TOPICAL REVIEW

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Topical Review

Strategies to improve ellagic acid bioavailability: from natural or semisynthetic derivatives to nanotechnological approaches based on innovative carriers

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Abstract

Ellagic acid (EA) is a polyphenolic compound whose dietary consumption is mainly associated with the intake of red fruits, including pomegranates, strawberries, blackberries, blackcurrants, raspberries, grapes or dried fruits, like walnuts and almonds. A number of studies indicate that EA exerts health-beneficial effects against several chronic pathologies associated with oxidative damage, including different kinds of cancer, cardiovascular and neurodegenerative diseases. Furthermore, EA possesses wound-healing properties, antibacterial and antiviral effects, and acts as a systemic antioxidant. However, clinical applications of this polyphenol have been hampered and prevented by its poor water solubility (9.7 ± 3.2 μg ml^{-1} in water) and pharmacokinetic profile (limited absorption rate and plasma half-life <1 h after ingestion of pomegranate juice), properties due to the chemical nature of the organic heterotetracyclic compound. Little has been reported on efficient strategies to enhance EA poor oral bioavailability, including chemical structure modifications, encapsulation within nano-microspheres to be used as carriers, and molecular dispersion in polymer matrices. In this review we summarize the experimental approaches investigated so far in order to improve EA pharmacokinetics, supporting the hypothesis that enhancement in EA solubility is a feasible route for increasing its oral absorption.

Keywords: ellagic acid, bioavailability, polymeric nano- and microspheres, drug delivery, health promotion, cancer, melanoma

(Some figures may appear in colour only in the online journal)

[3] These authors contributed equally

1. Introduction

Ellagic acid (EA) is a polyphenolic flavonoid detected in pomegranates, berries (blackberries, blackcurrants, raspberries, strawberries, grapes) and dried fruits (walnuts, almonds) [1–3], as well as in distilled beverages, like cognac, rum and scotch whisky [4].

Several studies have demonstrated that EA has significant health-beneficial effects against chronic diseases associated with oxidative damage [5, 6], including different kinds of cancer [7, 8], cardiovascular diseases [9] and neurodegenerative disorders [10]. Furthermore, EA has wound-healing properties, promoting blood coagulation through the activation of factor XII of the intrinsic cascade [11], as well as antimicrobial or antiviral activities [12–15]. Therefore, EA is regarded as a high-value antioxidant, anti-inflammatory and chemopreventive agent, and it is widely employed in food, cosmetic and pharmaceutical industries [16].

However, some drawbacks associated with the chemical structure of this heterocyclic polyphenol, including both a lipophilic and a hydrophilic portion, like poor water solubility [17], limited oral bioavailability and short plasma half-life, hamper EA clinical applications and strictly limit its potential as a systemic drug. Moreover, even if EA is the main consumed polyphenol, the average individual intake is extremely low (i.e. 343 mg/year) and insufficient to achieve the plasma concentrations necessary for specific tumour prevention [18]. Currently, some companies are marketing capsules and tablets containing EA-rich extracts isolated from pomegranates, red raspberries, red raspberry seeds or an Indian plant (*T. chebula*), or United States Pharmacopeia (USP) grade EA (blended with herb extracts) [19]. Nevertheless, despite the fact that several studies have evaluated the EA clinical potential, its bioavailability has not received much attention [19]. Overcoming EA pharmacokinetic limitations represents a great challenge for the study of its actual beneficial effects. Three main strategies can be followed to fully exploit EA therapeutic potential: (i) use of natural or semisynthetic derivatives; (ii) encapsulation within proper delivery systems able to increase EA solubility, stability and bioavailability; (iii) formulation of molecular dispersions in polymer matrices.

In this review, we provide a complete overview about EA origin, chemistry, health-beneficial properties, applications, and, mainly, the strategies to improve its pharmacokinetics.

1.1. Origin and chemistry of ellagic acid

First discovered by the chemist Henri Braconnot in 1831 and first synthesized by heating gallic acid with arsenic acid or silver oxide by Julius Löwe in 1868, EA (2,3,7,8-tetrahydroxy[1]-benzopyranol[5,4,3-cde]benzopyran-5,10-dione; MW $= 302\ \mathrm{g \cdot mol^{-1}}$) is a naturally occurring compound [20] which belongs to the ellagitannins (ETs) family. The ETs, together with gallotannins (GTs), constitute the family of hydrolyzable tannins (HTs), highly studied phytochemicals because of their role in the health-promoting effects of pomegranate juice and extract, which have gained considerable attention in recent decades. The HTs are classified as ETs and GTs according to the phenolic acids esterified to the core cyclic polyol molecule, which is often a glucose; in total, more than 60 HTs have been detected from pomegranate by mass spectrometry and/or nuclear magnetic resonance [21].

From a chemical point of view, EA is a dimer of gallic acid, characterized by four fused rings (two of which are lactones) and four hydroxyl groups (figure 1). Due to its chemical structure, EA has both lipophilic (6-member hydrocarbon rings) and hydrophilic (hydroxyl groups and lactone rings) properties [22]. Its unique structure renders EA able to accept electrons from various donors, thus contributing to different antioxidant redox reactions [23]. Moreover, EA can be naturally present as free, glycosylated and/or acylated compounds, or as hydrolyzable ET polymers, usually esterified with glucose. Macroscopically, this odourless weak acid exists in the form of cream-coloured needles or yellow powder [24].

The chemical nature of EA accounts for its poor solubility ($9.7 \pm 3.2\ \mu\mathrm{g\ ml^{-1}}$ in water and $33.1 \pm 15.5\ \mu\mathrm{g\ ml^{-1}}$ in phosphate buffer at pH 7.4) [17] and for its low bioavailability after oral ingestion. In a study in which ACI rats received black raspberry powder (5% w/w, corresponding to $75\ \mathrm{mg\ l^{-1}}$ EA) in their diet, EA oral absorption was around 0.2% of the administered dose, as assessed through analysis of plasma samples by solvent extractions and HPLC [25]. Similar pharmacokinetic studies performed in humans confirmed that the rate of oral EA absorption was <1%, after ingestion of pomegranate juice or freeze-dried black raspberries [26, 27].

Metabolism by the gastrointestinal microbiota further reduces the EA absorption rate [26, 28]. The family of microbial metabolites obtained from EA is called urolithins (figure 1): opening of a lactone ring and elimination of a carboxyl group lead to the generation of urolithinD, which in turn is further metabolized to generate urolithinC, A and B, by removal of 1, 2, or 3 hydroxyl groups, respectively [29, 30].

Urolithins have a higher absorption rate, likely because of their more lipophilic nature, and result 25–80-fold more bioavailable than EA [31]. Therefore, the health-beneficial effects of EA-containing products are likely due to these derived ETs-catabolites [32, 33], which, once absorbed, can reach different body compartments. Actually, urolithins represent the first natural evidence of the possibility of improving EA solubility, bioavailability and beneficial activity on human health through its chemical manipulation.

1.2. Biological properties and clinical applications of ellagic acid

Both EA and ETs have shown antioxidant, anti-inflammatory, and anti-carcinogenic effects in animal and human models, suggesting a potential preventive/therapeutic role for cancer and chronic diseases (figure 2) [8, 9, 34].

EA antioxidant activity can be considered comparable to that of well-known essential vitamins, like ascorbic acid and α-tocopherol [35], and more efficient against reactive oxygen

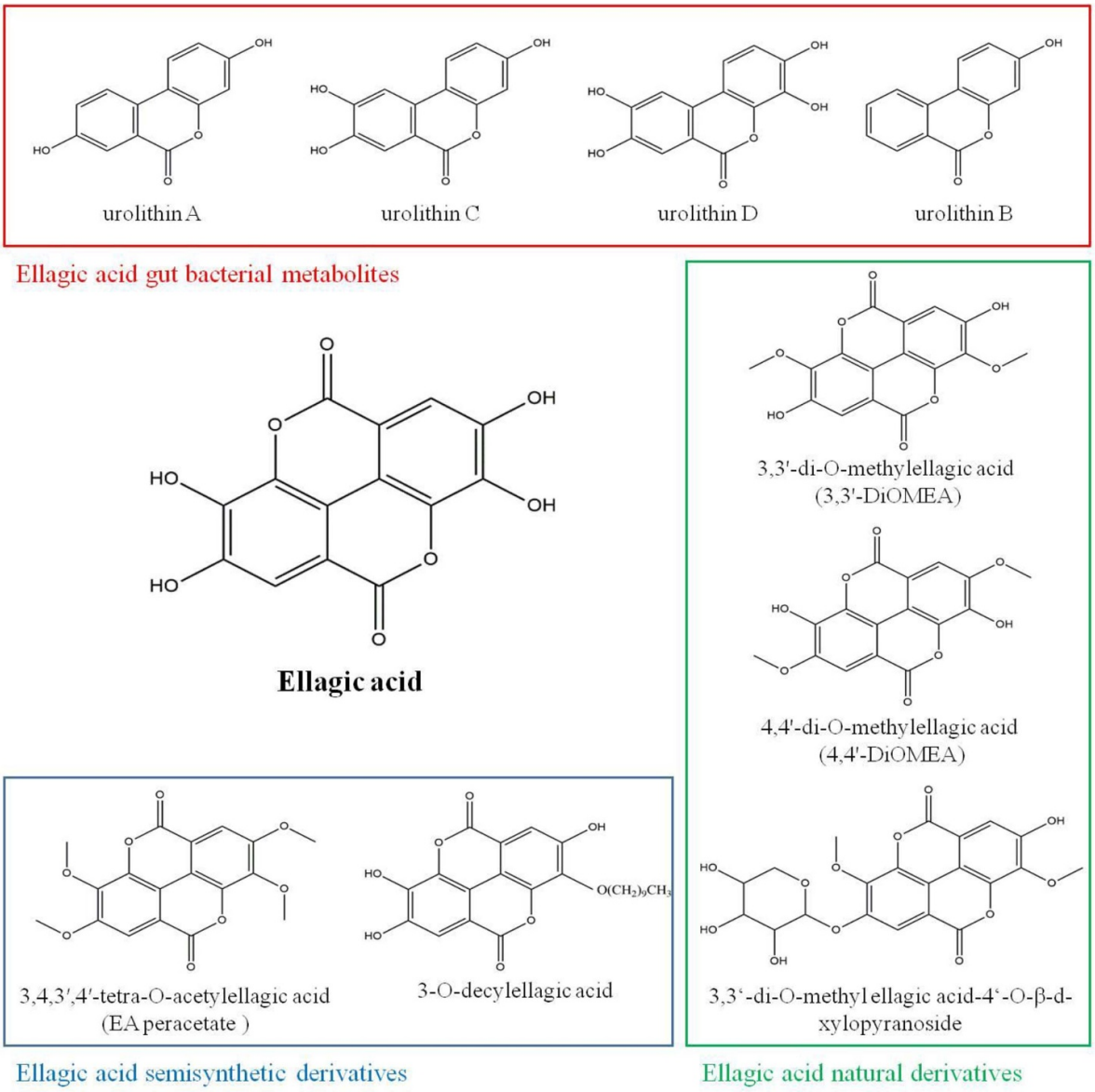

Figure 1. Molecular structure of ellagic acid (EA), intestinal metabolites (urolithins) and natural or semisynthetic derivatives, which gained attention in studies aimed at testing their potential health-promoting effects.

species (ROS) than reactive nitrogen species [36]. Furthermore, phenolic compounds like EA are able to hinder the pro-oxidative action of metals (copper, iron, nickel, cadmium) by chelation [37, 38] and directly interact with DNA causing a significant decrease of 8-oxo-2-deoxyguanosine levels, a typical marker of oxidative DNA damage [39–41]. Finally, it has been demonstrated that EA increases the expression/activity of the antioxidant enzymes superoxide dismutase (SOD1), glutathione peroxidase (GPX1), glutathione reductase (GR) and catalase (CAT) [42] and a role has been postulated for EA in the treatment of cirrhosis induced by chemical agents, like carbon tetrachloride [43].

EA anti-inflammatory activity supports its therapeutic potential against many chronic inflammatory diseases, like contact dermatitis and pancreatitis [44, 45]. EA has also been found to prevent activation and function of pancreatic stellate cells (a crucial cell type involved in pancreatic fibrosis) [46], to reduce the pro-inflammatory cytokine IL-6 expression and to increase the anti-inflammatory cytokine IL-10 levels in the bronchoalveolar lavage fluids of acid-induced acute lung injury models [47]. The transcription factor NF-κB, which plays a central role in inflammation and immunity, has been considered a potential target of EA anti-inflammatory effects, as demonstrated in a murine ulcerative colitis experimental model, where the polyphenol was included in the normal diet (0.5%) [48]. Other studies have also confirmed the involvement of NF-κB modulation in EA ability to decrease the serum levels of several pro-inflammatory cytokines [49–52]. Furthermore, EA modulates the expression of cyclooxygenase-2 (COX-2), a pro-inflammatory enzyme whose gene transcription is controlled by NF-κB [53], and binds with the high-affinity COX-2 active site [54], thus directly inhibiting its enzymatic activity (i.e. the synthesis of pro-inflammatory prostaglandins). Moreover, EA

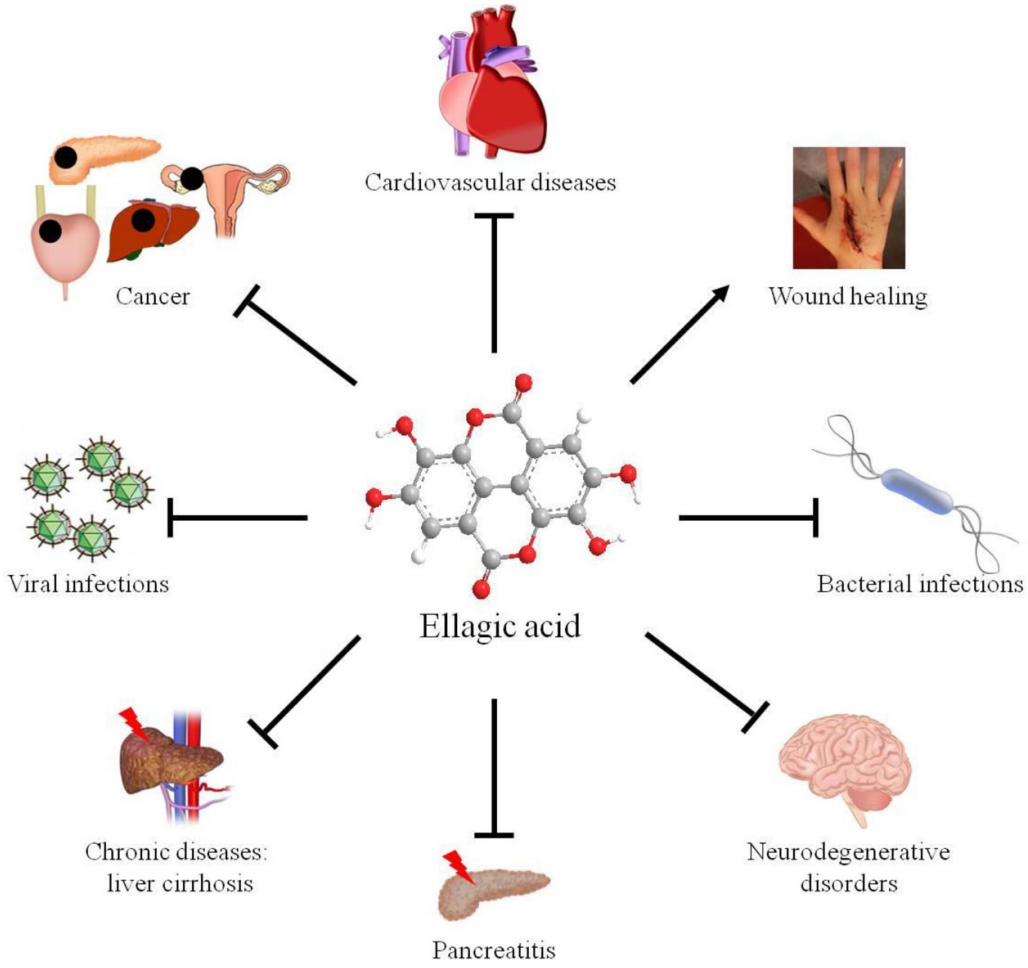

Figure 2. Potential clinical applications of EA: arrow indicates the promotion of a physiological process; horizontal bars indicate the inhibition of pathological conditions.

has been shown to inhibit the expression of vascular cell adhesion molecule 1 (VCAM1), intercellular adhesion molecule 1 (ICAM1) [55] and endothelial leucocyte adhesion molecule (E-selectin) [56], proteins which are required for the adhesion of circulating leukocytes to the vascular endothelium, a crucial step for white blood cell extravasation during the inflammatory response.

Finally, EA is considered as a promising chemopreventive and/or chemotherapeutic compound, since it is able to exert a significant antitumour effect against prostate, colon, pancreas, breast, ovarian and bladder cancers, lymphoma, hepatocellular carcinoma and glioblastoma [8]. Several mechanisms contribute to the antitumour activity of EA, including inhibition of cell proliferation, angiogenesis and extracellular matrix invasion, induction of caspase-dependent apoptosis and modulation of other processes required for tumour formation, progression and metastasis.

Interestingly, EA applications in the cosmetic sector have been reported, by producing a self-assembled supramolecular system based on green-synthetized gold nanoparticles (AuNPs), obtained by using *Punica granatum* juice for EA adsorption on their surface and chitosan (CS) as a wrapping agent [57]. High antioxidant [around 80% and 60% from the DPPH (2,2-diphenyl-1-picrylhydrazylhydrate) and ABTS (2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)) assays, respectively], skin lightening (tyrosinase inhibition of around 50%) and sunscreen (Sun Protection Factor of 20) properties were demonstrated, suggesting potentially promising applications in the cosmetic and biomedical fields for the obtained system.

2. Strategies to overcome ellagic acid limitations

Due to its extremely low water solubility (<10 μg ml^{-1}), oral bioavailability and intestinal permeability (0.13 $\times$ 10^{-6}), EA is categorized as a class IV drug of the biopharmaceutical classification system [17, 58]. The scarce solubility of EA derives from its high crystallinity degree (it is highly thermostable and its melting point is more than 300 °C), and, in particular, from its planar and symmetrical crystalline structure, with an extensive hydrogen-bonding [59]. Therefore, EA is soluble in dimethyl sulphoxide (DMSO), N-methyl pyrrolidone (NMP), pyridine, polyethylene glycol 200 (PEG200), polyethylene glycol 400 (PEG400) and triethanolamine, but it is difficult to solubilize in water as well as in organic

solvents like methanol (~671 μg ml^{-1}), which is a prerequisite for a pharmaceutical entity to be formulated into a dosage form [17].

With respect to its pharmacokinetic properties, EA is poorly absorbed after oral administration, and primary absorption takes place in the stomach and upper small intestine. Rapid elimination of the absorbed compound is due to a marked first-pass metabolism and low enterohepatic recirculation [60], finally resulting in a short plasma half-life and in the achievement of therapeutically irrelevant tissue concentrations [61]. In Sprague-Dawley rats treated orally with EA (50 mg kg^{-1}), plasma levels peaked at about 30 min, with a C_{max} of 93.6 ng ml^{-1}. The area under the curve (AUC, which measures the drug concentration in the systemic circulation as a function of time) was 457.2 ng ml^{-1} $\times$ h, indicating a poor absorption [62]. In human healthy volunteers receiving oral administration of black raspberries (45 g day^{-1} for 7 days), the maximal EA concentration in plasma was reached at 1–2 h, while in the urine it appeared within 4 h after ingestion; overall, less than 1% was absorbed [63]. Unabsorbed EA is converted to urolithins by intestinal metabolism [29], whereas absorbed EA is metabolized in the liver to methyl esters, dimethyl esters and glucuronides, which are removed by the kidney 1–5 h after absorption [64, 65].

The unfavourable pharmacokinetic properties of EA make it difficult to translate the therapeutic potential of EA-based drugs into an effective clinical treatment. With the purpose of finding suitable strategies to overcome EA pharmacokinetics and to increase EA bioavailability, different approaches can be pursued:

(1) use of natural or semisynthetic derivatives;
(2) development of drug delivery systems to vehiculate EA;
(3) formulation of molecular dispersions in polymer matrices.

2.1. Ellagic acid derivatives

From the 1980s to date, several studies focusing on the beneficial properties of natural and semisynthetic EA derivatives (see figure 1) have been published, with the aim of identifying the structural modifications that might result in the improvement of the absorption rate following oral administration.

Initial information in such a context derived from a study in which the effects of EA and some of its more lipophilic derivatives were tested, concerning their influence on the mutagenicity of (±)-7β, 8α-di-hydroxy-9α10α-epoxy-7,8,9,10-etrahydrobenz[a]pyrene in a *Salmonella typhimurium* strain. As a result, EA, 3,3′-di-*O*-methylellagic acid (3,3′-DiOMEA), 4,4′-di-*O*-methylellagic acid (4,4′-DiOMEA) and 3-*O*-decylellagic acid demonstrated similar anti-mutagenic effects [66]. These findings suggest that it is possible to deduce qualitative rules for predicting the activity of EA analogues, taking into account their chemical differences from the parental compound [67]. Conversely, two other semisynthetic derivatives, such as 3,3′-di-beta-D-glucopyranosylellagic acid decaacetate and 3,3′-di-n-octyl-4,4′-dihexanoylellagic acid, were less effective than EA in inhibiting lung tumour formation after exposure of A/J mice to benzo[a]pyrene [68]. Interestingly, the peracetate derivative (3,4,3,4-tetra-*O*-acetylellagic acid) was more efficient than EA in protecting bone marrow and lungs from genotoxicity induced by aflatoxin B_1 [69]. The same compound significantly suppressed melanoma growth and exerted immunostimulating effects in syngeneic C7BL/6 mice *in vivo,* to a higher extent than EA. Moreover, it induced apoptotic cell death through BCL-2 down-regulation *in vitro* in B16 melanoma cells. Unfortunately, EA peracetate still maintains poor water solubility [70].

3,3′-di-*O*-methylEA-4′-*O*-β-d-xylopyranoside, a natural EA derivative obtained from the acetone extract of the Chinese traditional herb *Euphorbia hylonoma* (Euphorbiaceae), was found to arrest the cell cycle in the G0/G1 phase, trigger apoptosis and inhibit extracellular matrix invasion in HepG2 human hepatocellular carcinoma cells [71].

Other studies have evaluated EA *in vivo* metabolites to elucidate possible structure-activity relationships potentially involved in their antiproliferative effects on tumour cells. All urolithins exerted antiproliferative activity on a panel of colon cancer cell lines, although with different potency (urolithinA > urolithinC > urolithinD > urolithinB) [72]. Interestingly, the only differential hydroxyl substitution of urolithinA and urolithinB led to a markedly different antiproliferative activity, suggesting that the additional—OH at position 8 in urolithinA is crucial for its biological activity. Consistently, another study demonstrated that the presence of a—OH group at the position 8, but not at the position 3, favours the interaction with the drug efflux transporter/breast cancer resistance protein ABCG2/BCRP [73]. On the other hand, considering that urolithins are produced by the opening and decarboxylation of one of the EA lactone rings and that urolithinA is more active than both EA and 3,3′-DiOMEA, the lactone ring seems to be not essential for the antiproliferative activity. Instead, the DiOMEA derivatives have a methoxy group in place of an alcohol group of EA, resulting in decreased molecular polarity [74]. The 4,4′-DiOMEA was the most effective compound in inhibiting colon cancer cell growth, compared to the 3,3′ derivative [74]. This observation further supported the pivotal role of the—OH groups in the 4,4′ positions, providing another rule for the structure-based drug design of EA derivatives with enhanced anticancer activity. Moreover, 4,4′-DiOMEA inhibited the proliferation of a colon cancer cell line resistant to 5-fluorouracil (SW-620-5FuR), with marginal activity against normal cells. In conclusion, the structural modifications of EA to obtain 4,4′-DiOMEA represent promising strategies for the development of new EA-based anticancer drugs with improved antitumour effects [74].

2.2. Nanoparticle-based approaches for EA bioavailability enhancement

Recently, several micro- and nanodevices have gained attention as promising drug delivery systems aimed at enhancing drug bioavailability [75, 76] (figure 3).

These specific drug delivery systems represent a nanotechnology-based approach involving biocompatible materials, mainly biopolymers [77]. In detail, different

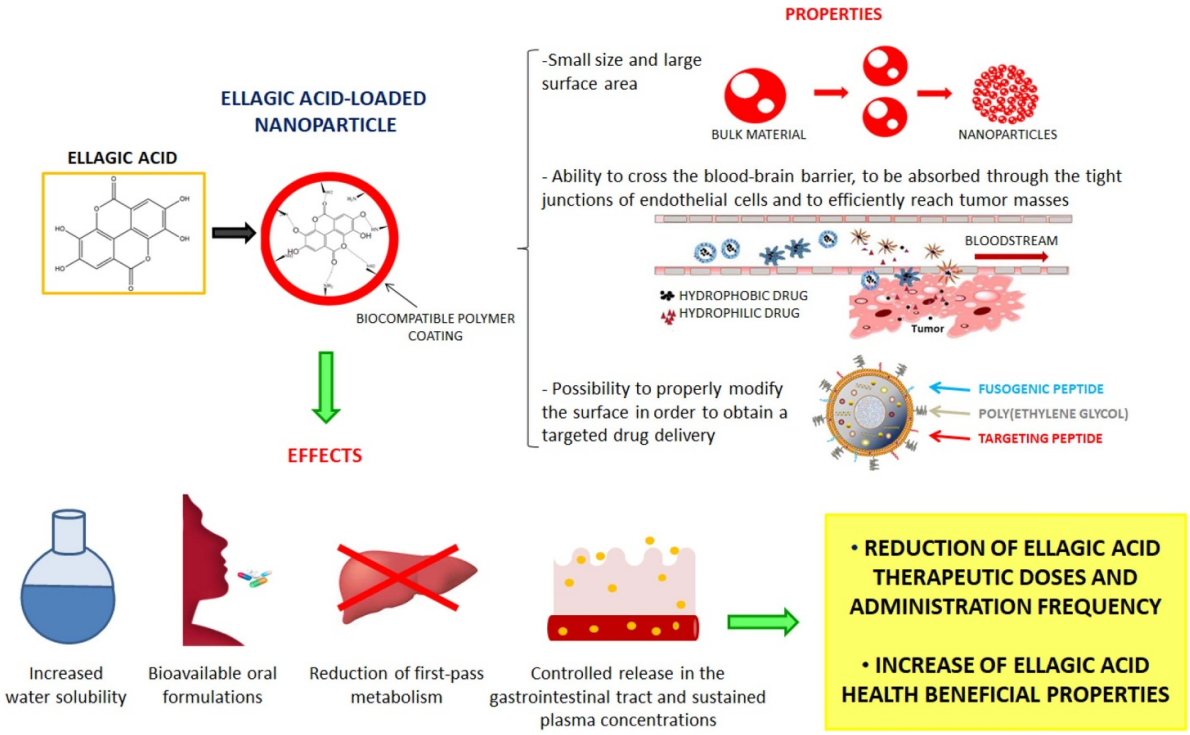

Figure 3. Correlation between the EA encapsulating nanoparticles properties, the enhancement of EA water solubility, and the improvement of its pharmacokinetic profile.

biocompatible polymers have been used in formulations aimed at increasing patient adherence [78, 79], for example by covering unpleasant tastes and odours. Furthermore, specific systems can be designed to achieve targeted drug release and control the active principle local release in the gastrointestinal tract.

Up to now, several EA micro- or nanoparticulate systems have been proposed, including microspheres [80–82], nanoparticles [83–88], pH-dependent microassemblies [89], nano-sized metalla-cages [90], zinc layered hydroxide nanohybrid [91] and nanogels [92], following different procedures such as emulsion–diffusion–evaporation [85, 86, 93], spray drying [62], co-precipitation [62], rotary evaporation [62] and ionic gelation [84] (figure 3).

In particular, many studies were aimed at developing drug delivery systems to achieve therapeutically relevant concentrations of EA in the bloodstream and potentiate its anticancer activity. Polymer-based nanoparticles, human bovine serum albumin-EA complexes encapsulated into thermosensitive liposomes [94], complexes with cyclodextrins [95], encapsulation within niosomes [96], and nano-sized metalla cages [90], molecular dispersion within dendrimers [97] are examples of drug delivery systems developed to reach these desirable goals [90, 95, 98] (figure 4).

2.2.1. Encapsulation within polymeric spheres Biopolymers have attracted great interest in the field of food and drug delivery systems, in particular for the preparation of micro-/nanocarriers [99, 100] aimed at increasing drug bioavailability [101], thanks to their specific uptake mechanism. Indeed, these devices are able to be taken up in the systemic circulation from the gastrointestinal tract by transcytosis [102] and to prevent the degradation and first-pass metabolism of the encapsulated drugs [78, 103]. In addition, they are able to sustain drug release in the plasma for longer time periods, thus allowing less frequent administration and reduction of potential drug side effects.

Among the several available biopolymers, CS and poly(d,l-lactic-co-glycolic acid) (PLGA) were widely employed for EA delivery (table 1).

Several studies reported encapsulation of EA within CS nanoparticles by ionotropic gelation. Spherical nanoparticles (average diameter size of 176 nm), with a drug-encapsulation efficacy of 94 $\pm$ 1.0% and a loading-efficiency of 33 $\pm$ 2.1%, were obtained [84]. The same authors observed a sustained release of EA from the nanoparticles and cytotoxic effects against the KB human oral epidermal cancer cell line, with very low IC_{50} values compared to free EA. In another study, EA-loaded CS nanoparticles induced rapid blood coagulation and clot retraction, suggesting a possible use as an effective anti-haemorrhagic system [104]. Moreover, similar nanoparticles inhibited hamster buccal pouch tumourigenesis induced by 7,12-dimethylbenz(a)anthracene (DMBA). This effect was attributed to the activation of both intrinsic and extrinsic apoptotic pathways, as a consequence of a sustained delivery of EA molecules [105].

In addition to CS, also chitin (Ch) and schizophyllan (SPG) were used to encapsulate EA [106]. The obtained Ch and SPG particles were characterized by a loading capacity of 79.52% and 30.08%, an average size of 39.82 nm and 217.8 nm and zeta potentials of -9.14 mV and $+27$ mV, respectively. EA release from both EA/SPG-NPs and EA/Ch-NPs

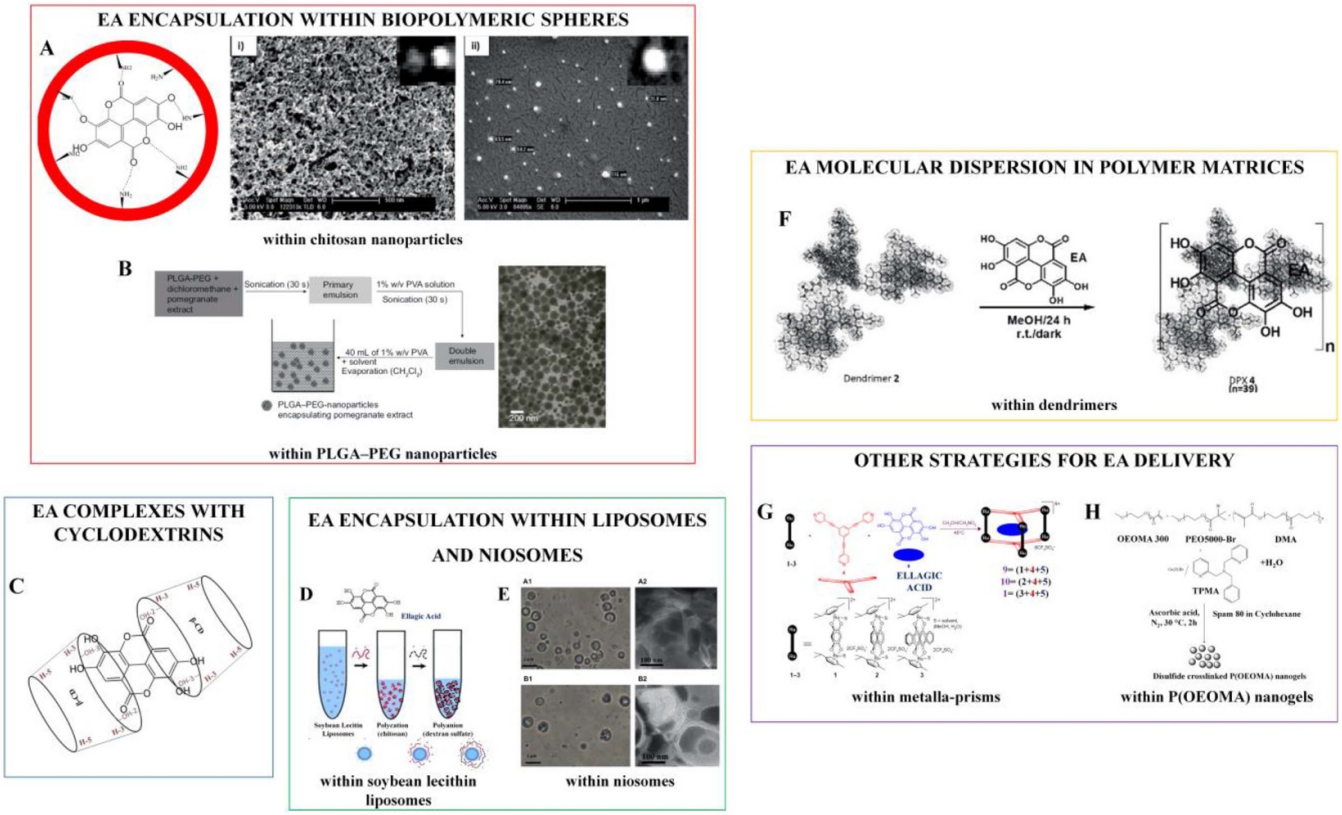

Figure 4. Possible EA carrier strategies. (A) EA encapsulation within CS nanoparticles; (B) EA encapsulation within PLGA–PEG nanoparticles; (C) EA inclusion within cyclodextrins; (D) EA encapsulation within soybean lecithin liposomes coated with biopolymers via layer-by-layer electrostatic deposition; (E) photomicrographs of EA-loaded niosomes containing 15% v/v PEG and 10% v/v DMSO (A1, A2) or 1% v/v NMP (B1, B2) ((A1, B1) acquired by optical microscope and (A2, B2) acquired by transmission electron microscopy); (F) EA molecular dispersion within dendrimers; (G) EA encapsulation within metalla prisma; (H) schematic representation of the synthesis of poly(oligo(ethylene oxide) methyl ether methacrylate) (P(OEOMA)) nanogels via inverse miniemulsion generated by atom transfer radical polymerization (ATRP). (A) Reprinted from [84], Copyright (2013), with permission from Elsevier. (B) Reproduced from [88]. CC BY 3.0. (C) Reprinted from [95], Copyright (2016), with permission from Elsevier. (D) Reprinted from [19], Copyright (2010), with permission from Elsevier. (E) Reproduced from [96]. CC BY 3.0. (F) Reproduced from [97] with permission of The Royal Society of Chemistry. (G) Reproduced from [90]. CC BY 3.0. (H) Reproduced from [92]. CC BY 3.0.

was higher in 96% ethanol than in different digestive system media (pH range 1.5–7.4). As expected, free EA presented greater scavenging activity compared to both EA/SPG-NP and EA/Ch-NP. However, EA/Ch-NPs showed higher activity than free EA at pH 7.4, whereas EA and EA/SPG-NPs scavenging activities decreased by raising the pH of the media. EA-loaded Ch and SPG NPs also inhibited the proliferation of MCF-7 breast cancer cells with IC_{50} values of 115 μg ml^{-1} and 60 μg ml^{-1}, respectively.

Another low-cost polysaccharide, karaya gum (KG), was used to encapsulate pomegranate-derived EA by the spray drying method. This application of KG was suggested by its complex and branched structure, emulsifier action, cohesive and adhesive properties. The obtained microcapsules (size between 1.69 and 4.55 μm) allowed to envisage potential applications in the food and pharmaceutical sectors [107].

Several studies were carried out to address the design and realization of PLGA particles loaded with EA [83, 86, 87, 93]. In an initial study, EA-loaded PLGA nanoparticles for oral administration were produced by emulsion–diffusion–evaporation, using PEG400 as a co-solvent to solubilize the drug and three different stabilizers [polyvinyl alcohol (PVA), didodecyldimethylammonium bromide (DMAB) and a mixture of PVA-CS in different relative ratios] [83]. The highest encapsulation efficiency (67.49% w/w) was obtained using PVA-CS 70:30, with average particle size of 500 nm, while the lowest encapsulation efficiency (41.73%) was revealed using DMAB. In detail, concerning the different PVA-CS ratios, it was observed that the zeta potential and the particle size increased with the CS amount, whereas the drug encapsulation efficiency decreased using PVA-CS 50:50. Since a better drug release can be obtained by using carriers characterized by low dimensions and high encapsulation efficiency, the PVA-CS 80:20 was identified as the optimal ratio to obtain a carrier that could allow the study of the influence of different initial drug loading amounts. A decrement of the drug encapsulation efficiency, associated to an increase of the particle size, was revealed with the increment of the initial drug loading from 5 to 15%. Successively, the same authors [93] produced EA-loaded nanoparticles using, in addition to DMAB, PVA/PVA-CS mixtures, and the same CS as a stabilizer. The use of DMAB as a stabilizer made it possible

Table 1. EA carrier systems: production process, physicochemical properties and biological effects.

	EA delivery system	Production process	Physico-chemical properties	Experimental model	Biological effect	Ref.
Poly-saccharides based systems	CS nanoparticles	Ionotropic gelation	-Good drug-encapsulation and loading-efficiency -Sustained drug release	Human oral epidermal carcinoma cell line (KB)	Anti-proliferative and pro-apoptotic activity	[84]
			-Initial rapid release of EA from chitosan matrix	Fresh whole rat blood	Anti-haemorrhagic activity	[104]
				DMBA-induced hamster buccal pouch oncogenesis model	Inhibition of tumour progression by apoptosis induction	[105]
	Ch nanofibers	Mixing and refrigeration	-EA loading capacity of 79.52% -Average size of 39.82 nm -Zeta potential of −9.14 mV -EA release higher in 96% ethanol than in different digestive system media (pH range 1.5–7.4) -Lower scavenging activity than free EA, except at pH 7.4	Human MCF-7 breast cancer cells	Growth inhibition (IC_{50} 115 μg ml^{-1})	[106]
	KG microcapsules	Spray drying	-Size between 1.69 and 4.55 μm	–	—	[106]
	SPG nanoparticles	Inverse emulsion (water-in-oil (w/o)) method	-EA loading capacity of 30.08% -Average size of 217.8 nm -Zeta potentials of +27 mV -EA release higher in 96% ethanol than in different digestive system media (pH range 1.5–7.4) -Decrease of EA and EA/SPG-NP scavenging activities by increasing pH	Human MCF-7 breast cancer cells	Growth inhibition (IC_{50}: 60 μg ml^{-1})	[107]
Polyesters based systems	PLGA nanoparticles	Emulsion-diffusion-evaporation technique	-Spherical and homogeneous nanoparticles -High encapsulation efficiency -Influence of the used stabilizer on the particle size, encapsulation efficiency and zeta potential -Decrement of the drug encapsulation efficiency, associated to an increase of the particle size and size distribution	A cell free system	–	[83]

Table 1. (Continued)

	EA delivery system	Production process	Physico-chemical properties	Experimental model	Biological effect	Ref.
	PLGA nanoparticles	Emulsion-diffusion-evaporation technique	-Different dimension and zeta potential on the basis of the used stabilizer -Rapid initial release of EA -Successive slower sustained release -Release rate increment in the following order: PVA > PVA–CS > DMAB, on the basis of the used stabilizer	-*In vivo* tests in rats -Yeast cell culture and a cell free system	–75, 73 and 87% of intestinal permeation in rats, using PVA, PVA–CS blend and DMAB as stabilizer, respectively -Good free radical scavenging effect	[83]
	PLGA and PCL nanoparticles	Emulsion-diffusion-evaporation technique	-Influence of the used stabilizer (i.e. DMAB, PVA) on the particle size and encapsulation efficiency -Faster EA *in vitro* release in the case of PVA-stabilized particles -Remarkably higher EA intestinal uptake in the case of DMAB-stabilized nanoparticles	*In vivo* tests in rats	-Improved EA oral bioavailability -Ability to prevent cyclosporine A-induced nephrotoxicity at 3-fold lower dose compared to free EA suspension -Antioxidant properties	[93]
	PLGA nanoparticles with the co-encapsulation of EA and coenzyme Q_{10} (CoQ_{10})	Emulsion technique	-Improved antioxidant properties compared to the suspension formulation	*In vivo* tests in rats	-Improved efficacy of EA and coenzyme Q10 in high fat diet induced hyperlipidaemia -More effective at 3-fold lower dose in reducing cholesterol, glucose and triglycerides levels and in improving endothelial function than the free compounds	[86]
	PCL nanoparticles	Emulsion-diffusion-evaporation technique	-High loading efficiencies -Diffusion-based release	Human colon cancer cell lines (Caco-2 and HCT-116)	-Cancer cells uptake -Reduction of cell viability -Enhancement of oral bioavailability *in vivo*	[87]
NIPAAm-PEG acrylate polymeric based systems	NIPAAm-PEG acrylate dual-loaded core shell nanoparticles	Membrane dialysis method	-Particle size between 140 ± 2 nm and 230 ± 3 -Entrapment efficiencies of total drug (paclitaxel and EA), paclitaxel, and EA of 80%, 62.3%, and 37.7%, respectively -Controlled *in vitro* release of the two drugs over a longer period of time at a higher temperature	MCF-7 breast cancer cell line	-Very high cellular uptake -Higher cytotoxicity than free EA	[108]

Table 1. (Continued)

	EA delivery system	Production process	Physico-chemical properties	Experimental model	Biological effect	Ref.
Blend systems	PLGA–PEG nanoparticles	Double emulsion–solvent evaporation method	–	Human breast cancer cell line (MCF-7)	-Nanoparticles intracellular uptake -Cancer cell growth inhibition	[108]
	CS functionalised PLGA and CS- PEG decorated PLGA nanoparticles	Oil-in-water (o/w) single emulsion solvent evaporation method	-PLGA-CS-PEG as optimal nanoprototype -Average diameter in the range 150–300 nm	Human hepatocellular carcinoma (HepG2) and colorectal cancer (HCT-116) cell lines	Potentiation of apoptosis-mediated cancer cell death	[88]

to obtain more stable, monodispersed particles with lower dimensions (average diameter of 148.5 nm) and higher zeta potential values as compared to the use of PVA (average diameter 269.7 nm) and PVA-CS (average diameter 359.6 nm in the case of PVA-CS 80:20). Concerning EA release from nanoparticles in pH 7.4 phosphate buffer, it was rapid at the beginning and presented a successive slower sustained profile, with the following order: PVA > PVA-CS > DMAB. The slowest release rate from the PLGA-DMAB particles was ascribed to higher DMAB hydrophobicity with respect to PVA, whereas in the case of PVA-CS, it was due to the CS insolubility at alkaline pH. The analysis of the *in situ* intestinal permeability of free EA and EA encapsulated within PLGA nanoparticles in rats revealed a 66, 75, 73 and 87% permeation rate in the case of free EA or encapsulated EA using PVA, PVA-CS and DMAB, respectively [93].

Encapsulation of EA was also performed within PLGA and polycaprolactone (PCL) nanoparticles, following a comparable procedure (emulsion-diffusion-evaporation method, using DMAB and PVA as stabilizers, and PEG400 as co-solvent for EA solubilization) [86]. The type of used stabilizer strongly affected the particle size and encapsulation efficiency: particles with ~120 or ~290 nm average diameter and ~50% or ~60% encapsulation index were obtained with DMAB and PVA, respectively. The same particles were able to sustain EA release in phosphate buffer *in vitro* over a period of 20 days and the release was faster from PVA-stabilized particles. *In situ* permeation studies in a rat model showed a remarkably higher EA intestinal absorption in the case of DMAB-stabilized nanoparticles, compared to PVA-stabilized particles. Finally, the designed nanoparticles prevented cyclosporine A-induced nephrotoxicity in rats at a three-fold lower dose than free EA suspension, due to the improved EA oral bioavailability and maintained antioxidant properties.

The co-encapsulation of two antioxidants, i.e. EA and coenzyme Q10 (10% w/w with respect to polymer) within PLGA nanoparticles (average diameter size of 260 nm) was also proposed [87]. In particular, the possible synergism between EA and coenzyme Q10 was investigated, in terms of beneficial effects on hyperlipidemia in high-fat diet fed rats. After 2 weeks of treatment, the nanoparticulate strategy seemed more promising and better performing than the oral suspension formulation of the same combination. In fact, the nanoparticles were equally or more effective at a three-fold lower dose in decreasing cholesterol, glucose and triglycerides levels and in stimulating endothelial functions.

Another polyester widely employed for the production of drug delivery particles, mentioned above in combination with PLGA, is PCL. EA-loaded PCL nanoparticles (average diameter size of 193 nm), with high entrapment and loading efficiencies, were produced by means of the emulsion–diffusion–evaporation technique [109]. *In vitro* cellular uptake and nuclear localization of these nanoparticles was demonstrated through fluorometric imaging in Caco-2 and HCT-116 human colon cancer cells. Moreover, the EA-containing nanoparticles were more cytotoxic (6.9-fold) than the free EA molecule. Oral administration of EA-loaded nanoparticles to New Zealand white rabbits resulted in a significant increase of the absorption rate and AUC (3.6-fold), compared to free EA.

Even the combination of different polymers to encapsulate poorly soluble drugs has been extensively investigated [88, 98, 110]. For instance, PLGA–PEG nanoparticles were proposed as carriers of pomegranate extract or individual polyphenols, such as punicalagin or EA, by using the double emulsion–solvent evaporation method. This method led to the production of spherical monodispersed nanoparticles with an average diameter of 150–200 nm [88]. The resulting EA-loaded nanoparticles were efficiently taken up by MCF-7 human breast cancer cells, with a maximum uptake at 24 h, and showed enhanced anti-proliferative effects (from 2 to 12-fold), compared to free EA.

In another study, CS and CS-PEG decorated PLGA nanoplatforms were investigated as carriers not only for EA, but also for two other bioactive compounds, i.e. quercetin and gallic acid, in order to protect them from phagocytosis and ensure their delivery to the target site [98]. The PLGA-CS-PEG nanoprototype (average diameter in the range 150–300 nm) was identified as the optimal one. In fact, this delivery system remarkably decreased the EA IC_{50} values in HepG2 human hepatocellular carcinoma cells. In particular, no change in EA IC_{50} value was detected when delivered through PLGA nanoparticles, while a 1.5- and 2.7-fold decrease was observed for EA-encapsulated PLGA-CS and PLGA-CS-PEG nanoparticles, respectively, thus evidencing that the functionalization with CS and PEG improved EA cell penetration.

Other authors developed dual-loaded core shell nanoparticles (particle size between 140 ± 2 nm and 230 ± 3 nm), based on the temperature-sensitive amphiphilic copolymer poly(*N*-isopropylacrylamide) (NIPAAm))-PEG acrylate, loaded with the chemotherapeutic agent paclitaxel and EA by membrane dialysis method [108]. The entrapment efficiencies of the drug combination, paclitaxel, and EA were of 80%, 62.3%, and 37.7%, respectively. Furthermore, nanoparticles showed a controlled and improved *in vitro* drug release over a longer period of time at a higher temperature. This co-delivery system also displayed very high cellular uptake that resulted in increased cytotoxicity against MCF-7 cells, in comparison to paclitaxel used as single agent; furthermore, it is likely that such nanoparticles might also represent a suitable strategy to overcome efflux-mediated drug resistance.

2.2.2. Complexes with cyclodextrins Many authors have used cyclodextrins, a family of cyclic oligosaccharides, in order to obtain complexes with EA (table 2). For example, methylated cyclodextrin inclusion complex allowed the enhancement of EA levels more than twice in the lung tissue, supporting the possibility of increasing its bioavailability by microencapsulating substances [111]. The use of methyl-β-cyclodextrin (Me-β-CD) as a carrier increased EA levels in plasma (7-fold) and pancreas (5.8-fold) of the treated rats, compared to the treatment with free EA, suggesting improved bioavailability and tissue distribution [112].

Another study evaluated the influence of β-cyclodextrin (β-CD) microspheres loaded with EA on the growth of HepG2 cells, demonstrating a dose- and time-dependent inhibition of cell proliferation, due to DNA damage and apoptosis [82]. Consistently, EA-loaded β-CD microspheres enhanced the antioxidant activity of EA and preserved its antimicrobial effects [115].

The EA-hydroxypropyl-β-CD inclusion complex, obtained with the mechanism of inclusion complexation through the freeze-drying method, also appeared to be a promising strategy to increase the anti-inflammatory/antioxidant activity of EA. This complex exerted a significant antioxidant activity on carrageenan-induced rat paw oedema [114] and anti-arthritis activity in a rat model, with reduction of hyperalgesia, oxidative stress and pro-inflammatory cytokines levels [113]. Remarkably enhanced EA solubility and *in vitro* dissolution by complexation with β-CD with respect to free EA were also evidenced [95]. Moreover, the complexation with β-CD positively influenced EA *in vitro* anti-inflammatory effects by protecting cells from protein denaturation and membrane lysis [95, 114].

EA-loaded β-CD NPs were proposed as an alternative antiprotozoal agent [116]. Indeed, the authors demonstrated the growth-inhibitory action *in vitro* against four *Babesia* species and *Theileria* parasites, and the chemotherapeutic efficacy *in vivo* in mice against *B. microti*. The cytotoxicity was evaluated in *in vitro* tests with Madin-Darby bovine kidney (MDBK), mouse embryonic fibroblast (NIH/3T3) and human foreskin fibroblast (HFF) cell lines, evidencing that EA loaded β-CD NPs were able to influence the cell viability with a half-maximal effective concentration (EC_{50}) higher than 800 μM.

Recently, a pomegranate EA-hydroxypropyl-β-CD inclusion complex was prepared by the stirring-ultrasonic method. This complex was able to inhibit *S. aureus* (Gram-positive bacterium) and *E. coli* (Gram-negative bacterium) growth, with an EA dose-dependent profile [117].

Thus, considering all the collected data, it is possible to conclude that cyclodextrins could be suitable delivery systems to improve EA bioavailability.

2.2.3. Encapsulation within liposomes and niosomes Liposomes consist of spherical bilayer vesicles formed by dispersion of polar lipids in aqueous solvents. Recently they have been largely utilized in biomedical, food and agricultural industries as carrier systems for both water and oil-soluble molecules, such as antimicrobials, flavours, antioxidants and bioactive agents [118]. The use of phospholipids from natural sources is gaining a lot of attention, since it allows a remarkable reduction in production costs with respect to synthetic phospholipids, thus favouring large-scale industrial applications. Reports about the use of liposomes for EA encapsulation are summarized in table 3.

Unfortunately, liposomal systems tend to leak and lose the encapsulated components over time [121] and undergo gradual coalescence, particularly in low pH environments, which reduce surface charges [122]. Thus, in an attempt to overcome these drawbacks, soybean lecithin liposomes were coated with alternating layers of positively charged CS and negatively charged dextran, by means of layer-by-layer electrostatic deposition [19]. The obtained spherical monodispersed nanoparticles with four bilayers of biopolymers presented an apparent hydrodynamic diameter of 386.5 ± 25.9 nm and surface charge of −30.66 ± 1.55 mV. This system showed better thermal and pH stability, as well as better release properties, good encapsulation efficiency and sustained release of EA [19]. Moreover, thermosensitive liposomal particles have been produced, for the co-delivery of nab-paclitaxel (paclitaxel bound to human serum albumin) and human serum albumin–EA complexes, improving drug blood retention and tumour growth inhibition *in vivo*. Indeed, after achieving the locally heated tumours, these systems rapidly release the complexes, facilitating their accumulation and matrix penetration [94].

Lately, niosomes have been considered as an efficient alternative to the liposomal drug carriers for the encapsulation of several biomolecules [123], including EA (table 3). They consist of vesicular colloidal drug carriers obtained by the self-assembly of non-ionic surfactants into vesicles, resembling the liposomes architecture [124]. This kind of carrier has been mainly exploited as dermal and transdermal drug delivery system [125–128]. EA-loaded niosomal formulations, obtained by using the reverse phase evaporation method, with Span 60, Tween 60, their mixtures and cholesterol as surfactants/vesicle forming agents, solulan C24 as steric stabilizer, and PEG400, propylene glycol or methanol as solubilizer, were designed for dermal delivery. The obtained spherical multilamellar vesicles showed a good percentage of entrapment efficiency [96, 120] and were stable after four months of storage at 4 °C

Table 2. Cyclodextrin complexes: physicochemical properties and biological effects.

Complex	Physico-chemical properties	Experimental model	Biological effect	Ref.
Methylated cyclodextrin inclusion complex	–	*In vivo* tests in mice	Two-fold increment of EA level in the lung tissue	[111]
Methyl-beta-cyclodextrin (Me-β-CD) complex	–	*In vivo* tests in rats	-Increment of EA level up to 5.8-fold in the pancreas -Increment of EA plasma levels up to 7-fold -Higher EA content in the duodenum	[113]
Hydroxypropyl-β-CD complex	–	*In vivo* tests in rats	Anti-arthritis activity by attenuation of hyperalgesia, oxidative stress and pro-inflammatory cytokines	[112]
Hydroxypropyl-β-CDcomplex	–	*In vivo* tests in rats	Enhanced anti-inflammatory and anti-oxidant activity	[114]
β-CD complex	Remarkably enhanced solubility and *in vitro* dissolution of EA	Fresh whole human blood	Protection of erythrocytes from membrane lysis	[95]
β-CD microspheres	–	Human liver cancer cell line (HepG2)	Inhibition of tumour cells proliferation, DNA damage and p53 up-regulation	[82]
β-CD and (2-hydroxypropyl)-β-CD complexes	-Rapid release of EA in the aqueous medium at 25 °C -Enhanced EA water solubility -Higher EA stability -Enhanced antioxidant activity	Fungi, gram-negative and gram-positive bacteria	Preservation of the antimicrobial activity	[115]
β-CD nanoparticles	–	Madin-Darby bovine kidney (MDBK), mouse embryonic fibroblast (NIH/3T3) and human foreskin fibroblast (HFF) cell lines	-Growth-inhibitory action *in vitro* against four *Babesia* species and *Theileria* parasites -Chemotherapeutic efficacy *in vivo* against *B. microti* -Cytotoxicity with a half-maximal effective concentration (EC_{50}) higher than 800 μM	[116]
Hydroxypropyl-β-CD inclusion complex	–	*S. aureus* and *E. coli*	Ability to inhibit bacteria growth, with an EA dose-dependent profile	[117]

[96]. Furthermore, in an *in vitro* skin permeation and distribution test, the niosomes delivered higher EA amounts into the deeper layer of the skin, as compared to free EA [120]. DMSO or NMP, tested as skin penetration enhancers, improved the EA entrapment efficiency and the EA permeation through the human skin from the EA-loaded niosomes [96]. In particular, DMSO made it possible to achieve the highest EA amount in the epidermis (penetration depth between 30–90 μm); conversely, NMP led to the highest EA amount in the acceptor medium resembling the skin condition, i.e. a mixture of isotonic phosphate buffer pH 5.5 and isopropyl alcohol (ratio 90:10, % v/v), and could be used for EA dermal delivery (penetration depth of 90–120 μm).

Recently, nanoliposomes have been tested as EA carriers to prevent its degradation and improve its antioxidant properties [119]. EA encapsulated within nanoliposomes demonstrated a higher ability to prevent *in vitro* lipid peroxidation than free EA, and *in vivo* experiments evidenced that both free EA and encapsulated EA were able to avoid rat liver damage induced by the alkylating agent cyclophosphamide.

2.3. Ellagic acid molecular dispersion in polymer matrices

Molecular dispersion within polymer matrices (amorphous solid dispersion, ASD) is considered another appealing modality to increase drug oral bioavailability [129, 130]. Taking into account that low water solubility can be ascribed to high melting temperature and, thus, high crystallinity, it is expected that embedding EA in the metastable amorphous state within a polymer matrix would successfully improve its bioavailability. Effective ASD delivery systems should be able to stabilize the released drug against crystallization even under supersaturated concentrations, as it occurs in the gastrointestinal tract. Thus, the polymer to be used for ASD device must have proper water solubility at least in the g ml^{-1} range.

Table 3. Liposomal/niosomal systems: physicochemical properties and biological effects.

EA liposomal/niosomal system	Physicochemical properties	Experimental model	Biological effect	Ref.
Soybean lecithin liposomes coated with alternating layers of positively charged chitosan and negatively charged dextran	-Better thermal stability -Better pH stability and release properties	A cell free system	–	[19]
Thermosensitive liposomes for co-delivery of human serum albumin-paclitaxel and human serum albumin-EA complexes		Murine pancreatic cancer	Strong tumour growth inhibition and apoptosis *in vivo*, in combination with heat	[94]
Nanoliposomes	-Improved stability -Enhanced antioxidant properties -Higher ability to prevent *in vitro* lipid peroxidation than free EA	–	Ability to prevent rat liver damage induced by cyclophosphamide for both free EA and encapsulated EA in *in vivo* experiments and increased hepato-protective action against cyclophosphamide-induced liver damage	[119]
Niosomes	-Spherical multilamellar vesicles with polydispersity index (PI) values lower than 0.4 -High entrapment efficiency -Delivery of higher amount of EA into the skin deeper layer compared to free EA solution -Improvement of EA entrapment efficiency, depending on the used skin penetration enhancers (i.e. DMSO and NMP)	*Ex vivo* human epidermis and underlying dermis	Improved skin permeation and entrapment compared to free EA	[96, 120]

Drug solid dispersions within polymers are usually prepared starting from a solution by means of different technologies, such as freeze-drying, spray-drying, co-precipitation, rotary evaporation and film casting, or by co-extrusion. The commonly used polymeric matrices are hydrophilic polymers, including the hydrosoluble polyvinylpyrrolidinone (PVP), water-swellable and/or dispersible polymers like cellulose acetate phthalate [131], hydroxypropylmethylcellulose acetate succinate (HPMCAS) [132], and carboxymethylcellulose acetate butyrate (CMCAB) [133, 134]. Also cellulose-carboxyalkanoates have been proposed as crystallization inhibitors [135, 136] and ASD polymers [137, 138], due to their acceptable toxicity profile, high glass transition temperatures, and the ability of the pendent carboxyl group to trigger pH-influenced drug release and generate strong hydrogen bonding with the drug.

Different carboxyl-containing cellulose derivatives [i.e. the relatively hydrophobic CMCAB, the highly hydrophobic cellulose acetate adipate propionate (CAAdP), and the hydrophilic HPMCAS] were tested for their ability to form ASDs with EA (up to 25 wt. %) [59]. The EA dissolution from ASDs was then compared to that obtained from pure crystalline EA and EA/PVP solid dispersions [59], taking into account that these polymers present different abilities to solubilize EA from ASDs (e.g. at pH 6.8 PVP » HPMCAS » CMCAB). The investigated ASDs demonstrated a remarkably better stability towards crystallization and EA concentrations in comparison with pure crystalline EA. The cellulose derivative ASDs also showed extremely slow (<4%) EA release at pH 1.2 and faster, though incomplete, drug release at pH 6.8 (up to 35% for HPMCAS solid dispersions). Among the different carboxyl-containing cellulose derivatives, HPMCAS most effectively stabilized EA towards chemical degradation and recrystallization in solution. Indeed, the release from ASDs in pure CAAdP or CMCAB was extremely slow and did not guarantee sufficient EA dissolution, whereas release from the more hydrosoluble polymers (PVP and HPMCAS) made it possible to achieve very high EA concentrations. However, EA was dissolved from ASD in PVP rapidly and almost completely (up to 92%) at pH 6.8, but was also released at pH 1.2, with

consequent fast recrystallization. Thus, HPMCAS was identified as the most promising matrix for EA amorphous solid dispersion, stabilization, solubilization, and bioavailability improvement.

Alfei *et al* [97] prepared other three different ASD based formulations: (i) EA solid microdispersion, characterised by 22% w/w drug loading, and a 30-fold improved water solubility, as well a marked radical scavenging activity, using water and low methoxylated pectin as food compatible excipient, by means of spray drying technology; (ii) EA nanodispersions (60–70 nm) using a strongly hydrophilic dendriplex, containing non-polyamidoamine; (iii) an amphiphilic dendriplex with 46 and 53% w/w drug loading and good antioxidant power. The EA solubility improvement was remarkably greater than that observed before, with an increment of 300–1000-fold in water and of 75-fold in ethanol, suggesting consequent enhanced bioavailability, and good antioxidant power.

2.4. Other strategies for EA delivery

In addition to the previously described approaches (i.e. encapsulation, complexation and dispersion), further strategies have been proposed in order to enhance the EA bioavailability and therapeutic action. For example, Montes *et al* [139] produced EA microparticles by a supercritical antisolvent process, followed by a successive co-precipitation with eudragit as a coating agent. These EA microparticles dissolved more rapidly than raw EA, faster in simulated gastric juice than in simulated intestinal fluid. The co-precipitates of EA and eudragit resulted in spherical microparticles of eudragit, surrounding sticks and flowers of EA, characterized by a quicker release of EA with respect to only EA made microparticles.

Micronization of EA was found to increase its solubility, by means of anti-solvent precipitation process, with NMP as solvent and deionized water as anti-solvent; a following lyophilization process was carried out in order to obtain a freeze-dried powder. The resulting submicrometric EA powder (m-EA; mean particle size of 429.2 $\pm$ 7.6 nm) was characterized by the same chemical structure of raw EA, but with greatly reduced crystallinity and higher 2,2-diphenyl-1-picrylhydrazyl radical scavenging activity. Moreover, m-EA presented dissolution rate, solubility and bioavailability approximately 2-, 6.5- and 2-fold higher, respectively, compared with orally administered EA, and its physical stability was demonstrated through x-ray diffraction measurements [140]. Thus, the anti-solvent precipitation method was recognized as a promising strategy, since it is rapid, needs low equipment requirements, and can be easily scaled up, with respect to the processes commonly used for EA encapsulation, such as emulsion–diffusion–evaporation [83, 85, 86], spray drying [59], co-precipitation [59], rotary evaporation [59] and ionic gelation [84] methods.

EA NPs, produced by means of antisolvent precipitation using a syringe pump (APSP) method, were also demonstrated to be able to enhance EA solubility and bioavailability. Needle-shaped or rod-like crystal structures with a good dispersion [116] were obtained and showed growth inhibition only on HFF cells, with an EC_{50} value of 790 $\pm$ 5.4 μM, but not on the other tested models, i.e. MDBK and NIH/3T3 cell lines.

Some authors proposed the use of gel carriers for EA delivery (table 4). A CS/β-glycerophosphate thermo-sensitive gel was produced to encapsulate EA and its antitumour effects on brain cancer cells (human U87 glioblastoma and rat C6 glioma cell lines) was investigated. Results suggested that gels containing 1% EA (w/v) significantly reduced glioma cell viability and increased the EA release rate by 2.5-fold [110]. Biodegradable disulfide crosslinked PEG-based nanogel (poly(oligo(ethylene oxide) methyl ether methacrylate)) [P(OEOMA)], synthesized via AGET (activator generated electron transfer) and ATRP (atom transfer radical polymerization), was employed to encapsulate EA (10–20 wt. %) [92]. The average size increased from 144.6 $\pm$ 39.5 nm for neat nanogels to 217.8 $\pm$ 105.5 and 633 $\pm$ 160.1 nm with the EA amount, at the lowest and highest drug loading level, respectively. The encapsulation efficiency was about 25% and 23.5% for EA stoichiometric amounts of 10 and 20 wt. %, respectively, and the radical scavenging activity of the nanogels was demonstrated using the HeLa human cervical cancer cell line.

Also EA–phospholipid complexes based on the self-nanoemulsifying drug delivery system (SNEDDS), by an anti-solvent, with a mean globule size of 106 $\pm$ 0.2 nm and cloud point at 83–85 °C, showed improved EA lipophilicity, higher oral bioavailability, *in vitro* drug release, and permeation in *ex vivo* studies, with respect to EA suspension [141].

Similarly, an innovative food-grade EA based self-nanoemulsifying system (EA-SNEDS), based on 45 wt.% PEG, 45 wt.% polysorbate, 10 wt.% caprylic/capric triacylglycerol, was developed [142] and characterized by a mean droplet size of around 120 nm, for potential applications in dietary supplements and functional foods. Pharmacokinetic studies in the rat model indicated that the EA oral bioavailability was enhanced 6.6- and 3.2-fold with respect to aqueous suspensions and pomegranate extract, respectively.

Another strategy to improve the EA solubility is represented by the development of supersaturatable self-microemulsifying drug delivery system (S-SMEDDS). Zheng *et al* [143] proposed a 10% ethyl oleate, 67.5% Tween 80, 22.5% PEG400, 0.5% PVP K30 and 4 mg g^{-1} EA S-SMEDDS, obtaining spherical particles with a droplet size of about 40 nm. Faster dissolution and quicker EA release from S-SMEDDS than from SMEDDS were revealed in *in vitro* dissolution studies. Furthermore, the EA-loaded S-SMEDDS showed remarkably higher *in vitro* and *in vivo* antioxidant abilities than free EA at the same concentrations. This interesting experimental evidence was ascribed to the use of a small amount of PVP K30 as precipitation inhibitor, since it was able to efficiently avoid EA nucleation.

Very recently, micellar nanodelivery tools, based on D-α-tocopheryl polyethylene glycol succinate (TPGS), were formulated for EA distribution by using a film-hydration method

Table 4. Other strategies for EA delivery.

EA delivery system	Production process	Physico-chemical properties	Experimental model	Biological effect	Ref.
CS/β-glycerophosphate (thermo-sensitive gel)	Dialysis	Increment of EA release rate by 2.5-fold in the presence of lysozyme	Brain cancer cells (U87 human glioblastoma cell line and C6 rat glioma cells)	Inhibition of cancer cell growth in a concentration-dependent manner	[110]
Biodegradable disulfide crosslinked PEG-based nanogels	AGET (activator generated electron transfer) and ATRP (atom transfer radical polymerization)	-Increase in nanogels size with the EA amount -Quite good encapsulation efficiency (23–25%)	Human cervical cancer cell line (Hela)	-No cytotoxicity -Radical scavenging ability	[92]
Nano-sized metalla prisms	Self-assembly	–	Human hepatocellular (SK-hep-1), gastric (AGS) and lung (A549) carcinoma cell lines	Macrophage-dependent anticancer activity through modulation of cytokine expression (G-CSF and Rantes)	[90]
Submicrometric EA powder	Anti-solvent precipitation process, followed by lyophilization	-EA powder physical stability -Greatly reduced crystallinity with respect to raw EA	*In vivo* EA plasma concentration in rats	-Dissolution rate, solubility and bioavailability approximately 2-, 6.5- and 2-fold higher, respectively, compared to free EA	[140]
EA–phospholipid complexes	Anti-solvent method	-Improved EA lipophilicity -Higher *in vitro* EA release	*Ex vivo* tests on rat stomach and small intestine	-Higher EA oral bioavailability and increased permeation	[141]
EA microparticles	Supercritical antisolvent process, with a subsequent coprecipitation,	-Faster EA dissolution from EA microparticles than raw EA and in simulated gastric fluid than in simulated intestinal fluid -Quicker release of EA from the co-precipitates of EA and eudragit with respect to EA microparticles	A cell free system	–	[139]
EA nanoparticles	Antisolvent precipitation using a syringe pump (APSP) method	-Needle-shaped or rod-like crystal structures -Good dispersion	Four *Babesia* species and *Theileria* parasites -*B. microti in vivo* chemotherapeutic efficacy in mice -Madin-Darby bovine kidney (MDBK), mouse embryonic fibroblasts (NIH/3T3) and human foreskin fibroblasts (HFF)	-High antiprotozoal activity *in vitro* -High chemotherapeutic efficacy *in vivo* -Growth inhibition on HFF with an EC_{50} value of 790 $\pm$ 5.4 μM	[116]
EA/PEG/polysorbate/caprylic/capric triacylglycerol self-nanoemulsifying system	Self-emulsion	-Mean droplet size of around 120 nm -Enhanced EA oral bioavailability (6.6- and 3.2-fold with respect to aqueous suspensions and pomegranate extract, respectively)	*In vivo* studies in rat	–	[142]
Self-nanoemulsifying drug delivery system (SNEDDS), based on the phospholipid complex technique	–	-Enhanced lipophilicity -Mean globule size: 106 $\pm$ 0.2 nm -Cloud point: 83–85 °C -Increasing drug loading	*Ex vivo* tests on rat stomach and small intestine	Increased permeability compared to free EA	[141]

Table 4. (Continued)

EA delivery system	Production process	Physico-chemical properties	Experimental model	Biological effect	Ref.
		-Higher *in vitro* drug release and permeation compared to EA suspension -Enhanced EA release and oral bioavailability			
EA/ethyl oleate/Tween 80/PEG400%/PVP K30S-SMEDDS	Self-emulsion	-Spherical particles with a droplet size of about 40 nm -Faster EA dissolution and release -Remarkably higher *in vitro* and *in vivo* antioxidant abilities than free EA at the same concentration	–	–	[143]
Micellar nano-delivery tool for EA, based on D-α-tocopheryl polyethylene glycol succinate (TPGS)	Film-hydration method	-Spherical nanoparticles (diameter of 113.2 $\pm$ 23 nm, PDI of 0.260 $\pm$ 0.038) -Drug-encapsulation efficiency of 88.67% $\pm$ 3.21 -Sustained *in vitro* release profile in phosphate-buffer saline	Human ovarian cancer cells (OVACR3 cell line)	-Enhanced EA bioavailability, and anticancer activity -Higher cytotoxicity than free drug and TPGS, with a dose dependent profile (IC_{50} value of 12.36 μM) -Ability to inhibit the G1 phase of cell cycle, inducing cancer cells apoptosis	[144]
Lactoferrin–chondroitin sulfate nanocomplex for doxorubicin and EA targeted co-delivery	–	-Particles of 192.3 nm -Faster release of EA, followed by doxorubicin	Human A549 lung cancer cells	-Higher cytotoxicity and cell internalization mediated via Tf and CD44 receptors	[145].
EA loaded SLNs	Hot homogenization technique	-Particles with an average size of 96 nm and an encapsulation efficiency of 88% -A burst EA release in the first hours, followed by a sustained release until 72 h in *in vitro* drug release study	Human prostate cancer cell line (PC3)	Ability to inhibit cells growth in a lower IC_{50} value with respect to free EA (i.e. 61 μM *vs* 82 μM after 48 h and 51 μM *vs* 65 μM after 72 h, respectively)	[146]
EA and vancomycin loaded SLNs	Solvent evaporation-ultrasonication technique	-Particles of 164 nm, with a zeta potential of 14.2 mV -Vancomycin and EA entrapment efficiency of 35.6% and 94.8%, respectively	*In vivo* tests on a group of animals treated with vancomycin-EA SLNs and a control group (treated with free vancomycin)	Non-significant differences between levels of all tested kidney functions parameters (i.e. serum creatinine, urea, glucose, calcium, sodium, and potassium)	[147]

[144]. Spherical nanoparticles (diameter of 113.2 $\pm$ 23 nm, polydispersion index (PDI) of 0.260 $\pm$ 0.038) with a drug-encapsulation efficiency of 88.67% $\pm$ 3.21 were obtained and a sustained *in vitro* release profile, with 67.8% cumulative release within 12 h, was revealed in phosphate-buffer saline. The enhanced EA bioavailability and anticancer activity were demonstrated by the decreased fluorescence unit in ROS activity assay, and by *in vitro* tests with human ovarian cancer cells (OVACR3 cell line), evidencing higher cytotoxicity than that of free drug and TPGS, with a dose-dependent profile (IC_{50} value of 12.36 μM). It was postulated that the EA-loaded TPGS micelles were able to stop the G1 phase of the cell cycle, probably through the suppression of p15 and p21 genes expression and the induction of apoptosis.

Doxorubicin and EA loaded lactoferrin–chondroitin sulfate nanocomplexes were produced for the targeted drug co-delivery to lung cancer [145]. The obtained particles of

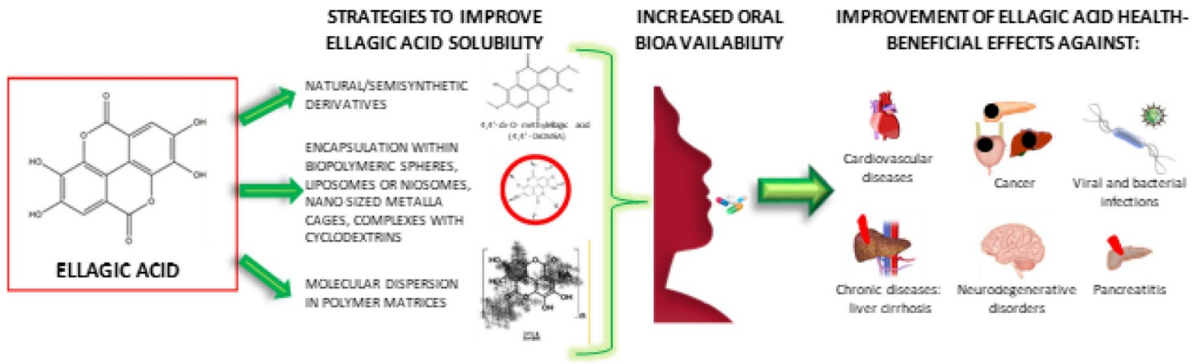

Figure 5. Proposed strategies to improve EA solubility, and, thus, its bioavailability and expected improvement of its health benefits.

192.3 nm showed a faster release of EA and higher cytotoxicity and internalization into A549 lung cancer cells, mediated via transferrin (Tf) and CD44 receptors.

Recently, solid lipid nanoparticles (SLNs) have been proposed as EA delivery systems [146, 147]. SLNs with an average size of 96 nm and an encapsulation efficiency of 88%, obtained by hot homogenization technique, improved EA bioavailability and anticancer activity against the PC3 human prostate cancer cell line [146]. In detail, a burst EA release in the first hours, followed by a sustained release until 72 h, was recorded by an *in vitro* drug release assay. Moreover, cytotoxicity tests demonstrated that EA-loaded SLNs were able to inhibit the prostate cancer cells growth at a lower IC_{50} value with respect to free EA (i.e. 61 μM *vs* 82 μM for 48 h and 51 μM *vs* 65 μM for 72 h, respectively). SLNs, produced by means of a solvent evaporation-ultrasonication technique, were employed for the co-delivery of EA and vancomycin loaded SLNs, in order to reduce/avoid nephrotoxicity of vancomycin, thanks to EA kidney protective action [147]. The obtained particles were characterized by particle size of 164 nm, zeta potential of 14.2 mV and vancomycin and EA entrapment efficiency of 35.6% and 94.8%, respectively. Through *in vivo* tests carried out on a group of animals treated with vancomycin-EA SLNs and a control group (treated with free vancomycin), non-significant differences between levels of all tested kidney function parameters (i.e. serum creatinine, urea, glucose, calcium, sodium, and potassium) were revealed. On the other hand, the group treated with free vancomycin presented remarkable differences in all tested parameters.

Finally, a non-polymeric system, based on the use of nano-sized metalla-cages, was also proposed [90]. Unlike free EA, EA encapsulated in metalla-prisms was able to induce cytotoxic effects in A549 human lung cancer cells and to modulate the expression levels of proteins involved in the immune response.

3. Concluding remarks and future perspectives

EA is a polyphenolic flavonoid present in different edible fruits and seeds, which exerts interesting pharmacological effects, such as protection against inflammation, diabetes, cardiovascular and liver diseases and cancer, as well as neurodegenerative disorders (figure 2).

EA occurs in nature as a free molecule or as complex polymers called ETs. After ingestion of polyphenols containing foods and beverages, a small amount of free EA is directly absorbed in the stomach. ETs, which are resistant to gastric metabolism, are hydrolysed in the small intestine. This intestinal uptake occurs by passive diffusion, based on a concentration gradient not involving specific transporters. Absorbed EA is then converted to inactive metabolites, which are eliminated through the urine 1–5 h after ingestion, while the unabsorbed EA is metabolized by the gut microbiota in the colon, giving a family of EA natural derivatives known as urolithins.

In general, low absorption and rapid elimination, i.e. poor bioavailability after oral administration, characterize EA pharmacokinetics. Moreover, the worldwide intake of EA in humans largely varies, but it is usually below the desirable levels to show clinical effects.

In such a context, several chemical derivatives or new EA delivery formulations have been proposed, including the encapsulation within nanocarriers and the molecular dispersion within polymer matrices, in order to improve the pharmacokinetic features and the therapeutic efficacy of EA (figure 5). Briefly, in recent years, several EA containing micro- or nanoparticulate systems have been developed, including microspheres, nanoparticles, pH-dependent microassemblies, nano-sized metalla-cages, zinc layered hydroxide nanohybrid and nanogels. The possibility to increase EA bioavailability and efficacy through nanotechnology-based delivery systems was demonstrated by several studies, supporting the hypothesis that the improvement in EA solubility is a feasible approach to enhance its oral bioavailability and, consequently, its therapeutic efficacy. However, the same studies have also highlighted the requirement of further and deeper investigation to validate this approach [98]. The use of nanocarriers can be considered a relatively innovative, recent and in continuous evolution nanotechnological approach, particularly as promising tools for cancer treatment [148]. However, a lot of challenges must be faced, and several criticisms have to be addressed, such as the biodistribution, the biocompatibility, the improvement of the localization, and the *in vivo* efficacy. Indeed, the real clinical application and commercialization of drug nanocarriers require an accurate analysis of the safety profile [77]; more studies focused on the cytotoxic aspects and

the comprehension of the underneath biological mechanisms are strictly required. The design of molecularly engineered biopolymers, as well as of smart materials, able to sense and selectively reply to specific physiological and biological signals, has been aimed at overcoming the remarkable limits of achieving efficient administration of therapeutics, promoting a controlled intracellular delivery of both hydrophobic drugs and macromolecular biotherapeutics, such as proteins and nucleic acids [76].

An attractive approach to be pursued in the future concerning the clinical applications of drug delivery systems loaded with EA is represented by the incorporation of tumour-targeting ligands on the particles surface [109]. Such a strategy should allow us to enhance the EA concentration at the tumour site after systemic administration, and, thus, to implement the EA clinical relevance. At the same time, the clinical application of such targeted systems could be prevented by the stability of nanomaterials, the development of multi-drug resistance, and the dysregulated accumulation of cancer cells [148]. For these reasons, new strategies have been and are actually being proposed, such as the obtainment of core–shell structures [108], and the coating/decoration of the nanoparticles shell with multiple chemically or physically active components to allow a targeted delivery of different drugs and combine their properties [94, 108, 145, 147].

Moreover, it would be very interesting to apply wireless technology to transdermally implantable drug delivery devices as a non-invasive strategy to allow the *in situ* release encapsulated drugs and molecules [149, 150], by using wirelessly controlled microchips, micropumps, microvalves, and magnetic robots [151].

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