Chapter

Food Ellagitannins: Structure, Metabolomic Fate, and Biological Properties

Karen Johana Ortega Villalba, Fabrice Vaillant Barka, Carlos Vélez Pasos and Pablo Emilio Rodríguez

Abstract

Food sources of ellagitannins (ETs) are numerous, and dietary intake of these compounds is estimated up to 12 mg/day in some countries, even though ETs have been considered in the past as not bioavailable like other tannins and were mostly neglected by nutritionists. Nonetheless, new insights show that ETs are bioconverted by microbiota in the gut into metabolites called urolithins, which are bioavailable and can reach relatively high physiological concentration in the body up to 7 days after ingestion. According to the initial structure of ETs in the food source, the extent of bioconversion into urolithins may differ but all urolithins are susceptible to exert potential health benefits. Nonetheless, due to the intervention of microbiota, the production and excretion of urolithins are highly variable according to individuals, which have led to the classification of consumers into metabotype. According to metabotype, the potential health benefits of ellagitannins may differ among consumers. In in vitro, cellular and animal studies, numerous health benefits of ellagitannins and urolithins are reported mainly for the chemoprevention of hormone-dependent cancer and cardiovascular disease. Nonetheless, ellagitannins deserve closer attention from the scientific community to unravel more biological properties of this particular compound.

Keywords: ellagitannins, urolithins, microbiota, metabotype, chemoprevention

1. Introduction

Ellagitannins are food compounds that were quite neglected by nutritionists until last decade. As part of tannins, they had no good reputation and they were considered as antinutritional compounds. But new scientific insights have changed these perspectives, and ellagitannins now attract the attention of food scientists, nutritionists and consumers since the number of published papers on these compounds has considerably increased during the last decade. Ellagitannin is a hydrolyzable polymer contrary to the rest of the family of tannins and can be hydrolyzed to more simple monomers that can be eventually metabolized and that can become bioavailable with subsequent exposition of the body to these metabolites. For sure, if ellagitannins are widely present in nature, only few food sources are reported with relatively high content of this compound, and consequently exposition of consumers to food ellagitannins is relatively low, especially in the Western diet. But given...
the health potential of ETs, ET-rich food now belongs to the select group of functional foods, and their consumption should be considerably enhanced in the future. Actually, given the main food source of ellagitannins such as berries and nuts, we can easily assume that the exposure to this compound and their metabolites was considerably higher in the hunter-gatherer diet than in modern time. Without presuming that an increase in ET intake would reduce significantly the impact of certain chronic diseases due to modern lifestyle, it is reasonable to argue that ETs have been part of our evolutionary history and they could potentially perform health care functions. New scientific insights presented in this chapter on the in vivo metabolisms of ellagitannins and the potential biological activities of generated metabolites tend to support this hypothesis. This review presents the main food source of ellagitannins, their general chemical structure, and how technologies and storage could eventually affect ellagitannin composition in processed foods. Then, we will review the metabolomic fate and the bioavailability of ellagitannins in humans, which is strongly related to the performance of intestinal microbiota, and finally, we will present a summary of the main biological activities, attributed to ETs and their derived metabolites.

2. Food occurrence of ellagitannins

Ellagitannins (ETs) are with gallotannins part of the hydrolyzable tannins and constitute the largest group among more than 500 hydrolyzable tannins characterized until now [1]. To date, more than 1000 natural ellagitannins have been identified in nature [2] but most of them are not preponderant in foods. The main ETs identified in foods (specially in fruits, nuts, and seeds) are punicalagin, sanguin H6, lambertianin C, pedunculagin, vescalagin, castalagin, casuarictin and potentillin (seeds) [3].

Examples of concentration and ellagitannins identified in some foods are presented in Table 1. The occurrence of ETs in foods is restricted to a few fruits, such as berries of the genus *Rubus* (cloudberry, raspberry, blackberry, blueberry, and cranberry) and the genus *Fragaria* (strawberry), pomegranate, nuts (walnuts and almonds), seeds, and oak-aged wines [1, 6–8]. Recently, other ET food sources of

| Food source                  | Ellagitannins                  | Content equ. EA (mg/100 g) |
|------------------------------|--------------------------------|----------------------------|
| Blackberries (*Rubus spp.*)  | Sanguin H6, lambertianin D [7] | 150–270 [3]                |
| Strawberries (*Fragaria ananassa*) | Casuarictin, pedunculagin, sanguin H6 [7, 8] | 71–83 [3]                |
| Cloudberries (*Rubus chamaemorus*) | Sanguin H6, lambertianin C [7] | 312 [3]                |
| Raspberries (*Rubus idaeus*)  | Sanguin H6, sanguin H10, lambertianin C [7, 9] | 326 [10]                |
| Pomegranate (*Punica granatum*) | Punicalagin [7] | 58–177 [3]                |
| Guava (*Psidium friedrichshianum*) | Pedunculagin, castalin, and vescalain [5] | 63 [5]                |
| Jabuticaba (*Myrciaria jaboticaba*) | Sanguin H6-H10, lambertianin C [4] | 900 [11]                |
| Muscadine grapes (*Vitis rotundifolia*) | Sanguin H5 [7] | 3–91 [7]                |
| Purple Grumixama cherry (*Eugenia brasiliensis*) | Pedunculagin, strictinin, castalagin, vescalagin [12] | 16 [12]                |
| Chestnuts (*Castanea sativa*)  | Castalagin [7] | 149 [13]                |
| Pecans (*Carya illinoinensis*)  | Pedunculagin [7] | 316 [13]                |
| Walnuts (*Juglans regia*)     | Pedunculagin, casuarictin [14] | 864 [13]                |

Table 1. Main food source of ellagitannins.
local importance have been identified such as jabuticaba [4], guava, [5] and grumixama cherries [12]. It is interesting to note that according to a Brazilian research team, Jabuticaba berries from a particular variety cultivated in south Brazil have the highest registered ET content in fruits. Berries have almost three times more equivalent EA content than walnuts and pecans and at least 15 times more than other fruits and nuts [6]. In the berries from the genus *Rubus* and genus *Fragaria*, total equ. EA content represents the most important compounds with 50–88% of total phenolic. Also, ET content can be considerably affected by variety, ripeness, fruit parts, geographic origin, climate, season, cultural practices, and mineral nutrition [6].

ET daily intake is generally low and has been estimated around 5 mg/day for Western diets with major contributors being the red berries mainly strawberries, followed by raspberries and blackberries. Given the significant seasonality of the production of these fruits, the exposure to ellagitannins is very uneven during the year. In the Scandinavian countries, where the consumption of berries increases considerably in summer, daily intake can reach up to 12 mg/day [6, 9] with cloudberry, raspberry, rose hip, strawberry, and sea buckthorn being the main contributors with content from 1 to 330 mg/100 g (fresh weight basis).

3. Chemical structure of ellagitannins

ETs are esters of hexahydroxydiphenic acid (HHDP) and a polyol, usually glucose or quinic acid [3, 15, 16], that when they are hydrolyzed spontaneously suffer lactonization to form ellagic acid [10, 17] (Figure 1).

Chemical structure diversity among ETs is huge and is due to the possible variations in position, frequency, and stereochemistry of the HHDP units, galloylation extent, and/or anomic stereochemistry of sugar moieties [17]. Thus, due to seemingly endless structural variations among ellagitannin, elucidating their native structure is often a challenge [17]. According to their chemical structure, ETs can readily undergo different chemical reactions such as transformation, isomerization and oligomerization, which finally determine overall physico-chemical properties, hydrolytic susceptibility, and finally biological activity in vivo [7].

The important structural diversity of ET structure is due to the different possible extent of galloylation and formation of aromatic C-glycosides, the number of intramolecular C-C coupling of galloyl groups and hydrolytic cleavage of galloyl-derived aromatic rings, the level of dehydrogenation, and oligomerization via oxidative C-O [2, 17]. According to the number of HHDP groups linked to sugar moiety, ETs can be classified into monomeric, oligomeric, and polymeric ellagitannins [18].

---

Figure 1.
Basic structures of ellagitannins: (A) HHDP acid (R radical); (B) galloyl unit (G radical); (C) ellagic acid.
ETs are generally hydrolyzable in acidic or basic solutions. Even though ETs are quite resistant to acid hydrolysis, neutral or slightly alkaline pH (from 7.0 to 7.3) are the best conditions for ET hydrolysis to occur [19]. During hydrolysis, the ester bounds in the polymer are cleaved and HHDP is released followed by a spontaneous lactonization of free HHDP unit into free ellagic acid or derivatives [20]. This reaction is mainly used for the detection and quantification of ellagitannins, as ET content in food samples is often expressed as ellagic acid equivalents (Figure 2).

Acidic and basic hydrolysis of ETs can also occur during food processing, storage, and passage through the stomach and duodenum [10, 16, 21]. Although most ETs are hydrolyzable, further C—C coupling of polyphenolic residue with the polyol unit, such as in the case of vescalagin, can prevent hydrolysis [22]. In addition, ETs can undergo polymerization reactions during maturation of fruits or thermo-physical treatments, which can make them insoluble and eventually attached covalently to cell wall fragments [21]. Nonetheless, most often acidic or basic hydrolysis will
allow generating ellagic acid (EA) from ET even in mild conditions. As a consequence, EA, the dimeric derivative of gallic acid, is often spontaneously present in its free form in plants, next to ET [23].

3.1 Structural changes of ETs and EA during process and storage

Different studies have pointed out that there are important changes in ETs’ composition during processing and storage with marked subsequent consequences on the bioavailability and bioactivity of these compounds [24, 25].

Mazur et al. [26] noticed a decrease of 7% of lambertianin C in red raspberry jam after 6 months of storage at 20°C in dark; meanwhile, ellagic acid derivatives and total phenolics increased by 47%. The reason was the spontaneous hydrolysis of ellagitannins to ellagic acid that may occur during storage. Authors showed also that according to the genotype of raspberry, losses of ET were more or less important. On the other hand, one ellagitannins, the sanguin H6, remains remarkably stable during storage in this case [26]. Nonetheless, in another study, stored pasteurized blackberry juice showed after 6 months at 25°C a 46% loss in sanguin H6/lambertianin D, 42% loss in lambertianin C, and 72% loss in lambertianin D. Like previously, the total amount of EA measured after hydrolysis registered only minimal changes, which evidenced the spontaneous depolymerization of ETs into EA during storage. At 5°C, half-life (t<sub>1/2</sub>) of sanguin H6 and lambertianin C was almost comparable (around 80 days), but when stored at 45°C, t<sub>1/2</sub> was four times higher for sanguin than for lambertianin [25]. Sanguin H6 is a dimer and lambertianin C a trimer, which could explain the higher stability of this compound during storage at relatively high temperature. At freezing temperature, no changes at all were observed over a 6-month period [24]. We can conclude that stability of ellagitannins during storage of processed foods depends on their chemical structure as well as the composition of the food matrix.

Between different processing alternatives evaluated by Hager et al. [24], canning, pureeing, and freezing had little effect on blackberry (cv. Apache) ellagitannins, but the removal of seeds in the press-cake generates a loss of up to 70%, and if juice is microfiltered, 12% more loss can be registered. In that case, some ellagitannins appear to be associated with cell fragments and with the mucilage that surrounds the seeds. In the case of Costa Rican guava, pressing appears to increase the content of some ETs. After pressing, an increase in pedunculagin isomer 1 of 25% was observed, while castalagin isomers presented a significant decrease (40%). Authors suggest that castalagin decrease may be linked to degradation and not to isomerization of the compounds, since no increase in vescalagin content was observed [5]. Milling appeared to enhance the content of pedunculagin isomer 1 and castalagin isomers by 34 and 31%, respectively. Actually, another study on the effects of mechanical and enzymatic pretreatments on the extraction of ellagitannins from blackberries showed that enzymatic treatment (pectinase and cellulase) combined with continuous pressing enhanced significantly ET content in the juice (from 437 to 982 mg ellagic acid equivalents/100 g (dry basis)) [27].

Critical steps on ET content during classical industrial processing of blackberry-based beverage in glass bottles were evaluated. Hot-filling that is characterized by long-term exposure of the beverage to high temperature was the operation that most degraded ellagitannins with losses of 80% in lambertianin C and 50% in sanguin H6 in the final product. Again, sanguin H6 showed a higher thermal stability than lambertianin. It was also observed that the intensity of thermal treatment during process affects stability of ETs during storage [25]. But, when dealing with equivalent total EA content after hydrolysis, no changes were observed. On the
other hand, in another food source, the ripe Costa Rican guava (Psidium friedrich-sthalianum Nied), different pasteurization treatments (71.1°C for 4 s and 60°C for 8.2 min) were found to not affect ETS' final content. In this case, the composition in geraniin, vescalagin, and pedunculagin isomers remained basically constant during the process [5]. The analysis of these results shows that thermal stability at high temperature is also affected by the chemical structure of ET.

In other processing operations such as osmotic dehydration in 50–65°Bx sucrose solutions (30°C), in the case of blackberry, 80% of ellagitannins were retained after 1 h, while losses reached up to 45% after 3 h. The concentrations of the two main ellagitannins, lambertianin C and sanguin H6, revealed similar patterns of variation. On the contrary, due to a much lower molecular weight, the loss of free ellagic acid reached up to 50% after 1 h of osmotic dehydration [23].

4. Metabolomic fate and bioavailability of ETS and EA

Many studies have proven that ETs are not bioavailable as such, and they have never been detected in human plasma after normal consumption of ET-rich foods [28, 29]. Ellagitannins are probably not bioavailable because of their size (above 634 Da for one of the simplest ellagitannins, the sanguin H4 (C_{27}H_{22}O_{18}), up to 3740 Da for lambertianin D (C_{164}H_{106}O_{104})). Their relatively high polarity and the presence of a C▬C linkage could also explain this situation. During ingestion, ETs can also bind some proteins in saliva and cause astringency, and in this case, they may not be metabolized further [30]. Also, some ellagitannins are resistant to acid and basic hydrolysis in the GI tract and they can reach almost intact the large intestine [31]. However, for most ETs sensitive to acidic and basic hydrolysis in the stomach and the duodenum, respectively, they release free ellagic acid, which is at its turn poorly bioavailable. In the human digestive system, the bioavailability of EA derivatives depends on the part of gastrointestinal tract in which these compounds are released [7]. In stomach or small intestine, only low level of absorption could occur, and if EA can be detected in plasma and urine between 1 and 5 h after ingestion of dietary ETs, generally as methyl and dimethyl ethers or glucuronic acid conjugates, all these EA derivatives are always found at very low concentrations [29, 32, 33]. Low bioavailability of EA is probably due to low water solubility, and to its ability to bind irreversibly to cellular DNA and proteins, or to form poorly soluble complexes with calcium and magnesium ions which affects transcellular absorption [3, 33, 34].

The extent of the degradation of ETs in the upper GI tract depends on their chemical structure, the food matrix, and their susceptibility to acid/base hydrolysis in the stomach and duodenum [29]. Therefore, some ETs can reach the intestine where they can exert potential biological activity and eventually some can be partially converted into EA by enzymes from microbiota [35].

In the lower GI tract, released EAs can be partially metabolized by gut microbiota into urolithins (Uro, dibenzopyran-6-one metabolites) through reduction of one of the two lactone groups followed by decarboxylation and sequential dehydroxylation involving a step-by-step reduction to tetrahydroxy (urolithin D), trihydroxy (urolithin C), dihydroxy (urolithin A and iso-urolithin A), and monohydroxy dibenzopyranones (urolithin B) (Figure 3) [21, 35–37].

Urolithins appear to be the main plasma and urinary biomarker after consumption of ET-rich food (Table 2). Specifically, urolithin A and B and their phase II metabolites are the main metabolites in plasma and urine [10, 13] detected at micromolar concentration level. They can also be found at much higher concentration in some tissues or organs such as prostate gland and colon where they can accumulate [38, 39]. Persistence of urolithins in the body has been reported for long periods
after a single intake of ET-rich food. Urolithins in urine have been detected up to 7 days [58] after dietary ET intake, and this long persistence in the body is attributed to the involvement of microbiota and enterohepatic recirculation [9, 40–42]. Therefore, urolithins have been proposed to be responsible for biological activity of ETs [38] as they remain in the body at relatively low concentrations but during a long time with potential homeopathic-like effect. However, the concentration of urolithins in plasma, urine, and feces varies considerably between individuals [38, 46, 47]. Actually, the huge inter-individual variability of microbiota composition affects the production of urolithins, which is mediated by microbiota. During different studies, some individuals were labeled “low excreters” of urolithins after ingestion of ET-rich food, while other individuals were labeled as “high excreters of urolithins A or B.” Therefore, recently, a stratification of individuals according to their urolithin excretion status in urine has been proposed. Three metabotypes were defined: metabotype A, which includes main excreters of urolithin A; metabotype B with main excreters of urolithin A and B; and metabotype 0 corresponding to low urolithin excreters [31]. This classification appeared to be consistent across multiple intervention studies, independent of the ET food source, and health status of participants [46]. The distribution of urolithin metabotypes in adult population varies probably according to geography, but in a Western adult population taking into consideration a large cohort of individuals, UM-A is the most abundant metabotype with 55% followed by UM-B (34%) and UM-0 (11%) [47]. Nonetheless, a recent study reported by Cortés-Marín and coworkers [47] showed for the first time in a Caucasian cohort (5–90 years, n = 839) that age could determine the individual’s capacity to metabolize EA into urolithins A and B, even though the percentage of the population with low ability to excrete urolithins (metabotype 0) remains around 10% of the population whatever the age considered. The percentage of individual with metabotype A was higher in the case of children (80%) and decreased steadily after adolescence while metabotype B increased [47]. Authors also reported a significant association between increased physical activity and prevalence of UM-B especially between 5 and 18 years. On the other hand, no correlation of a specific metabotype with gender, body mass index, weight, health status, and diet was observed [47]. Nonetheless, most studies tend to show a strong persistence of metabotype status for adults even though recent research showed that individuals with UM-0 status have managed to become urolithin excreters of UM-A or UM-B after a long-term
exposure (up to 6 months) to a high ET source, a pomegranate-concentrated extract [48]. Thus, it seems that microbiota ability to catalyze the production of urolithins could be influenced by long-term exposure to ET-rich food by promoting growth of the bacteria involved in the urolithin metabolism [40]. Nonetheless, it was not reported if the change of metabotype remains persistent after the end of the study, when diet comes back to normal.

Recently, an attempt to find a correlation between urolithin metabotypes and enterotypes of the human gut microbiome proposed by the Human Microbiome Project (HMP) [39] has been made by Romo-Vaquero and coworkers [49].
following a cohort of 249 healthy volunteers after walnut or pomegranate extract ingestion for 3 days. Results showed that urolithin metabotypes and enterotypes (enterotype 1 (preponderance of Bacteroides), enterotype 2 (preponderance of Prevotella), or enterotype 3 (preponderance of Ruminococcus)) were not coincident. Only for enterotype 2, UM-A was slightly higher than UM-B. Nonetheless, a higher diversity of microorganisms in UM-B individual with respect to UM-A, and even more with respect to UM-0, was found. Actually, urolithin B production requires a more complex enzymatic arsenal than urolithin A. It was observed that a higher relative importance of microorganisms from the Coriobacteriaceae family tends to be correlated with a higher preponderance of UM-B with respect to UM-A and even more with respect to UM-0. Two bacterial strains isolated from human microbiota, *Gordonibacter urolithinfaciens* and *Gordonibacter pamelaeae* from Eggerthellaceae family, which was previously considered as part of Coriobacteriaceae family, showed ability in vitro to transform EA into urolithin C [50]. Recently, a specific strain also isolated from human microbiota was able to further metabolize EA up to isourolithin-A and was named as a consequence *Ellagibacter isourolithinifaciens* [50, 51]. Nonetheless, until now, no other bacterial strains that could metabolize EA to urolithins B have been reported.

Another factor that can impact the rate of urolithin production in vivo is the food source and the chemical structure of ingested ETs. For example, more urolithins in prostate from patients who consumed walnuts rather than in patients who consumed pomegranate juice, even when the latter had a higher ET content, were found. [14]. Also, it appears that there is a kind of saturation of the metabolic pathways as the amount of urolithins excreted in vivo remains apparently independent of the quantity of ETs ingested. This was observed for different food sources of ETs consumed in normal quantities such as strawberries, raspberries, walnuts, and oak-aged red wine [52]. Probably, there exists a consumption threshold below which urolithin excretion cannot be detected.

At last, the bioavailability of ETs and EA could be affected by food processing. In a clinical study, 16 healthy volunteers consumed approximately the same quantity of ET but in different presentation: pomegranate juice (PJ), pomegranate polyphenol liquid extract (POMxl), and pomegranate polyphenol powder extract (POMxp). As a result, there were no statistical differences in the level of EA in plasma between the three interventions over a 6-h period. Only, POMxp presented a longer lag-time to reach the peak of maximum concentration compared to PJ and POMxl [53]. A similar study was performed with 20 healthy volunteers comparing pasteurized strawberry juice (80°C for 5 min) and the equivalent fresh fruits. In this case, processing did not affect the urinary excretion of urolithins. Although the amount of free EA was increased 2.5-fold during processing, no effect on the urinary excretion of urolithins was observed [40]. Actually, further researches are required for a more definitive assessment on the effect of processing on the production and excretion of urolithins.

5. Main biological activities of ETs and their metabolites

Ellagitannins, ellagic acid, and their metabolites have been reported to exhibit numerous beneficial effects on human health including anti-inflammatory, anticancer, antioxidant, prebiotic, and cardioprotective properties [21, 54]. However, in vitro studies with cells or in vivo studies with animals could give inconsistent or untranslatable information about bioactivity of these metabolites in humans. Abundant literature shows for example the impact of ETs and EA on cells from organs that are not part of the GI tract and the results are absolutely controversial and inconsistent with actual knowledge. The potential health effect of ETs and possibly EA can only be exerted
within the GI tract, as these compounds are poorly bioavailable. On the other hand, urolithin production is mediated by microbiota and studies on animals can hardly be extrapolated to humans, except in the case of germ-free animals used in human microbiota-related researches. Therefore, in this review, even though research studies are much more scarce, we will report results of biological activities of ETs and EA only related with the GI tract, and for urolithins, given the importance of microbiota in their metabolism, we will focus only on the results of clinical trials with humans.

5.1 Effect of ETs and EA in GI tract

In in vitro model of colon cancer, ellagic acid was found to have a significant antiproliferative effect inducing apoptosis of cancer Caco-2 cells via a mitochondrial pathway and without side effects on normal colon cells [55]. In another study in rats, EA showed anti-inflammatory properties by iNOS, COX-2, TNF-α, and IL-6 downregulation due to NF-κB repression. Authors conclude that EA may exert a chemopreventive effect on colon carcinogenesis [56]. Furthermore, ETs and EA have a high antioxidant activity (even higher than urolithins) and could be highly efficient to scavenge oxygen free radicals and eventually prevent inflammation and colon cancer [21]. At last, in nasopharyngeal carcinoma cell lines (NPC-BM1), EA has showed ability to downregulate Bcl-2 and DNA fragmentation, by increasing caspase-3 enzymatic activity, which reduces telomerase activity [57].

5.2 Effect of urolithins

Numerous studies have demonstrated the metabolism of EA into urolithins, in approximately 12–24 h, with persistence of urolithins up to 4–7 days in urine after dietary intervention [9, 41, 42, 58], and research interest has shifted to the potential effect of urolithins on health. Actually, urolithins may exert a much more consistent effect at the systemic level than EA with concentration in body fluids at least one order of magnitude higher in body fluids. Actually, EA has been reported in plasma at concentration around some nanomoles per liter, while urolithins have been reported at concentration level up to 80 μmol/l [58].

5.2.1 Anti-inflammatory effect

Inflammation is a primary defensive response against harmful factors that involved different mechanisms including the immune system cells [8]. The impact of urolithins on inflammatory processes has been well established on various in vivo and in vitro models [59–61]. In in vitro models, urolithin aglycones have been tested, while in vivo glucuronide conjugates of urolithins are the predominant metabolites present in plasma, tissues, and urine [62]. Urolithin aglycone is highly bioactive against inflammation, but some authors suggest that urolithin conjugate may be even more active. In a study, in which urolithin conjugates (iso-Uro-A-gluc, Uro-A-gluc, and Uro-B-gluc) were isolated from urine of a volunteer after ingestion of pomegranate juice (0.5 L/day), walnuts (30 g/day), hazelnuts (30 g/day), and fresh raspberries (200 g/day) for 5 days, the cleavage of glucuronides by endogenous β-glucuronidases released by human neutrophils was observed. β-Glucuronidase is an enzyme that is released from inflammatory cells and the lysosomes of necrotic cells, and high levels can be found in most solid tumors. Therefore, a wide number of structurally diverse glucuronide prodrugs have been designed with the aim of enhancing the selectivity of cancer chemotherapy. The results suggest that the selective activation of urolithin glucuronides by β-glucuronidase could locally increase the concentration of bioactive urolithin aglycones. More clinical trials are needed to
better understand the anti-inflammatory response attributed to urolithin [62] and the impact on the suppression of the immune responses, especially on inflammation-associated diseases, like cardiovascular diseases and cancer [63].

5.2.2 Chemoprevention of cancers

Several in vitro and in vivo (animal or human) studies have reported a protective effect of urolithins on prostate cancer [64–66]. However, recent clinical interventions have pointed out inconsistent results. A recent review compiles the data of clinical trial studies after consumption of pomegranate juice or extracts and discusses whether urolithin could inhibit or slow the growth of prostate cancer in patients. The authors reported a significant increase in urolithin A in prostate but a nonsignificant reduction in 8-hydroxy-2-deoxyguanosine, a marker of oxidation in cancer tissue, for neoadjuvant patients subjected to radical prostatectomy after pomegranate intake (1200 mg polyphenols/day) compared with placebo in a large trial (4 weeks, n = 33) [67]. Similar results with muscadine grape skin extract have evidenced no benefit on recurrent prostate cancer patients in spite of urolithin A increase [68]. Nonetheless, authors [67] have noted in a specific group of patients (named AA genotype), which has been previously associated with more hostile prostate cancer and more sensitivity to antioxidants, a significant increase in a prostate-specific antigen doubling times (PSADT), an antigen that is claimed to slow tumor growth.

After an acute intake of grumixama cherry juice (Brazilian) by healthy women (n = 10), the antiproliferative activity of urolithins against breast cancer cells (MDA-MB-231) was evaluated. The extracts of urine exhibited seven urolithins, mainly urolithin C and urolithin A. Those extracts obtained during 2–4 h after juice intake presented the highest inhibition of proliferation of MDA-MB 231 breast cancer cells. This inhibition was attributed to a significant G2/M cell cycle arrest (apoptosis) occurred in MDA-MB-231 cells, and was demonstrated by the increase in sub-G0/G1 populations. Additionally, the authors linked this inhibition to a possible synergy among anthocyanins and urolithins [12]. Then, the modulation of the positive-estrogen receptor in breast cancer cells (MCF7) is probably one of the potential actions of urolithin conjugates. On the other hand, in a study realized with breast cancer patients (n = 19) who consumed a mixed extract (493.4 mg phenolics/day) containing pomegranate, orange, lemon, olive, cocoa, grape seed extracts plus resveratrol, theobromine, and caffeine, it was shown that the main metabolites detected in breast tissues were urolithin-A-3-O-glucuronide. Nonetheless, no antiproliferative or estrogenic/antiestrogenic activities in MCF-7 breast cancer cells were reported [69].

Ellagitannin gut microbiota-derived metabolites have shown a wide range of colon anticancer effects both in cellular and animal studies [70–72]. However, the current clinical evidence that confirms their colorectal cancer (CRC) chemopreventive effect in humans is still very weak. A study evaluated the modification of microRNAs (miRs) expression, one CRC biomarker, in normal and malignant colonic tissues from CRC patients after pomegranate extract intake (900 mg/day before surgery). As a result, pomegranate consumption seems to moderate the modulation of various specific miRs in colon tissue, but there was no association between tissue urolithins and the detected miRs changes, which were attributed to a possibly critical surgery alteration in miRs levels that did not allow to discriminate between malignant and normal tissues [73]. Another more recent study in 35 patients with colorectal cancer (CRC), daily supplemented with pomegranate extracts, was conducted to evaluate the expression of various CRC-related genes in normal and cancerous colon tissues. Before (biopsies) and posterior (surgical samples) to pomegranate intake (5–35 days). Despite the consumption of pomegranate extract was significantly associated with a balancing effect in the expression
of genes regulated by the experimental protocol, these results were not associated with the individual metabotypes or the levels of urolithins and EA in the colon tissues. Consequently, the in vitro effects were not reproduced in vivo evidencing discrepancy between results [70]. In general, we can conclude that there is a lack of clinical interventions with ET-rich food in humans; besides, these kinds of studies are essential to corroborate the real effect of urolithins on cancer.

5.2.3 Reducing risks of cardiovascular disease (CVD)

The gut microbiota is frequently presented as a key factor in the evolution of obesity and cardiovascular disorders (CVD) [74]. One clinical study clustered urolithin metabotypes (UMs) of 18 healthy overweight/obese subjects with the aim of correlating metabotype status with CVD biomarkers after pomegranate extract consumption. In baseline and before UM clustering, the whole group exhibited mild dyslipidemia, and after clustering, only the serum lipid profile of UM-B individuals (n = 15) showed moderate risk values in total cholesterol, intermediate-LDL-cholesterol, as well as other serum lipids related to CVD risk. After ET intervention, only blood biomarkers of UM-B subjects were improved after pomegranate extract intake, reducing their CVD risk. Interestingly, a dose-dependent behavior was notable only in UM-B patients [48].

Another experiment comparing healthy patients with patients with metabolic syndrome (MetS), both consuming walnuts, showed that urolithin A only was inversely correlated with glycaemia in MetS individuals. Additionally, when MetS patients with UM-A were treated with statin, their lipid profile became similar to healthy individuals. This was not the case for individuals with UM-B [74].

Another study showed that the increasing relative importance within the microbiota of bacteria from the Coriobacteriaceae family such as Olsenella, Senegalimassilia, and Slackia, which characterized UM-B status, was positively correlated with blood cholesterol levels and normal BMI [49].

Endothelial dysfunction and inflammation are both usual events that occur in the development of atherosclerosis. The correlation between the plasma urolithin metabolites and improvement in endothelial function after red raspberry intake was reported. Endothelial function measured as flow media vasodilation (FMD) presented two peaks, first at 1–2 h after intake, linked with EA plasma peak concentration, and second peak at 24 h, associated with urolithin-3-glucuronide and urolithin-A-sulfate absorption peaks. Similar results were reported by other authors in cranberry and blueberry juice interventions [75], but it was shown that effect was the same when consuming 200 or 400 g of raspberries. Additional distinctive key factors in atherosclerosis development have been reported, as the capacity of monocytes to adhere to endothelial cells and the uptake and efflux of cholesterol by macrophages. In vitro, urolithins and EA were able to reduce adhesion of THP-1 monocytes to human umbilical vein endothelial cells and reduce secretion of sVCAM-1 and IL-6, a cellular adhesion molecule and a pro-inflammation cytokine, respectively. Also, urolithin C and EA were associated with decreased accumulation of cholesterol in THP-1–derived macrophages [76]. Attenuation of THP-1 also was reported in the presence of urolithin A in endothelial cells and also reduced considerably the expressions of ICAM-1 and MCP-1, an intercellular adhesion molecule and a monocyte chemotactic protein, respectively [77].

6. Concluding remarks

Ellagitannins are present in considerable amounts only in some specific food sources such as berries and nuts, but some tropical fruits deserve attention. Their
diverse structure can be modified during food processing resulting in free ET and EA derivatives, which are poorly bioavailable. After ingestion, most ETs are spontaneously converted into EA, which is poorly bioavailable and can be used as substrate by gut microbiota. The main products resulting from the action of gut microbiota on EA are urolithins. The main biomarkers in blood and urine of ET-rich food exposure are urolithins A and B. Nonetheless, there is an important interindividual variability in the excretion of urolithins, and this observation has led to the classification of the population in three metabotypes: the “low urolithin” excreters that represent approximately 10% of the population; the “urolithin A” excreters, the most important group with approximately 55% of individuals; and finally, the “urolithin A and B excreters” that represent around 35% of the population. The metabotype status appears to be quite persistent although it can change during life span and the constant exposure to ET-rich food appears to increase urolithin production. Microorganisms from the Coriobacteriaceae family were identified as urolithin producers and the relative importance of this family within the microbiota was apparently correlated with the metabotype. The stratification of individuals by their metabotype was essential to overcome inconsistencies during clinical trial, and it must be taken into account in all future intervention studies. The positive biological effects of ETs and EA at the level of the GI tract are consistent and reported by various authors. For urolithins, the panorama is more confused, and more long-term clinical intervention studies with human are required. Nonetheless, at the end of this review, the potential health effect of ET-rich foods is definitely promising and they deserve to be part of a healthy diet as functional foods.

**Acknowledgements**

This publication was jointly financed by the International Research Center in Agronomy for Development (CIRAD), Montpellier, France, and the Colombian Research Cooperation in Agronomy (AGROSAVIA), Colombia. Karen Johana Ortega is a PhD student with a scholarship granted by the Colombian government through Colciencias 727-2015 announcement.

**Conflict of interest**

The authors confirm that there is no conflict of interest.
Author details

Karen Johana Ortega Villalba1, Fabrice Vaillant Barka2,3*, Carlos Vélez Pasos1 and Pablo Emilio Rodríguez2

1 Universidad del Valle, Cali, Colombia

2 Colombian Agropecuary Research Corporation (AGROSAVIA), C.I. La Selva, Rionegro, Colombia

3 International Research Center in Agronomy for Development (CIRAD), Montpellier, France

*Address all correspondence to: fabrice.vaillant@cirad.fr

© 2019 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.
References

[1] Yoshida T, Amakura Y, Yoshimura M. Structural features and biological properties of ellagitannins in some plant families of the order Myrtales. International Journal of Molecular Sciences. 2010;11:79-106

[2] Yamada H, Wakamori S. Structural revisions in natural ellagitannins. Molecules. 2018;23:1-46

[3] Smeriglio A, Barreca D, Bellocco E, Trombetta D. Proanthocyanidins and hydrolysable tannins: Occurrence, dietary intake and pharmacological effects. British Journal of Pharmacology. 2017;174(11):1244-1262

[4] Alezandro MR, Dubé P, Desjardins Y, Lajolo FM, Genovese MI. Comparative study of chemical and phenolic composition of two species of Jaboticaba: Myrciaria jaboticaba (Vell.) berg and Myrciaria cauliflora (Mart.) O. Berg. Food Research International. 2013;54(1):468-477. DOI: 10.1016/j.foodres.2013.07.018

[5] Rojas-garbanzo C, Winter J, Montero ML, Zimmermann BF, 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-MSn. Journal of Food Composition and Analysis. 2019;75:26-42. DOI: 10.1016/j.jfca.2018.09.012

[6] Bakkalbasi E, Mentes O, Artik N. Food ellagitannins—Occurrence, effects of processing and storage. Critical Reviews in Food Science and Nutrition. 2009;49(3):283-298

[7] Lipińska L, Klewicka E, Sójka M. Structure, occurrence and biological activity of ellagitannins: A general review. Acta Scientiarum Polonorum. Technologia Alimentaria. 2014;13(3):289-299

[8] Lorenzo M, Munekata PE, Putnik P. Sources, chemistry, and biological potential of ellagitannins and ellagic acid derivatives. In: Studies in Natural Products Chemistry. Elsevier Inc; 2018. pp 189-221. DOI: 10.1016/B978-0-444-64181-6.00006-1

[9] Bresciani L, Lean MEJ, Borges G, Calani L, Pereira-Caro G, Crozier A, et al. New insights into the bioavailability of red raspberry anthocyanins and ellagitannins. Free Radical Biology & Medicine. 2015;89:758-769. DOI: 10.1016/j.freeradbiomed.2015.10.400

[10] Koponen JM, Happonen AM, Mattila PH, Torronen AR. Contents of anthocyanins and ellagitannins in selected foods consumed in Finland. Journal of Agricultural and Food Chemistry. 2007;55:1612-1619

[11] Roquim M, Granato D, Inés M. Jaboticaba (Myrciaria jaboticaba (Vell.) Berg), a Brazilian grape-like fruit, improves plasma lipid profile in streptozotocin-mediated oxidative stress in diabetic rats. Food Research International. 2013;54(1):650-659. DOI: 10.1016/j.foodres.2013.07.041

[12] Teixeira LL. 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 brasiensis Lam.). Food & Function. 2017;8(6):2266-2274

[13] Abe LT, Lajolo FM, Genovese MI. Comparison of phenol content and antioxidant capacity of nuts. Food Science and Technology. 2010;30(1):254-259

[14] González-Sarrías A, Giménez-Bastida JA, García-Conesa MT, Gómez-Sánchez MB, García-Talavera NV,
Gil-Izquierdo 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. Molecular Nutrition & Food Research. 2010;54:311-322

[15] Adamczyk B, Simon J, Kitunen V, Adamczyk S. Tannins and their complex interaction with different organic nitrogen compounds and enzymes: Old paradigms versus recent advances. ChemistryOpen. 2017:610-614

[16] Clifford MN, Scalbert A. Ellagitannins—Nature, occurrence and dietary burden. Journal of the Science of Food and Agriculture. 2000;80:1118-1125

[17] Quideau S, Feldman KS. Ellagitannin chemistry. Chemical Reviews. 1996;96:475-503

[18] Aguilera-Carbo A, Augur C, Prado-Barragan LA, Favela-Torres E, Aguilar CN. Microbial production of ellagic acid and biodegradation of ellagitannins. Applied Microbiology and Biotechnology. 2008;78:189-199

[19] Larrosa M, Tomás-Barberán FA, Espín JC. The dietary hydrolysable tannin punicalagin releases ellagic acid that induces apoptosis in human colon adenocarcinoma Caco-2 cells by using the mitochondrial pathway. The Journal of Nutritional Biochemistry. 2006;17(9):611-625

[20] Okuda T, Ito H. Tannins of constant structure in medicinal and food plants—Hydrolyzable tannins and polyphenols related to tannins. Molecules. 2011;2191-2217

[21] Landete JM. Ellagitannins, ellagic acid and their derived metabolites: A review about source, metabolism, functions and health. Food Reasearch International. 2011;44(5):1150-1160. DOI: 10.1016/j.foodres.2011.04.027

[22] Khanbabae K, Van RT. Tannins: Classification and definition. The Royal Society of Chemistry. 2001;18:641-649

[23] Sójka A, Karlińska E, Klewicki R. Ellagitannin and anthocyanin retention in osmotically dehydrated blackberries. Food Science and Technology Research. 2017;23(6):801-810. Available from: https://www.jstage.jst.go.jp/article/fstr/23/6/23_801/_article

[24] Hager TJ, Howard LR, Prior RL. Processing and storage effects on the ellagitannin composition of processed blackberry products. Journal of Agricultural and Food Chemistry. 2010;58(22):11749-11754

[25] Gancel AL, Feneuil A, Acosta O, Pérez AM, Vaillant F. Impact of industrial processing and storage on major polyphenols and the antioxidant capacity of tropical highland blackberry (Rubus adenotrichus). Food Research International. 2011;44(7):2243-2251. DOI: 10.1016/j.foodres.2010.06.013

[26] Mazur SP, Nes A, Wold A, Remberg SF, Martinsen BK, Aaby K. Effect of genotype and storage time on stability of colour, phenolic compounds and ascorbic acid in red raspberry (Rubus idaeus L.) jams. Acta Agriculturae Scandinavica. 2014;64(5):442-453

[27] Soto M, Acosta O, Vaillant F, Pérez A. Effects of mechanical and enzymatic pretreatments on extraction of polyphenols from blackberry fruits. Journal of Food Engineering. 2015;39(5):492-500

[28] Sebestyén Z, Jakab E, Badea E, Barta-Rajnai E, Şendrea C, Czégény Z. Thermal degradation study of vegetable tannins and vegetable tanned leathers. Journal of Analytical and Applied Pyrolysis. 2019;138:178-187. DOI: 10.1016/j.jaap.2018.12.022
[29] García-Muñoz C, Vaillant F. Metabolic fate of ellagitannins: Implications for health, and research perspectives for innovative functional foods. Critical Reviews in Food Science and Nutrition. 2014;54(12):1584-1598

[30] Mena P, Calani L, Bruni R, Del RD. Bioactivation of high-molecular-weight polyphenols by the gut microbiome. In: Diet-Microbe Interactions in the Gut. Elsevier Inc; 2015. pp. 73-102. DOI: 10.1016/B978-0-12-407825-3.00006-X

[31] Sandhu AK, Miller MG, Thangthaeng N, Scott TM, Shukitt-Hale B, Edirisinghe I, et al. Metabolic fate of strawberry polyphenols after chronic intake in healthy older adults. Food & Function. 2018;9(1):96-106

[32] Andrade MA, Lima V, Sanches A, Vilarinho F, Conceição M, Khwaldia K, et al. Pomegranate and grape by-products and their active compounds: Are they a valuable source for food applications? Trends in Food Science & Technology. 2019;86(January):68-84. DOI: 10.1016/j.tifs.2019.02.010

[33] Nuñez-Sánchez MA, García-Villalba R, Monedero-Saiz T, García-Talavera NV, Gómez-Sánchez MB, Sánchez-Álvarez C, et al. Targeted metabolic profiling of pomegranate polyphenols and urolithins in plasma, urine and colon tissues from colorectal cancer patients. Molecular Nutrition & Food Research. 2014;58(6):1199-1211

[34] Serrano J, Puupponen-pimiä R, Dauer A, Aura AM. Tannins: Current knowledge of food sources, intake, bioavailability and biological effects. Molecular Nutrition & Food Research. 2009;53:S310-S329

[35] Aguilar-Zárate P, Wong-Paz JE, Buenrostro-Figueroa JJ, Ascacio JA, Contreras-Esquivel JC, Aguilar CN. Ellagitannins: Bioavailability, purification and biotechnological degradation. Mini Reviews in Medicinal Chemistry. 2018;18(15):1244-1252

[36] Zhang X, Sandhu A, Edirisinghe I, Burton-Freeman B. An exploratory study of red raspberry (Rubus idaeus L.) (poly)phenols/metabolites in human biological samples. Food & Function. 2018;9(2):806-818

[37] Milala J, Kosmala M, Fotschki B. Ellagitannins from strawberries with different degrees of polymerization showed different metabolism through gastrointestinal tract of rats. Journal of Agricultural and Food Chemistry. 2017;65:10738-10748

[38] Liberal J, Carmo A, Gomes C, Cruz MT, Batista MT. Urolithins impair cell proliferation, arrest the cell cycle and induce apoptosis in UMUC3 bladder cancer cells. Investigational New Drugs. 2017;35(6):671-681

[39] García-Villalba R, Beltrán D, Espín JC, Selma MV, Tomás-Barberán FA. Time course production of urolithins from ellagic acid by human gut microbiota. Journal of Agricultural and Food Chemistry. 2013;61(37):8797-8806

[40] Truchado P, Larrosa M, Cerda B, Toma FA. Strawberry processing does not affect the production and urinary excretion of urolithins, ellagic acid metabolites, in humans. Journal of Agricultural and Food Chemistry. 2012;60(23):5749-5754

[41] Seeram NP, Henning SM, 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 hours. The Journal of Nutrition. 2006;136:2481-2485

[42] Cerdá B, Espín JC, Parra S, Martínez P, Tomás Barberán FA. 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. European Journal of Nutrition. 2004;43(4):205-220

[43] Mulero J, Tomás-barberán FA, Carlos J. Identifying the limits for ellagic acid bioavailability: A crossover pharmacokinetic study in healthy volunteers after consumption of pomegranate extracts. Journal of Functional Foods. 2015;19:225-235. DOI: 10.1016/j.jff.2015.09.019

[44] Gu J, Thomas-Ahner JM, Riedl KM, Bailey MT, Vodovotz Y, Schwartz SJ, et al. Dietary black raspberries impact the colonic microbiome and phytochemical metabolites in mice. Molecular Nutrition & Food Research. 2019;63(8):1800636. DOI: 10.1002/mnfr.201800636

[45] García-Villalba R, Vissenaekens H, Pitart J, Romo-Vaquero M, Espín JC, Grootaert C, et al. The gastrointestinal simulation model TWIN-SHIME® shows differences between human urolithin-metabotypes in gut microbiota composition, pomegranate polyphenol metabolism, and transport along the intestinal tract. Journal of Agricultural and Food Chemistry. 2017;65(27):5480-5493

[46] Chambers K, Id EC, Pinto P, Ristic AK, Hollands WJ, Kroon PA, et al. Meta-analysis of the effects of foods and derived products containing ellagitannins and anthocyanins on cardiometabolic biomarkers: Analysis of factors influencing variability of the individual responses. International Journal of Molecular Sciences. 2018

[47] Cortés-Martín A, García-Villalba R, González-Sarrías A, Romo-Vaquero M, Loria-Kohenb V, Ramírez-de-Molina A, et al. The gut microbiota urolithin metabolotypes revisited: The human metabolism of ellagic acid is mainly determined by aging. Food & Function. 2018;9(8):4100-4106

[48] González-Sarrías A, García-Villalba R, Romo-Vaquero M, Alasalvar C, Orem A, Zafrilla P, et al. Clustering according to urolithin metabotype explains the interindividual variability in the improvement of cardiovascular risk biomarkers in overweight-obese individuals consuming pomegranate: A randomised clinical trial. Molecular Nutrition & Food Research. 2017;61(5):1600830

[49] Romo-Vaqueroa M, Cortés-Martína A, Loria-Kohenb V, Ramírez-de-Molina A, García-Mantrana I, Colladoc MC, et al. Deciphering the human gut microbiome of urolithin metabolites: Association with enterotypes and potential cardiometabolic health. Molecular Nutrition & Food Research. 2019;63(4):e1800958

[50] Selma MV, Beltrán D, Luna MC, Romo-Vaquero M, García-Villalba R, Mira A, et al. Isolation of human intestinal bacteria capable of producing the bioactive metabolite iso-urolithin A from ellagic acid. Frontiers in Microbiology. 2017;8:1521

[51] Romo-vaquero M, Espín JC, Tom FA, Selma MV. Ellagibacter isourolithinifaciens gen. nov., sp. nov., a new member of the family Eggerthellaceae, isolated from human gut. International Journal of Systematic and Evolutionary Microbiology. 2018;68(5):1707-1712

[52] Cerdá B, Tómas-Barberán FA, Espín JC. Metabolism of antioxidant and chemopreventive ellagitannins from strawberries, raspberries, walnuts, and oak-aged wine in humans: Identification of biomarkers and individual variability. Journal of Agricultural and Food Chemistry. 2005;53:227-235

[53] Seeram NP, Zhang Y, Mckeever R, Henning SM, Lee R, Suchard MA, et al. Ellagitannin metabolites in human subjects. Journal of Medicinal Food. 2008;11(2):390-394
[54] Cortés-Martín A, Selma MV, Espín JC, García-Villalba R. The human metabolism of nuts proanthocyanidins does not reveal urinary metabolites consistent with distinctive gut microbiota metabolotypes. Molecular Nutrition & Food Research. 2019;63(2):e1800-e1819

[55] Derosa G, Maffioli P, Sahebkar A. Anti-inflammatory nutraceuticals and chronic diseases. In: Advances in Experimental Medicine and Biology. 2016. pp. 473-479. Available from: http://link.springer.com/10.1007/978-3-319-41334-1

[56] Umesalma S, Sudhandiran G. Differential inhibitory effects of the polyphenol ellagic acid on inflammatory mediators NF-κB, iNOS, COX-2, TNF-α, and IL-6 in 1,2-dimethylyhydrazine-induced rat colon carcinogenesis. Basic & Clinical Pharmacology & Toxicology. 2010;107(2):650-655

[57] Ahire V, Mishra KP, Kulkarni G. Ellagic acid: A potent radio-sensitizer in cancer radiotherapy. Cancer Research Frontiers. 2016;2(2):141-155

[58] 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 Research International. 2014;55:161-169. DOI: 10.1016/j.foodres.2013.10.049

[59] Lee G, Park J, Lee E, Ahn J, Kim H. Anti-inflammatory and antioxidant mechanisms of urolithin B in activated microglia. Phytomedicine. 2019;55:50-57. DOI: 10.1016/j.phymed.2018.06.032

[60] Singh R, Chandrashekarappa S, Bodduluri SR, Baby BV, Hegde B, Kotla NG, et al. Microbial metabolite through the Nrf2 pathway. Nature Communications. 2019;10(1):1-18. DOI: 10.1038/s41467-018-07859-7

[61] Boakye YD, Groyer L, Heiss EH. An increased autophagic flux contributes to the anti-inflammatory potential of urolithin A in macrophages. Biochimica et Biophysica Acta. 2017;1862(1):61-70. DOI: 10.1016/j.bbagen.2017.10.006

[62] Piwowarski JP, Stanisławska I, Granica S, Staﬁńska J, Kiss AK. Phase II conjugates of urolithins isolated from human urine and potential role of β-glucuronidases in their disposition. Drug Metabolism and Disposition. 2017;45(6):657-665

[63] Kiss AK, Piwowarski JP. Ellagitanins, gallotannins and their metabolites—The contribution to the anti-inflammatory effect of food products and medicinal plants. Current Medicinal Chemistry. 2018;25(37):4946-4967

[64] Dahiya NR, Chandrasekaran B, Kolluru V, Ankem M, Damodaran C, Vadhanam MV. A natural molecule, urolithin A, downregulates androgen receptor activation and suppresses growth of prostate cancer. Molecular Carcinogenesis. 2018;57(10):1332-1341

[65] Granica S, Piwowarski JP, Czarnocki Z, Kiss AK. The activity of urolithin A and M4 valerolactone, colonic microbiota metabolites of polyphenols, in a prostate cancer in vitro model. Planta Medica. 2019:118-125

[66] Zhou B, Wang J, Zheng G, Qiu Z. Methylated urolithin A, the modified ellagitanin-derived metabolite, suppresses cell viability of DU145 human prostate cancer cells via targeting miR-21. Food and Chemical Toxicology. 2016;97:375-384. DOI: 10.1016/j.fct.2016.10.005

[67] Paller CJ, Pantuck A, Carducci MA. A review of pomegranate in prostate cancer. Prostate Cancer and Prostatic Diseases. 2017;20(3):265-270. DOI: 10.1038/pcan.2017.19
[68] Paller CJ, Zhou XC, Heath EI, Taplin M, Mayer TM, Stein MN, et al. Muscadine grape skin extract (MPX) in men with biochemically recurrent prostate cancer: A randomized, multicenter, placebo-controlled clinical trial. Clinical Cancer Research. 2017;24(2):306-315

[69] Ávila-Gálvez MÁ, García-Villalba R, Martínez-Díaz F, Ocaña B, Monedero-Saiz T, Torrecillas-Sánchez A, et al. Metabolic profiling of dietary polyphenols and methylxanthines in normal and malignant mammary tissues from breast cancer patients. Molecular Nutrition & Food Research. 2019;Jan;28:e1801239

[70] Nuñez-Sánchez MA, González-Sarrías A, García-Villalba R, Monedero-Saiz T, García-Talavera NV, Gómez-Sánchez MB, et al. Gene expression changes in colon tissues from colorectal cancer patients following the intake of an ellagitannin-containing pomegranate extract: A randomized clinical trial. The Journal of Nutritional Biochemistry. 2017;42:126-133. DOI: 10.1016/j.jnutbio.2017.01.014

[71] Nuñez-Sánchez MÁ, Karmokar A, González-Sarrías A, García-Villalba R, Tomás-Barberán FA, García-Conesa MT, et al. In vivo relevant mixed urolithins and ellagic acid inhibit phenotypic and molecular colon cancer stem cell features: A new potentiality for ellagitannin metabolites against cancer. Food and Chemical Toxicology. 2016;92:8-16. DOI: 10.1016/j.fct.2016.03.011

[72] Cho H, Jung H, Lee H, Yi C, Kwak H, Hwang KT. Chemopreventive activity of ellagitannins and their derivatives from black raspberry seeds on HT-29 colon cancer cells. Food & Function. 2015;6(5):1675-1683

[73] Nuñez-Sánchez MA, Dávalos A, González-Sarrías A, Casas-Agustench P, Visioli F, Monedero-Saiz T, et al. MicroRNAs expression in normal and malignant colon tissues as biomarkers of colorectal cancer and in response to pomegranate extracts consumption: Critical issues to discern between modulatory effects and.

[74] Selma MV, González-Sarrías A, Salas-Salvadó J, Andrés C, Alasalvar C, Örem A, et al. The gut microbiota metabolism of pomegranate or walnut ellagitannins yields two urolithin-metabotypes that correlate with cardiometabolic risk biomarkers: Comparison between normoweight, overweight-obesity and metabolic syndrome. Clinical Nutrition. 2017;37(3):897-905. DOI: 10.1016/j.clinu.2017.03.012

[75] Heiss C, Rodriguez-Mateos A, Istas G, Feliciano RP, García-Villalba R, Weber T, et al. Plasma urolithin metabolites correlate with improvements in endothelial function after red raspberry consumption: A double-blind randomized controlled trial. Archives of Biochemistry and Biophysics. 2018;651:43-51. DOI: 10.1016/j.abb.2018.05.016

[76] Brighenti F, Bernini F, López-Gutiérrez N, Mena P, Marino V, Piemontese A, et al. Antiatherogenic effects of ellagic acid and urolithins in vitro. Archives of Biochemistry and Biophysics. 2016;599:42-50

[77] Han QA, Yan C, Wang L, Li G, Xu Y, Xia X. Urolithin A attenuates ox-LDL-induced endothelial dysfunction partly by modulating microRNA-27 and ERK/PPAR-γ pathway. Molecular Nutrition & Food Research. 2016;60(9):1933-1943