Applications of Ellagic Acid and Its Derivatives

Subjects: Biochemical Research Methods

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Ellagitannins (ETs), characterized by their diversity and chemical complexity, belong to the class of hydrolysable tannins that, via hydrolysis under acidic or alkaline conditions, can yield ellagic acid (EA). They are mostly found as a part of extractives in angiosperms. As known antioxidants and chelators, EA and EA derivatives are drawing an increasing interest towards extensive technical and biomedical applications.

Keywords: ellagic acid ; ellagitannins ; urolithins ; antioxidant properties ; biological activity ; bioavailability

1. Introduction

Ellagic acid (EA) (**Figure 1**), belongs to the class of polyphenol extractives (tannins) widely spread among dicotyledons [1]. In plants, EA is predominately found ester-linked to sugars in the composition of hydrolysable tannins called ellagitannins (ETs). Among hydrolysable tannins, with more than a 1000 identified molecules, ETs form the largest group [2][3]. As other tannins, ETs are secondary metabolites of higher plants [2] and act as a part of the defense mechanism against microbial and animal attacks due to their astringent capacity and the ability to form complexes with proteins and polysaccharides [1]. During plant chemical processing, both under acidic or basic conditions, ester bonds of ETs are hydrolyzed, yielding a hexahydroxydiphenoyl (HHDP) group, which spontaneously lactonizes into the almost water-insoluble ellagic acid (EA).

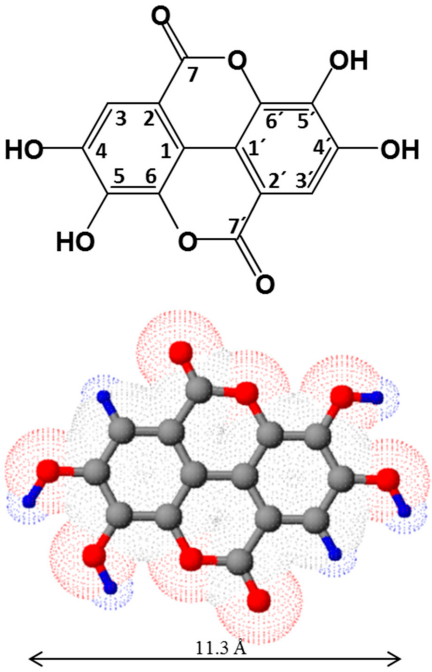

Figure 1. Chemical structure of ellagic acid.

Hydrolysable tannins have long been known for their use in leather tanning processes [1][4]. Nonetheless, today the growing interest in these compounds is mainly associated with the consumption and development of new products offering beneficial health effects linked to phenolic antioxidant properties [5]. Accordingly, owing to beneficial health effects against many oxidative-linked chronic diseases, including cancer and neurodegenerative diseases, EA has generated a noticeable scientific interest [6][7][8][9][10][11][12][13].

2. The Chemistry of Ellagic Acid and Ellagitannins

2.1. Structure and Physico-Chemical Properties of Ellagic Acid

Ellagic acid (EA), first noticed by Chevreul in the gallnut (noix de galle in french), was described in 1818 by Braconnot [14], who named the acid by reversing the word “galle” [15]. EA consists of a dimeric derivative of gallic acid with a molecular weight of 302.194 g/mol. According to IUPAC nomenclature, EA is identified as 2,3,7,8-tetrahydroxychromeno[5,4,3-cde]chromene-5,10-dione, though the most common designation in chemistry may be found based on diphenic acid classification (4,4′,5,5′,6,6′-hexahydroxydiphenic acid 2,6,2′,6′-dilactone). EA comprises four free OH groups and two acyloxy groups linked to a core of fused aromatic rings (**Figure 1**), keeping a near planar structure with molecular symmetry C_{2h} and crystallizing in the monoclinic cell, space group $P2_1/c$ [16]. EA dihydrate forms triclinic crystals representing characteristics of the *P*1 space group [17]. Concomitants and eventual metal complexes explain the variety of different crystalline groups of EA isolated from natural sources [18].

The assignments to proton and carbon resonances in NMR spectra of EA are widely reported [18][19]. Electron-donating groups enhance EA’s electron density, bestowing EA to participate in hydrogen bonding and π–π interactions. Thus, such characteristics are directly related to EA’s diversity in terms of practical uses. The four phenolic and two lactone groups form the hydrophilic part, while two phenyl rings represent the hydrophobic part, hence EA exhibits amphiphilic character (**Figure 1**). Given its low polarity, EA is only sparingly soluble in aqueous media (9.7 µg/mL at 37 °C) [20]. Meanwhile, the solubility of EA is increased substantially in methanol (671 µg/mL at 37 °C) [20]. EA’s high solubility in pyridine has also been documented [18][20]. The most promising results for pharmaceutical use include *N*-methyl pyrrolidone (skin penetration enhancer for transdermal use), polyethylene glycol 400 (vehicle for parenteral dosage forms) and triethanolamine (salt formation in injectable and topical preparations) with small amounts of water [20].

The free radical scavenging activity of phenolics is influenced by the pH of the surrounding medium [21]. EA can be partially or fully ionized, suggesting that ions could also be involved in the antioxidant activity and underlining the importance of EA protolytic equilibria studies. All four phenolic groups can suffer deprotonation, which would suggest four pK_a values. However, due to symmetric phenolic substituents in EA, usually two pK_a values assigned to 4-/4′-OH and 5-/5′-OH are referred. Simić and co-workers [22] clearly detected two acidity constants pK_{a1} and pK_{a2} of 5.42 and 6.76, respectively, confirming the diprotic nature of EA. Therefore, three different regions were recognized, depending on different dominating species: unionized molecule (H_4A), monoanion (H_3A^-), and dianion (H_2A^{2-}).

Free radical scavenging activity of EA relates to the phenolic H-atom transfer (HAT), single electron transfer followed by proton transfer (SET-PT), and sequential proton loss electron transfer (SPLET) mechanisms. By analyzing the energy requirements for bond dissociation enthalpy (BDE), adiabatic ionization potential (IP), O-H proton dissociation enthalpy (PDE), proton affinity (PA), and electron transfer enthalpy (ETE), it is possible to indicate which mechanism is thermodynamically favored and identify the active site for radical inactivation [23][24]. Thus, BDE characterizes the HAT mechanism; IP and PDE the SET-PT mechanism; finally, PA and ETE the SPLET mechanism. Marković and co-workers [23] calculated these parameters for ellagic acid and its phenoxide anions, bringing some insightful conclusions regarding the antiradical mechanism of EA.

2.2. Structure of Ellagitannins

ET’s complexity and diversity are directly linked to their biosynthetic variability, and there are limitless possible structures as a result thereof. In fact, more than 1000 ETs have been identified to date. Some ET structures, characteristic groups and their precursor, β-pentagalloyl glucose, are depicted in **Figure 2**. ETs are formed via oxidative C-C coupling of at least two galloyl units of the β-pentagalloyl glucose (**Figure 2**), leading to an axially chiral HHDP unit [1]. Further steps can lead to the formation of a second HHDP group (e.g., Casuarictin, **Figure 2**) or to the cleavage of the formed HHDP or galloyl groups (e.g., Corilagin, **Figure 2**). Trimer and tetramer forms of the galloyl group can result from a further oxidative coupling. Such is the case of Castalagin and Vescalagin (**Figure 2**), which have a nonahydroxytriphenoyl (NHTP) group, also known as flavogallonyl. HHDP groups can also suffer further oxidation to form other units, such as dehydrohexahydroxydiphenoyl (DHHDP) (e.g., Mallotusinic acid in **Figure 2**) or chebuloyl (e.g., Chebulagic acid in **Figure 2**). C-O bonding of HHDP groups is another possibility, resulting in sanguisorboyl, tergalloyl and valoneoyl groups (**Figure 2**), among others [25]. Thus, via the oxidative C-O coupling between galloyl and hexahydroxydiphenoyl moieties, ET monomers can form dimers, trimers and tetramers with molecular weights up to several thousands of Da (e.g., Sanguiin H-6, a Casuarictin dimer, in **Figure 2**). The nature of the bonds between monomers, either biphenyl or diarylether, sets up a method for their classification [25]. Lastly, ETs can give rise to hybrid structures by joining with other classes of molecules: e.g., Epiacutissimin B (**Figure 2**), a flavano-ellagitannin, has epicatechin at the C-1 center of the open-chain glucose core [26].

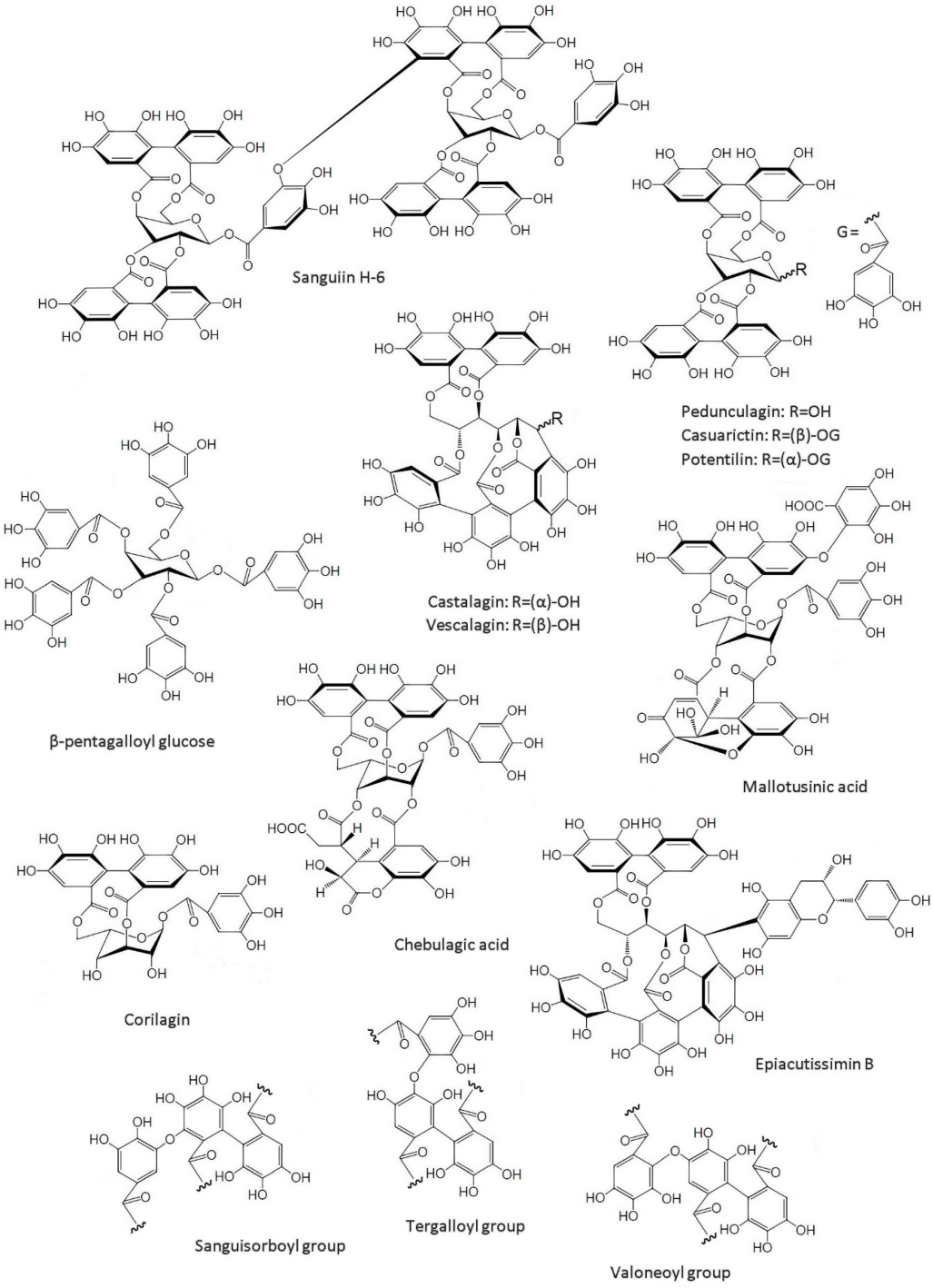

Figure 2. Example of some ellagitannin structures and their precursor, β-pentagalloyl glucose.

It is certain that the pentagalloyl glucose oxidation pathway plays a central role in ellagitannins biosynthesis, but differing structural principles have been recognized for this class, which still leave many gaps, not only in the identification of enzymes catalyzing the synthesis of different linkage types, but also regarding some physiological aspects, such as seasonal variation of metabolite concentrations and enzyme activities [27]. Detailed postulations on ET's biosynthesis fall outside of the scope of this review and can be found elsewhere [1][27]. Additionally, a detailed discussion on structural revisions of some ETs can be found in a recent review [3], reinforcing once again the complexity and structural diversity of this tannin class.

3. Sources of Ellagic Acid and Ellagitannins

ETs are known constituents of numerous species of economic importance [1]. They are abundant in berries of the family *Rosaceae* such as cloudberry, raspberry and strawberry. They seem to have most of their EA in the form of ETs, as the relative amount of free EA and its glycosides is rather low [28][29]. In general, the amount of EA/ET in fruits can range from 100 to 1500 mg·kg^{-1} and contributes substantially to the dietary intake [20]. Kakadu plum, with up to 140.2 g·kg^{-1} (dw) of EA, is probably the richest edible source [30][31]. Other important sources of ETs include walnuts [32], pecans [33], camu-camu fruits [34], pomegranates [35], and muscadine grapes [36]. The amounts of EA/ETs found in different fruits, nuts and

woods are summarized in **Table 1**. Notably, pomegranate peel has been considered as a prominent source of raw material for industrial exploitation [37].

Many medicinal plants used for their antioxidant, anti-diarrheic and anti-microbial activities contain ETs. Some notable examples include Agrimoniin (*Agrimonia pilosa*), Camelliatannin A (*Camelia japonica*), Casuarictin (*Liquidambar formosana*), Chebulinic acid (*Terminalia chebula*), Cornussin A (*Cornus officinalis*), Gemin-A (*Geum japonicum*), Geraniin (*Geranium thunbergii*), Granatin B (*Punica granatum*), Mallotusinic acid (*Mallotus japonicas*), Oenothein B (*Oenothera erythrosepala*) and Rugosin (*Rosa rugosa*) [25]. Lastly, EA, methyl derivatives of EA, and glycosides of both, are the components of the tannin extractives of *Eucalyptus* species [38]. Therefore, EA is also present in agro-forest and industrial residues (e.g., in cork, tree bark and wood) [39]. In fact, Santos and co-workers [40] reported 512.8 mg·kg^{-1} (dw) of EA in Brazilian *E. grandis* and these values are in accordance with their previous findings. Moreover, using the capillary zone electrophoresis (CZE) analytical procedure, reliable determinations have been made of EA in *E. globulus* wood: 1100 ± 600 mg·kg^{-1} (dw) [41]. Usually, eucalypt bark contains 3–5 times higher EA/ETs than wood [42]. Besides *Eucalyptus*, EA/ETs are also widely present in *Quercus* [43], *Acacia* [44] and *Castanea* [45] species, among some other angiosperms [46]. It is noteworthy that the abundance of EA and ETs in wood and bark is comparable or even higher than in most agricultural sources (**Table 1**).

Table 1. Sources of EA and its content (mg·kg^{-1}) in different fruits, nuts, seeds and woods *.

Source	Latin Name	Total ET/EA #	Free EA	Ref.
Fruits				
Arctic bramble	*Rubus arcticus*	3900 (fw)	-	[29]
Blackberry	*Rubus ursinus*	1500 ± 140 (dw)	-	[47]
Camu-camu fruit:				
Pulp powder		258.5 ± 4.3 (dw) *	56.0 ± 1.1 (dw)	
Flour		5656.6 ± 11.3 (dw) *	764.9 ± 4.9 (dw)	
Peel	*Myrciaria dubia*	71.4 (fw) *	Nd	[34]
Pulp		67.3 (fw) *	Nd	
Seeds		2819.8 (fw) *	50.4 (fw)	
Cloudberry	*Rubus chamaemorus*	3600 (fw)	-	[29]
		3151 (fw)	-	[28]
Cranberries	*Vaccinium*	120 ± 4 (dw)	-	[47]
Guava	*Psidium guajava L.*	57.2–306 (dw)	-	[48]

Source	Latin Name	Total ET/EA [#]	Free EA	Ref.
Kakadu plum	*Terminalia ferdinandiana*	30,510–140,250 (dw)	-	[30]
		8796.0 ± 156.0 (dw)	6206.0 ± 22.0 (dw)	[31]
Muscadine grapes	*Vitis rotundifolia*	360–912 (fw)	-	[36]
Pomegranate:				
Mesocarp	*Punica granatum*	40,595.4 ± 4434.2 (dw)	234.2 ± 13.0 (dw)	[35]
Peel		43,979.0 ± 394.8 (dw)	637.7 ± 32.8 (dw)	
Red raspberry	*Rubus idaeus*	1500 ± 100 (dw)	-	[47]
		1900–2700 (fw)	-	[29]
		2637–3309 (fw)	-	[28]
Rose hip	*Rosa rugosa*	1096 (fw)	-	[28]
Strawberry	*Fragaria ananassa*	630 ± 90 (dw)	-	[47]
		650–850 (fw)	-	[29]
		683–853 (fw)	-	[28]
Processed Fruits				
Pomegranate juice	-	87–2118.3 ($mg \cdot L^{-1}$)	2.1–7.7 ($mg \cdot L^{-1}$)	[35]
Raspberry jam	-	764 (fw)	-	[28]
Strawberry jam	-	245 (fw)	-	[28]
Seeds and Nuts				
Pecans	*Carya illinoensis*	330 ± 0.3 (dw)	-	[47]
Walnuts	*Juglans nigra*	590 ± 0.3 (dw)	-	[47]
Wood				

Source	Latin Name	Total ET/EA [#]	Free EA	Ref.
Blue gum	*Eucalyptus globulus*	-	500–1700 (dw)	[41]
Common Oak	*Quercus robur*	-	81–228 (dw)	[49]
Pyrenean oak	*Quercus pyrenaica*	-	66–219 (dw)	[49]
Rose gum	*Eucalyptus grandis*	-	280–512 (dw)	[40]
Sessile oak	*Quercus petraea*	-	109–198 (dw)	[49]
Sweet chestnut	*Castanea sativa*	-	74–140 (dw)	[49]
White oak	*Quercus alba*	-	132–277 (dw)	[49]
Wood bark				
Blue gum	*Eucalyptus globulus*	-	471 (dw)	[50]
(Hybrid) eucalypt	*Eucalyptus urograndis*	-	2243–2307 (dw)	[51]
Maidens Gum	*Eucalyptus maidenii*	-	1130–1178 (dw)	[51]
Oak	*Quercus robur* + *Quercus petraea*	-	2200–3700 (dw)	[52]
Sweet chestnut	*Castanea sativa*	-	4300–9300 (dw)	[53]
Rose Gum	*Eucalyptus grandis*	-	2639–2721 (dw)	[51]
Other sources				
Eucalypt leaves	*Eucalyptus globulus*	3320.0 ± 80.0 (dw)	-	[54]
Filtrates from unbleached kraft wood	*Eucalyptus globulus*	-	98 ± 0.7 (mg/L)	[41]
Sulphite spent liquor	*Eucalyptus globulus*	-	1165.5 (mg/L)	[55]

[#]—total EA after ETs hydrolysis; all values are presented as mg per kg of source (dw = dry weight or fw = full weight). *—Total ET + Total EA derivatives.

The industrial importance of *Eucalyptus* species for cellulosic pulp production in South Europe, Australia, Asia, South America, and South Africa predetermines a particular interest in these angiosperms [56]. Since eucalypt wood is used in pulping processes after the preliminary removal of bark, the latter can be considered as a large source of ETs as well. EA is present in the different industrial streams from the production of both kraft [41] and sulphite [57] pulps. Furthermore, significant amounts of EA and its metal salts, in the form of undesirable waste by-products (pitch deposits, effluents, etc.), are readily available from the pulp industry [58][59][41]. Thus, in addition to fruits, nuts and herbs, the pulping industry can

furnish EA in a large scale. Accordingly, contrary to agricultural sources, the pulping industry represents an all-season large-scale underutilized source of EA and its derivatives.

4. Technical Applications of Ellagic Acid

The major applications of EA and its derivatives are limited to medicinal and nutritional purposes. Nevertheless, in recent years, more studies have been contemplating different technical applications. Thus, due to its particular chemical and structural features, EA reveals prospective industrial significance for the synthesis of new bioengineered materials. Zhang and co-workers [60] reported the synthesis of a macroporous ellagitannic acid ion-exchange resin for the easy removal of Cu^{2+}, Fe^{3+}, Ce^{3+} and La^{3+} from solutions. Later, Przewloka and Shearer [61] reported EA and water-soluble ellagates' utilization for the removal of divalent ionic metal ions from aqueous solution, confirming the potential of EA and its derivatives as metal chelants. Furthermore, Reitze, in collaboration with Przewloka and Shearer [62], reported the synthesis of several potential EA-based polymer precursors, including monomers and oligomers, offering new options for polymer applications.

More recently, Wang and co-workers [63] developed conductivity-based sensors via the assembling of EA molecules through π-π interaction and hydrogen bonding between EA molecules. Due to the near planar structure of EA, the obtained nanostructures exhibit a 1D dimensional structure, whose conductivity and fluorescence selectively change in the presence of nitrobenzene, indicating the potential of these nanomaterials for the detection of explosive chemicals. EA and catechols, in combination with lignin, were reported as a part of all-solid potentiometric chemical sensor for the selective detection of Cu^{2+} in aqueous solutions [64]. The sensing membrane, composed of tannin-lignin-based polyurethane doped by multi-walled carbon nanotubes (MWCNT), demonstrated long-term stability. It has been suggested that EA and catechol play a determining role in the specific chelation of Cu^{2+}, contributing to the ionic sensing mechanism. According to the results of another work, due to good redox properties and high thermal stability (up to 400 °C), EA (50 wt.%) mixed with acetylene black (40 wt.%) and polyvinylidene fluoride (PVDF, 10 wt.%), resulted in an efficient organic electrode material for rechargeable Li-ion batteries [18].

Barnaby and co-workers [65] reported the biomimetic synthesis of shape-controlled Ag-nanoparticles (NPs) in the presence of EA as the chelating agent. These EA-based Ag-NPs complexes exhibited enhanced antibacterial properties when compared to Ag-NPs or EA used separately. The development of the Ag nanochains in the presence of EA was achieved by a template free method without the need for high temperatures or reducing agents. Furthermore, the production of EA-based microassemblies, used afterwards as templates for the growth of CdSe nanoparticles, was reported [66]. The thermal stability and efficiency of these EA-based nanocomposites to photodegrade alizarin red (a model toxic aromatic compound) was confirmed, suggesting that these nanocomposites have potential applications in the degradation of environmental pollutants such as toxic aromatic compounds.

In order to enhance EA bioavailability and maximize its activity, attempts have been made to develop a delivery system using a chitosan polymer in composite films [67], collagen and chitosan-based scaffolds [68] and nanocapsules [69][70]. Apart from biomedical applications, more recently, Vilela and co-workers [71] have proposed chitosan/EA films as promising eco-friendly active food packaging material. Another interesting application of EA is for copigmentation in enhancement of color properties in wines [72]. Apparently, the technical applications of EA and its derivatives can be expanded as their availability in the market increases.

5. Bioavailability of Ellagitannins and Ellagic Acid

There are numerous factors that can influence EA bioavailability: low solubility in aqueous media under gastric conditions, *in vivo* hydrolysis of ETs to release EA, the type of ET as EA precursor, limited intestinal absorption and/or transport and the catabolism of EA by the gut microbiota to produce urolithins. Furthermore, EA pharmacokinetics revealed high inter-individual variability [73]. In addition, González-Sarrías and coworkers [73] conclude that EA's bioavailability is not enhanced by a higher intake and hardly exceeds 100 nM in human plasma. Conversely, urolithins can attain bloodstream concentrations at the micromolar level [74]. As previously mentioned, ETs are hydrolyzed to EA and the latter is either absorbed or transformed via lactone-ring cleavage, decarboxylation, and, after that, de-hydroxylation reactions resulting in dibenzo[*b,d*]pyran-6-one derivatives, with different phenolic hydroxylation patterns, known as urolithins (**Figure 3**). Methylated and glucuronidated counterparts such as urolithin A glucuronide, urolithin-C glucuronide, urolithin-C methyl ether glucuronide, and dimethyl ellagic acid glucuronide have been found in human plasma after the consumption of different sources of ellagitannins [75]. Urolithins have a higher bioavailability and it is debatable whether urolithins formed *in vivo* are the main reason for the effects attributed to the ETs [74]. Given this background, it should be considered that cultured cells representing systemic tissues and organs may not be in direct contact *in vivo* with food ETs or EA [76]. In

fact, it can be the cause of discrepancies between *in vitro* and *in vivo* results, which can also be linked to the inter-individual variability in quality and quantity of urolithin production [77].

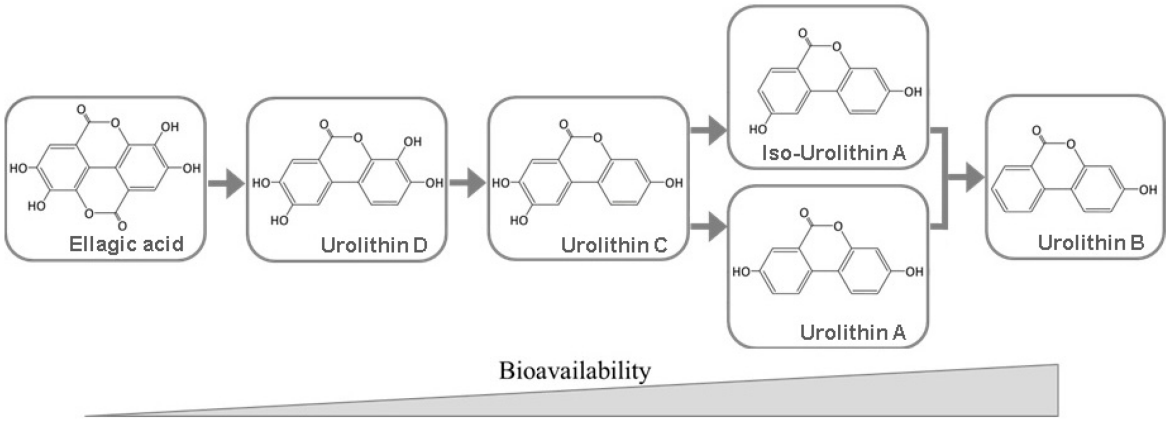

Figure 3. Urolithins derived from ellagic acid and their relative bioavailability.

6. Biomedical Applications

The above-mentioned structural features of EA, ETs and derivatives have a vital role in maintaining cellular homeostasis and bestowing these compounds with preventive and protective properties in many biological systems and cell types. It has been reported a wide range of possible biomedical/pharmaceutical applications, which are briefly summarized in Table 2.

Table 2. Possible biological effects of EA and its derivatives.

Activity	Active Compound	Main Features	Ref.
Antibacterial (Gram-Positive)	Commercial extract of pomegranate byproduct (POMx) and punicalagin	Inhibited the growth of pathogenic *Clostridium* and *Staphyloccocus aureus*	[78]
Antibacterial (Gram-Positive)	Ellagic acid	Action against *Bacillus luteus* and *Listeria monocytogenes*	[79]
Antibacterial (Gram-Negative)	Tellimagrandin I	Time- and dose-dependent bactericidal activity against *Helicobacter pylori*	[80]
Antibacterial (Gram-Negative)	Ellagic acid	EA—cyclodextrin complex expressed activity against *Escherichia coli* and *Pseudomonas aeruginosa*	[79]
Antimycobacterial	Punicalagin	Inhibited the growth of *Mycobacterium tuberculosis* typus humanus ATCC 27294 and patient strain of *Mycobacterium tuberculosis* sensitive to the standard antituberculosis drugs	[81]
Antileishmanial	Geraniin, phyllanthusiin B and elaeocarpusin	Exhibited effect against protozoa *Leishmania donovani,* comparable to that of the amphotericin B	[82]

Activity	Active Compound	Main Features	Ref.
Antimalarial	Ellagic acid	*In vitro* against all *Plasmodium falciparum* strains. *In vivo* against *Plasmodium vinckei petteri*; potentiates the activity of chloroquine, mefloquine, artesunate and atovaquone	[83]
Antibabesial	Ellagic acid	*In vivo* against *Babesia microti;* EA nanoparticles as an alternative antiparasitic agent	[84]
Antifungal	Candelitannin (ellagitannin) isolated from *E. antisyphilitica* Zucc.	Effective against *Alternaria alternata*, *Fusarium oxyzporum*, *Colletotrichum gloeosporoides* and *Rhizoctnia solani*	[85]
Antifungal	Ellagic acid	Action against *Candida albicans*	[79]
Antiviral	Castalagin, vescalagin and grandinin.	Action against acyclovir (ACV)—resistant strains of *Herpes simplex* virus HSV^{-1} and HSV-2; synergistic effects when used in combination with ACV	[86]
Prebiotic effect	Commercial extract of pomegranate byproduct (POMx) and punicalagin	Enhanced growth of *Bifidobacterium breve* and *Bifidobacterium infantis*	[78]
Anti-inflammatory	Ellagic acid, gallic acid and punicalagin A&B	Potential inhibition of LPS-induced NO, PGE-2 and IL-6 production	[87]
Anti-inflammatory	Ellagic acid	Enhancement of EA's anti-inflammatory properties *in vivo* by inclusion complex of EA with hydroxypropyl-β-cyclodextrin	[88]
Treatment of Type 2 diabetes mellitus	Ellagic acid and ETs from *Agrimonia pilosa* Ledeb.	Inhibition of protein tyrosine phosphatases (PTP1B)	[13]
Prevention of diabetic complications	Ellagic acid	ALR2 (aldose reductase) inhibition and antiglycating effect of EA could possibly delay progression of cataract	[89]
Anticancerous agent	Ellagic acid	Inhibition of SphK1 (sphingosine kinase 1)	[11]
Antiangiogenic and antiproliferative effect	Ellagic acid	Reduction in metastatic potential of bladder cancer and enhancement of the efficacy of anti-VEGF-A therapies	[7]
Gastroprotective	Ellagitannin-rich fraction obtained from *E. citriodora*	Possibly due to their antioxidant, anti-inflammatory and anti-apoptotic properties. Partially mediated by attenuating induced oxidative stress and by the reduction of pro-inflammatory markers.	[90]
Hepatoprotective	Ellagic acid	Suppression of caspase-3, bcl-2, NF-kB and Nrf-2	[6]

Activity	Active Compound	Main Features	Ref.
Antiarrhythmic	Ellagic acid	Antilipid peroxidation property and antihyperlipidemic activity through 3-hydroxy-3 methyl glutaryl CoA reductase inhibition; cardioprotective effect	[91]
Antiasthmatic	*L. pacari* extract and ellagic acid	Effective eosinophilic inflammation suppressors	[92]
Antihyperlipidemic	Ellagic acid	EA-CoQ10 nanoparticles effectively attenuated induced hyperlipidemia in rats	[93]
Antiepileptic	Ellagic acid	Possibly achieved through increase of brain GABA levels	[9]
Antianxiety	Ellagic acid	Possible involvement of GABAergic system in the anxiolytic action	[10]
Antidepressant	Ellagic acid	Possible interaction through adrenergic and serotonergic systems or through inhibition of inducible NOS	[8]
Neuroprotective in SAD	Ellagic acid	Diminished oxidative stress profile, pro-inflammatory markers, acetylcholinesterase activity, and amyloid-β plaque level in induced SAD (Sporadic Alzheimer's Disease) rats	[12]
Skin-whitening agent	Ellagic acid	EA acts as an alternative substrate of tyrosinase, inhibiting the melanogenesis process	[94]

There is still a focus on EA as a test compound and the results are promising, however EA derivatives and ETs have also been thoroughly investigated and it seems that they are yet to reveal their full potential. Reports of their activity on pathogens include infectious agents such as bacterium, virus, fungus and even protozoa [84][79][78][80][81][82][83][85][86]. Remarkably, prebiotic effects were also registered [78]. It is worth noting that C-glucosidic ellagitannins, active against Acyclovir (ACV)—resistant strains of the *Herpes simplex* virus, exhibited synergistic effects when used in combination with ACV [86]. It should also be noted that pre-treatment with ellagitannin-rich fraction obtained from *Eucalyptus citriodora*, at a dose of 100 mg/kg, resulted in higher gastroprotection (99.6% in ethanol-induced acute gastric ulceration) than that of the omeprazole, a widely known proton pump inhibitor. Notably, the authors point out that ETs were found to be the major active components responsible for the marked antioxidant, anti-inflammatory and gastroprotective properties [90]. Finally, the involvement of EA/ETs in the GABAergic system, inhibition of key enzymes such as aldose reductase, acethylcholinesterase and protein tyrosine phosphatases, suppression of pro-inflammatory markers, and interaction with adrenergic and serotonergic systems, establish a solid foundation for possible breakthroughs in treatments and/or prevention of many illnesses and related clinical complications [9][10][12][13][89].

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