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Review

Urolithins and Their Precursors Ellagic Acid and Ellagitannins: Natural Sources, Extraction and Methods for Their Determination

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Abstract: In the present review, we discuss the occurrence of ellagitannins (ETs) and ellagic acid (EA) and methods for their isolation from plant materials. We summarize analytical methods, including high-performance liquid chromatography–ultraviolet (HPLC–UV) and liquid chromatography–mass spectrometry (LC–MS), for the determination of ETs, EA and their bioactive metabolites urolithins (Uros) in samples of plant and food origin, as well as in biological samples, such as plasma, urine and feces. In addition, the current interest in the bioactivities of Uros is discussed in brief.

Keywords: ellagic acid; ellagitannins; HPLC-UV; LC-MS; urolithins

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1. Introduction

Ellagitannins (ETs) are a group of tannins widely spread in plants, in particular in fruits, including pomegranate, cloudberries and strawberries [1–3]. They are complex molecules characterized by structural diversity. When foods rich in ETs are consumed, ETs are first hydrolyzed into ellagic acid (EA) in the stomach and small intestine [4]. Then, EA may be converted into urolithins (Uros) by the action of the intestinal flora [4,5]. The consumption of foods rich in ETs and EA has been associated with beneficial effects on human health. As a consequence, a plethora of studies have been performed to shed light on the bioactivities of ETs, EA and Uros [6–10]. Recently, an increasing interest has been focused on the bioactivities of Uros and clinical trials have led Uro supplements to enter into the market [11].

Due to the diverse biological effects of ETs, EA and Uros, there is a high interest in the isolation of such components from various natural sources, their bio-transformations in the human organism, the study of their bioactivities and analytical methods for their detection and determination. The aim of the present review is to summarize the natural sources of ETs and EA, discussing methods for the extraction and isolation of ETs and EA from various sources. Furthermore, a detailed summary of the analytical methods developed for the determination of ETs, EA and Uros in plants, foods and biological samples is presented.

2. Ellagitannins and Ellagic Acid

2.1. Natural Sources and Occurrence of ETs and EA

ETs are naturally occurring compounds of medicinal and biological interest found in dicotyledonous and angiosperms plants [12]. They belong to the hydrolyzable tannins and possess a complex chemical structure, which renders them susceptible to various chemical reactions, including transformation, isomerization, and oligomerization [2]. ETs are esters of gallic acid and are typically constructed by hexahydroxydiphenic acid units (HHDP), connected usually to a D-glucose moiety. However, fructose, xylose, galactose and quinic

acid have also been reported to connect to HHDP [1,13,14]. The HHDP units may be linked to more than one sugar moiety; therefore, monomeric, dimeric, oligomeric and polymeric ETs are formed [15]. The exposure of ETs to an acidic or basic environment result in the formation of EA via hydrolysis/lactonization reactions. Representative ETs are punicalin and punicalagin, which are abundant in pomegranate, and their structures are depicted in Figure 1. Upon their hydrolysis, followed by dehydration/lactonization, EA is formed (Figure 1).

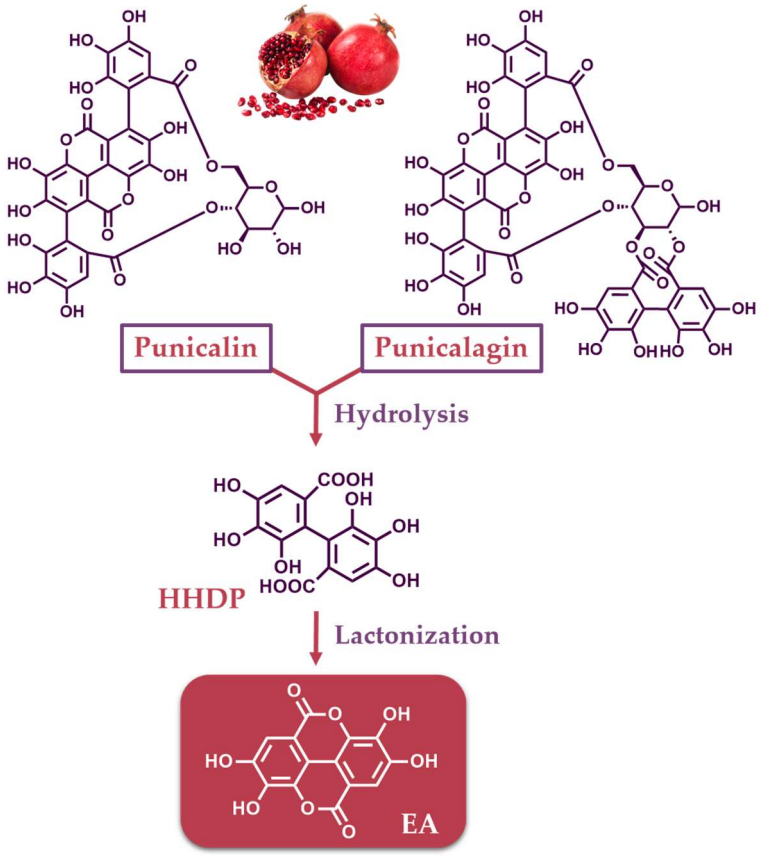

Figure 1. Structures of ETs found in pomegranate (punicalin and punicalagin) and their conversion to EA.

EA, first described two centuries ago [16], is a chromene-dione derivative, which can be considered as a dimeric derivative of gallic acid. It is named 2,3,7,8-tetrahydroxy-chromeno [5,4,3-cde]chromene-5,10-dione according to IUPAC nomenclature, However, it is also known as 4,4′,5,5′,6,6′-hexahydroxydiphenic acid 2,6,2′,6′-dilactone (Figure 1). It consists of a pair of lactone rings as a part of a tetracyclic core, carrying four free-hydroxyl phenolic groups, therefore exhibiting an amphiphilic character. Due to the lactone functionalities and the phenolic groups, it may act as a hydrogen bond acceptor or donor, respectively.

More than 1000 ETs have been detected to occur in many plants; nevertheless, few of them are fit for human consumption. Fruits including strawberries, berries, pomegranate, and nuts and seeds are rich in edible ETs, within which raspberries and cloudberries are the most abundant sources, as are processed foods, including fruit-derived beverages, jams and cakes (Table 1) [1,3,17]. In general, fruits of the genus Rubus are the most studied for their content in ETs and EA. Among them, raspberries of different species, such as *R. idaeus* [18–21], *R. occidentalis*, and *R. ursinusxidaeus* [21], have been investigated showing an ETs/EA content ranging from 16 to 17.92 mg/g. Similarly, strawberries from different varieties, for example, Honeoye, Jonsok, Polka [22], and Senga saengana [23], showed a diversity in their content of ETs/EA that ranges from 0.12 to 5.64 mg/g. Impressive is the content in ETs/EA of *Artic bramble*, a perennial plant whose fruits can also been used for the

preparation of jam, liqueur, and tea. According to Määttä-Riihinen et al., the concentration of ETs/EA reaches 24.91 mg/g [22]. In addition, other kinds of fruits native to tropical countries have been found to contain significant amounts of ETs and EA. *Myrciaria jaboticaba* (Myrtaceae) and *Myrciaria dubia* (Myrtaceae), commonly known as camu-camu, have been reported as rich sources of EA and ETs [24,25]. Another source of ETs and EA is wine. Oak wood releases tannins which are transferred to wine during its storage for maturation purposes in oak barrels [26,27].

The use of herbs containing ETs dates back to traditional medicine. Some examples are *Geranium thunbergia* (Geraniaceae) and *Mallotus japonicus* (Euphorbiaceae). Both plants produce geranin and have been widely used in Japan for treatment against diarrhea and to treat stomach ulcers, respectively [28]. Furthermore, the fruits of *Terminalia chebula* (Combretaceae) that contain chebulinic acid, chebulagic acid and terchebin, have been traditionally used in Indian and Iranian folk medicine to combat chronic diseases, such as dementia, diabetes, etc. [29].

Given the importance of ETs for their health beneficial properties, as has been documented by traditional medicine, some authors examined their presence in the non-edible parts of fruits. In a recent study, Torgbo et al. found that the peel of *Nephelium lappaceum* L., (Sapindaceae), a tropical fruit of Southeast Asia, contains in major quantities, with respect to other compounds, ETs such as geraniin and corilagin and their metabolites, including gallic acid and EA [30]. Similarly, de Vasconcelos et al. showed that ETs and EA are abundant in the pericarp and the integument of chestnut fruit [31]. In addition, Kaneshima et al. reported the presence of ETs, such as grandinin, vescalagin, castalagin and others, in camu-camu seeds and peels [32]. Therefore, obviously, the rational use of these by-products may lead the pharmaceutical, nutraceutical and cosmetic industries to the development of valuable products for human health. Furthermore, many scientific papers discuss various plant species for their significant amount in ETs and EA [1–3,17]. Plant families, such as Myrtaceae, Rosaceae, Asteraceae and Fagaceae, are reported to include several plant genera, which produce ETs and EA [33,34].

Apparently, a diversity between the concentration of these secondary metabolites is evident between the various fruits, foods, and the plant species, as presented in Table 1. The presence of many raspberries and other fruit varieties as well as the species diversity and the genetic diversity within the species contribute to these differences. However, there are also other factors to consider, including the handling of the sample for specific experimental purposes, climate variations and the developmental stage of the material under study.

2.2. Bioavailability of ETs and EA

Generally, data on the recommended daily intake of ETs and EA are not yet available. Though toxicity studies evaluate ETs and EA as safe, their pharmacokinetic behavior is still obscure. Therefore, caution should be taken by consumers, although the no-observed-effect level (NOEL) of EA in in vivo studies involving rats has been established at 3.254 mg/kg/day [35].

Although ETs are found in many natural products, their low bioavailability limits their use. ETs are generally large molecules, among which the molecular weight of Lambertianin D reaches 3740 Da [36]. The presence of the HHDP moiety(ies) in their structure, formed by C-C bond connection between adjacent galloyl residues, in addition to their polar nature, renders them components with low bioavailability. As mentioned above, most ETs are subjected to acidic or basic hydrolysis at the gastrointestinal tract to form EA through the hydrolysis of the ester bonds of ETs, enhanced by the enzyme ellagitannin acyl hydrolase [37]. However, ETs resistant to hydrolysis end intact to the large intestine [38]. Similarly to ETs, EA has also a low bioavailability both because of its poor water solubility and its capacity to bind irreversibly to cellular DNA and serum proteins, which results in complexes of large molecular weight that do not penetrate cell membranes [39,40]. However, in vivo under physiological conditions, EA is metabolized in the gut microbiota to Uros.

Table 1. Ellagitannins and ellagic acid content.

Source	Family/Genus	Content	Solvent System	Extraction Method	Reference
			Fruits		
Cloudberries	Rosaceae/*Rubus*	3.15 mg/g [a]	Aqueous methanol (acidified)	Reflux (20 h)	[18]
		18.25 mg/g [a]	Ethyl acetate/Methanol	Vortex	[22]
		10.90–16.30 mg/g [a]	70% aqueous acetone	Solid–liquid extraction	[41]
		2.63–3.30 mg/g [a]	Aqueous methanol (acidified)	Reflux (20 h)	[18]
		1.55 mg/g [a]	70% aqueous acetone	Solid–liquid extraction	[42]
		0.16–3.26 mg/g [a]	-	-	[13]
		16.92 mg/g [a]	60% acetone (acidified)	Sonication (5 min)	[19]
		1.5 mg/g [b]	Methanol	Soxhlet	[43]
Raspberries	Rosaceae/*Rubus*	10.65–13.84 mg/g [a]	Ethyl acetate/Methanol	Vortex	[22]
		7.67–9.31 mg/g [a]	Methanol (acidified)	-	[44]
		1.35–5.47 mg/g [a]	Methanol (acidified)	Magnetic stirring (1 h)	[20]
		16.92–17.54 mg/g [a]	70% aqueous acetone	Solid–liquid extraction	[41]
		47–90 mg/g [b]	Methanol	Solid–liquid extraction (24 h)	[21]
		1.6 mg/g [b]		Reflux (20 h)	
		0.71 mg/g [b]	Aqueous methanol (1:2) (acidified)	Reflux (2 h)	[45]
		8.58–17.92 mg/g [a]	Aqueous methanol(acidified)	Vortex + sonication (5 min)	[23]
			70% aqueous acetone (acidified)		[46]
Rose Hip	Rosaceae/*Rosa*	1.09 [a]	Aqueous methanol (acidified)	Reflux (20 h)	[18]
		0.68–0.85 mg/g [a]	Aqueous methanol (acidified)	Reflux (20 h)	[18]
		0.71–0.83 mg/g [a]	-	-	[13]
		0.63 mg/g [b]	Methanol	Soxhlet	[43]
		0.64 mg/g [a]	Methanol	Sonication (10 min)	[47]
		4.51–5.64 mg/g [a]	Ethyl acetate	Vigorous mixing	[22]
		0.13–0.32 mg/g [a]	Methanol	Agitation (30 min)	[48]
Strawberries	Rosaceae/*Fragaria*	0.12–1.29 mg/g [a]	70% aqueous acetone	Solid–liquid extraction	[49]
		0.31 mg/g [a]	Aqueous methanol (1:2) (acidified)	Reflux (20 h)	[45]
		0.40 mg/g [a]	Aqueous methanol (acidified)	Reflux (2 h)	[23]
		0.81–1.84 mg/g [a]	70% aqueous acetone	Solid–liquid extraction	[41]
		0.29 mg/g [a]	70% aqueous acetone	Sonication (10 min)	[50]
		0.77 mg/g [a]	Aqueous methanol (acidified)	Reflux (20 h)	[18]
		0.75–0.79 mg/g [a]	Aqueous methanol (acidified)	Reflux (20 h)	[18]
		3.43 mg/g [a]	70% aqueous acetone	Solid–liquid extraction	[42]
Blackberry	Rosaceae/*Rubus*	1.5–2.7 mg/g [a]	-	-	[13]
		0.63 mg/g [a]	80% aqueous methanol (acidified)	Sonication (10 min)	[51]
Arctic Bramble	Rosaceae/*Rubus*	24.91 mg/g [a]	Ethyl acetate	Vigorous mixing	[22]

Table 1. *Cont.*

Source	Family/Genus	Content	Solvent System	Extraction Method	Reference
Caneberries	Rosaceae/*Rubus*	8.7–32.2 mg/g [b]	Methanol	Solid–liquid extraction (24 h)	[52]
Rose Hip	Rosaceae/*Rosa*	1.09 mg/g [a]	Aqueous methanol (acidified)	Reflux (20 h)	[18]
Boysenberry	Rubeae/*Rubus*	1.68 mg/g [a]	Methanol	Sonication (10 min)	[47]
Cranberries	Ericaceae/*Vaccinium*	0.12 mg/g [b]	Methanol	Soxhlet	[43]
		0.58–1.77 mg/g [a]	-	-	[13]
		40.59 mg/g (mesocarp) [a]	80% aqueous methanol (acidified)	Stirring	[53]
		43.98 mg/g (peel) [a]			
Pomegranate	Lythraceae/*Punica*	1.25 mg/g [a]	Deionized water	Pressurized water extraction	[54]
		46.63 mg/g (fruit) [a]	Ethyl acetate	-	[55]
		81.23 mg/g (peel) [a]		Solid–liquid extraction	
		5.21–26.25 mmol/L [a]	Water		[56]
Guava	Myrtaceae/*Psidium*	0.20–0.25 mg/g [a]	-	-	[13]
Sea Buckthorn	Elaeagnaceae/*Hippophae*	0.01 mg/g [a]	Aqueous methanol (acidified)	Reflux (20 h)	[18]
Kakadu Plum Fruit	Combretaceae/*Terminalia*	8.80 mg/g [a]	Methanol	Sonication (10 min)	[47]
		10.69 mg/g [b]	Methanol	Sonication (10 min)	[57]
		0.43 mg/g (seeds) [b]	Methanol: water (4:1) acidified	Sonication (1 h)	
Grapes	Vitaceae/*Vitis*	0.46–0.49 mg/g (skin) [a]			[58]
		0.16–0.22 mg/g [a]			
Longan Seed	Sapindaceae/*Dimocarpus*	1.56 mg/g [b]	50% aqueous ethanol	Water bath (1 h)	[59]
Mango Kernel	Anacardiaceae/*Mangifera*	0.031–1.18 mg/g [b]	50% aqueous ethanol	Water bath (1 h)	[59]
		0.34–0.74 mg/g [b]	50% aqueous methanol	Water bath (1 h)	
Pecan Kernels	Juglandaceae/*Carya*	20.96–86.21 mg/g [b]	80% aqueous methanol	Solid–liquid extraction	[60]
		0.33 mg/g [b]	Methanol	Soxhlet	[43]
		1.61–24.9 mg/kg (raw) [b]	70% aqueous methanol	Vortex mixer (30 min)	[61]
		4.30–22.1 mg/kg (boiled) [b]			
		4.31–21.1 mg/kg (roasted) [b]			
Nuts	Fagaceae/*Castanea*	1.49 mg/g [a]			
		8.23 mg/g [a]	70% aqueous acetone	Ice bath	[62]
		0.36–0.59 mg/g [a]	-	-	[13]
		0.59 mg/g [b]	Methanol	Soxhlet	[43]
		0.40 mg/g [a]	Aqueous acetone (acidified)	Soxhlet	[63]
		3.01 mg/g [a]	70% aqueous acetone	Ice bath	[62]
Pecan	Juglandaceae/*Carya*	0.11–0.33 mg/g [a]	-	-	[13]
		0.70 mg/g [a]	Water	Reflux	[64]
		0.22 mg/g [a]	Aqueous acetone (acidified)	Soxhlet	[63]

Table 1. *Cont.*

Source	Family/Genus	Content	Solvent System	Extraction Method	Reference
		Medicinal and aromatic plants			
Psidium friedrichsthalianum-Nied	Myrtaceae/*Psidium*	2.43 mg/g (peel) [a] 3.06 mg/g (flesh) [a]	Methanol: water (9:1) acidified	Sonication	[65]
(*Psidium guajava* L.)	Myrtaceae/*Psidium*	5.72–30.6 mg/100 g [b]	Methanol	Shaking (30 min)	[66]
Myrciaria jaboticaba (Vell.) Berg	Myrtaceae/*Plinia*	9.1 mg/g [a]	70% aqueous methanol	Extraction (2 h)	[67]
		45.5–124.4 mg/g [a]	50% aqueous acetone	Overhead stirrer	[68]
Myrciaria cauliflora	Myrtaceae/*Plinia*	7.6 mg/g (peel) [a] 161.9 mg/g (seed) [a] 8.78 mg/g (pulp) [a]	50% aqueous acetone	Overhead stirrer	[69]
Myrciaria dubia	Myrtaceae/*Plinia*	7.14 mg/100 g (peel) [a] 6.73 mg/100 g (pulp) [a] 381.98 mg/100 g (seeds) [a]	50% aqueous methanol (acidified) 50% aqueous methanol (acidified)	Vortex + sonication (15 min)	[70]
Eucalyptus grandis	Myrtaceae/*Eucalyptus*	47.75 mg/g (extract) [b] 2.22 mg/g (drywood) [b]	Dichloromethane/50% aqueous methanol	Soxhlet/Stirring (24 h)	[33]
Eucalyptus globulus	Myrtaceae/Eucalyptus	4.95–5.08 mg/g (extract) [b] 0.42–0.71 mg/g (bark) [b]	Dichloromethane/50% aqueous methanol	Soxhlet/Stirring (24 h)	[71]
Myrtus communis L.	Myrtaceae/Myrtus	1.028–2.584 mmol/L (leaves) [a]	Water	Solid–liquid extraction	[56]
Feijoa sellowiana	Myrtaceae/Feijoa	12.04 µg/g (leaves) [b] 7.64 µg/g (flowerbuds) [b] 4.77 µg/g (branches) [b] 4,53 µg/g (fruits) [b]	70% aqueous acetone/ethyl acetate/n-butanol	Solid–liquid extraction	[72]
Plinia peruviana	Myrtaceae/*Plinia*	152.3 µg/mL [b]	50% aqueous ethanol	Ultra pressure	[73]
Fragaria × *ananassa* Duch	Rosaceae/*Fragaria*	33.18–151.78 mg/g (leaves) [a] 1.79–19.3 mg/g (roots) [a] 2.96–18.56 mg/g (fruits) [a]	Acetone:water (3:1) acidified	Vortex + sonication (15 min)	[74]
Prunus avium	Rosaceae/*Prunus*	0.059 mg/g [a]	Methanol	Sonication (30 min)	[34]
Potentilla tormentilla	Rosaceae/*Potentilla*	6.8–49.33 mg/g (rhizomes) [a]	50% aqueous methanol	Sonication (15 min)	[75]
Agrimonia asiatica	Rosaceae/*Agrimonia*	63.61 mg/g [a]	Water	Stirring + sonication (60 min)	[76]
Mangifera indica L.	Anacardiaceae/*Mangifera*	0.018–0.13 mg/g [b] 0.14 mg/g (peel) [b] 0.41 mg/g (seed) [b]	80% aqueous methanol Ethanol: Water (1:1) Acetone: Water (1:1)	Sonication (15 min) - -	[77] [78]

Table 1. *Cont.*

Source	Family/Genus	Content	Solvent System	Extraction Method	Reference
Syzygium cumini Lam	Myrtaceae/*Syzygium*	0.00–0.26 mg/g [a]	Methanol:Water (60:37) (acidified)	Homogenization	[79]
Myrciaria floribunda	Myrtaceae/Myrciaria	2.21 mg/g [b]	80% aqueous methanol	Liquid-solid extraction	[80]
Myrtus communis L.	Myrtaceae/Myrtus	8.54 mg/g [a]	71% aqueous ethanol	Pressurized-liquid extraction	[81]
Syzygium cumini L.	Myrtaceae/Syzygium	0.13–0.36 µg/g (pulp) [b] 18.65–32.70 µg/g (seed) [b] 7.14–15.30 µg/g (seed coat) [b] 34.60–48.37 µg/g (kernel) [b]	Petroleum ether/ethyl acetate/methanol/water	Soxhlet	[82]
Juglans regia L.	Juglandaceae/*Juglans*	412.9–552.9 mg/g [a]	Methanol	Vortex + sonication ice water (60 min)	[83]
Terminalia ferdinandiana	Combretaceae/*Terminalia*	30.51–140.25 mg/g [a]	80% aqueous methanol (acidified)	Vortex + sonication (15 min)	[84]
Quercus alba	Fagaceae/*Quercus*	1.06 mg/g [a] 3.95 mg/g [a]	80% aqueous methanol Ethanol:Water (62.5: 37.5)	Sonication (30 min) Stirring	[34] [85]
Quercus petraea	Fagaceae/*Quercus*	2.51 mg/g [a]	80% aqueous methanol	Sonication (30 min)	[34]
Quercus pyrenaica	Fagaceae/*Quercus*	2.94 mg/g [a]	80% aqueous methanol	Sonication (30 min)	[34]
Quercus robur	Fagaceae/*Quercus*	4.07 mg/g [a] 8.36 mg/g [a]	80% aqueous methanol Ethanol:Water (62.5: 37.5)	Sonication (30 min) Stirring	[34] [85]
Castanea sativa	Fagaceae/*Castanea*	8.91 mg/g [a]	80% aqueous methanol	Sonication (30 min)	[34]
Castanea crenata	Fagaceae/*Castanea*	2.26 mg/g [b]	80% aqueous methanol	Maceration (48 h)	[86]
Terminalia chebula Retz	Combretaceae/Terminalia	174.43 mg/g [a]	Water	Boil	[87]
Phyllanthus amarus	Phyllanthaceae/*Phyllanthus*	444.21 µg/mL [a]	80% aqueous ethanol	Soak (9 days)	[88]
Quassia undulata	Simaroubacea/*Quassia*	2.49 mg/g [b]	Cold water	Soak (24 h)	[89]
Acalypha hispida	Euphorbiaceae/*Acalypha*	1.19–5.41 mg/g [b]	Ethanol	Soak (72 h)	[90]
Baccharis trinervis	Asteraceae/*Baccharis*	1.35–9.74 mg/g [b]	Hot water	Infusion (15 min)	[91]
Carpobrotus edulis	Aizoaceae/*Carpobrotus*	0.45 µg/g [b] 0.55 µg/g [b]	Water Aqueous ethanol (1:1)	Stirring (30 min)	[92]
Clematis orientalis	Ranunculaceae/*Clematis*	0.46 mg/g [b]	80% aqueous methanol.Hexane	Shaking	[93]
Clematis ispahanica	Ranunculaceae/*Clematis*	0.81 mg/g [b]	Chloroform	Shaking	[93]
Hippophae rhamnoides L.	Elaeagnaceae/*Hippophae*	4.94–6.72 mg/g [b]	80% aqueous methanol	Homogenization + sonication (20 min)	[94]
Euterpe edulis	Arecaceae/*Euterpe*	1.40 mg/g [a]	70% aqueous ethanol (acidified)	Shaking	[95]
Juglans nigra L.	Juglandaceae/*Juglans*	9.05–98.41 µg/g [b]	methanol	Sonication in cool water (60 min)	[96]

Table 1. *Cont.*

Source	Family/Genus	Content	Solvent System	Extraction Method	Reference
Sterculia striata	Malvaceae/*Sterculia*	0.049 mg/g (nut) [b]	water	Sonication (60 min)	[97]
		0.046 mg/g (shell) [b]		Sonication (45 min)	
		0.032 mg/g (pelliche) [b]		Sonication (45 min)	
Juices/Wines/Liquors					
Pomegranate Juice	Lythraceae/*Punica*	26.5–33.2 mg/L [b]	-	-	[98]
		5.58 g/L [a]	-	-	[99]
		90.4–2071.0 mg/L [a]	-	-	[53]
		0.035–2.03 mmol/L [a]	Methanol	Shaking (3 min)	[100]
		1242.95 mg/L [a]	-	-	[101]
Jabuticaba juice	Myrtaceae/*Plinia*	24.37–143 mg/L [b]	Water	Steam extraction (30 min)	[102]
Eugenia brasiliensis Lam	Myrtaceae/*Eugenia*	146.1 mg/L [a]	Water	Homogenization	[103]
Muscadine juice	Vitaceae/*Vitis*	9.08–107.31 mg/L [a]	Ethyl acetate	-	[104]
guava juice	Myrtaceae/*Psidium*	1.41–1.48 mg/g [a]	-	Pasteurization	[65]
Raspberry juice	Rosaceae/*Rubus*	2.17–3.24 mg/g [a]	-	-	[46]
		2.27–77.76 mg/L [a]			[104]
Wine	Vitaceae/*Vitis*	20–50 mg/L [a]	-	-	[13]
		0.53–23.8 mg/L [a]	-	-	[105]
		7.88–11.61 mg/L [b]	Diethyl ether/ethyl acetate	-	[106]
		4.54–4.55 mg/L [a]	Diethyl ether/ethyl acetate	-	
Pomegranate wine lees	Lythraceae/*Punica*	4.36 mg/g [a]	70% aqueous methanol	Vortex/sonication (10 min)	[107]
Eucalyptus globulus	Myrtaceae/*Eucalyptus*	1165.5 mg/L [b]	Ethyl acetate	Liquid–liquid extraction (30 min)	[108]
Others					
Fruit pureé		8.8–43 mg/100 g [a]	80% ethanol	-	[109]
		8.5–44.1 mg/100 g [a]		-	
Strawberry Pureé		0.14–0.35 mg/g [a]	70% aqueous acetone	Sonication (10 min)	[50]
Kakadu Plum Fruit Pureé		11.65–14.96 mg/g [a]	Acetone	Sonication (10 min)	[57]
Strawberry Cake		25.21 mg/g [a]	70% aqueous acetone	Vortex/sonication (15 min)	[110]
				Vortex/sonication (5 min), Kept in dark (15 min)	
Strawberry Cake		17.70–81.01 mg/g [a]	70% aqueous acetone (acidified)		[46]
Strawberry Jam		0.17–0.29 mg/g [b]	Methanol:water (70:30) (acidified)	Homogenization in ice bath	[111]
		0.24 mg/g [a]	Aqueous methanol (acidified)	Reflux (20 h)	[18]
Raspberry jam		0.76 mg/g [a]	Aqueous methanol (acidified)	Reflux (20 h)	[18]

[a] Sum of ETs, EA and EA derivates; [b] EA.

2.3. Extraction ETs and EA from Natural Sources

Various solvents and methods have been used to extract ETs and EA from diverse sources. For example, Aaby et al. [50] extracted ETs and EA from strawberries through ultrasound-assisted extraction, using aqueous acetone as the extraction solvent. On the other hand, Abe et al. [24] observed that a treatment in an ice bath containing nuts and pecans with 80% aqueous acetone yielded higher amounts of total EA, compared to 80% aqueous ethanol. Similarly, Alagan et al. [88] successfully extracted a significant quantity of EA from the plant *Phyllanthus amarus* through soaking using 80% ethanol. Furthermore, Alañón et al. [34] extracted EA from three species of oak wood using methanol, while in another study by the same author, EA was extracted from mango seed kernel using an aqueous solution of methanol [77]. Both extractions were performed using a sonication process.

As shown in Table 1, the most useable extraction techniques are solid–liquid extraction, followed in some cases by sonication, or sonication alone. Solid–liquid extraction is a simple extraction technique, allowing the direct contact of the solid plant material with the solvent. Thus, it separates the soluble compounds found in a plant material and does not require further mechanical treatment of the samples. A Soxhlet apparatus is often used to achieve the isolation of the compounds; however, other procedures including maceration, stirring, and circular shaking have also been reported (Table 1). Pressurized water extraction has also been used to extract tannins. The main advantage of this method lies in its "green chemistry" characteristics. However, an important disadvantage to consider is that the high temperature used may deteriorate the presence of the analytes of interest. Indeed, Çam et al. [54] observed in their study that the optimal temperature to extract tannins is 40 °C. When the temperature was increased to 65 °C or 90 °C, the number of compounds decreased. Finally, ultrasound-assisted extraction is a common technique used to isolate plant secondary metabolites. In this case, time and sonication power are two variables of high importance, since they affect the yield of extractable compounds. Also critical is the selection of the extraction solvent, as well as the temperature of the water bath.

Most of the studies summarized in the present review use aqueous methanol as the extraction solvent in various % proportions. Both solvents' polarity is high, and their use can be explained by the fact % yield is increased when a polar solvent is used [112,113]. For this reason, some researchers use multiple solvents during the extraction process to facilitate the extraction of ETs and EA. For example, in the study of Määttä-Riihinen et al. [22], samples were first extracted with ethyl acetate, followed by methanol, which was applied to the solid residue. The same applies for the study of Häkkinen et al. [23] who used acidified aqueous methanol and then the solid residue was diluted to methanol. Nonetheless, data gathered in Table 1 also indicate that another solvent with intermediate polarity such as acetone, in combination with water, results in a high yield of ETs and EA content [41,46].

2.4. Analytical Techniques for the Determination of ETs and EA

The analytical identification, separation and quantification of ETs poses difficulties due to their structural complexity (high molecular weight), their high polarity, and in some cases the lack of commercial standards. Acidic hydrolysis has often been applied for the analysis of ETs with their quantification as equivalents of EA [114]. Theocharis et al. indicated that a maximum yield of EA can be obtained from strawberry samples with the use of a mixture of formic acid/water (80:20, v/v) and heating at 200 °C for 30 min, followed by microwave-assisted extraction (MAE) [115].

On some occasions, adsorption on macroporous resin columns can be used as an initial fractionation step. Usually, the column is washed with water for the removal of water-soluble impurities (i.e., sugar, proteins, etc.) and then gradually eluted with mixtures of ethanol and water [116,117]. This method has been applied to different samples, such as pomegranate husk extract, and for the phenolic profiling of *Duchesnea indica*, also known as the Indian strawberry [116,117].

High-performance liquid chromatography (HPLC) appears as the most utilized method for the separation and isolation of ETs and EA. Commonly, reverse phase RP-C18 chromatography is employed with polar mobile phases consisting of acidified acetonitrile or methanol and water containing formic or acetic acid [114,118]. Less frequently used columns include C6 phenyl columns [100] and diol columns [119]. Alternatively, fused-core columns have also been employed for the analysis of pomegranate polyphenols, where an improvement in the separation of constituents in a short time was reported, compared to conventional stationary phases [120,121]. Furthermore, a fused-core C18 column was used for the quantification of ETs in oak-aged red wine, achieving the simultaneous analysis of free EA [122]. Solely in the case of EA, high-performance thin layer chromatography (HPTLC) has been employed for quantitative analysis in different extracts and formulations with the use of mobile phases, usually consisting of toluene, ethyl acetate and formic acid [118,123].

In terms of detection, UV detectors such as diode array (DAD) detectors have been widely utilized for the routine identification and quantification of ETs and EA [114,118]. ETs and EA display characteristic UV spectra with maximum absorbance below 270 nm [124]. They have been frequently determined in pomegranate [124,125], strawberries [126,127], *Rubus* berries and their leaves [128,129], chestnuts [130], as well as waste products of walnuts, chestnuts, pomegranates [131], and pomegranate peels [132]. Mass spectrometry detectors also proved to be valuable tools mainly for the identification of ETs and EA, usually in combination with HPLC/DAD systems. Generally, the negative ion mode of electrospray ionization (ESI) has been employed. Some typical losses during the fragmentation of ETs include galloyl (152 Da), HHDP (302 Da), galloylglucose (332 Da), HHDP-glucose (482 Da), and galloyl-HHDP-glucose (634 Da) [133,134], while fragment ions of EA are frequently observed at m/z 284, 257, 229 and 201 [134]. Importantly, while ET commercial standards are scarce, several scientific groups focusing on the characterization and quantification of ETs often possess isolated compounds that can be used as standards for accurate quantitative determination [53,128,135–137]. Collectively, the tandem use of HPLC/DAD and ESI-MS is a technique that has been widely applied to the identification and quantification of ETs and EA found in different matrices, including raspberries [138], pomegranates [53,120], walnuts [139], wine [140], Madagascar's almonds [141], chestnut trunk samples [142], blueberries [143], Jabuticaba fruits [144], northern red oak (*Quercus rubra* L.) seeds [145], small burnet (*Sanguisorba minor* L.) [146] and Kakadu plum (*Terminalia ferdinandiana*) [137].

Finally, EA was previously determined through Capillary Electrophoresis (CE) in pomegranate rinds [147], industrial pulp samples and their filtrates [148], and Argentinian wines [149]. Fused-silica capillaries of 50 to 60 cm length were the most commonly used and the pH ranged between 8.4 and 9.1. All systems were equipped with a simple UV or DAD detector and the buffers used mostly consisted of boric acid or sodium tetraborate [147–149].

3. Urolithins

3.1. Production of Uros from ETs and EA Metabolism

Uros are bioactive metabolites containing a benzo-coumarin scaffold with differences in hydroxylation patterns. They are primarily produced by the gut microbiota in humans and some animals that receive ETs and EA through their diet [5]. Specifically, urolithin A (Uro-A) is one of the major metabolites of EA and it has exhibited a wide range of bioactivities, such as anti-inflammatory, antioxidant, anticancer, anti-diabetic and neuroprotective, among others [9,10,150–152].

The identification of the Uros formation pathway in humans has been studied and described by Tomas-Barberan et al. in human fecal fermentation studies, as well as in a gastrointestinal simulator model (TWIN-SHIME) [153,154]. The first step in this pathway is a lactone ring cleavage and a subsequent decarboxylation of EA, which is then converted into a pentahydroxy urolithin (Uro-M5) (Figure 2). Consecutive dehydroxylations, catalyzed by different dehydroxylase enzymes, lead to the formation of tetrahydroxy Uros (Uro-E, Uro-M6, Uro-M6R and Uro-D), trihydroxy Uros (Uro-M7, Uro-M7R, Uro-C and

Uro-CR) and dihydroxy Uros (Uro-A, isoUro-A and Uro-AR). Finally, the dehydroxylation of Uro-A or isoUro-A may lead to the monohydroxy Uro (Uro-B) [154].

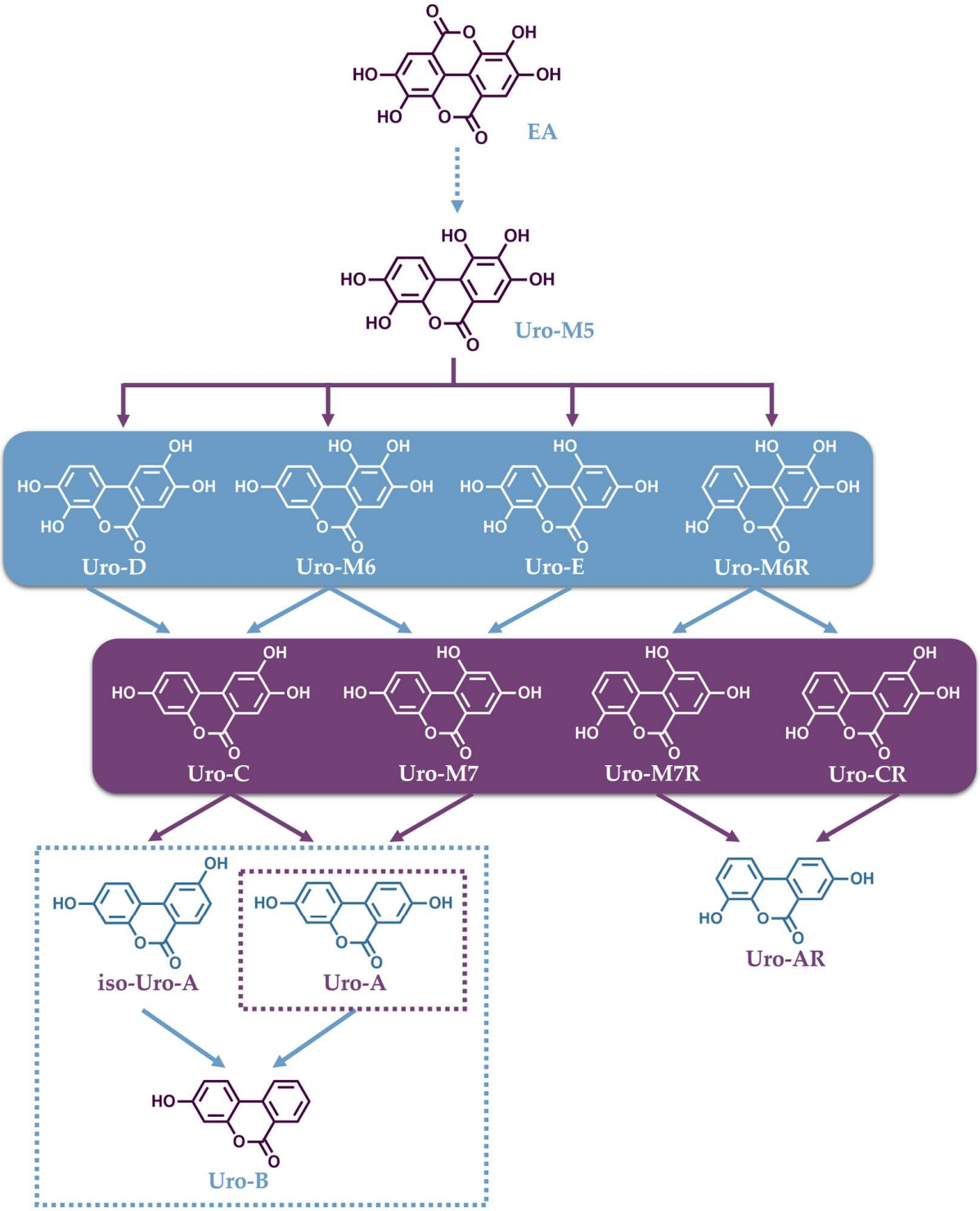

Figure 2. Catabolic pathway for the conversion of ellagic acid into urolithins.

The production of Uros, following ellagitannin-rich food intake, exhibits large variability throughout the population, because it is a process that depends on the gut microbiota composition of each individual. To date, three urolithin-producing metabotypes have been assigned to humans regarding their ability to produce Uros [155]. "Metabotype A" is assigned to individuals who only produce Uro-A conjugates, "metabotype B" to those who produce isoUro-A and/or Uro-B as well as Uro-A, and in individuals categorized as "metabotype 0", none of these urolithins are detected. As mentioned, the different metabotypes are associated with differences in the gut microbiome composition in healthy humans [156], which reportedly depends on aging [157]. In their study, Cortés-Martín et al. reported that individuals assigned with metabotype A represent approximately 70% and metabotype B 20% of the population at the ages between 5 and 30 years. In individuals older than 30 years, these two metabotypes tend to equate with a decline in metabotype A and an increase in metabotype B, while the percentage of metabotype 0 remained close to 10% [157].

The known gut bacteria that characterize different metabotypes by transforming EA to Uros mainly belong to the genera *Gordonibacter* and *Ellagibacter*, which belong to the Eggerthellaceae family. In a recent study, it was confirmed that the genus *Gordonibacter* metabolizes EA into Uro-M5, Uro-M6, and Uro-C, while *Ellagibacter* can convert EA into Uro-M5, Uro-M6, Uro-C and isoUro-A. Both genera could also convert Uro-D and Uro-M6 into Uro-C [158]. Importantly, a novel bacterium *Enterocloster bolteae* from the family Lachnospiraceae was isolated from human feces that could convert Uro-C and isoUro-A into Uro-A and Uro-B [158]. Then, co-cultures of these bacteria, which have complementary activities, were capable of cooperatively reproducing the Uro formation profiles associated with metabotype A and B individuals upon in vitro fermentation. The patented bacterial combinations could pave the way for future probiotic supplements for metabotype 0 individuals [158]. Finally, a new Uro, namely Uro-G, was discovered by the same team, and its occurrence was validated in human fecal samples following the intake of pomegranate ETs. Furthermore, it was indicated that Uro-G is produced from Uro-D in vivo by human *Enterocloster* species and it is the first urolithin bearing a catechol group in the A ring as well as solely one hydroxyl in the B ring, a feature that has not been found in human and animal samples until now [159]. In summary, the genera *Gordonibacter* and *Ellagibacter* can transform EA into different Uros through lactone-ring cleavage, decarboxylation, and further catechol dehydroxylations at 4- and 10-positions, as well as 8- only in the case of *Ellagibacter*, which can also produce Uro-A from Uro-G. In contrast, the *Enterocloster* genera is able to catalyze the dehydroxylation of hydroxyl groups at 9- and 10-positions in both aromatic rings, while Uro-G can only be obtained after the dehydroxylation of Uro-D catalyzed by the *Enterocloster* species that possesses 9-dehydroxylase activity [158].

3.2. Bioavailability of Uros and Their Metabolites

Uros are easily absorbed in the colon and undergo extensive phase II metabolism, resulting in glucuronide and sulfate conjugates that can reach plasma and systemic tissues, eventually being excreted in urine. In animals, the presence of a Uro conjugating in urine and plasma samples has been widely studied. Animals included in such studies were mainly rodents (rats and mice) [160–163], ruminants [164,165], pigs [166], and other mammals [164]. In humans, the levels of Uro-A and Uro-B conjugates have been determined in plasma and urine samples after the intake of ellagitannin-rich foods, such as raspberries [167–172], strawberries [167,173,174], walnuts [167,175–179], oak-aged wine [167], black tea [180], pomegranate products [175,178,181–187] and blackberry juice [188]. In studies regarding human plasma, the main Uro conjugates are detected at micromolar concentrations (Uro-A glucuronide up to 35 μM, Uro-B glucuronide 7.3 μM, and isoUro-A 0.745 μM, respectively) [153]. Moreover, in human urine samples, these metabolites reached concentrations up to 100 μM. Importantly, other conjugates of intermediate metabolites, such as Uro-C and Uro-D glucuronides, have been detected, but are generally less studied due to lack of commercial standards [188]. In some studies, the enzymatic hydrolysis

of Uro glucuronides and sulfates was employed, with the samples being treated with a β-glucuronidase/sulfatase solution and the Uros determined in total (conjugated and non-conjugated) [188–193]. The most common Uros, Uro-A, Uro-B and isoUro-A, have been identified and quantified in their non-conjugated form or as aglycones in the fecal samples or cecal digesta of rats and mice [189–191,194,195], ruminants [165], and other mammals, such as squirrels, beavers [164], and pigs [166]. In humans, the same non-conjugated metabolites have been determined in feces after the consumption of pomegranate extracts or walnuts [5,196,197]. In other human tissues, relatively high levels of Uro-A, -B, -C, -D and isoUro-A, and their glucuronide and sulfate conjugates (42 to 1671 ng/g tissue), were identified in normal and malignant colon tissues following pomegranate extract intake [183]. Furthermore, in human prostate samples, Uro-A glucuronide and Uro-B glucuronide were identified in trace amounts, the following consumption of walnuts or pomegranate juice [175].

Due to the inter-individual differences in Uro pharmacokinetics, bioavailable concentrations vary greatly between individuals. In recent years, physiologically based pharmacokinetic (PBPK) modeling has become an interesting alternative to animal testing, making use of existing physicochemical data and in vitro metabolism data in order to determine the tissue concentrations of chosen compounds. As an example, in a recent study of a PBPK model regarding the post-biotic supplementation of Uro-A, it was suggested that peak concentrations in most tissues were low (nanomolar range), supporting the safety of Uro-A to be used as a post-biotic supplement [198].

3.3. Extraction of Uros from Biological Samples

The importance of Uros and their health benefits as a result of ET and EA metabolism led to the development of appropriate analytical methods regarding their determination, mainly in biological samples. To serve this purpose, the first step was the selection of suitable extraction protocols considering the occurrence of conjugated and non-conjugated forms of Uros in combination with the distinct properties of different matrices. As a result, urine samples were often directly injected after dilution and/or filtration [164,170,172,175,176,178–180,182–185,187,190,197], while plasma, breast milk and tissue samples were extracted with solvents, such as MeOH and ACN (acidified with formic or hydrochloric acid in some cases), to facilitate protein precipitation [162,165,168–170,172,175–179,182,183,186,187,189,191,192,199–202]. Fecal samples were extracted with mixtures of MeOH/H_2O/HCl or formic acid [5,162,164,165,176,178,179,196], and in vitro fecal fermentation cultures were extracted with organic solvents, such as acetone, ethyl acetate or diethyl ether acidified with formic acid in some cases [203–207]. Solid-phase extraction (SPE) was also used as a cleanup technique in more complex matrices. Different cartridges (C18 Sep-pack, Supelclean LC-C18, Bond Elut C18, Oasis HLB, MCX) were chosen for the different samples, and in all cases, water was used as the washing solvent and MeOH as the elution solvent. In some cases, ninety-six well micro-elution SPE was employed, as it is useful for low volumes of samples and it can facilitate high-throughput sample processing [103,165–168,180,181,184,185,188,208–210].

3.4. Analytical Techniques for the Determination of Uros

The methodologies that have been employed throughout the years for the identification and quantification of Uros in biological fluids are summarized in Tables 2 and 3. Methods reported for the determination of Uros in samples originated from animals or in vitro cultures are shown in Table 2, while Table 3 summarizes studies on human biological samples. HPLC and UHPLC were the most common methods employed for the separation of Uros, using reverse phase columns with octadecyl-bonded stationary phases and isocratic or gradient mobile phases consisting of water mixed with acetonitrile or methanol with the addition of formic or acetic acid. In rare cases, a pentafluorophenylpropyl (F5) phase column and an ether-linked phenyl phase column were also successfully utilized for the separation of Uro conjugates [170,208]. The detection and quantification of analytes was usually achieved with the use of UV-diode array detec-

tors (DAD) or photodiode array detectors (PDA) coupled in series with mass spectrometers, such as ion traps (IT) [5,162,165–167,173,175,180,204,205,208,211], triple quadrupoles (QqQ) [168,171,172,174,189,190,192,193,196,199,200,209,212,213], and quadrupole-time of flight (QTOF) systems with electrospray ionization (ESI) sources [169,177–179,182,183,191,203,207]. In detail, the quantification of common Uros was primarily carried out in UV at specific wavelengths (305, 280, 330, 360 nm), and MS was employed for the identification of similar compounds based on differences in their fragmentation patterns. Intermediate Uros (Uro-D, Uro-M6 and Uro-M7), which have not been widely studied, were successfully characterized by Tomás-Barberán et al. with the use of three systems consisting of an LC coupled to a DAD and a QqQ or a QTOF detector. Following the validation of their methodology, it was applied in different biological samples, namely, urine, feces and plasma, after the consumption of ellagitannin-rich sources [178]. These metabolites have since been included in other studies; for example, Uro-M6, Uro-M7, Uro-C, and Uro-D were determined as increasing products of the catabolism of ETs from jaboticaba (*Myrciaria trunciflora*) fruit peel during in vitro colonic fermentation [203]. In a recent study investigating the supplementation of *Gordonibacter urolithinfaciens* in combination with EA in C57BL/6J mice, the predominant metabolites found in cecal content included Uro-C, Uro-M6/Uro-D, and Uro-A [190]. In fact, the co-administration of *Gordonibacter* with EA dramatically promoted EA catabolism and enhanced the production and systemic circulation of Uro-C and Uro-A in particular, especially when compared to the sole administration of EA, overcoming its known low bioavailability and poor absorption [190].

Finally, the presence of different isomers of Uro gluconorides has been previously described [178]. Their determination has not been achieved due to the limitations of the existing methods, mainly their resolution by reversed-phase HPLC. Recently, a novel method for the separation of such isomers using supercritical fluid chromatography (SFC) coupled to a UV detector was reported by Ares et al. utilizing a (S,S) Whelk-O 1 (150 × 4.6 mm, 3.5 µm) column with a mobile phase consisting of a mixture of carbon dioxide and 0.1% (*v*/*v*) trifluoroacetic acid in isopropanol (70:30; *v*/*v*) [214]. They were able to separate Uro-A 3- and 8-glucuronide, isoUro-A 3- and 9- glucuronide, and Uro-B 3-glucuronide in less than 15 min. This method was successfully applied in the analysis of these metabolites in urine samples from volunteers with different metabotypes and for the first time it was indicated that in metabotype B volunteers, the most common isomer of isoUro-A glucoronide was 3-, while both Uro-A glucuronide isomers were found to exist in similar quantities.

Table 2. Summary of reported analytical methods for the determination of urolithins in biological samples derived from animals or in vitro cultures.

Analyte	Sample Type—Origin	Analytical Technique	Instrumental Analysis	Column/Mobile Phase	Sample Preparation—Solvent Extraction	Ref.
Uro-A, Uro-B	Liver, kidney, heart, brain tissue and biofluids (blood and urine) of adult male rats.	UHPLC–MS/MS	Waters Acquity UPLC (Milford, MA, USA) equipped with a binary pump, autosampler, column compartment and an Acquity PDA eλ detector, coupled to a Waters Xevo TQ (Milford, MA, USA) triple quadrupole MS with an electrospray interface.	Waters Acquity UPLC column HSS T3 (100 mm × 2.1 mm, 1.8 mm, Milford, MA, USA). The mobile phase consisted of (A) water/formic acid (99.9:0.1, *v*/*v*) and (B) ACN/formic acid (99.9:0.1, *v*/*v*; flow rate 0.4 mL/min.	Extraction with 95% MeOH.	[212]
Uro-A Uro-A, Uro-B Uro-A-glucuronide	Cecal digesta (Wistar rats): intake of strawberry. Urine, plasma, cecal digesta (Wistar rats): intake of strawberry.	HPLC-PDA	HPLC Knauer Smartline system with photoDAD, (Knauer, Berlin, Germany).	Gemini C18 column (250 × 4.60 mm, 5 µm, Phenomenex, Torrance, CA USA). The mobile phase consisted of (A) 0.05% phosphoric acid in H_2O and (B) 0.05% phosphoric acid in 80% ACN; flow rate 1.25 mL/min.	Extraction with acetone.	[160,161,194]
Uro-A	Cecal digesta (Wistar rats): intake of blackberry.	HPLC-ESI-MS	Dionex UltiMate 3000 UHPLC coupled to a Thermo Scientific Q Exactive quadrupole ion trap MS (Thermo Fisher Scientific, Waltham, MA, USA).	Kinetex 110A C18 column (150 × 2.1 mm, 2.6 µm, Phenomenex, Torrance, CA USA). The mobile phase consisted of (A) 0.1% formic acid in H_2O and (B) 0.1% formic acid in ACN; flow rate 0.5 mL/min.	Extraction with acetone.	[195]
Uros (A, B, C, D, M5, M6 and M7)	Colonic fermentation samples.	HPLC-DAD-QTOFMS/MS	HPLC (CBM-20A Prominence, Shimadzu, Kyoto, Japan) equipped with a degasser (DGU20A5 prominence, Shimadzu, Japan) and column oven (CTO-20A Prominence, Shimadzu, Japan), coupled to DAD (SPDM-20A Prominence, Shimadzu, Japan) and connected to a QTOF MS analyzer and ESI (micrOTOF-QIII, Bruker Daltonics, Bremen, Germany).	C-18 Hypersil Gold column (150 mm × 4.6 mm; 5 µm, Thermo Fisher Scientific, Waltham, MA, USA). The mobile phase consisted of (A) 5% (*v*/*v*) methanol in acidified water (0.1% (*v*/*v*) of formic acid) and (B) 0.1% (*v*/*v*) of formic acid in ACN; flow rate 1.0 mL/min.	Extraction using an acidified acetone solution (0.35% formic acid, *v*/*v*).	[203]
Uro-A, -B, -C, -D	Plasma, liver, prostate, colon tissue and luminal content (C57BL/6 mice): intake of raspberries.	UPLC-MS/MS	UPLC system (ACQUITY, Waters, Milford, MA, USA) coupled to a triple quadrupole MS (Quattro Ultima, Waters, Milford, MA, USA).	BEH C18 Reverse Phase column (2.1 × 50 mm, 1.7 µm, ACQUITY UPLC, Waters). The mobile phase consisted of (A) 1% aqueous formic acid (*v*/*v*) and (B) 1% formic acid in ACN; flow rate 0.3 mL/min.	Samples were treated with β-glucuronidase/sulfatase (S9296, Sigma-Aldrich, St. Louis, MO, USA). Extraction with diethyl ether.	[189]
Uro-A and uro-B	Plasma (CD1 Harlan-Nossan male mice): intake of *E. angustifolium* extract.	UHPLC-MS/MS	Shimadzu Nexera UHPLC system with two LC 30 CE pumps, a SIL 30AC autosampler, a CTO 20AC column oven, and a CBM 20A controller. Coupled to a triple quadrupole LCMS 8050 (Shimadzu, Kyoto, Japan) with an ESI source.	ACQUITY UPLC® BEH C18 column (50 mm × 2.1 mm, 1.7 µm, Waters, Milford, MA, USA). The mobile phase consisted of (A) 0.1% aqueous acetic acid and (B) ACN plus 0.1% acetic acid; flow rate 0.5 mL/min.	Extraction with ice-cold acetonitrile acidified with 98% HCN and 2% HCOOH.	[199]

Table 2. *Cont.*

Analyte	Sample Type—Origin	Analytical Technique	Instrumental Analysis	Column/Mobile Phase	Sample Preparation—Solvent Extraction	Ref.
Uro-B, Uro-C	In vitro gastrointestinal digestion of raspberry extract.	HPLC-MS	Exactive™ Plus Orbitrap MS with an ESI Interface (Thermo Fisher Scientific Inc, USA).	Thermo Hypersil GOLD C18 column (100 mm × 2.1 mm, 3 µm, Thermo Fisher Scientific Inc., USA). The mobile phase consisted of (A) 1% formic acid in water and (B) 1% formic acid in ACN; flow rate 0.35 mL/min.	Filtration by 0.22 µm membrane and direct injection.	[211]
Uro-A	Samples of in vitro un-fermented/fermented pomegranate juice.	HPLC LC-MS/MS	HPLC Waters 1525 Q-Exactive LC-MS/MS (Thermo Fisher Scientific, Shanghai, China).	Hypersil GOLD C18 column (2.1 mm × 100 mm, 1.9 µm, Thermo Fisher Scientific, Shanghai, China). The mobile phase consisted of (A) 0.1% formic acid in water, and (B) ACN; flow rate 0.3 mL/min.	Extraction with diethyl ether and ethyl acetate.	[206]
Uro-A, -B, -C, -M5, -M6, isoUro-A	Samples of in vitro unfermented/fermented pomegranate peels.	HPLC-MS	LC-MS system (G2-XS QTof, Waters Corporation, Milford, MA, United States).	ACQUITY UPLC® BEH C18 column (100 mm × 2.1 mm, 1.7 µm, Waters, Milford, MA, USA). The mobile phase consisted of (A) 0.1% aqueous formic acid and (B) ACN plus 0.1% formic acid; flow rate 0.35 mL/min.	Extraction with ethyl acetate acidified with 1.5% formic acid.	[207]
Uro-M7, Uro-M6, Uro-D, -C, -A	Plasma, liver, cecal content, urine, brain, adipose tissue (C57BL/6J mice): supplementation of *Gordonibacter urolithinfaciens*.	UPLC-MS	Agilent 1290 Infinity II UHPLC system coupled to an Agilent 6460 Triple Quadrupole MS with an ESI source (Agilent Technologies Inc., Santa Clara, CA, USA).	ACQUITY UPLC® BEH C18 column (50 mm × 2.1 mm, 1.7 µm, Waters, Milford, MA, USA). The mobile phase consisted of (A) 0.05% aqueous formic acid and (B) ACN plus 0.05%; flow rate 0.45 mL/min.	Plasma, liver, cecal content, urine samples were treated with *β*-glucuronidase/sulfatase (S9296, Sigma-Aldrich, St. Louis, MO, USA). Extraction with ethyl acetate. Brain and adipose tissue were treated with *β*-glucuronidase/sulfatase. Extraction using an EMR-lipid 96-well plate.	[190]
Uro-A and conjugates	Plasma, liver, and feces (C57BL/6 mice).	HPLC-UV	HPLC system (SPD-M20A DAD, Shimadzu, Kyoto, Japan). UPLCESIMS (Thermo Scientific Orbitrap Elite Mass Spectrometer).	C18 HQ column (4.6 mm × 250 mm, 5 µm, Interchim, Montluçon, France). The mobile phase consisted of 50% MeOH and 50% ddH_2O (0.05% phosphoric acid); flow rate 1.0 mL/min.	Plasma: extraction with MeOH. Liver and feces: ultrasonication and extraction with MeOH:12N HCl:water (79.9: 0.1: 20, *v*/*v*/*v*).	[162]

Table 2. *Cont.*

Analyte	Sample Type—Origin	Analytical Technique	Instrumental Analysis	Column/Mobile Phase	Sample Preparation—Solvent Extraction	Ref.
Uros and their conjugates	Plasma, urine, feces, ruminal content from animals and beaver castoreum.	HPLC-DAD-MS/MS and HPLC-TOF-MS/MS	HPLC system with a binary pump (G1312A), an autosampler (G1313 A), a degasser (G1322A) and an Agilent 1100 series diode array and a mass detector in series (Agilent Technologies, Waldbronn, Germany). HPLC-TOF-MS Agilent 6220 system with an HPLC system Agilent 1200 series DAD (Agilent Technologies, Waldbronn, Germany).	LiChroCART (C_{18}) column (25 cm × 0.4 cm, 5 µm, Merck, Darmstadt, Germany). The mobile phase consisted of (A) 5% aqueous formic acid and (B) ACN; flow rate 1.0 mL/min.	Feces: extraction with MeOH/HCl/water (79.9:0.1:20, *v*/*v*/*v*).	[164]
Uro-A	Plasma, hippocampus and cortex (C57BL/6J mice).	HPLC-ESI-MS/MS	LC-MS/MS-18, TQ6500+ Triple quad (AB Sciex Pte. Ltd., USA) with an ESI interface (Waters, Milford, MA, USA).	Waters CORTECS T3 column (2.1 mm × 100 mm, 2.7 µm, Waters, Milford, MA, USA). The mobile phase consisted of (A) 0.1% formic acid in Milli-Q water and (B) 0.1% formic acid in MeOH; flow rate 0.50 mL/min.	Extraction with MeOH.	[201]
Uro-C	Rat plasma.	LC-ESI–MS/MS	Agilent 1100 LC system (Agilent Technologies, Les Ulis, France) coupled to an API 3000 tandem triple quadrupole MS (ABSciex, Courtaboeuf, France).	C18 Kinetex EVO column (2.1 × 150 mm, 2.6 µm, Phenomenex, Le Pecq, France). The mobile phase consisted of (A) 1% formic acid in water and (B) ACN; flow rate 0.20 mL/min.	Extraction with ethyl acetate.	[213]
Uro-A, -B, -C, -D and their conjugates	Plasma, urine, bile, intestinal lumen, feces, organs and tissues (iberian pigs).	HPLC-DAD-MS/MS	HPLC system (Agilent Technologies, Waldbronn, Germany) equipped with a DAD and an ion-trap mass detector in series with a binary pump and autosampler and an ESI system (Agilent Technologies, Waldbronn, Germany).	LiChroCART (C_{18}) column (25 cm × 0.4 cm, 5 µm, Merck, Darmstadt, Germany) The mobile phase consisted of (A) 1% aqueous formic acid and (B) ACN; flow rate 1.0 mL/min.	Filtration through a reverse phase C18 Sep-Pak cartridge (Millipore Corp., Burlington, MA, USA). Wash with distilled water (10 mL), elution with MeOH.	[166]
Uro-A and conjugates	Plasma and tissues (C57BL/6 wild-type mice). intake of pomegranate juice and extract.	HPLC-ESI/MS	LCQ Classic Finnigan system (ThermoFinnigan, San Jose, CA, USA), equipped with an Agilent HP 1100 series HPLC (Santa Clara, CA, USA) system consisting of an autosampler/injector, quaternary pump, column heater, and DAD.	Symmetry C18 column (100 mm × 2.1 mm, 3.5 µm, Waters, Milford, MA, USA). The mobile phase consisted of (A) 2% formic acid in water and (B) 2% formic acid in MeOH; flow rate 0.15 mL/min.	Homogenization in MeOH with 0.1% acetic acid.	[163]

Table 2. *Cont.*

Analyte	Sample Type—Origin	Analytical Technique	Instrumental Analysis	Column/Mobile Phase	Sample Preparation—Solvent Extraction	Ref.
Uro-A, -B, -C, -M6, isoUro-A and their conjugates	Rumen, feces, plasma and urine (brown swiss bulls).	HPLC-DAD-MS-MS	A HPLC system equipped with a photo-DAD (1100 series, Agilent Technologies, Waldbronn, Germany) in series with an ion-trap MS detector (Bruker Daltonics, Bremen, Germany).	LiChroCART (C_{18}) column (25 cm × 0.4 cm, 5 µm, Merck, Darmstadt, Germany). The mobile phase consisted of (A) 1% aqueous formic acid and (B) ACN; flow rate 1.0 mL/min.	Rumen: Sep-Pak C18 cartridge (Waters, Milford, MA, USA). Wash with distilled water, elution with MeOH. Feces: homogenization with MeOH:HCl:water (79.9/0.1/20, *v*/*v*/*v*). Plasma: extraction with ACN:formic acid (99:1, *v*/*v*).	[165]
Uro-A	Plasma and brain tissue (albino Wistar rats with PD)	UPLC-ESI-QTOF-MS	Agilent 1290 Infinity (Agilent, Les Ulis, France) equipped with an ESI-QTOF-MS (Agilent 6530 Accurate Mass, Agilent, Les Ulis, France).	Eclipse Plus C18 column (2.1 × 100 mm, 1.8 µm, Agilent, Les Ulis, France). The mobile phase consisted of (A) water with 0.1% formic acid and (B) methanol with 0.1% formic acid; flow rate 0.3 mL/min.	Plasma: extraction with ACN: formic acid (98:2, *v*/*v*) Brain: extraction with methanol:HCl (99.9:0.1 *v*/*v*). Samples were treated with β-glucuronidase/sulfatase (S9296, Sigma-Aldrich, Poznań, Poland).	[191]
Uro-M5, -M6, -A, -C, isoUro-A	In vitro cultures of *G. urolithinfaciens* and *E. isourolithinifaciens*.	HPLC-DAD-ESI-IT	Agilent 1100 HPLC system coupled to DAD (Agilent Technologies, Waldbronn, Germany) and an ion trap MS (Esquire 1100 with an ESI source, Brüker Daltoniks).	Poroshell 120 EC-C18 column (3 × 100 mm, 2.7 µm, Agilent Technologies, Waldbronn, Germany). The mobile phase consisted of (A) 1% aqueous formic acid (*v*/*v*) and (B) ACN; flow rate 0.5 mL/min.	Extraction with ethyl acetate.	[205]

Table 3. Summary of reported analytical methods for the determination of urolithins in human biological samples.

Analyte	Sample Type—Origin	Analytical Technique	Instrumental Analysis	Column/Mobile Phase	Sample Preparation—Solvent Extraction	Ref.
Uro-B-glucuronide and aglycone Uro-A	Urine (healthy volunteers): intake of strawberries, raspberries, walnuts, and oak-aged wine. Feces (healthy volunteers): intake of walnuts. Fecal suspensions.	LC-MS/MS	HPLC binary pump, autosampler, and degasser (Agilent Technologies, Waldbronn, Germany) coupled to an ion-trap MS equipped with an ESI system (Agilent Technologies, Waldbronn, Germany).	LiChroCART (C_{18}) column (25 cm × 0.4 cm, 5 µm, Merck, Darmstadt, Germany). The mobile phase consisted of (A) 5% aqueous formic acid and (B) MeOH; flow rate 1.0 mL/min.	Urine: Sep-Pak C-18 solid phase extraction cartridge (Waters Millipore, United States). Wash with water elution with MeOH. Feces: extraction with MeOH:H_2O:HCOOH (80:19.9:0.1, *v*/*v*). Fecal suspensions: extraction with diethyl ether.	[5,167]
Uro-A-glucuronide, Uro-B-glucuronide	Prostate, urine and plasma samples (prostate cancer patients): intake of pomegranate or walnuts.	HPLC-DAD-MS/MS	HPLC-DAD system (1200 series, Agilent) coupled to an HTC Ultra ion-trap mass detector (Bruker Daltonics, Bremen, Germany).	SB C18 Zorbax column (150 mm × 0.5 mm, 5 mm, Agilent Technologies, Waldbronn, Germany). The mobile phase consisted of (A) water/formic acid (99:1, *v*/*v*) and (B) ACN; flow rate 10.0 mL/min.	Prostate samples: extraction with cold MeOH:HCl:H_2O (79.9:0.1:20, *v*/*v*/*v*). Plasma: extraction with ACN.	[175]
Uro-A-glucuronide, Uro-B-glucuronide	Urine (human subjects): black tea intake	HPLC-PDA-FTMS^n	Accela HPLC tower connected to an LTQ/Orbitrap hybrid MS (Thermo Fisher Scientific).	Luna C18 column (2.0 × 150 mm, 3 mm, Phenomenex, Torrance, CA, USA). The mobile phase consisted of (A) water/formic acid (99.9:0.1, *v*/*v*) and (B) ACN/formic acid (99.9:0.1, *v*/*v*); flow rate 0.19 mL/min.	HLB SPE cartridge (OASIS, Waters, Milford, MA, USA). Wash with water, elution with MeOH.	[180]
Uro-A, B, C, D and their glucuronides	Urine, plasma, fecal samples (healthy volunteers): intake of walnuts.	HPLC-ESI-MS	Agilent 1100 HPLC, coupled to a HP1101 single-quadrupole, mass-selective detector (Agilent Technologies, Waldbronn, Germany).	RP-18 (250 mm × 4.5 mm, 5 µm, Latek, Eppelheim, Germany). The mobile phase consisted of (A) 2% acetic acid in water and (B) ACN.	Plasma: extraction with 0.2 M hydrochloric acid and EtOH. Feces: extraction with MeOH.	[176]
Uro-A, B, C, D, isoUro-A	Feces (healthy volunteers): intake of pomegranate juice.	UPLC–MS/MS	Waters Acquity Ultra-Performance^{TM} LC system (Waters, Milford, MA, USA), equipped with a binary pump system, coupled to a triple quadrupole detector (TQD) MS (Waters, Milford, MA, USA) with a Z-spray electrospray interface.	Acquity BEH C18 (100 mm × 2.1 mm, 1.7 µm, Waters, Milford, MA, USA). The mobile phase consisted of (A) Milli-Q water:acetic acid (99.8:0.2, *v*/*v*) and (B) ACN; flow rate 0.3 mL/min.	Extraction with MeOH/HCl/H_2O (79.9:0.1:20, *v*/*v*/*v*).	[196]
Uro-A	Stool and urine (healthy volunteers): intake of pomegranate juice.	HPLC-DAD	Surveyor HPLC system equipped with DAD, and an autosampler (Thermo Finnigan, San Jose, USA).	Agilent Zorbax SB C-18 column (250 × 4.6 mm, 5 µm, Agilent Technologies, Waldbronn, Germany). The mobile phase consisted of (A) 0.1% phosphoric acid in H_2O and (B) ACN; flow rate 0.75 mL/min.	Stool: extraction with DMSO. Samples were treated with β-glucuronidase/sulfatase.	[197]

Table 3. *Cont.*

Analyte	Sample Type—Origin	Analytical Technique	Instrumental Analysis	Column/Mobile Phase	Sample Preparation—Solvent Extraction	Ref.
Uro-A, -B, -C, -D	Urine and plasma (healthy men) Urine and plasma (prostate cancer patients)	UPLC-ESI-MS/MS	UPLC system (Acquity UPLC, Waters Corp., Milford, MA, USA) coupled to a triple quadrupole MS (Quattro Ultima, Waters Corp., Beverley, MA, USA).	BEH C18 (50 × 2.1 mm, 1.7 µm). The mobile phase consisted of (A) 1% formic acid in H_2O and (B) 1% formic acid in ACN; flow rate 0.75 mL/min.	Samples were treated with *β*-glucuronidase/sulfatase (S9626, Sigma Chem. Co., St Louis, MO, USA). Urine: extraction with diethyl ether. Plasma: extraction with 2:1 ACN:water.	[192]
Uro-A, -B, -C, -D and their conjugates	Urine and plasma (healthy subjects): intake of grumixama.	HPLC-MS	Prominence LC (Shimadzu, Japan) coupled to microTOF-Q II (Bruker Daltonics, Billerica, MA, USA).	Prodigy ODS3 column (250 × 4.60 mm, 5 µm, Phenomenex Ltd., Cheshire, UK). The mobile phase consisted of (A) 0.5% formic acid in H_2O and (B) 0.5% formic acid in ACN; flow rate 1.0 mL/min.	SPE in a C18 column (0.3 g, Supelclean LC-C18alkyl, Supelco, Bellefonte, PA, USA) and a CC6 polyamide column (Macherey-Nagel GmbH and Co., Duren, Germany). Wash with oxalic acid, elution with MeOH (5% TFA).	[103]
Uro-A, -B, isoUro-A glucuronides	Plasma (healthy older volunteers): intake of strawberry.	HPLC-MS	Agilent 1290 Infinity UHPLC system coupled to an Agilent 6460 Triple Quadrupole MS (Agilent Technologies, Santa Clara, CA, USA).	Poroshell 120 stablebond C18 column (2.1 mm × 150 mm, 2.7 µm). The mobile phase consisted of (A) 1% formic acid in H_2O and (B) ACN; flow rate 0.3 mL/min.	C18 SPE cartridges (Agilent Technologies, Santa Clara, CA, USA). Wash with water (1% formic acid). Elution with methanol (1% formic acid) and acetone (1% formic acid).	[174]
Uro-A, -B, isoUro-A and their conjugates	Plasma and urine (adults with prediabetes and insulin resistance): intake of fructo-oligosaccharide supplemepnts. Intake of red raspberries	UHPLC-QQQ	UHPLC system coupled with a triple quadrupole tandem MS model 6460 (UHPLC-QQQ, Agilent Technologies, Santa Clara, CA, USA)	Poroshell 120 SB-C18 Stable Bond column (2.1 × 150 mm, 2.7 µm). The mobile phase consisted of (A) 1% aqueous formic acid (*v*/*v*) and (B) ACN; flow rate 0.3 mL/min.	SPE C18 cartridges (Agilent Technologies, Waldbronn, Germany).	[168,209]
UA and conjugates	Fecal samples and plasma (healthy subjects): intake of pomegranate juice.	HPLC MS/MS	Agilent 1200 HPLC system (Agilent Technologies, Waldbronn, Germany) coupled to a TSQ Vantage triple-stage quadropole MS/MS (ThermoFisher Scientific, San Jose, CA, USA)	C18 reverse phase column (YMC Co., Ltd., Kyoto, Japan).	Plasma: SPE with a Bond-Elut focus plate (Agilent Technologies, Waldbronn, Germany). Wash with water, elution with MeOH.	[181]

Table 3. *Cont.*

Analyte	Sample Type—Origin	Analytical Technique	Instrumental Analysis	Column/Mobile Phase	Sample Preparation—Solvent Extraction	Ref.
Urolithin A, B, C, D, M6, M7, isoUroA and conjugates	Human breast milk: walnut Intake.	UPLC-ESI-QTOF	Agilent 1290 Infinity UPLC system coupled to a 6550 Accurate-Mass QTOF (Agilent Technologies, Waldbronn, Germany)	Poroshell 120 EC-C18 column (3 × 100 mm, 2.7 µm). The mobile phase consisted of (A) 0.1% aqueous formic acid (*v*/*v*) and (B) ACN plus 0.1% formic acid; flow rate 0.5 mL/min.	Extraction with ACN/formic acid (99:1, *v*/*v*).	[177]
Uro-A, -B, isoUro-A and conjugates	Plasma (subjects with T2DM): intake of red raspberry. Urine (subjects with metabolic syndrome): intake of pomegranate extract.	UPLC-ESI-QTOF-MS/MS	Agilent 1290 Infinity UPLC system coupled to a 6550 Accurate-Mass QTOF (Agilent Technologies, Waldbronn, Germany)	Poroshell 120 EC-C18 column (3 × 100 mm, 2.7 µm). The mobile phase consisted of (A) 0.1% aqueous formic acid (*v*/*v*) and (B) ACN plus 0.1% formic acid; flow rate 0.4 mL/min.	Extraction with ACN/formic acid (98:2, *v*/*v*).	[169,182]
Uro-A, -B	Plasma (healthy subjects): intake of pomegranate extract.	UHPLC-MS/MS	Agilent 1290 Infinity II LC (Agilent Technologies, Santa Clara, CA, USA), equipped with a binary solvent manager, sample manager, and heated column compartment coupled to a 6470 triple quadrupole MS detector.	Agilent ZORBAX Eclipse Plus C18 column (50 mm × 2.1 mm, 1.8 µm, Agilent Technologies, Santa Clara, CA, USA). The mobile phase consisted of (A) 0.1% aqueous formic acid and (B) ACN plus 0.1% formic acid; flow rate 0.4 mL/min.	Extraction with ACN (2% formic acid).	[200]
Uro-A and Uro-B aglycone, glucuronide and sulfate conjugates	Urine (adolescents with metabolic syndrome)	HPLC -LTQ-Orbitrap-HRMS	Accela chromatograph (Thermo Scientific, Hemel Hempstead, UK) equipped with a quaternary pump and a thermostated autosampler.	Kinetex F5 100 Å (50 × 4.6 mm, 2.6 µm, Phenomenex, Torrance, CA, USA). The mobile phase consisted of (A) 0.05% aqueous formic acid and (B) ACN plus 0.05% formic acid; flow rate 0.5 mL/min.	Oasis 96-well reversed-phase phase extraction plates (Waters, MA, USA). Wash with 1.5M formic acid and 0.5% MeOH, elution with MeOH.	[208]
Uro-A, -B, isoUro-A and their conjugates	Plasma, urine and colon tissue (colorectal cancer patients): intake of pomegranate extract.	UPLC-ESI-QTOF-MS/MS	Agilent 1290 Infinity UPLC system coupled to the 6550 Accurate-Mass quadrupole TOF MS (Agilent Technologies, Waldbronn, Germany).	Poroshell 120 EC-C18 column (3 × 100 mm, 2.7 µm). The mobile phase consisted of (A) 0.1% aqueous formic acid (*v*/*v*) and (B) ACN plus 0.1% formic acid; flow rate 0.4 mL/min.	Colon tissue: extraction with MeOH:HCl (99.9:0.1 *v*/*v*). Plasma samples: extraction with ACN:formic acid (98:2, *v*/*v*). Urine samples: dilution with water containing 0.1% formic acid.	[183]
Uro-A, -B, -C, -D and their conjugates	Urine (metabolic syndrome subjects): intake of nuts.	LC-PDA-QqQ-MS/MS	API 3000 triple-quadrupole MS (ABSciex, Concord, ON, Canada) equipped with a Turbo Ionspray source coupled to an Acquity UPLC with a Waters binary pump system (Waters, Milford, MA, USA).	Luna C18 analytical column (50 × 2.0 mm, 5 µm; Phenomenex, Torrance, CA, USA). The mobile phase consisted of (A) water/ACN/formic acid, 94.9:5:0.1 (*v*/*v*/*v*) and (B) ACN/formic acid, 99.9:0.1 (*v*/*v*); flow rate 0.4 mL/min.	Acidification with acetic acid, incubation with *β*-glucuronidase/sulfatase and solid-phase extraction (Oasis MCX 96-well plates, Waters, Mildford, MA, USA)	[193]

Table 3. *Cont.*

Analyte	Sample Type—Origin	Analytical Technique	Instrumental Analysis	Column/Mobile Phase	Sample Preparation—Solvent Extraction	Ref.
Uro-A glucuronide	Human plasma and urine: intake of strawberries.	HPLC-MS/MS	HPLC system equipped with a diode array absorbance detector and an autosampler (Thermo Finnigan, San Jose, CA, USA) coupled to an LCQ Advantage ion trap MS (Thermo Finnigan).	Agilent ZORBAX SB C18 column (150 mm × 2.1 mm, 5 µm, Agilent Technologies, Santa Clara, CA, USA). The mobile phase consisted of (A) 1% aqueous acetic acid and (B) ACN; flow rate 0.190 mL/min.	SPE cartridge (Sep-Pak C18 Plus, Waters)	[173]
Uro-A, Uro-B glucuronides	Plasma and urine (healthy volunteers): intake of pomegranate juice. Breast milk, plasma and urine (mothers and infants): intake of pomegranate juice.	LC-MS/MS	LCQ Classic Finnigan system (ThermoFinnigan, San Jose, CA, USA), equipped with an Agilent HP 1100 series HPLC (Santa Clara, CA, USA) system consisting of an autosampler/injector, quaternary pump, column heater, and DAD.	Symmetry C18 column (100 mm × 2.1 mm, 3.5 µm, Waters, Milford, MA, USA). The mobile phase consisted of (A) 2% formic acid in water and (B) 2% formic acid in MeOH; flow rate 0.15 mL/min.	Extraction with ACN and SPE on C18 cartridges (Waters WAT 036945). Wash with water and elution with MeOH.	[184,185]
Uro-A	Breast milk (healthy volunteers)	HPLC and HPLC-MS/MS	HPLC (1260 Series, Agilent Technologies, Waldbronn, Germany). HPLC-MS/MS (Thermo Fisher, Waltham, MA, USA).	ZORBAX SB-C18 column (250 × 4.6 mm, 5.0 µm, Agilent Technologies, Santa Clara, CA, USA). The mobile phase consisted of (A) 1% MeOH and (B) ACN; flow rate 1.0 mL/min.	Extraction with ACN:H_2O:HCOOH (80:19.9:0.1).	[202]
Uro-A, -B, -C, -D, -M7, isoUro-A and their conjugates	Urine, feces and plasma (healthy volunteers): intake of walnuts and pomegranate extract.	UPLC-ESI-QTOF-MS	Agilent 1290 Infinity UPLC system coupled to a 6550 Accurate-Mass QTOF (Agilent Technologies, Waldbronn, Germany).	Poroshell 120 EC-C18 column (3 × 100 mm, 2.7 µm, Agilent Technologies, Waldbronn, Germany). The mobile phase consisted of (A) 0.5% aqueous formic acid (*v*/*v*) and (B) ACN; flow rate 0.5 mL/min.	Urine: dilution with water containing 0.1% formic acid. Feces: homogenization with MeOH/H_2O (80:20) and 0.1% HCl. Plasma: extraction with ACN:formic acid (98:2, *v*/*v*).	[178,179]
Uro-A, -B and conjugates	Plasma (healthy volunteers): intake of pomegranate extract.	HPLC-MS	HPLC system (Agilent Technologies, Waldbronn, Germany) equipped with a DAD and mass detector in series with a binary pump and autosampler (Agilent Technologies, Waldbronn, Germany).	LiChroCART (C_{18}) column (25 cm × 0.4 cm, 5 µm, Merck, Darmstadt, Germany) The mobile phase consisted of (A) 5% aqueous formic acid and (B) MeOH; flow rate 1.0 mL/min.	Homogenization with MeOH:0.2 M HCl (1:1, *v*/*v*).	[186]
Uro-A and conjugates	Plasma and urine (healthy human subjects): intake of pomegranate juice and extract.	HPLC-ESI/MS	LCQ Classic Finnigan system (ThermoFinnigan, San Jose, CA, USA), equipped with an Agilent HP 1100 series HPLC (Santa Clara, CA, USA) system consisting of an autosampler/injector, quaternary pump, column heater, and DAD.	Symmetry C18 column (100 mm × 2.1 mm, 3.5 µm, Waters, Milford, MA, USA). The mobile phase consisted of (A) 2% formic acid in water and (B) 2% formic acid in MeOH; flow rate 0.15 mL/min.	Human plasma: extraction with ACN. Human urine: dilution with H_2O (2% formic acid)/methanol (9:1 *v*/*v*).	[187]

Table 3. *Cont.*

Analyte	Sample Type—Origin	Analytical Technique	Instrumental Analysis	Column/Mobile Phase	Sample Preparation—Solvent Extraction	Ref.
Uro-A, -B and conjugates	Plasma and urine (healthy volunteers and subjects with an ileostomy): intake of raspberries.	HPLC-PDA-MS^2	Surveyor HPLC system with an HPLC pump, PDA detector and an autosampler (Thermo Finnigan, San Jose, CA, USA).	Synergi RP-Polar (250 × 4.6 mm, 4 µm, Phenomenex, Macclesfield, UK). The mobile phase consisted of (A) 1% formic acid in water and (B) 1% formic acid in MeOH; flow rate 1.0 mL/min.	Homogenization in MeOH/water/formic acid (95:4:1, *v*/*v*/*v*).	[170]
Uro-A, -B, -M5, -M6, -M7, -C, isoUro-A and Uro-E and their conjugates	Feces and urine (healthy volunteers) and in vitro fermentation samples.	LC-UV/Vis and LC-MS/MS	A HPLC system equipped with a photo-DAD (1100 series, Agilent Technologies, Waldbronn, Germany) in series with an ion-trap MS detector (Bruker Daltonics, Bremen, Germany).	LiChroCART (C_{18}) column (25 cm × 0.4 cm, 5 µm, Merck, Darmstadt, Germany). The mobile phase consisted of (A) 1% aqueous formic acid and (B) ACN; flow rate 1.0 mL/min.	Feces: homogenization with MeOH/DMSO/H_2O (40:40:20) with 0.1% HCl. Human faecal suspensions: Extraction with ethyl acetate acidified with 1.5% formic acid.	[204]
Uro-A, -B, -C and their conjugates	Plasma (healthy volunteers): intake of French oak wood extract (Robuvit).	HPLC-ESI-MS/MS	Perkin-Elmer series 200 HPLC system coupled to an Applied Biosystems (Foster City, CA, USA) API 3200 instrument with a Turbo ion-spray source.	Restek Ultra C18 column (100 × 2.1 mm, 3 µm). The mobile phase consisted of (A) 1% aqueous formic acid and (B) ACN with 1% formic acid; flow rate 0.3 mL/min.	HLB solid-phase extraction cartridge (OASIS, Waters, Milford, MA, USA) Wash with water, elution with MeOH.	[210]
Uro-A, Uro-B, Uro-C, Uro-D, Uro-M5 and conjugates	Urine (healthy volunteers): intake of blackberry juice.	UPLC-DAD/ESI-Q-TOF/MS	Waters Acquity UPLC-PDA coupled to a Quadrupole Time-Of-Flight Mass Spectrometer (ESI-Q-TOF/MS) (Waters Synapt G1, Waters Corp., Milford, MA, USA).	ACQUITY UPLC C18 CSH (100 × 2.1 mm, 1.7 µm, Waters, Milford, MA, USA). The mobile phase consisted of (A) water/formic acid (99.9:0.1, *v*/*v*) and (B) ACN/formic acid (99.9/0.1 *v*/*v*); flow rate 0.4 mL/min.	SupelcleanTM LC-18 extraction cartridges (Supelco Analytical, USA). Wash with MilliQ water, elution with MeOH.	[188]
Uro-A and conjugates	Plasma and urine (human subjects): intake of raspberry drink.	UHPLC-QQQ	UHPLC system coupled with a 6460 Series Triple Quadrupole (QQQ) (Agilent Technologies, Santa Clara, CA, USA).	Poroshell C18 Stable Bond column (2.1 × 150 mm, 2.7 µm; Agilent Technologies, Santa Clara, CA, USA). The mobile phase consisted of (A) water with 1% formic acid and (B) ACN.	Plasma: SPE C18 cartridges (Agilent Technologies, Santa Clara, CA, USA) Urine: filtration with a 0.2 µm Polypropylene syringe filter (Whatman, Maidston, UK).	[171]
Uro-A, -B, -C, -D and conjugates	Urine and plasma (men with prostate cancer): consumption of black raspberry products.	HPLC-MS/MS	UPLC system (Acquity UPLC, Waters Corp., Milford, MA, USA) coupled to a triple quadrupole MS (Quattro Ultima, Waters Corp., Beverley, MA, USA).	BEH C18 column (50 × 2.1 mm, 1.7 µm). The mobile phase consisted of (A) water with 1% formic acid and (B) ACN with 1% formic acid; flow rate 0.75 mL/min.	Urine: samples were treated with *β*-glucuronidase/sulfatase (S9626, Sigma Chem. Co., St Louis, MO, USA). Extraction with diethyl ether. Plasma: extraction with ACN.	[172]

4. Current Research on the Bioactivities of Urolithins on Human Health

Recent studies have demonstrated the beneficial effects of Uro-A supplementation in human health and highlighted Uro-A as a promising healthspan promoting and anti-aging compound. Derived from ETs, Uro-A sustains cellular and tissue homeostasis primarily by inducing mitochondrial selective autophagy, known as mitophagy, as demonstrated in both in vitro and in vivo studies using mammalian cells, the nematode *Caenorhabditis elegans* and mouse models [215]. Mitophagy efficiency declines with age and in several age-associated pathologies, including myopathies, neurodegenerative diseases and autoimmunities, among others [9]. Notably, mitophagy induction restores the age-dependent mitochondrial damage and rejuvenates cellular fitness by promoting mitochondrial activity and energy metabolism, leading eventually to improved muscle function, neuronal homeostasis, healthspan and lifespan extension [9,10,216,217].

Emerging findings from in vivo animal models highlight the potential therapeutic effects of Uro-A supplementation on both tissue-specific diseases, such as neurodegenerative disorders, cardiovascular pathologies, and myopathies, and systemic diseases, including metabolic syndrome and cancer. In preclinical models of cardiac ischemia, atherosclerosis, and diabetic cardiomyopathy, Uro-A treatment has been shown to improve animals' physiology. Notably, in a mouse model of ischemia-reperfusion injury, pretreatment with Uro-A reduced infarct size and partially preserved ejection fraction. This was accompanied by decreased levels of circulating creatine kinase and lactate dehydrogenase, along with a reduction in apoptotic cells in the heart [218]. Additionally, Uro-A has been found to protect rats from atherosclerosis by lowering plasma lipid levels and reducing aortic lesions [219]. In models of diabetic cardiomyopathy, Uro-A enhanced myocardial contractility, underscoring its protective role in heart health [220].

Several studies have demonstrated the neuroprotective impact of Uro-A on various neurodegenerative conditions across species. Uro-A has been shown to enhance associative learning and memory in transgenic nematodes overexpressing the human amyloid-beta (Aβ1–42) and Tau proteins. It also improved learning, memory retention, neuronal survival, and neurogenesis in the hippocampus of APP/PS1 mice, a model of Alzheimer's disease (AD). Additionally, Uro-A reduced levels of insoluble Aβ1–42 plaques and phosphorylated Tau, which are significant biomarkers associated with the development and severity of AD [221,222]. In models of ischemic stroke and multiple sclerosis, Uro-A decreased infarct volume and neurological deficits, and diminished the incidence and severity of multiple sclerosis, as well as inflammation and demyelination [223,224]. Furthermore, UA displayed a robust anti-inflammatory effect, resulting in reduced levels of IL-1β, IL-6 and TNFα in brain samples from AD mice [221,222]. Further supporting its anti-inflammatory function, Uro-A enhanced microglial phagocytic activity and inhibited inflammasome activation, thereby regulating neuroinflammation in AD mice [221,225]. Expanding its therapeutic potential against inflammatory diseases, Uro-A administration showed protective effects against inflammatory bowel diseases, such as ulcerative colitis and Crohn's disease. These pathologies, caused by a deregulated immune system leading to chronic inflammation and microbial dysbiosis, displayed a reduction in colon inflammation markers and improved mucosal integrity in different mouse models [226–229].

In 2017, the first safety assessment of Uro-A in Wistar rats was reported, where Uro-A did not indicate any target organ toxicities, adverse effects or mortality after repeated oral doses in 28- and 90-day studies. The no-observed-adverse-effect level (NOAEL) was the highest dose tested, corresponding to 5% UA by weight in the diet, or 3451 mg/kg bw/day in males and 3826 mg/kg bw/day in females [230]. When these values are applied to humans, the estimated Uro-A value is approximately 600 mg Uro-A/kg bw, applying a scaling factor of 6.2 for rat-to-human conversion [231]. Moreover, the safety and efficacy of Uro-A were highlighted in its first-in-human clinical trial, establishing favorable bioavailability and no adverse effects at doses ranging from 250 to 2000 mg, which supports Uro-A use as a safe supplement ingredient [232]. In 2018, the U.S. Food and Drug Administration (FDA) officially recognized Uro-A as safe for inclusion in food

products and supplements at typical use levels of 250 mg/serving or 500 mg/serving up to a maximum of 500 mg/serving or 1000 mg/serving [233]. Additionally, in a randomized clinical trial in older adults where Uro-A was supplemented at doses of 1000 mg, it was well tolerated and its long-term supplementation benefited muscle endurance and plasma biomarkers [234]. Further supporting the beneficial effects of Uro-A on cellular and tissue homeostasis, a randomized clinical trial showed that middle-aged adults administered with Uro-A at doses of 500 and 1000 mg exhibited improvements in biomarkers related to mitochondrial function, cellular health, and muscle performance, confirming Uro-A's effectiveness in critical aspects of human physiology [235]. Notably, these trials underscore Uro-A potential for practical dietary interventions. Interestingly, in a study where the levels of Uro-A obtained from dietary supplementation were compared to natural dietary exposure in a healthy population, it was established that in order to achieve the equivalent dosing of 500 mg supplemented Uro-A from dietary exposure via pomegranate juice, an individual would need to drink approximately 1.5 L on average, as that would contain the necessary dietary precursors [181].

In terms of safety for the supplementation of Uro-A's precursors ETs and EA, limited information is available. As previously mentioned, in an EA subchronic toxicity study conducted on F344 rats, no treatment-related adverse effects or mortality were observed with an estimated no-observed-effect level (NOEL) of 3011 mg/kg bw for male rats and a NOAEL of 3254 mg/kg bw for female rats (5% in the diet) [35]. Importantly, in a study conducted in type 2 diabetic patients supplemented with EA for 8 weeks at doses of 180 mg/day, reduced levels of blood sugar, blood lipids, and insulin resistance were reported with no adverse effects being observed [236]. Regarding ETs, punacalagin was evaluated for its possible toxic effect in Sprague Dawley rats upon the repeated administration of a diet containing 20% pomegranate husk extract with an average of 6% punicalagin for 37 days. The mean oral consumption throughout the study was reported to be 4800 mg punicalagin/kg bw/day and no significant adverse effects were reported apart from a decrease in serum urea and triglyceride values, although these values remained within the normal range [237]. In another study, the acute oral median lethal dose (LD_{50}) of a pomegranate fruit extract containing 30% punicalagins in mice and rats was found to be greater than 5 g/kg body weight and the NOAEL for a subchronic 90-day study in Wistar rats treated with this extract was 600 mg/kg bw/day, which was the highest dose tested, presenting no toxicologically significant changes [238]. As an exception, in a study on ellagitannin metabolism following the consumption of jabuticaba fruit in a non-European population, 63% of subjects reported the occurrence of diarrhea, a side effect that was attributed to the high amount of ellagitannins consumed (1493 mg of ETs, EA and gallic acid in total) [239]. It is worth noting that numerous association studies involving diets and supplements rich in ETs, such as pomegranate and raspberry extracts, or walnuts, have reported health benefits linked to Uros production. For instance, the intake of a standardized oral pomegranate extract containing 75 mg of punicalagins was recently associated with an increase in short-chain fatty acid-producing bacteria in the gut, as well as improvements in the skin microbiome and reduction in skin wrinkles [240,241]. In conclusion, the diverse range of beneficial bioactivities attributed to Uros underscores their significant potential for future research and their promising role in enhancing human health.

5. Conclusions

Food and plant components contributing to health protection and promotion are currently of high interest. ETs, as well as EA, which is a product of ETs generated in the stomach and the small intestine, have been documented to offer beneficial health effects to humans. Accumulated data have revealed that these effects are exerted by Uros, which are the metabolic products of EA upon the action of the gut microbiota. As a consequence, analytical methods to study the presence of ETs and EA in plant and food sources are needed, permitting a detailed mapping of these bioactive components in natural sources and in processed foods. In parallel, understanding the generation of Uros within the

organism and the ability of each individual to efficiently convert EA in Uros requires reliable and sensitive methods for the determination of Uros in biological samples. Thus, a variety of HPLC and LC-MS methods have been developed, allowing the detection of ETs, EA and Uros in a variety of samples. Due to the pleiotropic activities of EA and Uros, this field of research is expected to be highly active in the coming years.

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References

1. Clifford, M.N.; Scalbert, A. Ellagitannins—Nature, occurrence and dietary burden. *J. Sci. Food Agric.* **2000**, *80*, 1118–1125. [CrossRef]
2. Lipińska, L.; Klewicka, E.; Sójka, M. The structure, occurrence and biological activity of ellagitannins: A general review. *Acta Sci. Pol. Technol. Aliment.* **2014**, *13*, 289–299. [CrossRef]
3. Lorenzo, J.M.; Munekata, P.E.; Putnik, P.; Kovačević, D.B.; Muchenje, V.; Barba, F.J. Sources, chemistry, and biological potential of ellagitannins and ellagic acid derivatives. *Stud. Nat. Prod. Chem.* **2019**, *60*, 189–221.
4. Zhang, M.; Cui, S.; Mao, B.; Zhang, Q.; Zhao, J.; Zhang, H.; Tang, X.; Chen, W. Ellagic acid and intestinal microflora metabolite urolithin A: A review on its sources, metabolic distribution, health benefits, and biotransformation. *Crit. Rev. Food Sci. Nutr.* **2023**, *63*, 6900–6922. [CrossRef] [PubMed]
5. Cerdá, B.; Periago, P.; Espín, J.C.; Tomás-Barberán, F.A. Identification of urolithin A as a metabolite produced by human colon microflora from ellagic acid and related compounds. *J. Agric. Food Chem.* **2005**, *53*, 5571–5576. [CrossRef]
6. Čižmáriková, M.; Michalková, R.; Mirossay, L.; Mojžišová, G.; Zigová, M.; Bardelčíková, A.; Mojžiš, J. Ellagic acid and cancer hallmarks: Insights from experimental evidence. *Biomolecules* **2023**, *13*, 1653. [CrossRef]
7. Gupta, A.; Singh, A.K.; Kumar, R.; Jamieson, S.; Pandey, A.K.; Bishayee, A. Neuroprotective potential of ellagic acid: A critical review. *Adv. Nutr.* **2021**, *12*, 1211–1238. [CrossRef] [PubMed]
8. Li, J.; Liao, R.; Zhang, S.; Weng, H.; Liu, Y.; Tao, T.; Yu, F.; Li, G.; Wu, J. Promising remedies for cardiovascular disease: Natural polyphenol ellagic acid and its metabolite urolithins. *Phytomedicine* **2023**, *116*, 154867. [CrossRef]
9. D'Amico, D.; Andreux, P.A.; Valdés, P.; Singh, A.; Rinsch, C.; Auwerx, J. Impact of the natural compound urolithin A on health, disease, and aging. *Trends Mol. Med.* **2021**, *27*, 687–699. [CrossRef]
10. An, L.; Lu, Q.; Wang, K.; Wang, Y. Urolithins: A prospective alternative against brain aging. *Nutrients* **2023**, *15*, 3884. [CrossRef]
11. Available online: https://www.mitopure.com/ (accessed on 3 April 2024).
12. Yoshida, T.; Amakura, Y.; Yoshimura, M. Structural Features and Biological Properties of Ellagitannins in Some Plant Families of the Order Myrtales. *Int. J. Mol. Sci.* **2010**, *11*, 79–106. [CrossRef] [PubMed]
13. Smeriglio, A.; Barreca, D.; Bellocco, E.; Trombetta, D. Proanthocyanidins and hydrolysable tannins: Occurrence, dietary intake and pharmacological effects. *Br. J. Pharmacol.* **2017**, *174*, 1244–1262. [CrossRef] [PubMed]
14. Okuda, T.; Yoshida, T.; Hatano, T. Ellagitannins as active constituents of medicinal plants. *Planta Med.* **1989**, *55*, 117–122. [CrossRef] [PubMed]
15. Aguilera-Carbo, A.; Augur, C.; Prado-Barragan, L.A.; Favela-Torres, E.; Aguilar, C.N. Microbial production of ellagic acid and biodegradation of ellagitannins. *Appl. Microbiol. Biotechnol.* **2008**, *78*, 189–199. [CrossRef] [PubMed]
16. Braconnot, H. Observations sur la préparation et la purification de l'acide gallique, et sur l'existence d'unacide nouveau dans la noix de galle. *Ann. Chim. Phys.* **1818**, *9*, 181–189.
17. Villalba, K.J.O.; Barka, F.V.; Pasos, C.V.; Rodríguez, P.E. Food ellagitannins: Structure, metabolomic fate, and biological properties. In *Tannins-Structural Properties, Biological Properties and Current Knowledge*; Aires, A., Ed.; IntechOpen: Rijeka, Croatia, 2020; pp. 26–46, ISBN 9781789847963.
18. Koponen, J.M.; Happonen, A.M.; Mattila, P.H.; Törrönen, A.R. Contents of anthocyanins and ellagitannins in selected foods consumed in Finland. *J. Agric. Food Chem.* **2007**, *55*, 1612–1619. [CrossRef] [PubMed]
19. Piechowiak, T.; Grzelak-Błaszczyk, K.; Sójka, M.; Balawejder, M. Changes in phenolic compounds profile and glutathione status in raspberry fruit during storage in ozone-enriched atmosphere. *Postharvest Biol. Technol.* **2020**, *168*, 111277. [CrossRef]

20. Sparzak, B.; Merino-Arevalo, M.; Vander Heyden, Y.; Krauze-Baranowska, M.; Majdan, M.; Fecka, I.; Głód, D.; Bączek, T. HPLC analysis of polyphenols in the fruits of *Rubus idaeus* L. (Rosaceae). *Nat. Prod. Res.* **2010**, *24*, 1811–1822. [CrossRef]
21. Wada, L.; Ou, B. Antioxidant activity and phenolic content of *Oregon caneberries*. *J. Agric. Food Chem.* **2002**, *50*, 3495–3500. [CrossRef]
22. Määttä-Riihinen, K.R.; Kamal-Eldin, A.; Törrönen, A.R. Identification and quantification of phenolic compounds in berries of Fragaria and *Rubus* species (family Rosaceae). *J. Agric. Food Chem.* **2004**, *52*, 6178–6187. [CrossRef]
23. Häkkinen, S.H.; Kärenlampi, S.O.; Mykkänen, H.M.; Heinonen, I.M.; Törrönen, A.R. Ellagic acid content in berries: Influence of domestic processing and storage. *Eur. Food Res. Technol.* **2000**, *212*, 75–80. [CrossRef]
24. Abe, L.T.; Lajolo, F.M.; Genovese, M.I. Potential dietary sources of ellagic acid and other antioxidants among fruits consumed in Brazil: Jabuticaba (*Myrciaria jaboticaba* (Vell.) Berg). *J. Sci. Food Agric.* **2012**, *92*, 1679–1687. [CrossRef]
25. Rodrigues, L.M.; Romanini, E.B.; Silva, E.; Pilau, E.J.; da Costa, S.C.; Madrona, G.S. Camu-camu bioactive compounds extraction by ecofriendly sequential processes (ultrasound assisted extraction and reverse osmosis). *Ultrason. Sonochem.* **2020**, *64*, 105017. [CrossRef]
26. Jourdes, M.; Michel, J.; Saucier, C.; Quideau, S.; Teissedre, P.L. Identification, amounts, and kinetics of extraction of C-glucosidic ellagitannins during wine aging in oak barrels or in stainless steel tanks with oak chips. *Anal. Bioanal. Chem.* **2011**, *401*, 1531–1539. [CrossRef]
27. Amarowicz, R.; Janiak, M. Hydrolysable tannins. In *Encyclopedia of Food Chemistry*; Melton, L., Shahidi, F., Varelis, P., Eds.; Elsevier: Amsterdam, The Netherlands, 2019; pp. 337–343, ISBN 9780128140451.
28. Okuda, T.; Yoshida, T.; Hatano, T.; Ito, H. Ellagitannins renewed the concept of tannins. In *Chemistry and Biology of Ellagitannins: An Underestimated Class of Bioactive Plant Polyphenols*; Quideau, S., Ed.; World Scientific: Hackensack, NJ, USA, 2009; pp. 1–54, ISBN 9789812797407.
29. Jokar, A.; Masoomi, F.; Sadeghpour, O.; Nassiri-Toosi, M.; Hamedi, S. Potential therapeutic applications for *Terminalia chebula* in Iranian traditional medicine. *J. Tradit. Chin. Med.* **2016**, *36*, 250–254. [CrossRef]
30. Torgbo, S.; Rugthaworn, P.; Sukatta, U.; Sukyai, P. Biological characterization and quantification of Rambutan (*Nephelium lappaceum* L.) peel extract as a potential source of valuable minerals and ellagitannins for industrial applications. *ACS Omega* **2022**, *7*, 34647–34656. [CrossRef]
31. Vasconcelos, M.C.B.M.; Bennett, R.N.; Quideau, S.; Jacquet, R.; Rosa, E.A.; Ferreira-Cardoso, J.V. Evaluating the potential of chestnut (*Castanea sativa* Mill.) fruit pericarp and integument as a source of tocopherols, pigments and polyphenols. *Ind. Crops Prod.* **2010**, *31*, 301–311. [CrossRef]
32. Kaneshima, T.; Myoda, T.; Nakata, M.; Fujimori, T.; Toeda, K.; Nishizawa, M. Antioxidant activity of C-Glycosidic ellagitannins from the seeds and peel of camu-camu (*Myrciaria dubia*). *LWT-Food Sci. Technol.* **2016**, *69*, 76–81. [CrossRef]
33. Santos, S.A.; Vilela, C.; Domingues, R.M.; Oliveira, C.S.; Villaverde, J.J.; Freire, C.S.; Neto, C.P.; Silvestre, A.J. Secondary metabolites from *Eucalyptus grandis* wood cultivated in Portugal, Brazil and South Africa. *Ind. Crops Prod.* **2017**, *95*, 357–364. [CrossRef]
34. Alañón, M.E.; Castro-Vázquez, L.; Díaz-Maroto, M.C.; Hermosín-Gutiérrez, I.; Gordon, M.H.; Pérez-Coello, M.S. Antioxidant capacity and phenolic composition of different woods used in cooperage. *Food Chem.* **2011**, *129*, 1584–1590. [CrossRef]
35. Tasaki, M.; Umemura, T.; Maeda, M.; Ishii, Y.; Okamura, T.; Inove, T.; Kuroiwa, Y.; Hirose, M.; Nishikawa, A. Safety assessment of ellagic acid, a food additive, in a subchronic toxicity study using F344 rats. *Food Chem. Toxicol.* **2008**, *46*, 1119–1124. [CrossRef] [PubMed]
36. Heber, D. Pomegranate Ellagitannins. In *Herbal Medicine: Biomolecular and Clinical Aspects*; Benzie, I.F.F., Wachtel-Galor, S., Eds.; CRC Press/Taylor & Francis: Boca Raton, FL, USA, 2011; Chapter 10, ISBN 9781439807132.
37. Buenrostro-Figueroa, J.; Mireles, M.; Ascacio-Valdés, J.A.; Aguilera-Carbo, A.; Sepúlveda, L.; Contreras-Esquivel, J.; Rodríguez-Herrera, R.; Aguilar, C.N. Enzymatic biotransformation of pomegranate ellagitannins: Initial approach to reaction conditions. *Iran. J. Biotechnol.* **2020**, *18*, 2305. [CrossRef] [PubMed]
38. Quideau, S.; Deffieux, D.; Douat-Casassus, C.; Pouységu, L. Plant polyphenols: Chemical properties, biological activities, and synthesis. *Angew. Chem. Int. Ed.* **2011**, *50*, 586–621. [CrossRef] [PubMed]
39. Liu, F.; Zhang, Y.; Yu, Q.; Shen, Y.; Zheng, Z.; Cheng, J.; Zhang, W.; Ye, Y. Exploration of the binding between ellagic acid, a potentially risky food additive, and bovine serum albumin. *Food Chem. Toxicol.* **2019**, *134*, 110867. [CrossRef] [PubMed]
40. Whitley, A.C.; Stoner, G.D.; Darby, M.V.; Walle, T. Intestinal epithelial cell accumulation of the cancer preventive polyphenol ellagic acid--extensive binding to protein and DNA. *Biochem. Pharmacol.* **2003**, *66*, 907–915. [CrossRef] [PubMed]
41. Kähkönen, M.P.; Hopia, A.I.; Heinonen, M. Berry phenolics and their antioxidant activity. *J. Agric. Food Chem.* **2001**, *49*, 4076–4082. [CrossRef] [PubMed]
42. Sangiovanni, E.; Vrhovsek, U.; Rossoni, G.; Colombo, E.; Brunelli, C.; Brembati, L.; Trivulzio, S.; Gasperotti, M.; Mattivi, F.; Bosisio, E.; et al. Ellagitannins from Rubus berries for the control of gastric inflammation: In vitro and in vivo studies. *PLoS ONE* **2013**, *8*, e71762. [CrossRef] [PubMed]
43. Daniel, E.M.; Krupnick, A.S.; Heur, Y.H.; Blinzler, J.A.; Nims, R.W.; Stoner, G.D. Extraction, stability, and quantitation of ellagic acid in various fruits and nuts. *J. Food Compos. Anal.* **1989**, *2*, 338–349. [CrossRef]

44. Bradish, C.M.; Yousef, G.G.; Ma, G.; Perkins-Veazie, P.; Fernandez, G.E. Anthocyanin, carotenoid, tocopherol, and ellagitannin content of red raspberry cultivars grown under field or high tunnel cultivation in the southeastern United States. *J. Amer. Soc. Hort. Sci.* **2015**, *140*, 163–171. [CrossRef]
45. Mattila, P.; Kumpulainen, J. Determination of free and total phenolic acids in plant-derived foods by HPLC with diode-array detection. *J. Agric. Food Chem.* **2002**, *50*, 3660–3667. [CrossRef]
46. Sójka, M.; Macierzyński, J.; Zaweracz, W.; Buczek, M. Transfer and mass balance of ellagitannins, anthocyanins, flavan-3-ols, and flavonols during the processing of red raspberries (*Rubus idaeus* L.) to juice. *J. Agric. Food Chem.* **2016**, *64*, 5549–5563. [CrossRef]
47. Williams, D.J.; Edwards, D.; Pun, S.; Chaliha, M.; Sultanbawa, Y. Profiling ellagic acid content: The importance of form and ascorbic acid levels. *Int. Food Res. J.* **2014**, *66*, 100–106. [CrossRef]
48. Diamanti, J.; Mazzoni, L.; Balducci, F.; Cappelletti, R.; Capocasa, F.; Battino, M.; Dobson, G.; Stewart, D.; Mezzetti, B. Use of wild genotypes in breeding program increases strawberry fruit sensorial and nutritional quality. *J. Agric. Food Chem.* **2014**, *62*, 3944–3953. [CrossRef]
49. Gasperotti, M.; Masuero, D.; Guella, G.; Palmieri, L.; Martinatti, P.; Pojer, E.; Mattivi, F.; Vrhovsek, U. Evolution of ellagitannin content and profile during fruit ripening in *Fragaria* spp. *J. Agric. Food Chem.* **2013**, *61*, 8597–8607. [CrossRef]
50. Aaby, K.; Wrolstad, R.E.; Ekeberg, D.; Skrede, G. Polyphenol composition and antioxidant activity in strawberry purees; Impact of achenelLevel and storage. *J. Agric. Food Chem.* **2007**, *55*, 5156–5166. [CrossRef]
51. Van de Velde, F.; Pirovani, M.E.; Drago, S.R. Bioaccessibility analysis of anthocyanins and ellagitannins from blackberry at simulated gastrointestinal and colonic levels. *J. Food Compos. Anal.* **2018**, *72*, 22–31. [CrossRef]
52. Bushman, B.S.; Phillips, B.; Isbell, T.; Ou, B.; Crane, J.M.; Knapp, S.J. Chemical composition of caneberry (*Rubus* spp.) seeds and oils and their antioxidant potential. *J. Agric. Food Chem.* **2004**, *52*, 7982–7987. [CrossRef]
53. Fischer, U.A.; Carle, R.; Kammerer, D.R. Identification and quantification of phenolic compounds from pomegranate (*Punica granatum* L.) peel, mesocarp, aril and differently produced juices by HPLC-DAD–ESI/MS^n. *Food Chem.* **2011**, *127*, 807–821. [CrossRef]
54. Çam, M.; Hışıl, Y. Pressurised water extraction of polyphenols from pomegranate peels. *Food Chem.* **2010**, *123*, 878–885. [CrossRef]
55. Masci, A.; Coccia, A.; Lendaro, E.; Mosca, L.; Paolicelli, P.; Cesa, S. Evaluation of different extraction methods from pomegranate whole fruit or peels and the antioxidant and antiproliferative activity of the polyphenolic fraction. *Food Chem.* **2016**, *202*, 59–69. [CrossRef]
56. Romani, A.; Campo, M.; Pinelli, P. HPLC/DAD/ESI-MS analyses and anti-radical activity of hydrolyzable tannins from different vegetal species. *Food Chem.* **2012**, *130*, 214–221. [CrossRef]
57. Williams, D.J.; Edwards, D.; Chaliha, M.; Sultanbawa, Y. Measuring the three forms of ellagic acid: Suitability of extraction solvents. *Chem. Pap.* **2016**, *70*, 144–152. [CrossRef]
58. You, Q.; Chen, F.; Sharp, J.L.; Wang, X.; You, Y.; Zhang, C. High-performance liquid chromatography–mass spectrometry and evaporative light-scattering detector to compare phenolic profiles of muscadine grapes. *J. Chromatogr. A* **2012**, *1240*, 96–103. [CrossRef]
59. Soong, Y.Y.; Barlow, P.J. Quantification of gallic acid and ellagic acid from longan (*Dimocarpus longan* Lour.) seed and mango (*Mangifera indica* L.) kernel and their effects on antioxidant activity. *Food Chem.* **2006**, *97*, 524–530. [CrossRef]
60. Malik, N.S.; Perez, J.L.; Lombardini, L.; Cornacchia, R.; Cisneros-Zevallos, L.; Braford, J. Phenolic compounds and fatty acid composition of organic and conventional grown pecan kernels. *J. Sci. Food Agric.* **2009**, *89*, 2207–2213. [CrossRef]
61. Gonçalves, B.; Borges, O.; Costa, H.S.; Bennett, R.; Santos, M.; Silva, A.P. Metabolite composition of chestnut (*Castanea sativa* Mill.) upon cooking: Proximate analysis, fibre, organic acids and phenolics. *Food Chem.* **2010**, *122*, 154–160. [CrossRef]
62. Abe, L.T.; Lajolo, F.M.; Genovese, M.I. Comparison of phenol content and antioxidant capacity of nuts. *LWT-Food Sci. Technol.* **2010**, *30*, 254–259. [CrossRef]
63. Gong, Y.; Pegg, R.B. Separation of ellagitannin-rich phenolics from US pecans and Chinese hickory nuts using fused-core HPLC columns and their characterization. *J. Agric. Food Chem.* **2017**, *65*, 5810–5820. [CrossRef]
64. Aires, A.; Carvalho, R.; Saavedra, M.J. Valorization of solid wastes from chestnut industry processing: Extraction and optimization of polyphenols, tannins and ellagitannins and its potential for adhesives, cosmetic and pharmaceutical industry. *J. Waste Manag.* **2016**, *48*, 457–464. [CrossRef]
65. Rojas-Garbanzo, C.; Winter, J.; Montero, M.L.; Zimmermann, B.F.; Schieber, A. Characterization of phytochemicals in Costa Rican guava (*Psidium friedrichsthalianum*-Nied.) fruit and stability of main compounds during juice processing-(U) HPLC-DAD-ESI-TQD-MS^n. *J. Food Compos. Anal.* **2019**, *75*, 26–42. [CrossRef]
66. Dos Santos, W.N.L.; da Silva Sauthier, M.C.; dos Santos, A.M.P.; de Andrade Santana, D.; Azevedo, R.S.A.; da Cruz Caldas, J. Simultaneous determination of 13 phenolic bioactive compounds in guava (*Psidium guajava* L.) by HPLC-PAD with evaluation using PCA and Neural Network Analysis (NNA). *Microchem. J.* **2017**, *133*, 583–592. [CrossRef]
67. Alezandro, M.R.; Granato, D.; Genovese, M.I. Jaboticaba (*Myrciaria jaboticaba* (Vell.) Berg), a Brazilian grape-like fruit, improves plasma lipid profile in streptozotocin-mediated oxidative stress in diabetic rats. *Int. Food Res. J.* **2013**, *54*, 650–659. [CrossRef]
68. Silva, R.M.; Pereira, L.D.; Véras, J.H.; do Vale, C.R.; Chen-Chen, L.; da Costa Santos, S. Protective effect and induction of DNA repair by *Myrciaria cauliflora* seed extract and pedunculagin on cyclophosphamide-induced genotoxicity. *Mutat. Res. Genet. Toxicol. Environ. Mutagen.* **2016**, *810*, 40–47. [CrossRef]

69. Pereira, L.D.; Barbosa, J.M.G.; Ribeiro da Silva, A.J.; Ferri, P.H.; Santos, S.C. Polyphenol and ellagitannin constituents of jabuticaba (*Myrciaria cauliflora*) and chemical variability at different stages of fruit development. *J. Agric. Food Chem.* **2017**, *65*, 1209–1219. [CrossRef]
70. Fracassetti, D.; Costa, C.; Moulay, L.; Tomás-Barberán, F.A. Ellagic acid derivatives, ellagitannins, proanthocyanidins and other phenolics, vitamin C and antioxidant capacity of two powder products from camu-camu fruit (*Myrciaria dubia*). *Food Chem.* **2013**, *139*, 578–588. [CrossRef]
71. Santos, S.A.; Freire, C.S.; Domingues, M.R.M.; Silvestre, A.J.; Neto, C.P. Characterization of phenolic components in polar extracts of *Eucalyptus globulus* Labill. bark by high-performance liquid chromatography–mass spectrometry. *J. Agric. Food Chem.* **2011**, *59*, 9386–9393. [CrossRef]
72. Aoyama, H.; Sakagami, H.; Hatano, T. Three new flavonoids, proanthocyanidin, and accompanying phenolic constituents from *Feijoa sellowiana*. *Biosci. Biotechnol. Biochem.* **2018**, *82*, 31–41. [CrossRef]
73. Mazzarino, L.; da Silva Pitz, H.; Lorenzen Voytena, A.P.; Dias Trevisan, A.C.; Ribeiro-Do-Valle, R.M.; Maraschin, M. Jaboticaba (*Plinia peruviana*) extract nanoemulsions: Development, stability, and in vitro antioxidant activity. *Drug Dev. Ind. Pharm.* **2018**, *44*, 643–651. [CrossRef]
74. Karlińska, E.; Masny, A.; Cieślak, M.; Macierzyński, J.; Pecio, Ł.; Stochmal, A.; Kosmala, M. Ellagitannins in roots, leaves, and fruits of strawberry (*Fragaria* × *ananassa* Duch.) vary with developmental stage and cultivar. *Sci. Hortic.* **2021**, *275*, 109665. [CrossRef]
75. Fecka, I.; Kucharska, A.Z.; Kowalczyk, A. Quantification of tannins and related polyphenols in commercial products of tormentil (*Potentilla tormentilla*). *PCA* **2015**, *26*, 353–366. [CrossRef]
76. Kashchenko, N.I.; Olennikov, D.N. Phenolome of asian agrimony tea (*Agrimonia asiatica* Juz., Rosaceae): LC-MS profile, α-glucosidase inhibitory potential and stability. *Foods* **2020**, *9*, 1348. [CrossRef]
77. Alañón, M.E.; Pimentel-Moral, S.; Arráez-Román, D.; Segura-Carretero, A. HPLC-DAD-Q-ToF-MS profiling of phenolic compounds from mango (*Mangifera indica* L.) seed kernel of different cultivars and maturation stages as a preliminary approach to determine functional and nutraceutical value. *Food Chem.* **2021**, *337*, 127764. [CrossRef]
78. Dorta, E.; González, M.; Lobo, M.G.; Sánchez-Moreno, C.; de Ancos, B. Screening of phenolic compounds in by-product extracts from mangoes (*Mangifera indica* L.) by HPLC-ESI-QTOF-MS and multivariate analysis for use as a food ingredient. *Int. Food Res. J.* **2014**, *57*, 51–60. [CrossRef]
79. Lestario, L.N.; Howard, L.R.; Brownmiller, C.; Stebbins, N.B.; Liyanage, R.; Lay, J.O. Changes in polyphenolics during maturation of Java plum (*Syzygium cumini* Lam.). *Int. Food Res. J.* **2017**, *100*, 385–391. [CrossRef]
80. de Oliveira, L.M.; Porte, A.; de Oliveira Godoy, R.L.; da Costa Souza, M.; Pacheco, S.; de Araujo Santiago, M.C.P.; Gouvêa, A.C.M.S.; da Silva de Mattos do Nascimento, L.; Borguini, R.G. Chemical characterization of *Myrciaria floribunda* (H. West ex Willd) fruit. *Food Chem.* **2018**, *248*, 247–252. [CrossRef]
81. Díaz-de-Cerio, E.; Arráez-Román, D.; Segura-Carretero, A.; Ferranti, P.; Nicoletti, R.; Perrotta, G.M.; Gómez-Caravaca, A.M. Establishment of pressurized-liquid extraction by response surface methodology approach coupled to HPLC-DAD-TOF-MS for the determination of phenolic compounds of myrtle leaves. *Anal. Bioanal. Chem.* **2018**, *410*, 3547–3557. [CrossRef]
82. Gajera, H.P.; Gevariya, S.N.; Hirpara, D.G.; Patel, S.V.; Golakiya, B.A. Antidiabetic and antioxidant functionality associated with phenolic constituents from fruit parts of indigenous black jamun (*Syzygium cumini* L.) landraces. *J. Food Technol.* **2017**, *54*, 3180–3191. [CrossRef]
83. Medic, A.; Jakopic, J.; Hudina, M.; Solar, A.; Veberic, R. Identification and quantification of the major phenolic constituents in Juglans regia L. peeled kernels and pellicles, using HPLC-MS/MS. *Food Chem.* **2021**, *352*, 129404. [CrossRef]
84. Konczak, I.; Maillot, F.; Dalar, A. Phytochemical divergence in 45 accessions of *Terminalia ferdinandiana* (Kakadu plum). *Food Chem.* **2014**, *151*, 248–256. [CrossRef]
85. Glabasnia, A.; Hofmann, T. Sensory-directed identification of taste-active ellagitannins in American (*Quercus alba* L.) and European oak wood (*Quercus robur* L.) and quantitative analysis in bourbon whiskey and oak-matured red wines. *J. Agric. Food Chem.* **2006**, *54*, 3380–3390. [CrossRef]
86. Tuyen, P.T.; Xuan, T.D.; Tu Anh, T.T.; Mai Van, T.; Ahmad, A.; Elzaawely, A.A.; Khanh, T.D. Weed suppressing potential and isolation of potent plant growth inhibitors from *Castanea crenata* Sieb. et Zucc. *Molecules* **2018**, *23*, 345. [CrossRef]
87. Pellati, F.; Bruni, R.; Righi, D.; Grandini, A.; Tognolini, M.; Pio Prencipe, F.; Poli, F.; Benvenuti, S.; Del Rio, D.; Rossi, D. Metabolite profiling of polyphenols in a *Terminalia chebula* Retzius ayurvedic decoction and evaluation of its chemopreventive activity. *J. Ethnopharmacol.* **2013**, *147*, 277–285. [CrossRef]
88. Alagan, A.; Jantan, I.; Kumolosasi, E.; Ogawa, S.; Abdullah, M.A.; Azmi, N. Protective effects of *Phyllanthus amarus* against lipopolysaccharide-induced neuroinflammation and cognitive impairment in rats. *Front. Pharmacol.* **2019**, *10*, 632. [CrossRef]
89. Odubanjo, V.O.; Ibukun, E.O.; Oboh, G.; Adefegha, S.A. Aqueous extracts of two tropical ethnobotanicals (*Tetrapleura tetraptera* and *Quassia undulata*) improved spatial and non-spatial working memories in scopolamine-induced amnesic rats: Influence of neuronal cholinergic and antioxidant systems. *Biomed. Pharmacother.* **2018**, *99*, 198–204. [CrossRef]
90. Siraj, M.A.; Shilpi, J.A.; Hossain, M.G.; Uddin, S.J.; Islam, M.K.; Jahan, I.A.; Hossain, H. Anti-inflammatory and antioxidant activity of *Acalypha hispida* leaf and analysis of its major bioactive polyphenols by HPLC. *Adv. Pharm. Bull.* **2016**, *6*, 275–283. [CrossRef]

91. Jaramillo-García, V.; Trindade, C.; Lima, E.; Guecheva, T.N.; Villela, I.; Martinez-Lopez, W.; Corrêa, D.S.; Ferraz, A.d.B.F.; Moura, S.; Sosa, M.Q.; et al. Chemical characterization and cytotoxic, genotoxic, and mutagenic properties of *Baccharis trinervis* (Lam, Persoon) from Colombia and Brazil. *J. Ethnopharmacol.* **2018**, *213*, 210–220. [CrossRef]
92. Hafsa, J.; Hammi, K.M.; Khedher, M.R.B.; Smach, M.A.; Charfeddine, B.; Limem, K.; Majdoub, H. Inhibition of protein glycation, antioxidant and antiproliferative activities of *Carpobrotus edulis* extracts. *Biomed. Pharmacother.* **2016**, *84*, 1496–1503. [CrossRef]
93. Karimi, E.; Ghorbani Nohooji, M.; Habibi, M.; Ebrahimi, M.; Mehrafarin, A.; Khalighi-Sigaroodi, F. Antioxidant potential assessment of phenolic and flavonoid rich fractions of *Clematis orientalis* and *Clematis ispahanica* (Ranunculaceae). *Nat. Prod. Res.* **2018**, *32*, 1991–1995. [CrossRef]
94. Cho, C.H.; Jang, H.; Lee, M.; Kang, H.; Heo, H.J.; Kim, D.O. Sea buckthorn (*Hippophae rhamnoides* L.) leaf extracts protect neuronal PC-12 cells from oxidative stress. *J. Microbiol. Biotechnol.* **2017**, *27*, 1257–1265. [CrossRef]
95. Vieira, G.S.; Marques, A.S.; Machado, M.T.; Silva, V.M.; Hubinger, M.D. Determination of anthocyanins and non-anthocyanin polyphenols by ultra performance liquid chromatography/electrospray ionization mass spectrometry (UPLC/ESI–MS) in jussara (*Euterpe edulis*) extracts. *J. Food Sci. Technol.* **2017**, *54*, 2135–2144. [CrossRef]
96. Vu, D.C.; Vo, P.H.; Coggeshall, M.V.; Lin, C.H. Identification and characterization of phenolic compounds in black walnut kernels. *J. Agric. Food Chem.* **2018**, *66*, 4503–4511. [CrossRef]
97. de Britto Policarpi, P.; Turcatto, L.; Demoliner, F.; Ferrari, R.A.; Bascuñan, V.L.A.F.; Ramos, J.C.; Jachmanián, J.; Vitali, L.; Micke, G.A.; Block, J.M. Nutritional potential, chemical profile and antioxidant activity of Chichá (*Sterculia striata*) nuts and its by-products. *Food Res. Int.* **2018**, *106*, 736–744. [CrossRef]
98. Gil, M.I.; Tomás-Barberán, F.A.; Hess-Pierce, B.; Holcroft, D.M.; Kader, A.A. Antioxidant activity of pomegranate juice and its relationship with phenolic composition and processing. *J. Agric. Food Chem.* **2000**, *48*, 4581–4589. [CrossRef]
99. Cerdá, B.; Espín, J.C.; Parra, S.; Martínez, P.; Tomás-Barberán, F.A. The potent in vitro antioxidant ellagitannins from pomegranate juice are metabolised into bioavailable but poor antioxidant hydroxy-6H-dibenzopyran-6-one derivatives by the colonic microflora of healthy humans. *Eur. J. Nutr.* **2004**, *43*, 205–220. [CrossRef] [PubMed]
100. Borges, G.; Mullen, W.; Crozier, A. Comparison of the polyphenolic composition and antioxidant activity of European commercial fruit juices. *Food Funct.* **2010**, *1*, 73. [CrossRef] [PubMed]
101. Vegara, S.; Martí, N.; Lorente, J.; Coll, L.; Streitenberger, S.; Valero, M.; Saura, D. Chemical guide parameters for *Punica granatum* cv.'Mollar'fruit juices processed at industrial scale. *Food Chem.* **2014**, *147*, 203–208. [CrossRef] [PubMed]
102. Inada, K.O.P.; Duarte, P.A.; Lapa, J.; Miguel, M.A.L.; Monteiro, M. Jabuticaba (*Myrciaria jaboticaba*) juice obtained by steam-extraction: Phenolic compound profile, antioxidant capacity, microbiological stability, and sensory acceptability. *J. Food Sci. Technol.* **2018**, *55*, 52–61. [CrossRef]
103. Teixeira, L.L.; Costa, G.R.; Dörr, F.A.; Ong, T.P.; Pinto, E.; Lajolo, F.M.; Hassimotto, N.M.A. Potential Antiproliferative Activity of Polyphenol Metabolites against Human Breast Cancer Cells and Their Urine Excretion Pattern in Healthy Subjects Following Acute Intake of a Polyphenol-Rich Juice of Grumixama (*Eugenia brasiliensis* Lam.). *Food Funct.* **2017**, *8*, 2266–2274. [CrossRef]
104. Lee, J.H.; Talcott, S.T. Ellagic acid and ellagitannins affect on sedimentation in muscadine juice and wine. *J. Agric. Food Chem.* **2002**, *50*, 3971–3976. [CrossRef]
105. Garcia-Estevez, I.; Escribano-Bailón, M.T.; Rivas-Gonzalo, J.C.; Alcalde-Eon, C. Validation of a mass spectrometry method to quantify oak ellagitannins in wine samples. *J. Agric. Food Chem.* **2012**, *60*, 1373–1379. [CrossRef]
106. Sanz, M.; de Simón, B.F.; Esteruelas, E.; Muñoz, Á.M.; Cadahía, E.; Hernández, M.T.; Estrella, I.; Martinez, J. Polyphenols in red wine aged in acacia (*Robinia pseudoacacia*) and oak (*Quercus petraea*) wood barrels. *Anal. Chim. Acta* **2012**, *732*, 83–90. [CrossRef] [PubMed]
107. Mena, P.; Ascacio-Valdés, J.A.; Gironés-Vilaplana, A.; Del Rio, D.; Moreno, D.A.; García-Viguera, C. Assessment of pomegranate wine lees as a valuable source for the recovery of (poly) phenolic compounds. *Food Chem.* **2014**, *145*, 327–334. [CrossRef] [PubMed]
108. Alexandri, M.; Papapostolou, H.; Vlysidis, A.; Gardeli, C.; Komaitis, M.; Papanikolaou, S.; Koutinas, A.A. Extraction of phenolic compounds and succinic acid production from spent sulphite liquor. *Chem. Technol. Biotechnol.* **2016**, *91*, 2751–2760. [CrossRef]
109. Bobinaitė, R.; Viskelis, P.; Bobinas, Č.; Mieželienė, A.; Alenčikienė, G.; Venskutonis, P.R. Raspberry marc extracts increase antioxidative potential, ellagic acid, ellagitannin and anthocyanin concentrations in fruit purees. *LWT-Food Sci. Technol.* **2016**, *66*, 460–467. [CrossRef]
110. Sójka, M.; Klimczak, E.; Macierzyński, J.; Kołodziejczyk, K. Nutrient and polyphenolic composition of industrial strawberry press cake. *Eur. Food Res. Technol.* **2013**, *237*, 995–1007. [CrossRef]
111. Da Silva Pinto, M.; Lajolo, F.M.; Genovese, M.I. Bioactive compounds and antioxidant capacity of strawberry jams. *Plant Foods Hum. Nutr.* **2007**, *62*, 127–131. [CrossRef] [PubMed]
112. Markom, M.; Hasan, M.; Daud, W.R.W.; Singh, H.; Jahim, J.M. Extraction of hydrolysable tannins from Phyllanthus niruri Linn.: Effects of solvents and extraction methods. *Sep. Purif. Technol.* **2007**, *52*, 487–496. [CrossRef]
113. Widyawati, P.S.; Dwi, T.; Budianta, W.; Kusuma, F.A.; Wijaya, E.L. Difference of Solvent Polarity to Phytochemical Content and Antioxidant Activity of *Pluchea indicia* Less Leaves Extracts. *Int. J. Pharmacogn. Phytochem. Res.* **2014**, *6*, 850–855.
114. Arapitsas, P. Hydrolyzable tannin analysis in food. *Food Chem.* **2012**, *135*, 1708–1717. [CrossRef]
115. Theocharis, G.; Andlauer, W. Innovative microwave-assisted hydrolysis of ellagitannins and quantification as ellagic acid equivalents. *Food Chem.* **2013**, *138*, 2430–2434. [CrossRef]

116. Abdulla, R.; Mansur, S.; Lai, H.; Ubul, A.; Sun, G.; Huang, G.; Aisa, H.A. Qualitative analysis of polyphenols in macroporous resin pretreated pomegranate husk extract by HPLC-QTOF-MS. *Phytochem. Anal.* **2017**, *28*, 465–473. [CrossRef] [PubMed]
117. Zhu, M.; Dong, X.; Guo, M. Phenolic profiling of *Duchesnea Indica* combining macroporous resin chromatography (MRC) with HPLC-ESI-MS/MS and ESI-IT-MS. *Molecules* **2015**, *20*, 22463–22475. [CrossRef] [PubMed]
118. Agrawal, O.D.; Kulkarni, Y.A. Mini-review of analytical methods used in quantification of ellagic acid. *Rev. Anal. Chem.* **2020**, *39*, 31–44. [CrossRef]
119. Furuuchi, R.; Yokoyama, T.; Watanabe, Y.; Hirayama, M. Identification and quantification of short oligomeric proanthocyanidins and other polyphenols in boysenberry seeds and juice. *J. Agric. Food Chem.* **2011**, *59*, 3738–3746. [CrossRef] [PubMed]
120. Brighenti, V.; Groothuis, S.F.; Prencipe, F.P.; Amir, R.; Benvenuti, S.; Pellati, F. Metabolite fingerprinting of *Punica granatum* L. (pomegranate) polyphenols by means of high-performance liquid chromatography with diode array and electrospray ionization-mass spectrometry detection. *J. Chromatogr. A* **2017**, *1480*, 20–31. [CrossRef] [PubMed]
121. Gómez-Caravaca, A.M.; Verardo, V.; Toselli, M.; Segura-Carretero, A.; Fernández-Gutiérrez, A.; Caboni, M.F. Determination of the major phenolic compounds in pomegranate juices by HPLC–DAD–ESI-MS. *J. Agric. Food Chem.* **2013**, *61*, 5328–5337. [CrossRef] [PubMed]
122. Navarro, M.; Kontoudakis, N.; Canals, J.M.; García-Romero, E.; Gómez-Alonso, S.; Zamora, F.; Hermosín-Gutiérrez, I. Improved method for the extraction and chromatographic analysis on a fused-core column of ellagitannins found in oak-aged wine. *Food Chem.* **2017**, *226*, 23–31. [CrossRef] [PubMed]
123. Godiyal, S.; Laddha, K. Validated high-performance thin-layer chromatographic method for quantification of gallic acid and ellagic acid in fruits of *Terminalia chebula*, *Phyllanthus emblica*, and *Quercus infectoria*. *J. Sep. Sci.* **2023**, *46*, 2200991. [CrossRef] [PubMed]
124. García-Villalba, R.; Espín, J.C.; Aaby, K.; Alasalvar, C.; Heinonen, M.; Jacobs, G.; Voorspoels, S.; Koivumäki, T.; Kroon, P.A.; Pelvan, E.; et al. Validated method for the characterization and quantification of extractable and nonextractable ellagitannins after acid hydrolysis in pomegranate fruits, juices, and extracts. *J. Agric. Food Chem.* **2015**, *63*, 6555–6566. [CrossRef]
125. Topalović, A.; Knežević, M.; Gačnik, S.; Mikulic-Petkovsek, M. Detailed chemical composition of juice from autochthonous pomegranate genotypes (*Punica granatum* L.) grown in different locations in Montenegro. *Food Chem.* **2020**, *330*, 127261. [CrossRef]
126. Da Silva Pinto, M.; Lajolo, F.M.; Genovese, M.I. Bioactive compounds and quantification of total ellagic acid in strawberries (*Fragaria* × *Ananassa* Duch.). *Food Chem.* **2008**, *107*, 1629–1635. [CrossRef]
127. Hejduk, A.; Sójka, M.; Klewicki, R. Stability of ellagitannins in processing products of selected *Fragaria* fruit during 12 months of storage. *Food Sci. Nutr.* **2023**, *11*, 1354–1366. [CrossRef] [PubMed]
128. Gasperotti, M.; Masuero, D.; Vrhovsek, U.; Guella, G.; Mattivi, F. Profiling and accurate quantification of *Rubus* ellagitannins and ellagic acid conjugates using direct UPLC-Q-TOF HDMS and HPLC-DAD analysis. *J. Agric. Food Chem.* **2010**, *58*, 4602–4616. [CrossRef] [PubMed]
129. Gudej, J.; Tomczyk, M. Determination of flavonoids, tannins and ellagic acid in leaves from *Rubus* L. species. *Arch. Pharm. Res.* **2004**, *27*, 1114–1119. [CrossRef] [PubMed]
130. Richard-Dazeur, C.; Jacolot, P.; Niquet-Léridon, C.; Goethals, L.; Barbezier, N.; Anton, P.M. HPLC-DAD Optimization of quantification of vescalagin, gallic and ellagic acid in chestnut tannins. *Heliyon* **2023**, *9*, e18993. [CrossRef] [PubMed]
131. Yalcin, G.; Demirbag, C.; Bahsi, I.; Ozgul, L.; Alkaya, D.B.; Onurlu, H.I.; Seyhan, S.A. *Determination of Ellagic Acid in the Wastes of Walnut, Chestnut, and Pomegranate Grown in Turkey. ACS Symposium Series*; Jayaprakasha, G.K., Patil, B.S., Gattuso, G., Eds.; American Chemical Society: Washington, DC, USA, 2018, 2018; Volume 1286, pp. 81–103, ISBN 9780841232969.
132. Kumar, N.; Pratibha; Neeraj; Sami, R.; Khojah, E.; Aljahani, A.H.; Al-Mushhin, A.A.M. Effects of drying methods and solvent extraction on quantification of major bioactive compounds in pomegranate peel waste using HPLC. *Sci. Rep.* **2022**, *12*, 8000. [CrossRef] [PubMed]
133. Aaby, K.; Ekeberg, D.; Skrede, G. Characterization of phenolic compounds in strawberry (*Fragaria* × *Ananassa*) fruits by different HPLC detectors and contribution of individual compounds to total antioxidant capacity. *J. Agric. Food Chem.* **2007**, *55*, 4395–4406. [CrossRef] [PubMed]
134. Yisimayili, Z.; Abdulla, R.; Tian, Q.; Wang, Y.; Chen, M.; Sun, Z.; Li, Z.; Liu, F.; Aisa, H.A.; Huang, C. A comprehensive study of pomegranate flowers polyphenols and metabolites in rat biological samples by high-performance liquid chromatography quadrupole time-of-flight mass spectrometry. *J. Chromatogr. A* **2019**, *1604*, 460472. [CrossRef]
135. Michel, J.; Jourdes, M.; Silva, M.A.; Giordanengo, T.; Mourey, N.; Teissedre, P.-L. Impact of concentration of ellagitannins in oak wood on their levels and organoleptic influence in red wine. *J. Agric. Food Chem.* **2011**, *59*, 5677–5683. [CrossRef]
136. Kool, M.M.; Comeskey, D.J.; Cooney, J.M.; McGhie, T.K. Structural identification of the main ellagitannins of a boysenberry (*Rubus loganbaccus* × *baileyanus* Britt.) extract by LC–ESI-MS/MS, MALDI-TOF-MS and NMR spectroscopy. *Food Chem.* **2010**, *119*, 1535–1543. [CrossRef]
137. Akter, S.; Hong, H.; Netzel, M.; Tinggi, U.; Fletcher, M.; Osborne, S.; Sultanbawa, Y. Determination of ellagic acid, punicalagin, and castalagin from *Terminalia ferdinandiana* (Kakadu Plum) by a validated UHPLC-PDA-MS/MS methodology. *Food Anal. Methods* **2021**, *14*, 2534–2544. [CrossRef]
138. Kula, M.; Majdan, M.; Głód, D.; Krauze-Baranowska, M. Phenolic composition of fruits from different cultivars of red and black raspberries grown in poland. *J. Food Compos. Anal.* **2016**, *52*, 74–82. [CrossRef]

139. Regueiro, J.; Sánchez-González, C.; Vallverdú-Queralt, A.; Simal-Gándara, J.; Lamuela-Raventós, R.; Izquierdo-Pulido, M. Comprehensive identification of walnut polyphenols by liquid chromatography coupled to linear ion trap–orbitrap mass spectrometry. *Food Chem.* **2014**, *152*, 340–348. [CrossRef] [PubMed]
140. Chen, R.; Li, J.; Yang, Z.; Gao, F.; Qi, P.; Li, X.; Zhu, F.; Li, J.; Zhang, J. Determination of ellagic acid in wine by solid-phase extraction–ultra-high performance liquid chromatography–tandem mass spectrometry. *Food Anal. Methods* **2019**, *12*, 1103–1110. [CrossRef]
141. Shahzad, M.N.; Ahmad, S.; Tousif, M.I.; Ahmad, I.; Rao, H.; Ahmad, B.; Basit, A. Profiling of phytochemicals from aerial parts of *Terminalia Neotaliala* using LC-ESI-MS2 and determination of antioxidant and enzyme inhibition activities. *PLoS ONE* **2022**, *17*, e0266094. [CrossRef] [PubMed]
142. Khatib, M.; Campo, M.; Bellumori, M.; Cecchi, L.; Vignolini, P.; Innocenti, M.; Mulinacci, N. Tannins from different parts of the chestnut trunk (*Castanea sativa* Mill.): A green and effective extraction method and their profiling by high-performance liquid chromatography-diode array detector-mass spectrometry. *ACS Food Sci. Technol.* **2023**, *3*, 1903–1912. [CrossRef]
143. Seyhan, S.; Yalcin, G.; Seyhan, S.A. The extraction and determination of ellagic acid and resveratrol in blueberry species by HPLC-DAD and LC-MS/MS. *J. Res. Pharm.* **2023**, *27*, 311–320. [CrossRef]
144. De Andrade Neves, N.; César Stringheta, P.; Ferreira Da Silva, I.; García-Romero, E.; Gómez-Alonso, S.; Hermosín-Gutiérrez, I. Identification and quantification of phenolic composition from different species of Jabuticaba (*Plinia* Spp.) by HPLC-DAD-ESI/MS^n. *Food Chem.* **2021**, *355*, 129605. [CrossRef] [PubMed]
145. Oracz, J.; Żyżelewicz, D.; Pacholczyk-Sienicka, B. UHPLC-DAD-ESI-HRMS/MS profile of phenolic compounds in northern red oak (*Quercus rubra* L., Syn. Q. Borealis F. Michx) seeds and its transformation during thermal processing. *Ind. Crops Prod.* **2022**, *189*, 115860. [CrossRef]
146. Finimundy, T.C.; Karkanis, A.; Fernandes, Â.; Petropoulos, S.A.; Calhelha, R.; Petrović, J.; Soković, M.; Rosa, E.; Barros, L.; Ferreira, I.C.F.R. Bioactive properties of *Sanguisorba minor* L. cultivated in central Greece under different fertilization regimes. *Food Chem.* **2020**, *327*, 127043. [CrossRef]
147. Zhou, B.; Wu, Z.; Li, X.; Zhang, J.; Hu, X. Analysis of ellagic acid in pomegranate rinds by capillary electrophoresis and high-performance liquid chromatography. *Phytochem. Anal.* **2008**, *19*, 86–89. [CrossRef]
148. Costa, E.V.; Lima, D.L.D.; Evtyugin, D.V.; Esteves, V.I. Development and application of a capillary electrophoresis method for the determination of ellagic acid in E. Globulus wood and in filtrates from E. Globulus kraft pulp. *Wood Sci. Technol.* **2014**, *48*, 99–108. [CrossRef]
149. Spisso, A.; Gomez, F.J.V.; Fernanda Silva, M. Determination of ellagic acid by capillary electrophoresis in Argentinian wines. *Electrophoresis* **2018**, *39*, 1621–1627. [CrossRef]
150. Wojciechowska, O.; Kujawska, M. Urolithin A in health and diseases: Prospects for Parkinson's disease management. *Antioxidants* **2023**, *12*, 1479. [CrossRef] [PubMed]
151. Raimundo, A.F.; Ferreira, S.; Tomás-Barberán, F.A.; Santos, C.N.; Menezes, R. Urolithins: Diet-derived bioavailable metabolites to tackle diabetes. *Nutrients* **2021**, *13*, 4285. [CrossRef] [PubMed]
152. García-Villalba, R.; Tomás-Barberán, F.A.; Iglesias-Aguirre, C.E.; Giménez-Bastida, J.A.; González-Sarrías, A.; Selma, M.V.; Espín, J.C. Ellagitannins, urolithins, and neuroprotection: Human evidence and the possible link to the gut microbiota. *Mol. Asp. Med.* **2023**, *89*, 101109. [CrossRef]
153. Tomás-Barberán, F.A.; González-Sarrías, A.; García-Villalba, R.; Núñez-Sánchez, M.A.; Selma, M.V.; García-Conesa, M.T.; Espín, J.C. Urolithins, the rescue of "old" metabolites to understand a "new" concept: Metabotypes as a nexus among phenolic metabolism, microbiota dysbiosis, and host health status. *Mol. Nutr. Food Res.* **2017**, *61*, 1500901. [CrossRef]
154. García-Villalba, R.; Selma, M.V.; Espín, J.C.; Tomás-Barberán, F.A. Identification of novel urolithin metabolites in human feces and urine after the intake of a pomegranate extract. *J. Agric. Food Chem.* **2019**, *67*, 11099–11107. [CrossRef]
155. Tomás-Barberán, F.A.; García-Villalba, R.; González-Sarrías, A.; Selma, M.V.; Espín, J.C. Ellagic acid metabolism by human gut microbiota: Consistent observation of three urolithin phenotypes in intervention trials, independent of food source, age, and health status. *J. Agric. Food Chem.* **2014**, *62*, 6535–6538. [CrossRef]
156. Romo-Vaquero, M.; García-Villalba, R.; González-Sarrías, A.; Beltrán, D.; Tomás-Barberán, F.A.; Espín, J.C.; Selma, M.V. Interindividual variability in the human metabolism of ellagic acid: Contribution of Gordonibacter to urolithin production. *J. Funct. Foods* **2015**, *17*, 785–791. [CrossRef]
157. Cortés-Martín, A.; García-Villalba, R.; González-Sarrías, A.; Romo-Vaquero, M.; Loria-Kohen, V.; Ramírez-de-Molina, A.; Tomás-Barberán, F.A.; Selma, M.V.; Espín, J.C. The gut microbiota urolithin metabotypes revisited: The human metabolism of ellagic acid is mainly determined by aging. *Food Funct.* **2018**, *9*, 4100–4106. [CrossRef] [PubMed]
158. Iglesias-Aguirre, C.E.; García-Villalba, R.; Beltrán, D.; Frutos-Lisón, M.D.; Espín, J.C.; Tomás-Barberán, F.A.; Selma, M.V. Gut bacteria involved in ellagic acid metabolism to yield human urolithin metabotypes revealed. *J. Agric. Food Chem.* **2023**, *71*, 4029–4035. [CrossRef]
159. Beltrán, D.; Frutos-Lisón, M.D.; García-Villalba, R.; Yuste, J.E.; García, V.; Espín, J.C.; Selma, M.V.; Tomás-Barberán, F.A. NMR spectroscopic identification of urolithin G, a novel trihydroxy urolithin produced by human intestinal *Enterocloster* Species. *J. Agric. Food Chem.* **2023**, *71*, 11921–11928. [CrossRef]

160. Milala, J.; Kosmala, M.; Karlińska, E.; Juśkiewicz, J.; Zduńczyk, Z.; Fotschki, B. Ellagitannins from strawberries with different degrees of polymerization showed different metabolism through gastrointestinal tract of rats. *J. Agric. Food Chem.* **2017**, *65*, 10738–10748. [CrossRef]
161. Żary-Sikorska, E.; Kosmala, M.; Milala, J.; Fotschki, B.; Ognik, K.; Juśkiewicz, J. Concentrations of blood serum and urinal ellagitannin metabolites depend largely on the post-intake time and duration of strawberry phenolics ingestion in rats. *Pol. J. Food Nutr. Sci.* **2019**, *69*, 379–386. [CrossRef]
162. Lin, I.-C.; Wu, J.-Y.; Fang, C.-Y.; Wang, S.-C.; Liu, Y.-W.; Ho, S.-T. Absorption and metabolism of urolithin A and ellagic acid in mice and their cytotoxicity in human colorectal cancer cells. *Evid. Based Complement. Alternat. Med.* **2023**, *2023*, 8264716. [CrossRef] [PubMed]
163. Seeram, N.P.; Aronson, W.J.; Zhang, Y.; Henning, S.M.; Moro, A.; Lee, R.; Sartippour, M.; Harris, D.M.; Rettig, M.; Suchard, M.A.; et al. Pomegranate ellagitannin-derived metabolites inhibit prostate cancer growth and localize to the mouse prostate gland. *J. Agric. Food Chem.* **2007**, *55*, 7732–7737. [CrossRef]
164. González-Barrio, R.; Truchado, P.; Ito, H.; Espín, J.C.; Tomás-Barberán, F.A. UV and MS Identification of urolithins and nasutins, the bioavailable metabolites of ellagitannins and ellagic acid in different mammals. *J. Agric. Food Chem.* **2011**, *59*, 1152–1162. [CrossRef]
165. González-Barrio, R.; Truchado, P.; García-Villalba, R.; Hervás, G.; Frutos, P.; Espín, J.C.; Tomás-Barberán, F.A. Metabolism of oak leaf ellagitannins and urolithin production in beef cattle. *J. Agric. Food Chem.* **2012**, *60*, 3068–3077. [CrossRef]
166. Espín, J.C.; González-Barrio, R.; Cerdá, B.; López-Bote, C.; Rey, A.I.; Tomás-Barberán, F.A. Iberian pig as a model to clarify obscure points in the bioavailability and metabolism of ellagitannins in humans. *J. Agric. Food Chem.* **2007**, *55*, 10476–10485. [CrossRef]
167. Cerdá, B.; Tomás-Barberán, F.A.; Espín, J.C. Metabolism of antioxidant and chemopreventive ellagitannins from strawberries, raspberries, walnuts, and oak-aged wine in humans: Identification of biomarkers and individual variability. *J. Agric. Food Chem.* **2005**, *53*, 227–235. [CrossRef] [PubMed]
168. Zhang, X.; Fan, J.; Xiao, D.; Edirisinghe, I.; Burton-Freeman, B.M.; Sandhu, A.K. Pharmacokinetic evaluation of red raspberry (poly)phenols from two doses and association with metabolic indices in adults with prediabetes and insulin resistance. *J. Agric. Food Chem.* **2021**, *69*, 9238–9248. [CrossRef]
169. Moreno Uclés, R.; González-Sarrías, A.; Espín, J.C.; Tomás-Barberán, F.A.; Janes, M.; Cheng, H.; Finley, J.; Greenway, F.; Losso, J.N. Effects of red raspberry polyphenols and metabolites on the biomarkers of inflammation and insulin resistance in type 2 diabetes: A pilot study. *Food Funct.* **2022**, *13*, 5166–5176. [CrossRef] [PubMed]
170. González-Barrio, R.; Borges, G.; Mullen, W.; Crozier, A. Bioavailability of anthocyanins and ellagitannins following consumption of raspberries by healthy humans and subjects with an ileostomy. *J. Agric. Food Chem.* **2010**, *58*, 3933–3939. [CrossRef]
171. Zhang, X.; Zhao, A.; Sandhu, A.K.; Edirisinghe, I.; Burton-Freeman, B.M. Functional deficits in gut microbiome of young and middle-aged adults with prediabetes apparent in metabolizing bioactive (poly)phenols. *Nutrients* **2020**, *12*, 3595. [CrossRef] [PubMed]
172. Roberts, K.M.; Grainger, E.M.; Thomas-Ahner, J.M.; Hinton, A.; Gu, J.; Riedl, K.; Vodovotz, Y.; Abaza, R.; Schwartz, S.J.; Clinton, S.K. Dose-dependent increases in ellagitannin metabolites as biomarkers of intake in humans consuming standardized black raspberry food products designed for clinical trials. *Mol. Nutr. Food Res.* **2020**, *64*, 1900800. [CrossRef]
173. Henning, S.M.; Seeram, N.P.; Zhang, Y.; Li, L.; Gao, K.; Lee, R.-P.; Wang, D.C.; Zerlin, A.; Karp, H.; Thames, G.; et al. Strawberry consumption is associated with increased antioxidant capacity in serum. *J. Med. Food* **2010**, *13*, 116–122. [CrossRef]
174. Sandhu, A.K.; Miller, M.G.; Thangthaeng, N.; Scott, T.M.; Shukitt-Hale, B.; Edirisinghe, I.; Burton-Freeman, B. Metabolic fate of strawberry polyphenols after chronic intake in healthy older adults. *Food Funct.* **2018**, *9*, 96–106. [CrossRef]
175. González-Sarrías, A.; Giménez-Bastida, J.A.; García-Conesa, M.T.; Gómez-Sánchez, M.B.; García-Talavera, N.V.; Gil-Izquierdo, A.; Sánchez-Álvarez, C.; Fontana-Compiano, L.O.; Morga-Egea, J.P.; Pastor-Quirante, F.A.; et al. Occurrence of urolithins, gut microbiota ellagic acid metabolites and proliferation markers expression response in the human prostate gland upon consumption of walnuts and pomegranate juice. *Mol. Nutr. Food Res.* **2010**, *54*, 311–322. [CrossRef]
176. Pfundstein, B.; Haubner, R.; Würtele, G.; Gehres, N.; Ulrich, C.M.; Owen, R.W. Pilot walnut intervention study of urolithin bioavailability in human volunteers. *J. Agric. Food Chem.* **2014**, *62*, 10264–10273. [CrossRef]
177. Cortés-Martín, A.; García-Villalba, R.; García-Mantrana, I.; Rodríguez-Varela, A.; Romo-Vaquero, M.; Collado, M.C.; Tomás-Barberán, F.A.; Espín, J.C.; Selma, M.V. Urolithins in human breast milk after walnut intake and kinetics of *Gordonibacter* colonization in newly born: The role of mothers' urolithin metabotypes. *J. Agric. Food Chem.* **2020**, *68*, 12606–12616. [CrossRef]
178. García-Villalba, R.; Espín, J.C.; Tomás-Barberán, F.A. Chromatographic and spectroscopic characterization of urolithins for their determination in biological samples after the intake of foods containing ellagitannins and ellagic acid. *J. Chromatogr. A* **2016**, *1428*, 162–175. [CrossRef] [PubMed]
179. García-Mantrana, I.; Calatayud, M.; Romo-Vaquero, M.; Espín, J.C.; Selma, M.V.; Collado, M.C. Urolithin metabotypes can determine the modulation of gut microbiota in healthy individuals by tracking walnuts consumption over three days. *Nutrients* **2019**, *11*, 2483. [CrossRef] [PubMed]
180. Van Der Hooft, J.J.J.; De Vos, R.C.H.; Mihaleva, V.; Bino, R.J.; Ridder, L.; De Roo, N.; Jacobs, D.M.; Van Duynhoven, J.P.M.; Vervoort, J. Structural elucidation and quantification of phenolic conjugates present in human urine after tea intake. *Anal. Chem.* **2012**, *84*, 7263–7271. [CrossRef]

181. Singh, A.; D'Amico, D.; Andreux, P.A.; Dunngalvin, G.; Kern, T.; Blanco-Bose, W.; Auwerx, J.; Aebischer, P.; Rinsch, C. Direct supplementation with urolithin A overcomes limitations of dietary exposure and gut microbiome variability in healthy adults to achieve consistent levels across the population. *Eur. J. Clin. Nutr.* **2022**, *76*, 297–308. [CrossRef] [PubMed]
182. Cortés-Martín, A.; Iglesias-Aguirre, C.E.; Meoro, A.; Selma, M.V.; Espín, J.C. Pharmacological therapy determines the gut microbiota modulation by a pomegranate extract nutraceutical in metabolic syndrome: A randomized clinical trial. *Mol. Nutr. Food Res.* **2021**, *65*, 2001048. [CrossRef]
183. Nuñez-Sánchez, M.A.; García-Villalba, R.; Monedero-Saiz, T.; García-Talavera, N.V.; Gómez-Sánchez, M.B.; Sánchez-Álvarez, C.; García-Albert, A.M.; Rodríguez-Gil, F.J.; Ruiz-Marín, M.; Pastor-Quirante, F.A.; et al. Targeted metabolic profiling of pomegranate polyphenols and urolithins in plasma, urine and colon tissues from colorectal cancer patients. *Mol. Nutr. Food Res.* **2014**, *58*, 1199–1211. [CrossRef]
184. Seeram, N.P.; Henning, S.M.; Zhang, Y.; Suchard, M.; Li, Z.; Heber, D. Pomegranate juice ellagitannin metabolites are present in human plasma and some persist in urine for up to 48 h. *J. Nutr.* **2006**, *136*, 2481–2485. [CrossRef]
185. Henning, S.M.; Yang, J.; Lee, R.-P.; Huang, J.; Thames, G.; Korn, M.; Ben-Nissan, D.; Heber, D.; Li, Z. Pomegranate juice alters the microbiota in breast milk and infant stool: A pilot study. *Food Funct.* **2022**, *13*, 5680–5689. [CrossRef]
186. Mertens-Talcott, S.U.; Jilma-Stohlawetz, P.; Rios, J.; Hingorani, L.; Derendorf, H. Absorption, metabolism, and antioxidant effects of pomegranate (*Punica granatum* L.) polyphenols after ingestion of a standardized extract in healthy human volunteers. *J. Agric. Food Chem.* **2006**, *54*, 8956–8961. [CrossRef]
187. Seeram, N.P.; Zhang, Y.; McKeever, R.; Henning, S.M.; Lee, R.; Suchard, M.A.; Li, Z.; Chen, S.; Thames, G.; Zerlin, A.; et al. Pomegranate juice and extracts provide similar levels of plasma and urinary ellagitannin metabolites in human subjects. *J. Med. Food* **2008**, *11*, 390–394. [CrossRef] [PubMed]
188. García-Muñoz, C.; Hernández, L.; Pérez, A.; Vaillant, F. Diversity of urinary excretion patterns of main ellagitannins' colonic metabolites after ingestion of tropical highland blackberry (*Rubus adenotrichus*) Juice. *Food Res. Inter.* **2014**, *55*, 161–169. [CrossRef]
189. Gu, J.; Thomas-Ahner, J.M.; Riedl, K.M.; Bailey, M.T.; Vodovotz, Y.; Schwartz, S.J.; Clinton, S.K. Dietary black raspberries impact the colonic microbiome and phytochemical metabolites in mice. *Mol. Nutr. Food Res.* **2019**, *63*, 1800636. [CrossRef] [PubMed]
190. Yang, Y.; Lee, P.-K.; Wong, H.-C.; Zhao, D. Oral supplementation of Gordonibacter Urolithinfaciens promotes ellagic acid metabolism and urolithin bioavailability in mice. *Food Chem.* **2024**, *437*, 137953. [CrossRef] [PubMed]
191. Kujawska, M.; Jourdes, M.; Kurpik, M.; Szulc, M.; Szaefer, H.; Chmielarz, P.; Kreiner, G.; Krajka-Kuźniak, V.; Mikołajczak, P.Ł.; Teissedre, P.-L.; et al. Neuroprotective effects of pomegranate juice against Parkinson's disease and presence of ellagitannins-derived metabolite—Urolithin A—In the brain. *Int. J. Mol. Sci.* **2019**, *21*, 202. [CrossRef] [PubMed]
192. Roberts, K.M.; Grainger, E.M.; Thomas-Ahner, J.M.; Hinton, A.; Gu, J.; Riedl, K.M.; Vodovotz, Y.; Abaza, R.; Schwartz, S.J.; Clinton, S.K. Application of a low polyphenol or low ellagitannin dietary intervention and its impact on ellagitannin metabolism in men. *Mol. Nutr. Food Res.* **2017**, *61*, 1600224. [CrossRef] [PubMed]
193. Tulipani, S.; Urpi-Sarda, M.; García-Villalba, R.; Rabassa, M.; López-Uriarte, P.; Bulló, M.; Jáuregui, O.; Tomás-Barberán, F.; Salas-Salvadó, J.; Espín, J.C.; et al. Urolithins are the main urinary microbial-derived phenolic metabolites discriminating a moderate consumption of nuts in free-living subjects with diagnosed metabolic syndrome. *J. Agric. Food Chem.* **2012**, *60*, 8930–8940. [CrossRef] [PubMed]
194. Jurgoński, A.; Juśkiewicz, J.; Fotschki, B.; Kołodziejczyk, K.; Milala, J.; Kosmala, M.; Grzelak-Błaszczyk, K.; Markiewicz, L. Metabolism of strawberry mono- and dimeric ellagitannins in rats fed a diet containing fructo-oligosaccharides. *Eur. J. Nutr.* **2017**, *56*, 853–864. [CrossRef]
195. Kosmala, M.; Jurgoński, A.; Juśkiewicz, J.; Karlińska, E.; Macierzyński, J.; Rój, E.; Zduńczyk, Z. Chemical composition of blackberry press cake, polyphenolic extract, and defatted seeds, and their effects on cecal fermentation, bacterial metabolites, and blood lipid profile in rats. *J. Agric. Food Chem.* **2017**, *65*, 5470–5479. [CrossRef]
196. Mosele, J.I.; Gosalbes, M.; Macià, A.; Rubió, L.; Vázquez-Castellanos, J.F.; Jiménez Hernández, N.; Moya, A.; Latorre, A.; Motilva, M. Effect of daily intake of pomegranate juice on fecal microbiota and feces metabolites from healthy volunteers. *Mol. Nutr. Food Res.* **2015**, *59*, 1942–1953. [CrossRef]
197. Li, Z.; Henning, S.M.; Lee, R.-P.; Lu, Q.-Y.; Summanen, P.H.; Thames, G.; Corbett, K.; Downes, J.; Tseng, C.-H.; Finegold, S.M.; et al. Pomegranate extract induces ellagitannin metabolite formation and changes stool microbiota in healthy volunteers. *Food Funct.* **2015**, *6*, 2487–2495. [CrossRef]
198. Aichinger, G.; Stevanoska, M.; Beekmann, K.; Sturla, S.J. Physiologically-based pharmacokinetic modeling of the postbiotic supplement urolithin A predicts its bioavailability is orders of magnitude lower than concentrations that induce toxicity, but also neuroprotective effects. *Mol. Nutr. Food Res.* **2023**, *67*, 2300009. [CrossRef] [PubMed]
199. Dacrema, M.; Sommella, E.; Santarcangelo, C.; Bruno, B.; Marano, M.G.; Insolia, V.; Saviano, A.; Campiglia, P.; Stornaiuolo, M.; Daglia, M. Metabolic profiling, in vitro bioaccessibility and in vivo bioavailability of a commercial bioactive *Epilobium angustifolium* L. extract. *Biomed. Pharmacother.* **2020**, *131*, 110670. [CrossRef]
200. Wang, Y.-H.; Mondal, G.; Khan, W.; Gurley, B.J.; Yates, C.R. Development of a liquid chromatography-tandem mass spectrometry (LC–MS/MS) method for characterizing pomegranate extract pharmacokinetics in humans. *J. Pharm. Biomed. Anal.* **2023**, *233*, 115477. [CrossRef] [PubMed]

201. Xiao, Y.; Li, K.; Zhang, H.; Li, Y.; Han, L.; Liu, H.; Wang, M. The profile of buckwheat tannins based on widely targeted metabolome analysis and pharmacokinetic study of ellagitannin metabolite urolithin A. *LWT-Food Sci. Technol.* **2022**, *156*, 113069. [CrossRef]
202. Liu, Q.; Liu, S.; Ye, Q.; Hou, X.; Yang, G.; Lu, J.; Hai, Y.; Shen, J.; Fang, Y. A novel streptococcus thermophilus FUA329 isolated from human breast milk capable of producing urolithin A from ellagic acid. *Foods* **2022**, *11*, 3280. [CrossRef]
203. Quatrin, A.; Rampelotto, C.; Pauletto, R.; Maurer, L.H.; Nichelle, S.M.; Klein, B.; Rodrigues, R.F.; Maróstica Junior, M.R.; Fonseca, B.D.S.; De Menezes, C.R.; et al. Bioaccessibility and catabolism of phenolic compounds from Jaboticaba (*Myrciaria trunciflora)* fruit peel during in vitro gastrointestinal digestion and colonic fermentation. *J. Funct. Foods* **2020**, *65*, 103714. [CrossRef]
204. García-Villalba, R.; Beltrán, D.; Espín, J.C.; Selma, M.V.; Tomás-Barberán, F.A. Time course production of urolithins from ellagic acid by human gut microbiota. *J. Agric. Food Chem.* **2013**, *61*, 8797–8806. [CrossRef]
205. García-Villalba, R.; Beltrán, D.; Frutos, M.D.; Selma, M.V.; Espín, J.C.; Tomás-Barberán, F.A. Metabolism of different dietary phenolic compounds by the urolithin-producing human-gut bacteria *Gordonibacter urolithinfaciens* and *Ellagibacter isourolithinifaciens*. *Food Funct.* **2020**, *11*, 7012–7022. [CrossRef]
206. Zhang, M.; Cui, S.; Mao, B.; Zhang, Q.; Zhao, J.; Tang, X.; Chen, W. Urolithin A produced by novel microbial fermentation possesses anti-aging effects by improving mitophagy and reducing reactive oxygen species in *Caenorhabditis elegans*. *J. Agric. Food Chem.* **2023**, *71*, 6348–6357. [CrossRef]
207. Liu, Q.; Hua, Z.; Chen, M.; Liu, S.; Ahmed, S.; Hou, X.; Yang, G.; Fang, Y. Changes in polyphenols and antioxidant properties of pomegranate peels fermented by urolithin A-producing *Streptococcus thermophilus* FUA329. *ACS Food Sci. Technol.* **2023**, *3*, 1383–1392. [CrossRef]
208. Laveriano-Santos, E.P.; Quifer-Rada, P.; Marhuenda-Muñoz, M.; Arancibia-Riveros, C.; Vallverdú-Queralt, A.; Tresserra-Rimbau, A.; Ruiz-León, A.M.; Casas, R.; Estruch, R.; Bodega, P.; et al. Microbial phenolic metabolites in urine are inversely linked to certain features of metabolic syndrome in spanish adolescents. *Antioxidants* **2022**, *11*, 2191. [CrossRef] [PubMed]
209. Zhang, X.; Sandhu, A.; Edirisinghe, I.; Burton-Freeman, B.M. Plasma and urinary (poly)phenolic profiles after 4-week red raspberry (*Rubus idaeus* L.) intake with or without fructo-oligosaccharide supplementation. *Molecules* **2020**, *25*, 4777. [CrossRef] [PubMed]
210. Natella, F.; Leoni, G.; Maldini, M.; Natarelli, L.; Comitato, R.; Schonlau, F.; Virgili, F.; Canali, R. Absorption, metabolism, and effects at transcriptome level of a standardized french oak wood extract, robuvit, in healthy volunteers: Pilot study. *J. Agric. Food Chem.* **2014**, *62*, 443–453. [CrossRef] [PubMed]
211. Hao, Y.; Yang, J.; Cui, J.; Fan, Y.; Li, N.; Wang, C.; Liu, Y.; Dong, Y. Stability and mechanism of phenolic compounds from raspberry extract under in vitro gastrointestinal digestion. *LWT-Food Sci. Technol.* **2021**, *139*, 110552. [CrossRef]
212. Gasperotti, M.; Masuero, D.; Guella, G.; Mattivi, F.; Vrhovsek, U. Development of a targeted method for twenty-three metabolites related to polyphenol gut microbial metabolism in biological samples, using SPE and UHPLC–ESI-MS/MS. *Talanta* **2014**, *128*, 221–230. [CrossRef] [PubMed]
213. Bayle, M.; Roques, C.; Marion, B.; Audran, M.; Oiry, C.; Bressolle-Gomeni, F.M.M.; Cros, G. Development and validation of a liquid chromatography-electrospray ionization-tandem mass spectrometry method for the determination of urolithin C in rat plasma and its application to a pharmacokinetic study. *J. Pharm. Biomed. Anal.* **2016**, *131*, 33–39. [CrossRef] [PubMed]
214. Ares, A.M.; Toribio, L.; García-Villalba, R.; Villalgordo, J.M.; Althobaiti, Y.; Tomás-Barberán, F.A.; Bernal, J. Separation of isomeric forms of urolithin glucuronides using supercritical fluid chromatography. *J. Agric. Food Chem.* **2023**, *71*, 3033–3039. [CrossRef]
215. Ryu, D.; Mouchiroud, L.; Andreux, P.A.; Katsyuba, E.; Moullan, N.; Nicolet-dit-Félix, A.A.; Williams, E.G.; Jha, P.; Lo Sasso, G.; Huzard, D.; et al. Urolithin A induces mitophagy and prolongs lifespan in *C. elegans* and increases muscle function in rodents. *Nat. Med.* **2016**, *22*, 879–888. [CrossRef]
216. Jiménez-Loygorri, J.I.; Villarejo-Zori, B.; Viedma-Poyatos, Á.; Zapata-Muñoz, J.; Benítez-Fernández, R.; Frutos-Lisón, M.D.; Tomás-Barberán, F.A.; Espín, J.C.; Area-Gómez, E.; Gomez-Duran, A.; et al. Mitophagy curtails cytosolic mtDNA-dependent activation of cGAS/STING inflammation during aging. *Nat. Commun.* **2024**, *15*, 830. [CrossRef]
217. Qin, X.; Li, H.; Zhao, H.; Fang, L.; Wang, X. Enhancing healthy aging with small molecules: A mitochondrial perspective. *Med. Res. Rev*, 2024, *online ahead of print*. [CrossRef]
218. Tang, L.; Mo, Y.; Li, Y.; Zhong, Y.; He, S.; Zhang, Y.; Tang, Y.; Fu, S.; Wang, X.; Chen, A. Urolithin A alleviates myocardial ischemia/reperfusion injury via PI3K/Akt pathway. *Biochem. Biophys. Res. Commun.* **2017**, *486*, 774–780. [CrossRef]
219. Cui, G.H.; Chen, W.Q.; Shen, Z.Y. Urolithin A shows anti-atherosclerotic activity via activation of class B scavenger receptor and activation of Nef_2 signaling pathway. *Pharmacol. Rep.* **2018**, *70*, 519–524. [CrossRef] [PubMed]
220. Savi, M.; Bocchi, L.; Mena, P.; Dall'Asta, M.; Crozier, A.; Brighenti, F.; Stilli, D.; Del Rio, D. In vivo administration of urolithin A and B prevents the occurrence of cardiac dysfunction in streptozotocin-induced diabetic rats. *Cardiovasc. Diabetol.* **2017**, *16*, 80. [CrossRef] [PubMed]
221. Fang, E.F.; Hou, Y.; Palikaras, K.; Adriaanse, B.A.; Kerr, J.S.; Yang, B.; Lautrup, S.; Hasan-Olive, M.M.; Caponio, D.; Dan, X.; et al. Mitophagy inhibits amyloid-β and tau pathology and reverses cognitive deficits in models of Alzheimer's disease. *Nat. Neurosci.* **2019**, *22*, 401–412. [CrossRef] [PubMed]
222. Gong, Z.; Huang, J.; Xu, B.; Ou, Z.; Zhang, L.; Lin, X.; Ye, X.; Kong, X.; Long, D.; Sun, X.; et al. Urolithin A attenuates memory impairment and neuroinflammation in APP/PS1 mice. *J. Neuroinflamm.* **2019**, *16*, 62. [CrossRef]

223. Shen, P.X.; Li, X.; Deng, S.Y.; Zhao, L.; Zhang, Y.Y.; Deng, X.; Han, B.; Yu, J.; Li, Y.; Wang, Z.Z.; et al. Urolithin A ameliorates experimental autoimmune encephalomyelitis by targeting aryl hydrocarbon receptor. *EBioMedicine* **2021**, *64*, 103227. [CrossRef] [PubMed]
224. Ahsan, A.; Zheng, Y.R.; Wu, X.L.; Tang, W.D.; Liu, M.R.; Ma, S.J.; Jiang, L.; Hu, W.W.; Zhang, X.N.; Chen, Z. Urolithin A-activated autophagy but not mitophagy protects against ischemic neuronal injury by inhibiting ER stress in vitro and in vivo. *CNS Neurosci. Ther.* **2019**, *25*, 976–986. [CrossRef]
225. Madsen, H.B.; Park, J.H.; Chu, X.; Hou, Y.; Li, Z.; Rasmussen, L.J.; Croteau, D.L.; Bohr, V.A.; Akbari, M. The cGAS-STING signaling pathway is modulated by urolithin A. *Mech. Ageing Dev.* **2024**, *217*, 111897. [CrossRef]
226. Singh, R.; Chandrashekharappa, S.; Bodduluri, S.R.; Baby, B.V.; Hegde, B.; Kotla, N.G.; Hiwale, A.A.; Saiyed, T.; Patel, P.; Vijay-Kumar, M.; et al. Enhancement of the gut barrier integrity by a microbial metabolite through the Nrf_2 pathway. *Nat. Commun.* **2019**, *10*, 89. [CrossRef]
227. Sairenji, T.; Collins, K.L.; Evans, D.V. An Update on inflammatory bowel disease. *Prim. Care* **2017**, *44*, 673–692. [CrossRef]
228. Larrosa, M.; González-Sarrías, A.; Yáñez-Gascón, M.J.; Selma, M.V.; Azorín-Ortuño, M.; Toti, S.; Tomás-Barberán, F.; Dolara, P.; Espín, J.C. Anti-inflammatory properties of a pomegranate extract and its metabolite urolithin-A in a colitis rat model and the effect of colon inflammation on phenolic metabolism. *J. Nutr. Biochem.* **2010**, *21*, 717–725. [CrossRef] [PubMed]
229. Zhang, Y.; Wei, S.; Zhang, H.; Jo, Y.; Kang, J.S.; Ha, K.T.; Joo, J.; Lee, H.J.; Ryu, D. Gut microbiota-generated metabolites: Missing puzzles to hosts' health, diseases, and aging. *BMB Rep.* **2024**, 6194. [CrossRef] [PubMed]
230. Heilman, J.; Andreux, P.; Tran, N.; Rinsch, C.; Blanco-Bose, W. Safety assessment of urolithin A, a metabolite produced by the human gut microbiota upon dietary intake of plant derived ellagitannins and ellagic acid. *Food Chem. Toxicol.* **2017**, *108*, 289–297. [CrossRef] [PubMed]
231. Nair, A.; Jacob, S. A simple practice guide for dose conversion between animals and human. *J. Basic Clin. Pharma.* **2016**, *7*, 27. [CrossRef] [PubMed]
232. Andreux, P.A.; Blanco-Bose, W.; Ryu, D.; Burdet, F.; Ibberson, M.; Aebischer, P.; Auwerx, J.; Singh, A.; Rinsch, C. The mitophagy activator urolithin A is safe and induces a molecular signature of improved mitochondrial and cellular health in humans. *Nat. Metab.* **2019**, *1*, 595–603. [CrossRef] [PubMed]
233. FDA. *GRAS Notice GRN No. 791: Urolithin A*; US Food and Drug Administration: Silver Spring, MD, USA, 2018.
234. Liu, S.; D'Amico, D.; Shankland, E.; Bhayana, S.; Garcia, J.M.; Aebischer, P.; Rinsch, C.; Singh, A.; Marcinek, D.J. Effect of urolithin A supplementation on muscle endurance and mitochondrial health in older adults: A randomized clinical trial. *JAMA Netw. Open* **2022**, *5*, e2144279. [CrossRef]
235. Singh, A.; D'Amico, D.; Andreux, P.A.; Fouassier, A.M.; Blanco-Bose, W.; Evans, M.; Aebischer, P.; Auwerx, J.; Rinsch, C. Urolithin A improves muscle strength, exercise performance, and biomarkers of mitochondrial health in a randomized trial in middle-aged adults. *Cell Rep. Med.* **2022**, *3*, 100633. [CrossRef]
236. Ghadimi, M.; Foroughi, F.; Hashemipour, S.; Rashidi Nooshabadi, M.; Ahmadi, M.H.; Ahadi Nezhad, B.; Khadem Haghighian, H. Randomized double-blind clinical trial examining the ellagic acid effects on glycemic status, insulin resistance, antioxidant, and inflammatory factors in patients with type 2 diabetes. *Phytother. Res.* **2021**, *35*, 1023–1032. [CrossRef]
237. Cerdá, B.; Cerón, J.J.; Tomás-Barberán, F.A.; Espín, J.C. Repeated oral administration of high doses of the pomegranate ellagitannin punicalagin to rats for 37 days is not toxic. *J. Agric. Food Chem.* **2003**, *51*, 3493–3501. [CrossRef]
238. Patel, C.; Dadhaniya, P.; Hingorani, L.; Soni, M.G. Safety assessment of pomegranate fruit extract: Acute and subchronic toxicity studies. *Food Chem. Toxicol.* **2008**, *46*, 2728–2735. [CrossRef]
239. Inada, K.O.P.; Tomás-Barberán, F.A.; Perrone, D.; Monteiro, M. Metabolism of ellagitannins from Jabuticaba (*Myrciaria jaboticaba*) in normoweight, overweight and obese Brazilians: Unexpected laxative effects influence urolithins urinary excretion and metabotype distribution. *J. Funct. Foods* **2019**, *57*, 299–308. [CrossRef]
240. Sivamani, R.K.; Chakkalakal, M.; Pan, A.; Nadora, D.; Min, M.; Dumont, A.; Burney, W.A.; Chambers, C.J. Prospective randomized, double-blind, placebo-controlled study of a standardized oral pomegranate extract on the gut microbiome and short-chain fatty acids. *Foods* **2023**, *13*, 15. [CrossRef] [PubMed]
241. Chakkalakal, M.; Nadora, D.; Gahoonia, N.; Dumont, A.; Burney, W.; Pan, A.; Chambers, C.J.; Sivamani, R.K. Prospective randomized double-blind placebo-controlled study of oral pomegranate extract on skin wrinkles, biophysical features, and the gut-skin axis. *J. Clin. Med.* **2022**, *11*, 6724. [CrossRef] [PubMed]