Biomolecular Research & Therapeutics

Conte et al., J Biomol Res Ther 2016, 5:2
http://dx.doi.org/10.4172/2167-7956.1000139

Review Article Open Access

Polyphenols Nanoencapsulation for Therapeutic Applications

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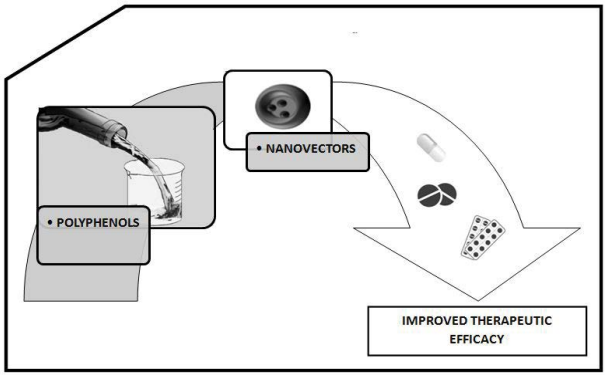
Abstract

Natural polyphenols are valuable compounds present in plants, fruits, legumes, chocolate, tea, wine and marine organisms possessing scavenging properties towards radical oxygen species. These abilities make polyphenols interesting either for the treatment of various diseases like inflammation and cancer or for anti-ageing purposes in cosmetic formulations. Unfortunately, such compounds lack in long-term stability, are very sensitive to light, and often present a low water solubility and poor bioavailability. To overcome these limitations and enhance polyphenols therapeutic applications, nanotechnology-based delivery systems have been developed, and among all, nanoencapsulation represented a promising strategy. This review described a recent overview of physicochemical nanoencapsulated polyphenols focusing on the most representative molecules such as resveratrol, quercetin, epigallocatechin-3-gallate, and curcumin.



Keywords: Nanotechnology; Polyphenols; Drug delivery; Bioavailability

Introduction

Polyphenols (PPH) are a large family of ubiquitous and varied molecules in the form of secondary metabolites of all vascular plants and several marine organisms. These natural compounds range from simple molecules to complex structures that have in common the presence of benzenic cycles bearing one or several hydroxy functions. These active principles play an important role in growth, reproduction, resistance to pathogens, predators and diseases [1]. In particular, these phytochemicals contribute importantly to the color and organoleptic properties of plants while, in the case of marine organisms, they act in the antioxidative response of microalgae and cyanobacteria against UV exposure [2]. Indeed, Klejdus et al. [2] showed that several classes of flavonoids, such as isoflavones, flavanones, flavonols and dihydrochalcones are found in microalgae and cyanobacteria despite of the fact that these organisms are evolutionary more primitive than terrestrial plants [2]. In medicine, polyphenols contribute to the promotion of health and reduction in the risk of common chronic diseases [3] (Figure 1).

Several studies show an inverse correlation between the consumption of polyphenols and the risk of major illness such as cancer, cardiovascular diseases, type 2 diabetes mellitus, neurodegenerative diseases and osteoporosis [4]. Such relationship is due to the PPH activity as potent effectors of biologic processes associated with the pathogenesis of human diseases. These effects also result from the ability of PPH to interact with proteins, enzymes, and membrane receptors modulating their activity in a specific way [5]. Among their properties, the strong free radical scavenging action mainly due to PPH ability to donate hydrogen atoms or electrons is probably the most studied [6,7]. Antioxidant effect of polyphenols can be achieved by several mechanisms of action such as molecular complexation with pro-oxidant proteins, chelation of metal ions or direct trapping of Reactive Oxygen Species (ROS). Moreover, polyphenols are recognized also for their ability to beneficially affect inflammation (e.g. by edema inhibition), to upregulate detoxification pathways or to modulate cell-signal transduction [8,9]. While PPH appear to have a dynamic interaction with gut microbiota, their efficacy in promoting health and reducing the risk of chronic diseases is dependent on their systemic bioavailability and metabolism. Generally, polyphenols have low bioavailability due to many intrinsic and extrinsic factors, including their chemical structure and molecular weight, low hydrosolubility, low stability in the gastrointestinal environment, extensive phase II metabolism and rapid elimination [10,11]. As a consequence, clinical applications of

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Received March 09, 2016; **Accepted** April 28, 2016; **Published** May 06, 2016

Citation: Conte R, Calarco A, Napoletano A, Valentino A, Margarucci S, et al. (2016) Polyphenols Nanoencapsulation for Therapeutic Applications. J Biomol Res Ther 5: 139. doi:10.4172/2167-7956.1000139

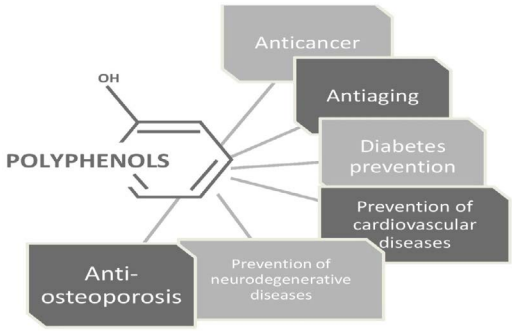


Figure 1: A schematic representation of therapeutic effects of Polyphenols.

PPH are limited. To avoid these drawbacks, nanodelivery systems able to maintain the structural integrity of the bioactive molecules have been developed [12-14]. Numerous nanoencapsulation methods have been developed based on physical (e.g. spray drying), physicochemical (e.g. ionic gelation, hydrophobic interactions, etc.) and chemical (e.g. *in situ* polymerization) principles. This review highlights the recent progress in the strategies for physicochemical nanoencapsulation of epigallocatechin-3-gallate, resveratrol, quercetin, ellagitannin, ellagic acid, phlorotannins, oleuropein, hydroxytyrosol and curcumin chosen as most representative examples of polyphenols molecules.

Classification of Polyphenols

Thousands of polyphenolic compounds have grouped together in various classes, depending to the basic chemical skeleton variations, such as degrees of oxidation, hydroxylation, methylation, glycosylation and the possible connections to other molecules (Table 1 and Figure 2). A simple sorting divides polyphenols in four classes: flavonoids (including the subclasses anthocyanidins, catechins, flavones, flavonols, flavanones and isoflavones), coumarins, stilbenes and tannins, although other constituents, like chalcones and lignans exhibit polyphenolic structures. Flavonoids are C15 compounds with the structure C6-C3-C6 in which two benzene rings are linked together by a group of three carbons. The arrangement of the C3 group determines how the compounds are classified. Typical flavonoids have A-, B- and C-ring typically depicted with the A-ring on the left-hand side.

The A-ring originates from the condensation of three malonyl-CoA molecules, and the B-ring originates from *p*-coumaroyl-CoA. The A-ring in most of flavonoids is either meta-dihydroxylated or meta-trihydroxylated. Substituents on A- and B- ring, along with the arrangement of the ring C-, differentiate the anthocyanidins, catechins, flavones, flavonols, flavanones and isoflavones. Coumarins, having C6-C3 skeleton with an oxygen heterocycle as part of the C3-unit, include isocoumarins, with a similar structure but reversed position of the oxygen and carbonyl groups within the oxygen heterocycle. Stilbenes, with a C6-C2-C6 structure, chemically are diarylethene, featured with a central ethane double bond substituted with phenyl groups on each carbon atoms of the double bond. Tannins comprise a group of compounds with a wide diversity in structure that is characterized by the ability to bind and precipitate proteins and to form complex molecules. Typically, these molecules require at least 12 hydroxyl groups and five phenyl groups to function as protein binders. Tannins are classified in three subgroups: condensed tannins, hydrolysable tannins and complex tannins, according to the type of linkage between simple units [15].

Polyphenols Bioavailability and the use of Nano Vectors

Polyphenols low bioavailability is mainly due to the low absorption in the human gastrointestinal (GI) tract following consumption, extensive biotransformation within the gut and rapid clearance from the body (Figure 3) [16]. In particular, many PPH are available as glycosylated compounds, and this form diminish their diffusion across barriers in the GI tract [10]. Other polyphenols cannot be absorbed from enterocytes because they are unstable in the acidic condition of the stomach and in the alkaline status of the small intestine [17]. Moreover, PPH are extensively transformed via phase II pathways, predominately methylation, glucuronidation and sulfation in the enterocytes of the small intestine, and then further metabolized in the liver, facilitating their quick excretion [10]. A number of strategies have been used to increase the chemical stability or permeability of these species. These approaches usually rely upon the addition of chemical additives such as reducing agents to maintain the structure, the use of dissolving agents to increase solubility [18], the interaction with inhibitors of phase I and/or II enzymes to escape biotransformation [19], the addition of complementary ingredients such as lipids or protein [20], the conjugation with promoiety groups [21]. More recently, encapsulation in nanovectors such as cyclodextrins, matrix systems, solid dispersions and liposomes has emerged as a novel strategy to improve poyphenols delivery, distribution and bioactivity [22]. Such systems differ for the internal structure (core-shell-like or matrix) and the physical state of the encapsulated active substances. Moreover, the effective use of nanoparticles as drug delivery systems require polyphenol encapsulation efficiency (EE) of, at least, sixty per cent (the percentage of drug entrapment efficiency is calculated according to the formula: Experimental drug loading/Theoretical drug loading x100).

Systems used for Nanoencapsulation

Nanotechnology is a science involving the formation of particles with diameters ranging from 1 to 1000 nm and for which the end product exhibits properties or phenomena attributable to its dimensions [12]. Nowadays, nanoencapsulation is an effective approach to improve solubility, minimize degradation process, reduce toxicity, and

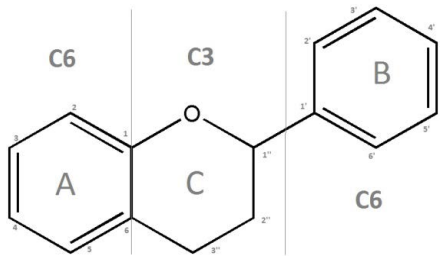


Figure 2: Basic chemical skeleton of typical Polyphenols.

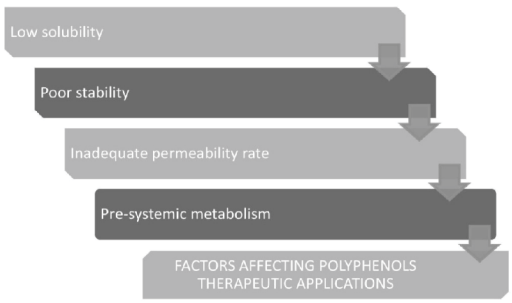


Figure 3: Factors affecting Polyphenols therapeutic applications.

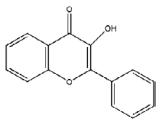
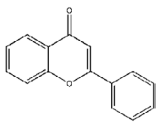
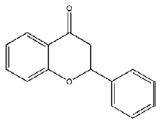
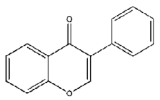
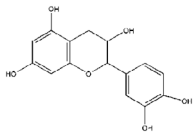
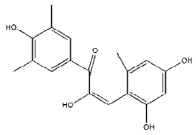
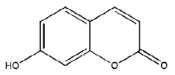
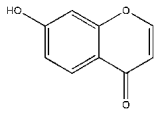
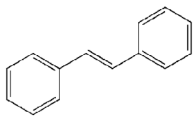
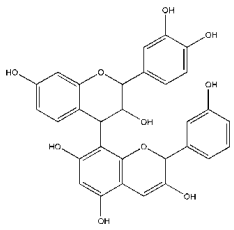
Polyphenols	Chemical Structure	Examples	Sources (List is not Exhaustive)
Flavonols		Myricetin, Quercetin, Kaempferol	Onions, broccoli, blueberries, red wine, tea
Flavones		Aspigenin, Luteolin, Tangeretin, Nobiletin	Parsley, celery, millet, wheat, skin of citrus
Flavanones		Hesperetin, Naringenin, Eriodictyol	Grapefruit, orange, lemon, tomatoes, mint
Isoflavones		Genistein, Daidzein, Glycitein	Leguminous plants, soya
Flavanols (Catechins)		Catechin, Epicatechin	Apricot, cherry, grape, peach, apple, green and black tea, red wine, cider
Anthocyanins		Cyanidin, Pelargonidin, Delphinidin, Petunidin	Red wine, aubergines, cabbage, beans, onions, radishes, fruit in general
Coumarins		Ombelliferone, Aesculetin, Scopoletin	Tonka bean, chestnut, Melilotus officinalis, Angelica officinalis
Isocoumarins		Isocoumarin	Tonka bean, chestnut, Melilotus officinalis, Angelica officinalis
Stilbenes		Resveratrol	Wine
Tannins		Ellagitannin, Ellagic acid and Phlorotannins	Plants (pomegranate) and brown algae

Table 1: Main classes of Polyphenols with structures and sources.

control the active absorption and biological response of polyphenols. Nanoencapsulation refers to several methods based on chemical, physical, and physiochemical principles. Chemical nanoencapsulation (e.g. interfacial and *in situ* polymerization methods) requires the polymerization of monomers at the interface of two immiscible substances through the addition of a cross-linker in the external phase [23]. Physical processes (e.g. air-suspension method, pan coating, spray drying, spray congealing, micro-orifice system, etc.) involve the interaction of the vector material with the molecules to be encapsulated when both are aerosolized or atomized [24]. Finally, physiochemical processes (e.g. coacervation, phase separation, complex emulsion, meltable dispersion and nanoprecipitation) form stable nanometer size drug nanosuspensions or nanoparticles through particle size reduction approaches [25]. The process versatility combined with the ability to increase loading capacities, persistence at the target sites and permeation and retention effect, make physiochemical methods interesting approaches to enhance PPH pharmacologic action [13,14,26]. Recently, several studies analyze nanoparticle-mediated delivery of polyphenols, based on biodegradable and biocompatible polymers able to encapsulate polyphenols in nanostructures such as cyclodextrins, nanospheres, nanocapsules, solid lipid nanoparticles, liposomes and micelles (Figure 4) [27-46].

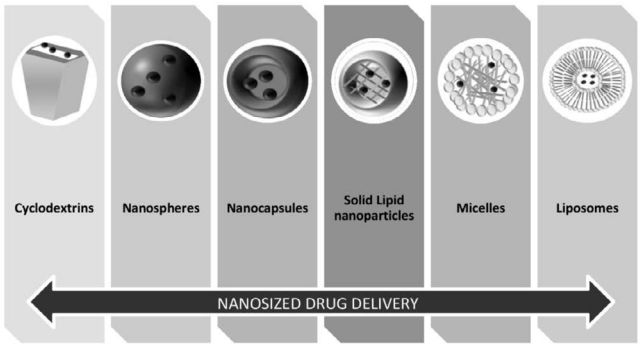


Figure 4: Schematic representation of nano-sized delivery systems for Polyphenols.

Cyclodextrins (CD) are a group of structurally related natural products formed during bacterial digestion of cellulose. They are structured as cyclic oligosaccharides consisting of (α-1,4)-linked α-D-glucopyranose units with lipophilic central cavity and hydrophilic outer surface. Specifically, the hydroxyl functions are orientated to the exterior and the central cavity is lined by the skeletal carbons and ethereal oxygens of the glucose residues. The natural α-, β- and γ- cyclodextrins (αCD, βCD and γCD) consist of six, seven, and eight glucopyranose units, respectively. These molecules have a limited aqueous solubility [27]. Effective NanoDDS are obtained using water-soluble cyclodextrin derivatives such as hydroxypropyl βCD and γCD, randomly methylated β-cyclodextrin (RMβCD), and sulfobutylether β-cyclodextrin sodium salt (SBEβCD) [28]. CD form complexes with molecules through inclusion into the CD cavity via van der Waals connections, hydrophobic interactions or hydrogen bonds. This complexation is enhanced when CD and drug have opposite charge and the temperature is low [29,30]. Another type of nanosized vectors are nanospheres (NS), structured with hydrophobic chains forming the inner part of the spheres and hydrophilic portions oriented on the surface. These NanoDDS have homogeneous solid matrices in which the polymer chains arrange in a "frozen" state phase-separated from the bulk solution [31]. Nanospheres allow a fine tuning of their properties through the use of different shell materials such as Poly-lactic acid (PLA), Poly-glycolic acid (PGA), Poly-lactic-co-glycolic acid (PLGA), poly ε-caprolactone (PCL), Chitosan (CS), Polyethylene glycol (PEG) and Eudragit (anionic copolymers based on methacrylic acid and methyl methacrylate). These polymers are widely used for the preparation of NS due to their biocompatibility and biodegradability [32]. Drugs are dissolved, entrapped, encapsulated, chemically bound or adsorbed to the constituent polymer matrix in order to be effectively delivered to the site of action [33]. Nanocapsules (NC) have similar composition but exhibit a core-shell structure in which the drug is confined within a cavity surrounded by a polymer membrane [34]. Nanocapsules can carry the active substance also on their surfaces or imbibed into the layer [35]. The cavity contains the active substances both in liquid or solid form [36]. Solid Lipid nanoparticles (SLNs) are vectors composed of high melting point lipids, as solid core, coated by aqueous surfactants. Examples of core lipids are fatty acids, acylglycerols and waxes, whereas phospholipids, sphingomyelins, bile salts and sterols are utilized as stabilizers [37]. SLNs have high biocompatibility, high bioavailability, physical stability, protection abilities of incorporated labile drugs from degradation, excellent tolerability, prevention of problems related with multiple routes of administration, avoidance of the use of organic solvents during the preparation and absence of problems concerning large scale production and sterilization [38,39]. However, common disadvantages of SLNs are particle growth, unpredictable gelation tendency, uncertain diffusion of the drug within the lipid matrix of the vector and unexpected dynamics of polymorphic transitions [40]. Liposomes (LS) are drug delivery systems that form spontaneously by hydration of lipid powder in aqueous medium produced from cholesterols, non-toxic surfactants, sphingolipids, glycolipids, long chain fatty acids and membrane proteins [41]. Liposomes have particle sizes ranging from 30 nm to several micrometers and consist of one or more lamellaes (phospholipidic bilayer membranes) surrounding aqueous units where the polar head groups are oriented in the pathway of the interior and exterior aqueous phases [42]. Self-aggregation of polar lipids is not limited to conventional bilayer structures, but they may self-assemble into various types of colloidal particles depending on molecular shape, temperature, and dispersion conditions [43]. Micelles (MC) are colloidal dispersions, with particle size ranging between 5 to 100 nm that form spontaneously at certain concentration and temperature values from amphiphilic agents. MC formation is driven by the decrease of free energy in the system because of the removal of hydrophobic fragments from the continuous phase, and the re-establishing of hydrogen bond network in water. Moreover, additional energy results from the formation of Van der Waals bonds between hydrophobic blocks in the core of the formed micelles. Hydrophobic fragments of amphiphilic molecules form the core of micelles, while hydrophilic portions the shells [44]. MC possesses high stability, good biocompatibility, and is able to solubilize a broad variety of poorly soluble pharmaceuticals [45]. Examples of amphiphilic agents used to form MC are Pluronic (Plu), Poly (ethylene glycol) (PEG), Poly (D,L-lactide-co-glycolide) (PLGA) and Polycaprolactone (PCL) [46].

Nanoparticles as Potential Delivery Systems of Polyphenols

Epigallocatechin-3-gallate (EGCG)

Epigallocatechin-3-gallate is a water-soluble flavanol found predominately in green tea leaves (*Camellia sinensis*) (Figure 5) that acts in the prevention of some forms of cancer, cardiovascular diseases, type 2 diabetes mellitus and osteoporosis. Epigallocatechin-3-gallate is highly susceptible to degradation in the intestinal milieu and via oxidative processes. Efforts to promote the intake, enhance the stability, and increase bioavailability of EGCG are directed to incorporate this flavanol into nanosized delivery vectors (Table 2).

Siddiqui et al. [47] reported the encapsulation of EGCG in poly (L-lactide)-poly (ethylene glycol), (PLA-PEG) nanoparticles and assessed its efficacy against human prostate cancer (PC3) cells both *in*

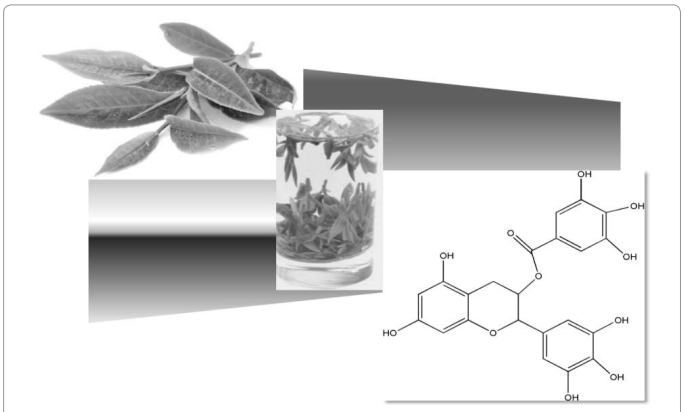


Figure 5: Epigallocatechin-3-gallate (EGCG) structure and natural derivation.

Nanovectors	Type of Delivery Systems	References
Polyester nanoparticles	Poly(L-lactide)-poly(ethylene glycol), (PLA-PEG) nanoparticles	[47]
	PLGA-PEG nanoparticles functionalized with the prostate-specific membrane antigen (PSMA) inhibitor on the surface	[49]
	PLGA biodegradable nanoparticles	[50]
Serum albumin nanoparticles	Bovine serum albumin (BSA) nanoparticles	[48]
Carbohydrate matrix	Carbohydrate matrix composed of maltodextrin (60%) and gum arabic (40%)	[51]
	Gelatin nanoparticles	[52]
	Chitosan nanoparticles	[53,54]

Table 2: Nano delivery systems for epigallocatechin gallate.

vitro and *in vivo*. The results showed that encapsulated EGCG retained its biological effectiveness with an over 10-fold dose advantage form exerting its efficacy in the inhibition of PC3 proliferation. Moreover, PLA-PEG nanoparticles were biocompatible and permitted the control of the time and rate of polymer degradation. Epigallocatechin-3-gallate was also incorporated in bovine serum albumin (BSA) nanoparticles (with a mean particle size of 200 nm) and their effect evaluated against PC3 cells [48]. In this work, PC3 cells lethality was positively correlated with the nanoparticles uptake amount. The specific targeting to prostate cancer cells was obtained also with Poly (lactide-co-glycolide)-Poly(ethylene glycol) (PLGA-PEG) nanoparticles encapsulating EGCG and functionalized with the prostate-specific membrane antigen (PSMA) inhibitor [49]. Other PLGA-based nanovectors for EGCG were synthesized by Italia et al. [50] with a loading efficiency of 70 % and high antioxidant efficiency *in vivo*. These nanoparticles, given by oral administration, acted 3 times more quickly of solutions of free epigallocatechin-3-gallate administered parenterally. A further nanosized delivery systems encapsulating epigallocatechin gallate is constituted by carbohydrate matrix composed of maltodextrin (60%) and gum arabic (40%) with EE of 85% [51]. These particles were able to inhibit steps of the tumorigenesis process. Smith et al. [52] immobilized EGCG on lipid-coated nanoparticles with a bioavailability, after encapsulation, increased twice-fold compared to that of the free form. Epigallocatechin gallate inside the membrane preserved its antioxidant activity and blocked the production of hepatocyte growth factor (HGF) from cancer cell lines MBA-MD-231. On these bases were prepared also gelatin nanoparticles loaded with EGCG with an interesting inhibitory effect on HGF-induced cell scattering [53]. Finally, epigallocatechin-3-gallate was encapsulated into chitosan nanoparticles (sizing 165 nm and exhibiting a zeta potential of 33 mV) by Dube et al. [54] in order to evaluate the ability of chitosan tripolyphosphate nanoparticles to increase EGCG stability and bioavailability. They found that EGCG-chitosan nanoparticles incubated in alkaline solution took more time to degrade to 50% of the initial level, compared to pure epigallocatechin. Moreover, Dube et al. found that chitosan tripolyphosphate EGCG exhibited a 1.8-fold greater absorption rate than the same dose of free EGCG in *ex vivo* mice experiments and that chitosan NP increased the relative oral bioavailability by 1.5-fold compared to the same dose of free EGCG in an *in vivo* absorption experiment on mice [55].

Quercetin (QC)

Quercetin is a semi-lipophilic flavonol ubiquitous in plants (Figure 6). In medicine, dietary supplementation of QC is promoted for prevention and treatment of cancer and this active principle is now largely utilized as a nutritional supplement and as a phytochemical remedy for a variety of diseases like diabetes, obesity, circulatory dysfunction, inflammation and mood disorders. Quercetin has a strong antioxidant activity which potentially enables it to quench free radicals from forming resonance-stabilized phenoxyl radicals but, like most flavonoids, it is extensively transformed via phase II metabolism for elimination from the body [56]. Nanosized vectors encapsulating quercetin were developed to improve its oral bioavailability and to enhance its antioxidant and anti-inflammatory action (Table 3).

Li et al. [57] reported the synthesis of solid lipid nanoparticles of 155 nm of size composed of soya lecithin, Tween-80 and PEG that encapsulate QC, with EE of 91%. These nanoparticles were able to increase the relative oral bioavailability of quercetin by 5.7 fold as compared to the free form. Lipid-coated Nano capsules were reported by Barras et al. [58], with a solubility 100 times higher respect to free quercetin, stable for more than ten weeks and with no degradation product being detected. Wu et al. [59] prepared nanosized QC delivery systems with aminoalkyl methacrylate copolymers sized 82 nm and with encapsulation efficiency of 99%. They resulted in a *in vitro* radical scavenging activity of quercetin nanoparticles toward di(phenyl)-(2,4,6-trinitrophenyl)iminoazanium (DPPH) radicals and superoxide anion enhanced by 883- and 1377- fold as compared to the free form. However, in recent years, an increasing number of works reported the synthesis of PLGA nanoparticles able to encapsulate QC. Indeed, Pool et al. [60] reported that quercetin encapsulated within PLGA displayed a more potent antioxidant action against peroxyl radical-induced lipid peroxidation and a greater capacity for chelating activity toward transient metals than free QC. Ghosh et al. [61] evaluated the antioxidant activity of a single pre-treatment of quercetin encapsulated into PLGA nanoparticles, administered orally to female rats, in the protection against injury from ROS produced in liver and brain tissue subsequent to a subcutaneous injection of arsenite. QC-PLGA nanoparticles provided full protection against the arsenite induced ROS injury, while free quercetin was ineffective. The same group

Nanovectors	Type of Delivery Systems	References
Solid lipid nanoparticles	SLNs composed of soya lecithin, Tween-80 and PEG	[57]
	Lipid-coated nanocapsules	[58]
Acrylic nanoparticles	Aminoalkyl methacrylate copolymers nanoparticles	[59]
Polyester nanoparticles	PLGA nanoparticles	[60-63]
	PLA nanoparticles	[64]
	Eudragit-polyvinilalchool nanoparticles	[59]
Cyclodextrines	2-(hydroxy-propyl)-β-cyclodextrines (HP-β-CD)	[65]

Table 3: Nano delivery systems for Quercetin.

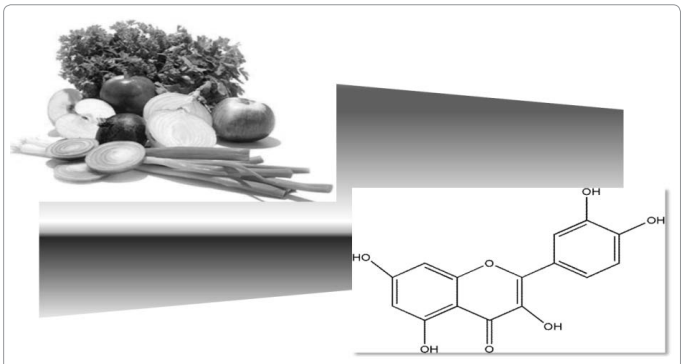


Figure 6: Quercetin structure and natural derivation.

reported a synergy between QC and meso-2,3-dimercaptosuccinic acid (a hydrophilic arsenic chelator), encapsulated together into PLGA nanoparticles, in the protection against arsenic induced damages [62]. In a rat model, Chakraborty et al. [63] examined the potency of a single dose of quercetin-PLGA nanoparticles administered orally prior to alcohol induced gastric ulcer in the protection against oxidative damages, demonstrating that QC-PLGA nanoparticles prevented 90 % of alcohol-induced ulceration as compared to the 20% of the free quercetin. QC encapsulated into PLA nanoparticles had increased antioxidant activity along with a slow and total release after 72 h, useful for potential therapeutic applications [64]. Similarly, Wu et al. [59] synthesized Eudragit-polyvinilalchool quercetin-loaded nanoparticles with particle size of 85 nm, good polydispersity, drug loading of around 99% and enhanced antioxidant activity. Lastly, QC and myricetin in 2-(hydroxy-propyl)-β-cyclodextrines (HP-β-CD) had improved bioavailability [65].

Resveratrol (RE)

Resveratrol, chemically known as 3,5,4'-trihydroxystilbene, is a naturally occurring polyphenol produced by a wide variety of plants in response to injury, UV Irradiation, ozone exposure and fungal attack (Figure 7) [66]. This polyphenol is an antioxidant [67], anti-inflammatory [68], anticancer [69], cell cycle inhibitor [70], anti-aging [68], neuroprotector [71] and cardioprotector [72] agent with application in the treatment of obesity and diabetes [73]. Moreover, it is used to stabilize polyester films for packaging and potential biomedical applications [74]. However, resveratrol has rapid and extensive metabolism [75] that affects its body distribution and bioavailability. Further, there is a significant person-to-person variability in drug absorption and metabolic processes depending on the hepatic function and on the metabolic activity of the local intestinal microflora [76]. To overcome these problems, in the recent years, several nano-drug delivery systems were synthesized (Table 4).

A good example is the liposomal formulation containing RE, with a good encapsulation efficiency of around 70% [77]. PEG-PCL resveratrol nanoparticles had enhanced loading efficiency and higher cytotoxicity to malignant glioma cells, compared with free resveratrol, and a good cellular uptake occurring by endocytosis [78]. Singh and Pai [79] reported sustained release of trans-resveratrol from orally administered PLGA nanoparticles (drug encapsulation efficiency more than 78%, with a particle size of about 170 nm). RE was detected in the rat plasma for up to 4 days with higher concentration in the systemic circulation and in the organs rich in mononuclear phagocyte system. The same authors encapsulated resveratrol in Eudragit RL 100 nanoparticles with a drug incorporation efficiency of 84% and the

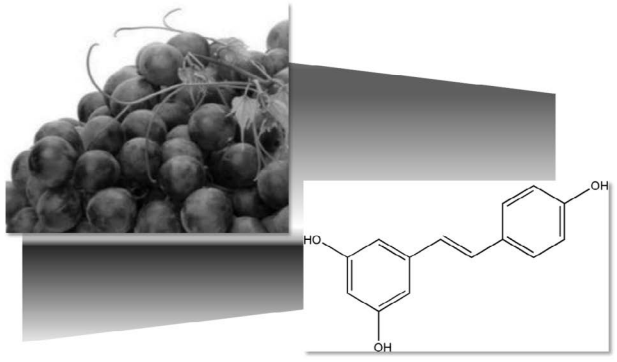


Figure 7: Resveratrol structure and natural derivation.

Nanovectors	Type of Delivery Systems	References
Liposomes	Cholesterol, dicetyl phosphate and lecithin liposomes	[77]
	Soy phosphatidylcholine liposomes	[43]
	Liposomal resveratrol formulation for intravenous administration	[84]
	Proliposomal formulation containing distearoyl phosphatidyl choline (DSPC)	[85]
Polyester nanoparticles	PEG-PCL nanoparticles	[78]
	PLGA nanoparticles	[79]
	Eudragit RL 100 nanoparticles	[80]
Carbohydrate matrix	Carboxymethyl chitosan nanoparticles	[81]
Solid Lipid nanoparticles	Stearic acid and Phospholipon® 90G SLNs	[39]
	Cetyl palmitate and polysorbate 60 SLNs	[40]
	Glyceryl behenate-based solid lipid nanoparticles	[83]
Micelles	PCL-PEG micelles	[86]
Cyclodextrins	Cyclodextrins based nanosponges	[87]

Table 4: Nano delivery systems for Resveratrol.

average size 180 nm. The *in vivo* studies of these vectors, in a rat model, showed that nanoparticles exhibited prolonged plasma levels up to 16 h, maintaining drug levels in the liver, spleen, heart, lungs, kidney and brain up to 24 h in comparison with free drug being cleared within 6 h [80]. Zu et al. [81] reported carboxymethyl chitosan nanoparticles as potential carrier for resveratrol. These nanoparticles (sized 155 nm and showing an encapsulation efficiency of 44%) improved the solubility of resveratrol, thereby greatly affecting the antioxidant activity of the drug. *In vivo* biodistribution study indicated higher body localization of drug loaded carboxymethyl chitosan nanoparticles, in comparison to free resveratrol solution in phosphate buffered saline (PBS) [81]. Additionally, were synthesized resveratrol loaded Solid Lipid nanoparticles with a controlled release profile, due to an initial burst release of 40% caused by the active principle associated with the particle shell, and a subsequent prolonged release of the drug located in the lipid matrix. In this system, the efficiency of the cellular uptake depended on the molecular interactions with the biological membrane organization, lipid rafts and the actin cytoskeleton invaginations for the receptor mediated entrance. Moreover, SLNs were able to carry RE to the nuclear target site [82]. Resveratrol loaded SLNs were also prepared by Pandita et al. [39] with a drug incorporation efficiency of 89% and average diameter of 134 nm. The drug delivery system showed prolonged release *in vitro* up to 120 h in a Wistar rat model, enhancing plasma bioavailability compared to free drug suspension. Other resveratrol-SLNs were produced using Polysorbate 60 as surfactant, with an entrapment efficiency of 70% and the particle size ranged between 150 and 250 nm: the drug release in simulated gastric fluid (SGF) was of 8% at 3 h [40]. Jose et al. [83] checked the brain targeting ability of glyceryl behenate-based solid lipid nanoparticles to utilize the potent anticancer properties of resveratrol. The *in vivo* biodistribution study using Wistar rats demonstrated that these SLNs significantly increased the brain concentration of RE. Moreover, these DDS had lower distribution to other tissues, proving the targeting abilities of this system. Resveratrol loaded soy phosphatidylcholine liposomes were synthesized by Pando et al. [43] to investigate the *ex vivo* percutaneous absorption of RE. Results indicated high cutaneous accumulation and low transdermal delivery of the drug. Moreover, Coimbra et al. [84] designed liposomal resveratrol formulation for

intravenous administration. The encapsulation process gave protection against trans–cis isomerization, with 70% trans-resveratrol still present after 16 min of UV light exposure compared to 10% when resveratrol is exposed in its free form. In addition, *in vivo*, intravenous injection of 5 mg/kg body weight of resveratrol in nude BALB/c female mice with subcutaneous head and neck squamous cell carcinoma led to a significant reduction in tumor volume [84]. Basavaraj et al. [85] produced resveratrol-loaded proliposomal formulation with entrapment efficiency of 20–23% and zeta potential of −22 mV containing distearoyl phosphatidyl choline (DSPC) with or without cholesterol. Faster drug release was observed in formulation without cholesterol and the release increased as the amount of DSPC in the formulation was enhanced. Lu et al. [86] produced resveratrol loaded micelles in which polycaprolactone (PCL) constituted the hydrophobic core and poly (ethylene glycol) (PEG) was the hydrophilic shell of micelles. This system showed a protective effect on adrenal gland PC12 cells against superoxide-induced damage during the phenomenon of oxidative stress. Finally, cyclodextrins-resveratrol complexes were used to increase the concentration of the polyphenol in aqueous solution, while maintaining its biological activity. For example, spherical CD-based nanosponges showed increasing solubility and stability, together with good drug encapsulation efficiency, compared to free RE [87].

Ellagitannin (ET), Ellagic acid (EAC) and Phlorotannins (PHT)

Ellagitannin, Ellagic acid and Phlorotannins are examples of the phenolic class of tannins, widely diffused in plant and marine organisms (Figure 8). In fact, ET and EAC are most present in the pomegranate (*Punica granatum*), a fruit-bearing shrub that originated in the region from Iran to northern India, while phlorotannins are isolated from algae. Ellagitannin and Ellagic acid decrease heart disease risk factors, affect LDL oxidation, macrophage oxidative status, foam cell formation [88,89] provoke the reduction of systolic blood pressure by inhibiting serum angiotensin-converting enzyme [90] and prevent cancer. These tannins show free-radical scavenging properties [91,92] and selectively inhibit the growth of breast, prostate, colon, lung tumors, and skin cancer [93,94]. Similar properties are found in phlorotannins, present in brown algae, formed by the polymerization of phloroglucinol. Specifically, the phlorotannins eckol, phlorofucofuroeckol A, dieckol and 8,8'-bieckol are isolated from the Laminariaceous brown algae *Eisenia bicyclis* (Kjellman) Setchell, *Ecklonia cava* Kjellman and *Ecklonia kurome* Okamura [95]. All these tannins have limited therapeutic applications due to low water solubility, inadequate permeability [96], poor absorption and instability [97]. Nanosized drug delivery systems mask the active substances inside the nanoparticulate network, thus preventing degradation and increasing bioavailability (Table 5).

For example, gelatin nanoparticles incorporating partially purified pomegranate (PPE) ellagitannins showed a good loading efficiency and the capacity of inducing a late stage of apoptosis and necrosis in the human promyelocytic leukemia cells (HL-60) [98]. Similar results were obtained with Chitosan nanoparticles containing ellagic acid [99] and with Ellagic acid-loaded PLGA nanoparticles [100]. In particular, Ellagic acid-Chitosan nanoparticles were spherical shaped with an average particle size of 176 nm, showing a drug-encapsulation and loading-efficiency of 94% and 33%, respectively. The *in vitro* drug release profile in the PBS medium showed sustained release of EAC from chitosan nanoparticles. Further, the therapeutic efficacy of Ellagic acid-Chitosan nanoparticles in human oral cancer cell line (KB) exhibited significant cytotoxicity in KB cells in a dose-dependent manner with a very low IC50 value compared to the free EAC [99]. Ellagic acid-loaded PLGA nanoparticles had a rapid initial release of EAC in pH 7.4 phosphate buffer, followed by a slower sustained release [100]. Further, the authors tested the influence of the stabilizers DMAB and PVA on the size, loading efficacy, release kinetics in PBS, stability, cytotoxic activities and *in situ* intestinal permeability of these nanoparticles [100]. Same study was conducted also on PLGA-PCL ellagic acid nanoparticles [101]. Both resulted on improved tannin bioavailability with potential therapeutic application due to the oral administration of smaller quantity of nanoparticles, compared to the free drug. Shirode et al. [102] synthesized poly (D,L-lactic-*co*-glycolic acid)–poly(ethylene glycol) (PLGA–PEG) nanoparticles, with an average diameter of 150-200 nm, loaded with pomegranate extract or with the individual polyphenol components (e.g. punicalagin or ellagic acid). Synthetized nanoparticles showed a 2- to 12-fold enhanced antiproliferative effect on MCF-7 and Hs578T breast cancer cells compared to free extracts [102]. Similarly, brown algal phlorotannins were encapsulated in lecithin unilamellar vesicles prepared by the extrusion method. These nanovectors maintained their activity on lipid peroxidation inhibition and radical scavenging activities and presented the advantage of the improved stability [95].

Oleuropein (OR) and Hydroxytyrosol (HYT)

Oleuropein and Hydroxytyrosol are phenolic compounds naturally present in olive fruits and leaves (Figure 9) [103]. Indeed, olive leaf extracts are rich in oleuropein, demethyloleuropein, oleuroside, verbascoside, non-glycosidic secoiridoids and ligstrosides as well as several flavonoids and biflavonoids. Also olive oil vegetation water (or olive mill waste water), obtained by centrifugation or sedimentation of the olive oil, contains these organic polyphenols. Such compounds have several pharmacological properties, including antioxidant, anti-inflammatory, anti-atherogenic, anticancer, antimicrobial, antiviral and cardioprotective effects. Oleuropein and hydroxytyrosol exhibit similar free radical-scavenger ability, but with different action mechanisms. *In vitro* studies, in a model system consisting of dipalmitoylphosphatidylcholine/linoleic acid unilamellar vesicles (DPPC/LA LUVs) and a water-soluble azo compound as a free radical generator (LP–LUV test) [104] revealed that hydroxytyrosol can serve

Nanovectors	Type of Delivery Systems	References
Carbohydrate matrix	Gelatin nanoparticles incorporating partially purified pomegranate (PPE) ellagitannins	[98]
	Chitosan nanoparticles	[99]
Polyester nanoparticles	PLGA nanoparticles	[100]
	PLGA-PCL nanoparticles	[101]
	PLGA–PEG nanoparticles	[102]
Liposomes	Lecithin unilamellar vesicles	[95]

Table 5: Nano delivery systems for Tannins.

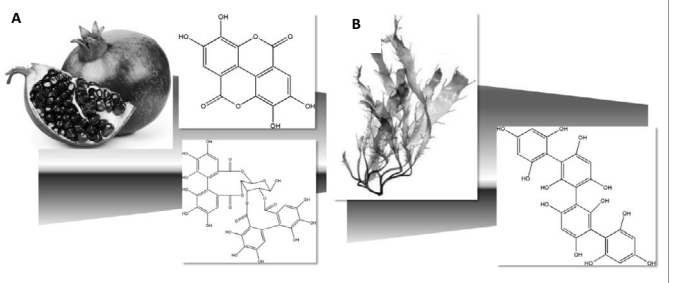


Figure 8: (A) Ellagic acid (up), Ellagitannin (down) and (B) Phlorotannin structures with their natural derivation.

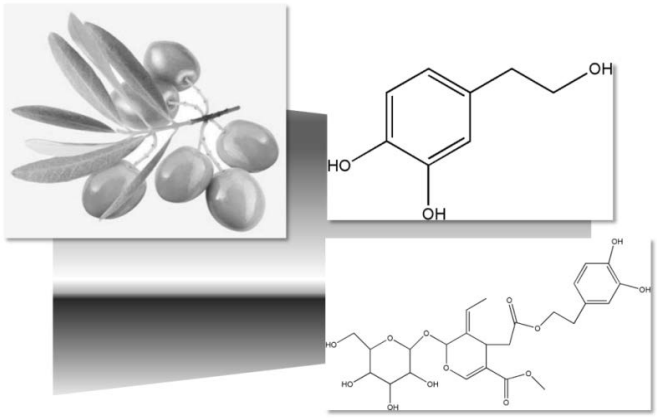


Figure 9: Hydroxytyrosol (up) and Oleuropein (down) structures and natural derivation.

as scavenger of aqueous peroxyl radicals near the membrane surface, while oleuropein acts also as a scavenger of chain-propagating lipid peroxyl radicals within the membranes. The pharmacologic activity of these active principles is enhanced by the use of nanotechnology as reported in Table 6.

Haghighi et al. [105] developed oleuropein-magnetic bovine serum albumin (BSA) nanoparticles with an initial burst and a sustained release. Hussain et al. [106] administered chitosan co-loaded hydrocortisone (HC) and hydroxytyrosol nanoparticles to provide additional anti-inflammatory and antioxidant benefits in the treatment of atopic dermatitis (AD). The co-loaded nanoparticles showed different particle sizes, zeta potentials, loading efficiencies, and morphology, when the pH of the chitosan solution was increased from 3.0 to 7.0. Moreover, they significantly increased the permeation of the drugs and showed higher epidermal and dermal accumulation of HC compared to commercial hydrocortisone formulations. *In vivo* studies resulted in the efficient control of transepidermal water loss, intensity of erythema and dermatitis index [106]. Similarly, a patent by Katas used [107] hydrocortisone and hydroxytyrosol loaded chitosan nanoparticles as local treatment of atopic dermatitis. Such nanovectors gave reduced side effects, increased efficiency of delivery, antibacterial properties and enhanced transepidermal penetration. Moreover, Siddique et al. [108] produced HC-HT co-loaded chitosan nanoparticles (HC–HT CSNPs) of 235 nm in size and with zeta potential +39.2 mV incorporated into aqueous cream (vehicle) to treat atopic dermatitis. This formulation was investigated *in vivo*, in albino Wistar rats, for acute dermal toxicity, dermal irritation and repeated dose toxicity. The results proved that HC–HT CS nanoparticles did not cause neither skin irritation, nor adverse-effect with respect to body weight, organ weight, feed consumption, blood hematological and biochemical, urinalysis, and histopathological parameters, when the HC–HT CS were used for 28 days at a dose of 1000 mg/body surface area per day. This study demonstrated that nanoencapsulation significantly reduced the toxic effects of HC. Qingxia Guan et al. [109] investigated the therapeutic efficiency of monomethoxy polyethylene glycol-poly (lactic co-glycolic acid) (mPEG-PLGA) nanoparticles co-loaded with syringopicroside and hydroxytyrosol prepared using a nanoprecipitation method. In particular, they analyzed the parameters of *in vivo* pharmacokinetics, biodistribution, fluorescence, endomicroscopy and cellular uptake. This vector (92 nm with a narrow polydispersity and a negative zeta potential of -24.5 mV) showed an encapsulation efficiency of ~ 33% and drug loading of 12%, that allows persisting drug plasma concentrations while the nanoparticles moved gradually into the cell, thereby increasing the available quantity. The *in vitro* effect resulted in the liver hepatocellular carcinoma (HepG2.2.15) cells proliferation inhibition [109]. Olive leaf extract containing oleuropein and hydroxytyrosol was encapsulated in β-CD, increasing the water solubility and antioxidant capacity of the encapsulated polyphenols [110]. Similarly, López-García et al. [111] studied the complexation of hydroxytyrosol with β-CD or HP-β-CD. Only β-CD appeared to be very strong photo-protectors of polyphenolic compounds subjected to ultraviolet radiation (λ=254 nm). Finally, Mohammadi et al. showed that water/oil/water emulsion with whey protein concentrate (WPC) and pectin complexes of olive leaf phenolic compounds result in a high stability and controlled release of the encapsulated compounds [112].

Curcumin (CU)

Curcumin is the principal polyphenol of the curcuminoid class of the Indian spice *Curcuma Longa* Linn., a plant typically grown and used in Southeast Asia (Figure 10) [113]. Curcumin lowers cholesterol, reduces platelet aggregation, inhibits the proliferation of cancer cells and improves digestion by increasing the flow of bile from the gallbladder [114]. Moreover, it has immunomodulatory, antiangiogenic and neuroprotective actions, antioxidant and anti-inflammatory abilities and the capacity to modulate the activity of several key transcription factors, cytokines, growth factors, kinases and other enzymes [115]. The activity of CU is correlated with the inhibition of the inducible nuclear factor kappa B (NF-kB) activation, and the suppression of cancer cell proliferation [116]. In addition, the clinical efficacy for rheumatoid arthritis, psoriasis, and postoperative inflammation of Curcumin is due to the reduction of NF-kB, cyclooxygenase 2 (COX2) and proinflammatory cytokines [117]. However, the pharmacological potential of CU is hampered by its low solubility, bioavailability, and stability [118]. In fact, Curcumin is sparingly soluble in water at

Nanovectors	Type of Delivery Systems	References
Serum albumin nanoparticles	Magnetic bovine serum albumin (BSA) nanoparticles	[105]
Carbohydrate matrix	Chitosan nanoparticles	[106]
	Chitosan nanoparticles incorporated into an aqueous cream	[107,108]
Polyester nanoparticles	mPEG-PLGA nanoparticles	[109]
Cyclodextrins	β-CD	[110]
	HP-β-CD	[111]
Micelles	whey protein concentrate (WPC) and pectin complexes	[112]

Table 6: Nano delivery systems for Oleuropein and Hydroxytyrosol.

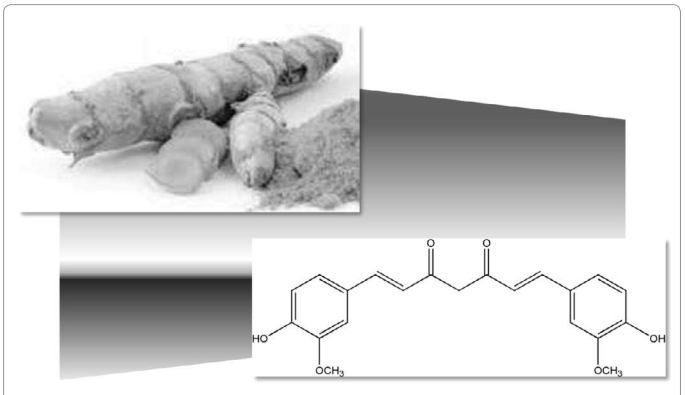


Figure 10: Curcumin structure and natural derivation.

acidic or neutral pH and slightly soluble under alkali conditions. For another CU is unstable in the gut and trace amounts of curcumin that pass through the gastrointestinal tract are rapidly degraded [118]. Nanotechnology permits to enhance the bioavailability of CU through the encapsulation of the drug in the hydrophobic domains of various types of nanovectors (Table 7).

β-Cyclodextrin-curcumin (CD-CUR) nanovectors inhibited telomerase gene expression in breast cancer cells. CD-CUR lowered the gene expression of telomerase more than free curcumin in breast cancer cells (T47D) in a time and dose dependent manner [119]. Similarly, Human Serum Albumin (HSA) possessed two affinity sites for curcumin [120] and literature studies revealed that Curcumin-HSA complexes had greater therapeutic effect than free CU, with no observable toxicity [121]. Self-assembled micelles containing Curcumin spontaneously formed in aqueous phase using Pluronic (Plu), poly(ethylene glycol) (PEG), Poly (D,L-lactide-co-glycolide) (PLGA), or polycaprolactone (PCL) with improved drug stability [44,122]. For example, Chen et al. [44] formulated curcumin in polyethylene glycol (PEG)-derivatized FTS (S-trans, trans-farnesylthiosalicylic acid)-based nanomicellar system. This nanovector had small size of around 20 nm. The nanomicellar curcumin demonstrated enhanced cytotoxicity towards several cancer cell lines *in vitro*. Moreover, intravenous application of curcumin-loaded micelles led to a significantly more effective inhibition of tumor growth in a syngeneic mouse breast cancer model (4T1.2) than free Curcumin. Similarly, Alizadeh et al. [123] synthesized diblock copolymer micelles made of oleoyl chloride and methoxy polyethylene glycol 2000 effective in inhibiting mammary and hepatocellular carcinoma cells proliferation *in vitro*. Moreover, tumor growth in micelles-treated mice was significantly suppressed and/or almost completely stopped at the end of the treatment [123]. Also, polymeric nanoparticles were structurally effective for embedding the water-insoluble curcumin. As the micelles, the most commonly used polymers included polylactic acid, polyglycolic acid, copolymer lactic acid/glycolic acid, polyethylene glycol, chitosan or a blend of these [124]. For example, bis-demethoxy curcumin analog loaded Chitosan–starch (BDMCA–CS) nanocomposite particles were developed by Subramanian et al. [125] by ionic gelation method. The entrapment efficiency and drug loading capacity were high and the *in vitro*-drug release showed a slow and sustained diffusion controlled release of the drug. Curcumin loaded PLGA nanoparticles; described by Verderio et al. [126] released intracellularly CU in a time and dose dependent manner at low drug concentration, yielding cell proliferation inhibition by G2/M cell arrest. Poly-(allylamine hydrochloride) (PAH), poly-(sodium 4-styrenesulfonate) (PSS) and chitosan nanocapsules loaded with curcumin were fabricated by Goethals et al. around a solid core/mesoporus (SC/MS) structure. These nanovectors resulted in high cytotoxicity in breast cancer MCF-7 cells due to effective curcumin loading and low particle aggregation [127]. Examples of liposomal delivery systems of CU were Diacyl phosphocholine liposomes and coated or uncoated flexible liposomal systems. Diacyl phosphocholine nanovectors had six molecules of phosphatidylcholine binding one molecule of Curcumin [128]. The drug was inserted into the membrane in a transbilayer orientation, anchored by hydrogen bonding to the phosphate group of phospholipids [129], increasing drug bioavailability. Similarly, Silica-coated flexible liposomes loaded with curcumin (CUR-SLNs) and curcumin-loaded flexible liposomes (CUR-FLs) without silica-coatings had higher bioavailability compared to that of free curcumin suspensions [130]. Other particularly suitable nanocarriers were Solid-lipid nanoparticles: Tiyaboonchai et al. [131] used Dioctyl sodium sulfosuccinate and Poloxamer 188 SLNs in a microemulsion technique to produce drug delivery systems sized less than 450 nm and showing up to 70% incorporation efficiency of curcuminoids. The same type of nanovectors were developed for the treatment of Alzheimer's disease by Kakkar and Kaur [37], and further improved by Mulik et al. [38], demonstrating how transferrin-mediated solid lipid nanoparticles containing curcumin had significant increases in apoptosis, cytotoxicity, ROS, and cellular uptake compared to a curcumin solubilized surfactant solutions and curcumin-loaded solid lipid nanoparticles, in breast cancer.

Nanovectors	Type of Delivery Systems	References
Cyclodextrins	β-Cyclodextrin	[119]
Serum albumin nanoparticles	Human Serum Albumin nanoparticles	[120,121]
Micelles	Polyethylene glycol (PEG)-derivatized FTS (S-*trans*, *trans*-farnesylthiosalicylic acid)-based nanomicellar system	[44]
	Pluronic	[122]
	Diblock Copolymer Micelles made of oleoyl chloride and methoxy polyethylene glycol 2000	[123]
Carbohydrate matrix	Chitosan–starch (BDMCA–CS) nanocomposite	[124]
Polyester nanoparticles	PLGA nanoparticles	[125]
	Poly-(allylamine hydrochloride) (PAH), poly-(sodium 4-styrenesulfonate) (PSS) and chitosan nanocapsules	[126]
Liposomes	Diacyl phosphocholine liposomes	[127,128]
	Flexible liposomes	[129]
Solid Lipid nanoparticles	Dioctyl sodium sulfosuccinate and Poloxamer 188 SLNs	[130]
	Transferrin-mediated solid lipid nanoparticles	[37,38]

Table 7: Nano delivery systems for Curcumin.

Conclusion

Polyphenols are among the most powerful active compounds synthesized by plants and marine organisms, and show a unique combination of chemical, biological and physiological activities. However, their limited stability and/or solubility, often combined with a poor bioavailability, have to be resolved in order to make these compounds able to answer growing demands in human health. In this review, the results of recent studies implementing various delivery techniques applied to polyphenolic compounds confirmed that nanoencapsulation is an interesting means to improve their activity. The various reported research revealed that physicochemical nanoencapsulation provided a significant protection against drastic conditions such as oxidation and thermal degradation, thereby contributing to increase the shelf life of the active ingredients. Furthermore, nanoparticles are also able to control the release, change the physical properties of the initial material, and improve the bioavailability of the polyphenolic compound. Future developments must be aimed to complete the characterization of absorption, distribution, metabolism and elimination behavior of nanosized systems carrying the polyphenols in order to potentiate their therapeutic applications.

Acknowledgement

We thank Dr. Orsolina Petillo for editing the manuscript and for administrative assistance. This work was supported by Progetto PON—"Ricerca e Competitività

2007–2013"—PON01_01802: "Sviluppo di molecole capaci di modulare vie metaboliche intracellulari redox-sensibili per la prevenzione e la cura di patologie infettive, tumorali, neurodegenerative e loro delivery mediante piattaforme nano tecnologiche", PON01_02512: "Ricerca e sviluppo di bioregolatori attivi sui meccanismi epigenetici dei processi infiammatori nelle malattie croniche e degenerative", PON03_00106: "Materiali Avanzati per la Ricerca ed il comparto Agroalimentare, Laboratorio Pubblico-Privato, MAReA" and PRIN 2012 (prot. 201288JKYY): "Nanotecnologie per variare i programmi di sviluppo osseo nella parete vasale per la prevenzione e trattamento delle patologie associate alla calcificazione ectopica arteriosa".

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Citation: Conte R, Calarco A, Napoletano A, Valentino A, Margarucci S, et al. (2016) Polyphenols Nanoencapsulation for Therapeutic Applications. J Biomol Res Ther 5: 139. doi:10.4172/2167-7956.1000139