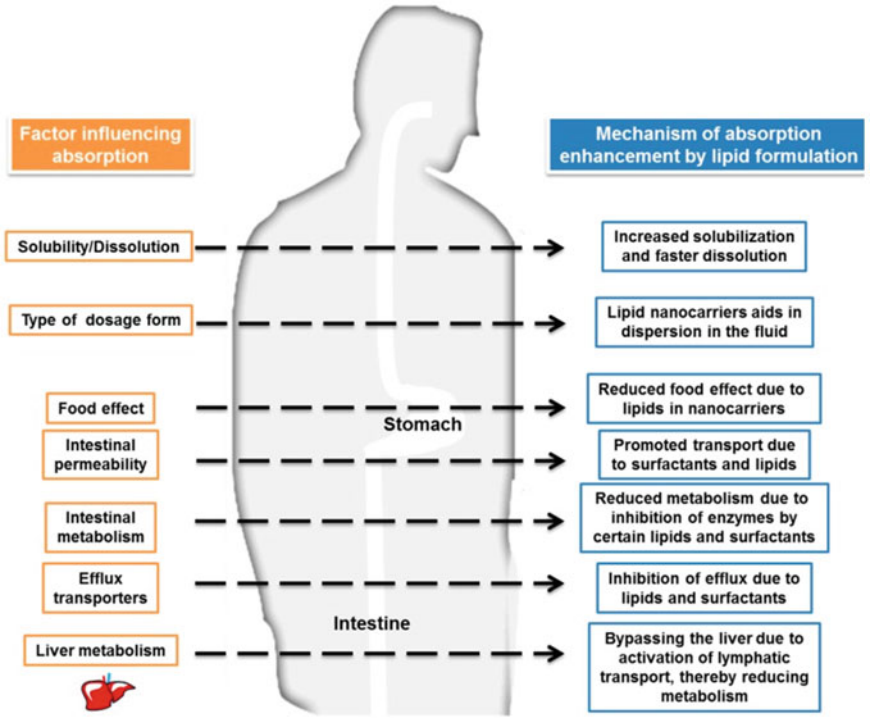


**Fig. 8.2** Possible mechanisms for enhancement of PBC bioavailability using lipid-based delivery systems. Reproduced from (Hsu et al. 2019) with permission from MDPI

by human body (Fig. 8.2). In addition, they can be digested to produce emulsions with high surface area that further may be enzymatically hydrolyzed to release active compound in easily absorbed form (Joyce et al. 2016), see also Fig. 8.3 for schematic representation.

### *8.2.1 Nanoemulsions*

Nanoemulsions (NE) are heterogeneous mixtures of oil droplets in aqueous solution that are further stabilized by an emulsifier (McClements 2011). They are generally produced by directed assembly of the compounds. Drug or active compound can be loaded into the oil cores of NE to improve oral administration (Kumar and Sarkar 2018). The mixture is kinetically stable with no flocculation or coalescence during long-term storage. Nanoemulsions are prepared of natural components or GRAS. Surfactants and co-surfactants are used in NE to reduce toxicity and increase stability of the compound. The most used particles of the nanoemulsions are peptides, proteins,

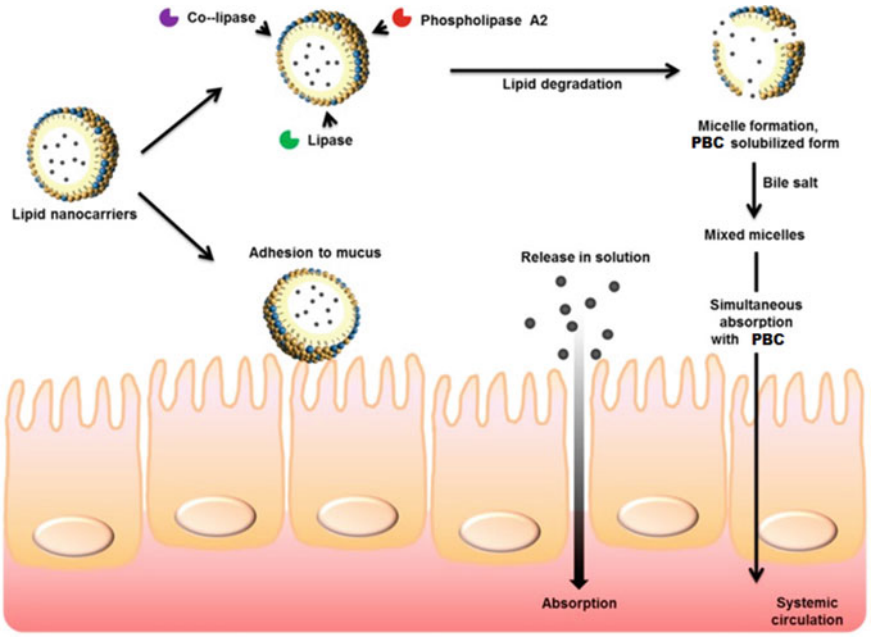


**Fig. 8.3** Possible pathways of gastrointestinal absorption of orally administered lipid NPs. Reproduced from (Hsu et al. 2019) with permission from MDPI

polysaccharides, phospholipids, and small molecule nonionic surfactants (Tagami and Ozeki 2017).

Three methods are mostly used to prepare NE which include phase inversion temperature synthesis, high-pressure homogenization, and **microfluidization** (Goh et al. 2015). The use of rapidly diffusing and electrostatically stabilized emulsifiers with low molecular weight can provide complete dispersity. The use of proper synthesis method in combination with surfactant gives the possibility to create tiny droplet size with large surface area. Thus, they can easily be absorbed in the gastrointestinal tract with significantly increased availability of bioactive compounds compared with conventional emulsions. Nanoemulsions increase bioavailability of PBCs due to increased solubilization, prolonged **gastric residence time**, stimulated lymphatic absorption, reduce the effects of efflux transporters, and inhibit metabolism (Salvia Trujillo et al. 2017).

An average size of NE particles varies from less than a nanometer to more than 400 nm and is strongly dependent on the compounds used. For example, curcumin-loaded NPs studied by Chen and colleagues were nanoemulsion prepared from ethanol, isopropyl myristate, tween 80, and tween 20 and had an average size of about 100 nm (Chen et al. 2013). Nanoemulsions of curcumin for cancer chemotherapy were prepared with soybean oil and hydrogenated L-α-phosphatidylcholine and has an average particle size of 55 nm (Anuchapreeda et al. 2012).

NE may carry out different types of compounds with different targets. Fat-soluble vitamins A, E, and D can be loaded within the oil core of liquid droplets and thus be protected from chemical and enzymatic degradation and released after ingestion. It has been shown that NE loaded with b-carotene was twice more effective. Nanoemulsions were tested to increase delivery of varied active compounds when applied orally, transdermal or intranasal administration. Lipid nanoformulation of antimalarial agent primaquin gave possibility to decrease amount of applied drug by 25% with respect to increase of liver drug concentration by 45% (Singh and Vingkar 2008). Oil-in-water nanoemulsions of anti-HIV protease inhibitor Saquinavir increased drug oral bioavailability and its brain disposition (Vyas et al. 2008). Oral administration of NE loaded with paclitaxel significantly increased amount of drug in the circulation and absorbed by kidneys, liver, and lungs (Tiwari and Amiji 2006). Intranasal administration of NE formulations of olanzapine and risperidone showed the ability of direct nose-to-brain transport that bypasses the blood–brain barrier with about four-fold increased efficacy (Kumar et al. 2008a, b). Finally, dermally applied celecoxib-loaded NE showed a significant decrease of inflammation (Baboota et al. 2007).

### *8.2.2 Self-emulsifying Drug Delivery Systems*

Mixtures of oils, surfactants, solvents, and compound spontaneously form nanoemulsions or microemulsions upon dilution with water under soft agitation (Chintalapudi et al. 2015; Knaub et al. 2019). These self-emulsifying drug delivery systems (SEDDS) can include particles with diameters from 20 to 300 nm. An exciting property of SEDDS is the possible formation of nanosized oils during self-assembly in the fluid of gastrointestinal tract (Dokania and Joshi 2015). Two main types of SEDDSs are self-nanoemulsifying (SNEDDSs) and self-microemulsifying drug delivery systems (SMEDDSs). SNEDDSs with the droplet size under 100 nm are generally opaque or translucent formulations. SMEDDSs are transparent microemulsions that become thermodynamically stable after ingestion. Droplet diameter, composition, lipid digestibility, and lipophilicity of the active compound affect its bioavailability when released from particles (Date et al. 2010). This type of nanocarriers are generally formulated by using lipids and surfactants, sometimes co-surfactants, that are generally recognized as safe according to FDA. Technically, SEDDSs can be produced by phase inversion composition, low-energy emulsification, solvent displacement, or phase inversion temperature methods (Date et al. 2010).

Significant volumes of typical emulsions have to be consumed to provide the therapeutically tractable amounts of bioactive compound. Emulsions include water that is required for their productions. Comparably large amount of water included may enhance hydrolysis and/or precipitation at long-term storage and in this way reduce stability and absorption after oral ingestion. Thus, oral administration SEDDS is an application of emulsion concentrate that does not require water for the production.

SEDDSs possess varied advantages for oral administration. These formulations improve physicochemical stability of delivered drug with possibility to be encapsulated with the vehicle to increase acceptability by recipient (Khan et al. 2012). Agitation required for the formation of nanoemulsions may be simply provided by digestive motility of GI tract. The spontaneous formation of an interface between the oil droplets and external phase is caused due to swelling of liquid crystalline phase that is formed between water and oil phases (Khan et al. 2012). An increased production of emulsion droplets may also be induced by excess amounts of the lipids in GI tract derived from SEDDSs. They trigger the secretion of bile acids into the lumen. Together with higher quantities of cholesterol and phospholipids in the presence of lipids and emulsifiers, the lipid-rich environment provides intensive formation of droplets. Thus, drugs or bioactive compounds with low solubility initially loaded into SEDDS will be incorporated in micelles that are characterized by high absorption rate.

Ingested SEDDSs provide increased bioavailability by increasing the stability of bioactive compound in the gastro-intestinal environment via minimizing the first-pass effects (Chatterjee et al. 2016). Also, formulations inhibit efflux mediated by P-glycoprotein (Negi et al. 2013). Finally, there is methodologically simple production of SEDDSs and simple delivery by the oral consumption with low intersubject variability and effects caused by food ingestion.

SEDDSs have to be encapsulated into gelatin capsules for oral administration. However, the material of the shell might be incompatible with the formulation. This fact may cause the precipitation of the active ingredients, the requirements of storage at lower temperature, or changes of the preparation protocols (Dokania and Joshi 2015). These problems can be partially solved if liquid SEDDSs are converted into solid state. Thus, more stable and convenient forms for easier handling and delivery may be created by methods such as granulation, **freeze drying**, spray drying, or be achieved by adsorption to carriers.

SEDDS loaded with varied bioactive compounds or drugs with anti-fungal, anti-seizure, anticoagulant or anthelmetic properties were tested to treat inflammation, cancer, hypercholesterolemia, liver cirrhosis and bleeding in the brain. For example, SEDDs-based formulations of anti-inflammation low water-soluble drugs ketoprofen and celecoxib showed three- and four-fold higher effectivity at oral administration, respectively (Patil et al. 2004; Song et al. 2014). The paclitaxel SEDDS formulation showed about five-fold higher oral bioavailability of the drug compared with that of the orally dosed Taxol or SEDDS formulation without HPMC (Gao et al. 2003). In vivo treatment with nanocarriers-loaded atorvastatin significantly reduced serum lipid levels in a triton-induced hypercholesterolemia model in male Albino Wistar rats as compared with calcium salt (Kadu et al. 2011). Moreover, the in vivo study indicated ~ three-fold increased delivery when silybin-S-SEDDS produced in the presence of HPMC were used (Wei et al. 2012). A two-fold increased bioavailability of lipophilic CoQ10 was observed for the SEDDS compared to a powder formulation (Kommuru et al. 2001).

### *8.2.3 Solid Lipid NPs*

SLNs or solid lipid NPs represent another formulation and drug delivery system. This type of nanocarriers consists of solid lipid core matrix stabilized by surfactants or emulsifiers and thus may solubilize molecules with lipophilic properties (Muchow et al. 2008). The use of biodegradable and biocompatible solid lipids in the formulations of SLNs strongly increases their applicability and safety. Triglycerides, wax, fatty acids, cholesterol, and glycerol derivatives such as monostearate, palmitostearate, or behenate are combined with either natural or synthetic solid lipids to form stable SLNs nanosystems (Santo et al. 2013). SLNs can be produced by melting microemulsification, melting or cold homogenization. Solid lipids must be melted by hot homogenization before combining with other components (Weiss et al. 2008). However, if drug or active compound of formulation is sensitive to temperature, then cold homogenization may be used. SLNs are mostly spherical particles with average diameter 10–1000 nm.

Lipases in the stomach start to digestion orally applied SLNs. Simple mechanical mixing of particles with gastric fluids results in the formation of crude emulsion that can be further digested by intestinal fluids (Lin et al. 2017). Small size and properties of SLNs allow them to attach to gastrointestinal mucus and diffuse into intervillar space. Absorption of particles may be further increased by using emulsifiers that reduce membrane fluidity and coat the surface of SLNs. Moreover, chemically labile bioactive compounds can be partially protected by solid state of the lipid. Also, slower digestion of SLNs may prolong release of the carried active compound (Dolatabadi et al. 2015).

Since there are obvious benefits of SLNs use for oral delivery of bioactive compounds, several disadvantages limit their broader application. Firstly, the loading space of active compound can be thereby reduced because solid lipids are densely packed into matrix (Dolatabadi et al. 2015). Secondly, partial loss of active compound may occur due to aggregation and gelation of particles during storage. Thirdly, the liquid lipid incorporation into the crystalline matrix can partially change the properties of the core due to “lattice defects” (Garcês et al. 2018). Finally, so called “burst escape” of the drug from the NPs may cause toxic effects. Thus, the SLN formulations have to be significantly improved to decrease the drawbacks of SLNs.

Solid lipid NPs of different formulations were successfully loaded with antibacterial, antifungal, antischistosomal, anti-inflammation, and antirheumatic drugs and compounds. SLN formulation of carvacrol showed significant benefits in rat with lung damage by partial prevention of oxidative stress and histological damages caused by smoke inhalation (Carvalho et al. 2019). An increased trans-resveratrol penetration through the skin for up to 45% was shown for NPs loaded with ionic liquid-melinjo seed extract (Trinovita et al. 2019). SLN formulations of antirheumatic drugs methotrexate and doxycycline with yield of 65–80% were characterized by sustained release of both drugs for about two days without any significant interaction suggesting their use to treat chronic inflammation (Vijaya and Ram Kishan 2018).

Interestingly, praziquantel-containing SLN formulation shows enhanced bioavailability and antischistosomal efficacy against murine *S. mansoni* infection. SLN-PZQ use is able to decrease applicable drug concentration by five-fold with a significantly higher reduction in hepatic and intestinal tissue egg amounts and strong disappearance of deposited immature eggs (Radwan et al. 2019). Treatment with SLN loaded with myricitrin abrogated diabetes-related changes by increasing the activities of antioxidant enzymes, and reducing levels of oxidative stress markers and apoptotic signatures (Ahangarpour et al. 2019).

### *8.2.4 Nanostructured Lipid Carriers*

Nanostructured lipid carriers (NLCs) consist of partially crystallized lipid particles dispersed in an aqueous phase including emulsifier (Khan et al. 2012). NLC may have some advantages in comparison with other colloidal carriers, for instance, NLC can be loaded with high amount of drug with increased encapsulation efficiency and stability. Carriers may further increase stability of bioactive compounds and their bioavailability. NLCs as second-generation lipid-based NPs consisted of solid and liquid lipids with improved physical stability. Moreover, the release of bioactive agents from NLCs can be easily modulated by adjusting the ratio between the liquid and solid lipids. A number of preparation methods are suitable for NLC production such as solvent evaporation or injection, emulsion–solvent diffusion, membrane extrusion, multiple or microemulsions, sonication, phase inversion high-pressure homogenization (McClements 2011). The latter does not require a solvent and thus is preferred over other methods. Moreover, this method is already well established and extensively used in pharmacology.

A nature of NLCs makes them especially useful for enhanced absorption in gastro-intestinal tract by lymphatic uptake via M cells (Managuli et al. 2018). NLCs promote absorption by increasing carrier transport through intestinal bulk fluid and brush border of enterocytes. Moreover, P-glycoprotein efflux can be inhibited by the components of NLC shell surfactants (Negi et al. 2013). Nanostructured lipid carriers were successfully used for oral, skin, eye, or lung drug applications. NLC-based gels loaded with celecoxib and valdecoxib were showed to be effective at treating inflammation and allied conditions in rats (Joshi and Patravale 2006, 2008). These formulations were two- and four-fold more effective as compared to other ones. Ibuprofen-containing NLCs displayed controlled-release property with four fold increase of ocular drug delivery (Li et al. 2008). NLC loaded with simvastatin, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor with beneficial effects on coronary diseases and mortality rate in patients with hypercholesterolemia, showed better release, pharmacokinetics, and increased bioavailability for about five-fold (Tiwari and Pathak 2011).

## 8.3 Nanoformulations of Anti-aging Drugs

Many lipid nano-delivery systems loaded with plant-based bioactive compounds such as resveratrol, genistein, quercetin, curcumin, and epigallocatechin-3-gallate (EGCG) (for chemical formulas, see Fig. 8.4) have been demonstrated to be efficacious in modulating oxidative stress and related chronic inflammation mediating most aging-associated disorders. Results from studies reporting antioxidant and anti-inflammation effects of these nano-delivery systems are discussed in subsections below.

### *8.3.1 Nano-curcumin*

Curcumin is a naturally occurring polyphenolic compound with a wide range of beneficial biological functions, including antioxidant, anti-inflammation, and anticancer activities (Sarker and Franks 2018). Its therapeutic potentials in combating aging-associated conditions, including chronic inflammation, hypertension, type 2 diabetes, atherosclerosis, cardiovascular and neurodegenerative diseases, osteoporosis, and also chronic kidney and ocular diseases are well documented (Kumar et al. 2010). Presently, the healthspan-promoting capacity of curcumin is increasingly investigated in clinical trials (Salehi et al. 2019). The clinical use of this compound is, however, limited because of its susceptible nature to high temperature, alkaline pH,

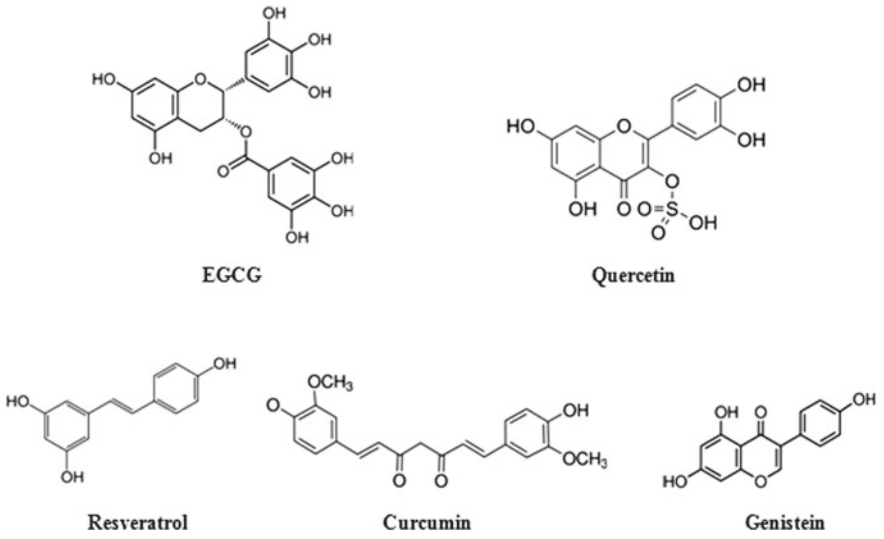


**Fig. 8.4** Chemical formulas of PBCs most commonly used to integrate in lipid nano-delivery systems

as well as presence of oxygen and light. Therefore, it is extremely difficult to maintain its bioactivity during processing, storage, and consumption (Nayak et al. 2016). Its therapeutic potential is, however, substantially limited through low aquatic solubility and gastrointestinal stability, leading to poor bioavailability (Kumar et al. 2010). Therefore, developing nano-delivery systems aimed at improving bioavailability of curcumin is considered as a promising therapeutic option now (Flora et al. 2013; Ahmad et al. 2016).

Recent advancements in the nanotechnology-based applications offer an opportunity to enhance the stability and bioactivity of curcumin to overcome its pharmacokinetic mismatch. Among various nano-delivery systems, lipid-based ones are the most well-studied delivery systems aimed at enhancing its stability and pharmacokinetic profile both for pharma and food applications (Nayak et al. 2016). Greater therapeutic potential of curcumin-loaded lipid nanoformulations in comparison to that of native curcumin was repeatedly reported in vitro *and* in vivo. Both its solubility and bioavailability were demonstrated to be significantly improved by encapsulating in nano-delivery systems, including the lipid ones, and it caused enhancement of its pharmacological activity (Shome et al. 2016). In particular, loading of curcumin in N-trimethyl chitosan surface-modified solid lipid NPs resulted in a substantial improvement of its oral bioavailability and brain distribution compared to those of free curcumin (Ramalingam and Ko 2015). In an induced cerebral ischemia rat model, the bioavailability of curcumin in the brain was shown to be 16 times greater if it was loaded in solid lipid NPs compared to that of the native curcumin (Kakkar et al. 2013). Therefore, the nano-delivery of curcumin is regarded now as an efficient approach to enhance its bioavailability in a target-specific manner and to improve its therapeutic potential in combating aging-related disorders. Some studies have indeed demonstrated the enhanced oral bioavailability of curcumin-loaded solid lipid NPs to the brain, highlighting its therapeutic potential to treat neurodegenerative disorders (Ramalingam and Ko 2015,2016; Sadegh Malvajerd et al. 2019). For example, in an aluminum-induced model of Alzheimer's disease, orally administered curcumin-loaded solid lipid NPs resulted in 32–155 times enhanced bioavailability of curcumin relative to the control mouse group, and also in abolishing of adverse behavioral changes and biochemical and histopathological alterations in the brain induced by exposure to aluminum (Kakkar and Kaur 2011). The protective potential of curcumin-loaded solid lipid NPs in ameliorating the complete Freund's adjuvant (CFA)-induced arthritis, supposedly due to attenuation of the antioxidative and anti-inflammation responses, has been also demonstrated (Arora et al. 2015). Recently, in a double-blind randomized placebo-controlled clinical trial, nano-curcumin improved glucose indices, lipid profiles, and ameliorated inflammation in overweight and obese patients with non-alcoholic fatty liver disease (Jazayeri Tehrani et al. 2019). In the study conducted in the breast cancer cell line, an evidence has also been obtained that loading curcumin into nanostructured lipid carriers can enhance its cell penetration and cytotoxic anticancer properties (Kamel et al. 2019).

### 8.3.2 Nano-auercetin

Quercetin is a flavonoid widely presented in a number of grains, fruits, and vegetables. Antioxidant, anti-inflammation, antihypertensive, anti-obesity, antidiabetic, anti-atherosclerotic, and anti-hypercholesterolemic properties of this compound were repeatedly reported (Anand David et al. 2016). However, its health benefits are substantially limited because of very low bioavailability (less than 2% after a single oral dose) that is attributed to its low absorption, and also extensive metabolism and fast elimination from the body (Kawabata et al. 2015; Ganesan et al. 2017). The estimated absorption of quercetin glucoside (the naturally occurring form of quercetin), ranges from 3 to 17% only of quercetin ingested in healthy persons (Li et al. 2016). The innovative nano-delivery approaches are developed now to overcome these challenges. For example, substantially enhanced bioavailability of quercetin-loaded solid lipid NPs compared to a pure quercetin powder was reported in Caco-2 cell study (Vijayakumar et al. 2017). The improved topical delivery of quercetin by nanostructured lipid carrier systems was also demonstrated (Bose and Michniak Kohn 2013). Some studies demonstrated a therapeutic potential of such NPs in combating aging-associated disorders such as the Alzheimer's disease. In a rat model of Alzheimer's disease, substantially better memory retention vis-à-vis was observed in animals intravenously administered with quercetin-loaded solid lipid NPs compared to that in animals administered with pure quercetin (Dhawan et al. 2011). Moreover, a higher delivery of quercetin to the brain along with the enhanced antioxidant effect in the brain cells was found in these NPs. In addition, a formulation of quercetin-based solid lipid NPs was shown to be more efficient than free quercetin in an ovariectomized rat model in restoring bone mineral density in osteopenic animals (Ahmad et al. 2016).

### 8.3.3 Nano-resveratrol

Resveratrol is a well-known polyphenolic compound with many anti-aging activities. Its anti-aging effects are believed to be attributed to the capacity to activate the mammalian silent information regulator 1 (SIRT1), and also to modulate the activity of proteins playing important regulatory roles in aging processes, including the Akt (protein kinase B), peroxisome proliferator-activated receptor coactivator-1α (PGC-1α), NFκβ, and the FOXO family members (Camins et al. 2009). Many of these activities are similar to those observed in **calorie restriction** (CR) treatments (Li et al. 2017). The effectivity and safety of resveratrol have been documented to date in 244 clinical trials, where the therapeutic potential of this compound in treating aging-associated conditions such as hypertension, obesity, metabolic syndrome, type 2 diabetes, cardiovascular disorders, stroke, chronic inflammation and kidney diseases, Alzheimer's disease, and cancer was shown (Berman et al. 2017; Singh et al. 2019).

The therapeutic applicability of resveratrol is, however, substantially limited because of its fast metabolism and poor bioavailability (Smoliga and Blanchard

2014), and also very low water solubility causing its poor absorption by oral administration (Chauhan 2015). To overcome these limitations, nanosized resveratrol-loaded formulations have been recently developed and investigated. For example, the bioavailability of *resveratrol loaded in* N-trimethyl chitosan-g-palmitic acid surface-modified solid lipid NPs was shown to be 3.8-fold higher than that from resveratrol suspension (Ramalingam et al. 2016). In male Wistar rats, two times higher bioavailability of the trans-resveratrol in the brain, kidney, and liver was observed through oral delivery with trans-resveratrol-loaded lipid core nanocapsules compared to the free trans-resveratrol (Frozza et al. 2010). Gastrointestinal safety has also been found to be significantly improved in the same animal model compared to the free trans-resveratrol. Since resveratrol is considered to be a promising candidate for the treatment of Alzheimer's disease due to its neuroprotective properties, the resveratrol-loaded solid lipid NPs functionalized with monoclonal antibodies against the transferrin receptor have been developed to enhance its bioavailability to the brain (Loureiro et al. 2017). These NP–antibody conjugates demonstrated increased cellular intake; therefore, they were proposed as promising nanocarriers to transport resveratrol to the brain tissues in efforts to treat Alzheimer's disease. Recently, solid lipid NPs loaded with resveratrol were shown to have therapeutic effect for protecting the myocardium and reducing the doxorubicin-induced cardiotoxicity in mice (Zhang et al. 2019). Oral administration of resveratrol-loaded solid lipid NPs also was found to improve insulin resistance through targeting expression of SNARE proteins in adipose and muscle tissues in rats with type 2 diabetes (Mohseni et al. 2019).

### *8.3.4 Nano-genistein*

Genistein is a phytoestrogenic isoflavone found in soy. It is known to be able to combat aging-associated pathological conditions such as oxidative stress, inflammation, osteoporosis, obesity, type 2 diabetes, neurodegenerative diseases, and several cancers (Saha et al. 2014). Its bioactivity is, however, substantially decreased due to a very low solubility and poor bioavailability. Moreover, since genistein is an estrogen-like substance, its high doses may cause toxicity and endocrine-disrupting effects (Patisaul 2017). Recently, innovative nanoscale materials, including the lipid ones, were developed with aim to improve the oral delivery and to overcome the potential toxic effects of this substance (Rassu et al. 2018). For instance, the oral bioavailability of genistein loaded in the solid lipid NPs was found to be significantly increased in rats compared to that of its suspension or bulk powders (Kim et al. 2017).

### 8.3.5 Nano-epigallocatechin-3-Gallate

Epigallocatechin-3-gallate (EGCG) is polyphenol compound (catechin) contained in green tea. This compound was shown to exhibit a lot of anti-aging and healthspan-promoting activities including antioxidant, anti-atherogenic, anti-inflammation, and anti-tumor ones (Khan and Mukhtar 2018). The epidemiological findings on these properties are, however, inconsistent and frequently conflicting with results of in vitro investigations. This contradiction is believed to be due to poor stability and low bioavailability of this compound (Krupkova et al. 2016; Chu et al. 2017). In order to enhance its bioavailability, innovative solid lipid NPs and other nanocarrier-based delivery systems have been recently developed (Granja et al. 2017; Dai et al. 2019). Encapsulating EGCG in lipid NPs is regarded as an appropriate approach to avoid the oxidation and **epimerization** of drugs, which are known to be common processes that result in reducing their bioavailability and, thereby, to limiting their therapeutic effectivity (Fangueiro et al. 2014). In a study by (Frias et al. 2016), EGCG loaded into solid lipid NPs (particle size ~300–400 nm) demonstrated higher stability and larger potential for oral delivery compared to those of non-processed EGCG. EGCG-loaded folic acid functionalized NPs were demonstrated to be biocompatible with epithelial Caco-2 cells, and EGCG transport across the intestinal barrier was estimated to be 1.8-fold higher than that of native EGCG (Granja et al. 2019). Two-fold larger oral bioavailability over free EGCG and improved ability to treat the Alzheimer's disease was also found in EGCG-loaded nanolipid particles (Smith et al. 2010). The EGCG-loaded lipid NPs (<300 nm) have also been shown to have a potential for the treatment of aging-related ocular diseases, such as dry eye, age-related macular degeneration, glaucoma, diabetic retinopathy, and macular oedema (Fangueiro et al. 2014).

### 8.3.6 Other Phytocompound-Based Lipid Nanocomposites

Enhancement of therapeutic potential was also found in several other phytocompound-based lipid nanocomposites compared to their pure constituents. Such effect was found, e.g., for puerarin which is the major bioactive constituent in kudzu roots widely used in China for the treatment of various cardiovascular disorders. Solid lipid NPs loaded with puerarin demonstrated three times higher bioavailability following oral administration in heart and brain tissues compared to the free puerarin (Luo et al. 2011). The same effect was observed for the alkaloid piperine which is the main active ingredient of black pepper. In a rat model of the complete Freund's adjuvant (CFA)-induced arthritis, either topical or oral administration of piperine-loaded solid lipid NPs caused significant reduction in TNFα protein levels, assuming that treatment with such NPs has antirheumatic therapeutic potential (Bhalekar et al. 2017). Improved therapeutic potential against myocardial ischemia–reperfusion injury has also been shown in rats treated with solid lipid NPs

loaded with the total flavonoid extract derived from *Dracocephalum moldavica L.* compared to that of the non-modified extract (Tan et al. 2017).

## 8.4 Summary and Outlooks

There is convincing evidence that PBCs have a substantial potential in preventing and treating various aging-associated chronic disorders. However, poor stability, solubility in the gastrointestinal tract, and bioavailability largely limit their clinical applications. Currently, many nanocarrier-based systems intended to delivery of PBCs to target organs are developed to protect them from premature enzymatic degradation and metabolism, enhance the solubility and stability, increase the absorption in the gastrointestinal tract, and also to prolong their circulation time, thereby limiting side effects of these compounds (Conte et al. 2017; Lai et al. 2020; Martínez Ballesta et al. 2018; Lai 2013; Jampilek et al. 2019). Phytonanotherapy represents a promising innovative approach that may provide an opportunity to overcome a lot of drawbacks intrinsic to conventional therapeutic strategies. PBC-loaded nanoformulations are believed to provide synergistic health benefits because such a therapeutic modality can be clinically equivalent to a standard treatment mode with conventional drugs, but with minimum side effects (Anand David et al. 2016). Thus, this approach may provide an approach alternative to therapeutic modalities commonly used for management of aging-associated pathological conditions and give an opportunity to overcome disadvantages related to the use of conventional medications. Among nanosystems aimed at delivering PBCs to target organs and tissues, lipid-based nano-delivery systems are the most well-studied systems aimed at enhancing the stability and pharmacokinetic profiles of PBCs in various pharmacological and food applications (Nayak et al. 2016). One beneficial feature of such delivery systems is that they can help in delivering PBCs to vital body organs, particularly the brain, following the oral delivery (for schematic representation, see Fig. 8.5). The available research evidence indeed suggests that bioavailability of PBCs loaded in nanocarriers can be up to 5–10 times higher than that of their bulk counterparts (Ganesan et al. 2017). In conclusion, it can be stated that substantial steps have been already taken to bringing a nonotechnology-based approach closer to application in clinical practice. In light of the unresolved questions, however, additional research is certainly needed to further improving the long-term safety, efficiency, and cost-effectiveness of PBC-loaded lipid nano-delivery systems.

**Important Notes**

- The development of efficient means for the human healthspan extension is a priority task for researchers worldwide.

- Phytobioactive compounds (PBCs) demonstrate anti-aging properties such as antioxidant, anti-inflammation, cardioprotective, and anti-tumor activities.
- The therapeutic efficiency of orally administered PBCs is, however, largely limited by their poor stability, solubility in the gastrointestinal tract, and bioavailability.
- Lipid-based nano-delivery systems are increasingly used now to enhance the bioactivity of PBCs and improve their potential in delaying and/or preventing aging-associated pathological conditions.
- PBC-loaded lipid nanocomposites provide many benefits over their conventional formulations, including improved solubility and stability, prolonged half-life, enhanced epithelium permeability, and bioavailability, and also improved tissue targeting and minimized side effects.

**Questions for Future Research**

- **How can nano-delivery designs be incorporated with optimized release profiles specific to physicochemical properties of the loaded PBCs?** For some PBC-loaded nano-delivery systems, the burst drug release may potentially cause cellular toxicity. The very slow drug release can, in turn, lead to inadequate therapeutic effect in treating the disease. Therefore, the development of innovative nano-delivery designs with optimized release profiles

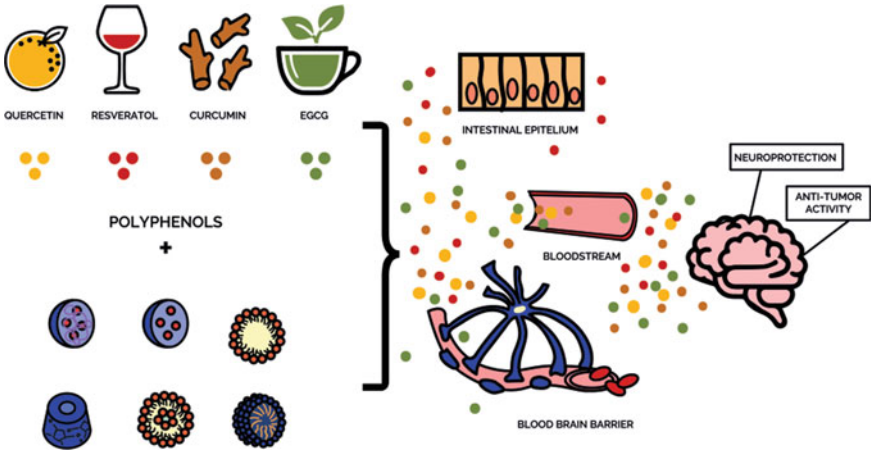


**Fig. 8.5** Schematic representation of lipid nanotechnology based systems used for brain delivery of PBCs

specific to physicochemical properties of loaded PBCs presents an important research challenge.

- **How safe can nanomaterials be used in anti-aging medicine?** Advances in research in nanomaterials have streamlined the development of biogerontological interventions, but currently studies on the biological safety of those materials are lacking. Nanomaterials that are being used to encapsulate PBCs need to be further thoroughly investigated to determine if these carriers themselves have any harmful effects, especially if they will be used over a long period of time by patients.
- **What is the fate of the nanomaterials after administration?** Right now, our understanding of the physiological fate of a nanomaterial after administration is insufficient. It is unclear whether these nanocomposites can be metabolized into potentially harmful products. An important question to be addressed is whether the orally administered nanomaterials may be completely degraded and excreted after delivering their drug load. In addition, it is important to determine whether lipid nanomaterials can bioaccumulate in the human body. Finally, there is a concern that nanomaterials may constitute a biohazard when excreted in urine or feces and accumulated in the environment. These have to be verified before applications of nanomaterials in clinical practice for tackling aging.

## Glossary

**Bioavailability** The fraction of absorbed drug or active compound reaching the systemic circulation.

**Calorie restriction** A reduction in calorie intake without malnutrition.

**Epimerization** A chemical process in which an epimer is converted to its chiral counterpart.

**Freeze drying** A method of removing water from a frozen material via sublimation of ice crystals.

**Gastric residence time** The length of time during which a material is kept in the stomach.

**Healthspan** The period of life spent in good health, free from the chronic diseases and disabilities of aging.

**Lipids** Organic molecules with hydrophobic or amphiphilic properties able to form structures such as vesicles, liposomes, or membranes in an aqueous environment.

**Microfluidization** A homogenization technique in which high pressure is applied to a fluid and is used to force the fluid to pass through microchannels. It is used extensively for generation of emulsions and nanoemulsions.

**Nanocarriers** Materials with particle size up to 100 nanometrers used to increase bioavailability of drugs with low solubility and absorption.

**Nano-delivery** Delivery of drugs or substances with nanocarriers.

**Phytobioactive compounds** Compounds of natural origin, being able to affect varied processes in biological systems.

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