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Chapter 15

GALLIC ACID BIOAVAILABILITY IN HUMANS

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ABSTRACT

Polyphenols are extensively metabolized either in tissues, once they are absorbed through the gut barrier or, for the non-absorbed fraction and the fraction re-excreted in the bile, by the colonic microflora. All polyphenols are conjugated in our body to form O-glucuronides, sulphate esters and O-methyl ethers. The formation of anionic derivatives by conjugation with glucuronides and sulphate groups facilitates their urinary and biliary excretion and explains their rapid elimination.

Animal studies first revealed the possible metabolic fate of gallic acid. In rats, rabbits and chickens the major urinary metabolite is 4-O-methylgallic acid, followed by pyrogallol (conjugated and unconjugated). Small amounts of conjugated 2-O-methylpyrogallol were also detected in rats. In sheep, resorcinol glucuronide is the major product of gallic acid metabolism and unconjugated pyrogallol and resorcinol comprise minor urinary metabolites.

Moreover, recent *in vitro* studies have reported phenolic acids to be main metabolites of anthocyanins after fecal fermentation. However, fragmentation of anthocyanins to phenolic acids in humans has not been studied in detail. One recently identified anthocyanin metabolite is 3-O-methylgallic acid, which is presumably the metabolite of petunidin-3-glucoside, but possibly also a demethylation product of malvidin-3-glucoside.

The few existing studies addressing the bioavailability of gallic acid in humans revealed that, compared to other polyphenols, this phenolic compound is extremely well absorbed. The most common metabolite of gallic acid identified in human biological fluids is 4-O-methylgallic acid, which was found to increase significantly in human

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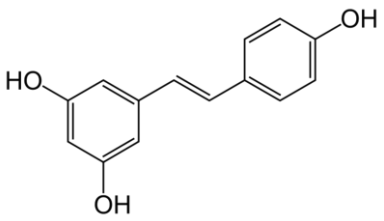
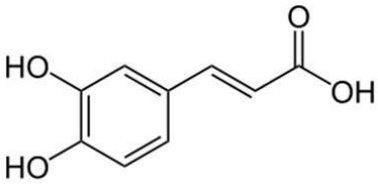
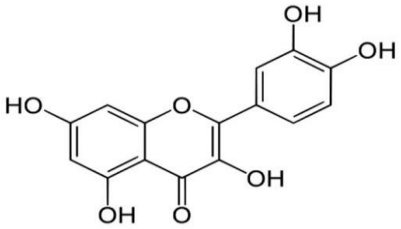
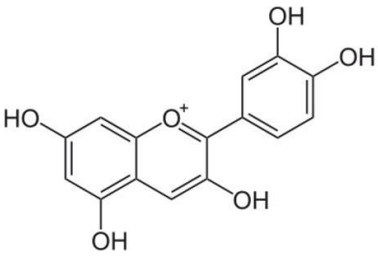
plasma within the first 4 h after consumption of a single dose of red wine or dealcoholized red wine. Plasma concentrations of free and glucuronidated forms of gallic acid and 4-O-methylgallic acid also increased after ingestion of 50 mg pure gallic acid, while gallic acid was rapidly absorbed after human administration with tea or acidum gallicum. Concerning the excretion of gallic acid, many studies have identified gallic acid and its metabolites in urinary samples. For example, after acute consumption of 3 cups of black tea, gallic acid was not detected in urine of subjects. However, three gallic acid methyl ethers, 4-O-methylgallic acid, 3-O-methylgallic acid and 3,4-O-dimethylgallic acid, were identified. A recent study on the bioavailability of phenolic compounds present in Corinthian raisins (*Vitis vinifera*) –containing 115.7 ng gallic acid per g- indicated that gallic acid is bioavailable in humans, as its concentrations in plasma increased one hour after raisins consumption. Overall, gallic acid concentrations in plasma were found to range between 2.2±0.9 to 9.9±4.6 (SEM) μg/L.

1. INTRODUCTION

Phenolic compounds, abundant in plant products, have the characteristic structure of at least one aromatic ring with one or more hydroxyl groups attached. Over 8000 phenolic structures have been reported and they are widely dispersed throughout the plant kingdom– many occurring in foods.

Phenolic compounds range from simple, low molecular weight, single aromatic ring compounds to the large and complex tannins and derived polyphenols. They can be classified by the number and arrangement of their carbon atoms and are commonly found conjugated to sugars and organic acids. Phenolics occurring naturally in healthy plant tissue can be classified into two groups, the flavonoids (i.e. the flavonol quercetin) and the non-flavonoids (i.e. caffeic acid or resveratrol or cyanidin) (Table 1).

Table 1. Characteristic flavonoid and non-flavonoid phenolic compounds

 resveratrol (stilbene)	 caffeic acid (phenolic acid)
 quercetin (flavonol)	 cyanidin (anthocyanin)

Traditionally processed foods and beverages, such as black tea, matured red wine, coffee and cocoa, may contain phenolic transformation products that are best described as ‘derived polyphenols’. Tannins are the active ingredients of traditional plant extracts used to convert hides to leather and occur widely in foods and beverages but at concentrations too low to tan hides.

Flavonoids are polyphenolic compounds comprising 15 carbons, with two aromatic rings connected by a three carbon bridge, hence C6–C3–C6. They are the most abundant of the phenolics and are found throughout the plant kingdom.

The main non-flavonoids of dietary significance are the C6–C1 phenolic acids, most notably gallic acid, which is the biosynthetic precursor of hydrolysable tannins, the C6–C3 hydroxycinammates and their conjugated derivatives, and the polyphenolic C6–C2–C6 stilbenes.

The most important food sources of phenolic compounds are fruit and vegetables, green and black tea, red wine, coffee, chocolate and extra virgin olive oil.

Herbs and spices, nuts, and algae are also potentially relevant sources of polyphenols, depending on culinary habits.

2. GALLIC ACID

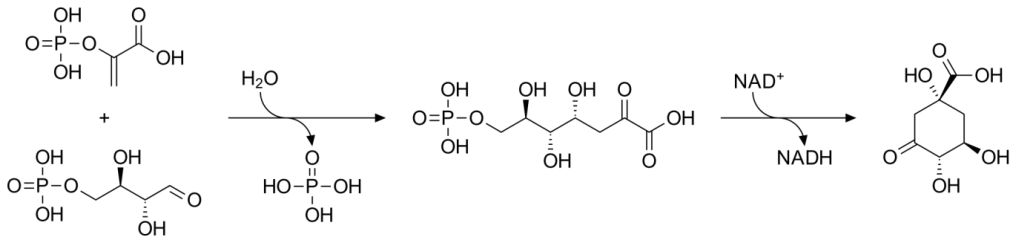
2.1. Biosynthesis

Gallic acid is synthesized via the shikimate pathway, a seven step metabolic route used by bacteria, fungi, algae, parasites and plants for the biosynthesis of aromatic amino acids (phenylalanine, tyrosine, and tryptophan).

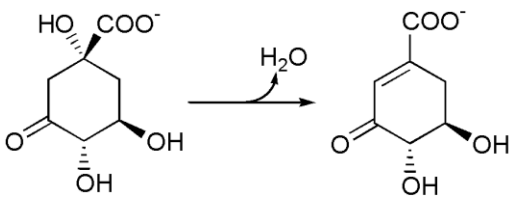
This pathway is not found in animals and in humans, hence the products of this pathway represent essential amino acids that must be obtained from the animal’s diet.

The first enzyme involved is the shikimate kinase, an enzyme that catalyzes the ATP-dependent phosphorylation of shikimate to form shikimate 3-phosphate.

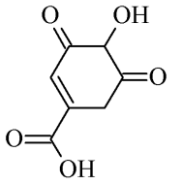
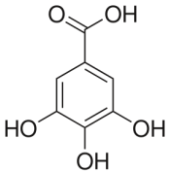
Biosynthesis of 3-dehydroquinate from phosphoenolpyruvate and erythrose-4-phosphate



Biosynthesis of 3-dehydroshikimate acid from 3-dehydroquinate



3-Dehydroshikimate under the action of the enzyme shikimate dehydrogenase is transformed in 3,5-didehydroshikimate and finally rearranged to gallic acid

 3,5-Didehydroshikimate	 Gallic acid

2.2. Natural Occurrence in Plants/Foods

Gallic acid is the commonest phenolic acid, and occurs widely as complex sugar esters in gallotannins such as 2-O-digalloyltetra-O-galloyl-glucose but these are found only to a limited extent in dietary components. Non-sugar galloyl esters in grapes, wine, mangoes, green tea and black tea are the major source of gallic acid in the human diet.

3. BIOAVAILABILITY OF GALLIC ACID

3.1. The Concept of Bioavailability

Bioavailability is defined as the amount of an ingested nutrient that is absorbed and available for physiological functions. Bioavailability is dependent on digestion, release from the food matrix, absorption by intestinal cells, and transportation to body cells. *Bioaccessibility* is the amount of an ingested nutrient that is potentially available for absorption. It is dependent only on digestion and release from the food matrix.

3.2. *In Vitro* Studies

In vitro screening methods for the determination of nutrient bioaccessibility and bioavailability from foods have been developed mostly during the last decades.

These methods can provide useful information, especially when the vast number of factors that potentially affect nutrient absorption is taken into consideration.

In vitro bioavailability methods could provide knowledge on possible interactions between nutrients and/or food components, the effects of luminal factors (including pH and enzymes), food preparation and processing practices, nature of the food matrix, on either micronutrient absorbability (a component of bioavailability) or on the potential for a nutrient to be absorbed (bioaccessibility).

Even if *in vitro* methods have many advantages compared to human or animal studies (less expensive, faster, better control of experimental variables) (Sandberg, 2005), they cannot be substituted for *in vivo* studies.

There are principally four *in vitro* methods for measuring bioaccessibility and/or bioavailability: solubility, dialyzability, or a gastrointestinal model for bioaccessibility, and the Caco-2 models for bioavailability (Table 2).

The main *in vitro* bioavailability method that has been used repeatedly to measure the bioaccessibility of polyphenols is *in vitro* solubility. This method has been used to test the bioaccessibility of various polyphenols in a plethora of foods.

Fogliano et al. (2011) examined the *in vitro* digestion of the water-insoluble cocoa fraction (WICF) with gastrointestinal enzymes as well as its bacterial fermentation in a human colonic model system. Experiments were carried out to investigate bioaccessibility and biotransformation of WICF polyphenols, respectively. In this study *in vitro* digestion solubilized 38.6% of WICF with pronase and Viscozyme L treatments releasing 51% of the total phenols from the insoluble material. Regarding biotransformation flavanols were converted into phenolic acids, including gallic acid, by the microbiota following a concentration gradient resulting in high concentrations of 3-hydroxyphenylpropionic acid (3-HPP) in the last gut compartment.

In the study of López de Lacey et al. (2012) who examined the bioaccessibility of polyphenols in green tea-agar films, most of the release of gallic acid occurred in the gastric phase of digestion, whereas little or no increase was observed in the duodenal phase.

Table 2. Characteristics of *in vitro* methods for measuring bioaccessibility and/or bioavailability

In vitro method	End point	Advantages	Limitations
Solubility	Bioaccessibility	Simple to do Relatively inexpensive Easy to conduct, equipment in all labs	Sometimes not a reliable indicator of bioavailability Cannot assess rate of uptake or absorption or transport kinetics Cannot measure nutrient or food component competition at the site of absorption
Dialyzability	Bioaccessibility	Simple to do Relatively inexpensive Easy to conduct, equipment in all labs	Cannot assess rate of uptake or absorption or transport kinetics Cannot measure nutrient or food component competition at the site of absorption
Gastrointestinal models	Bioaccessibility Bioavailability when coupled to intestinal cells	Incorporates many digestion parameters (peristalsis, churning, body temperature, etc.,) Allows the collection of digest at any step of the digestive system	Expensive Few validation studies
Caco-2 cell model	Bioavailability	Allows the study of nutrient or food component competition at the site of absorption	Requires trained personnel with knowledge of cell culture methods

Adjusted by Etcheverry et al., 2012.

The recovery from the film samples was significantly lower, irrespectively of the presence of gelatin. However, the interactions established between gallic acid and gelatin in this study seemed to be weak, allowing, therefore, an easy release of the phenolic compound. Consequently, in bioaccessibility experiments, the release of gallic acid is highly dependent on the matrix.

Recent *in vitro* studies have reported phenolic acids to be main metabolites of anthocyanins after fecal fermentation (Aura et al., 2005). However, fragmentation of anthocyanins to phenolic acids in humans has not been studied in detail.

One recently identified anthocyanin metabolite is 3-O-methylgallic acid, which is presumably the metabolite of petunidin-3-glucoside, but possibly also a demethylation product of malvidin-3-glucoside (Forester and Waterhouse, 2008).

3.3. Animal Studies

The use of animals in research is essential to the development of new and more effective methods for diagnosing and treating diseases that affect both humans and animals. Animal studies aiming at examining the bioavailability of phenolic compounds have been also conducted (Table 3).

Konishi et al. (2004) examined the absorption of orally administered gallic acid in rats to obtain serum pharmacokinetic profiles and to investigate their intestinal absorption characteristics *in vivo*. Specifically, rats were administered 100 μmol/kg body weight of gallic acid, and both gallic acid and its metabolites were subsequently quantified with a highly selective and sensitive colorimetric detection method using high-performance liquid chromatography-electrochemical detection. Gallic acid was shown to be slowly absorbed, with a tmax for intact gallic acid of 60 min and a Cmax of 0.71 μmol/L and the area under the curve for intact gallic acid was calculated from the serum concentration profile in the portal vein to be 42.6 μmol min L^{-1}. These findings are in good agreement with the results obtained in vitro using a Caco-2 cell system (Deprez et al., 2001). In a recent study, Ferruzzi et al. (2009) examined the bioavailability and brain deposition of a grape seed polyphenolic extract (GSPE) in Sprague Dawley rats.

Table 3. Studies of gallic acid bioavailability in Sprague Dawley rats fed on different nutritional sources of the phenolic acid

Supplementation	Identified compounds	Biological samples	Method	Reference
Gallic acid (100 μmol/kg body weight)	Gallic acid 4-Methyl gallic acid	Serum	HPLC-electrochemical detection	Konishi et al., 2004
Grape seed polyphenolic extract (GSPE) (50, 100, and 150 mg)	Gallic acid	Plasma	LC-UV-MS	Ferruzzi et al., 2009
Concentrated cranberry powder (3.3, 6.6, and 33 mg/kg of diet)	Gallic acid	Urine	LC-MS/MS	Prior et al., 2010

Plasma pharmacokinetic response of major GSPE phenolic components was measured following intragastric gavage of 50, 100, and 150 mg GSPE per kg body weight. Liquid chromatography-mass spectrometry (LC-MS) analysis identified gallic acid in plasma of rats gavaged acutely with GSPE. Additionally, 4-O-methylgallic acid and other metabolites of GSPE, such as 3-methylcatechin, were identified as circulating phenolic constituents. Cmax for individual GSPE constituents and their metabolites increased in a dose-dependent fashion (with increasing GSPE oral dose). Repeated daily exposure to GSPE was found to significantly increase bioavailability (defined as plasma area under the curve, AUC, 0-8 h) of gallic acid by 198% relative to animals receiving only a single acute GSPE dose. This study suggests that brain deposition of gallic acid is affected by repeated dosing of GSPE. The objective of another study by Prior et al. (2010) was to identify and quantify the urinary excretion of 19 phenolic acids and their conjugates in rats fed on three doses of a concentrated cranberry powder (3.3, 6.6, and 33 mg/kg of diet). The basic diet used contained very low amounts of any polyphenolic compounds. Among the phenolic acids studied, gallic acid was excreted in the urine in concentrations of 0.1-2 μg/mg creatinine, a relative low one compared to other phenolic acids.

3.4. Human Studies of Gallic Acid Bioavailability

There are only a few published studies concerning the bioavailability of gallic acid in humans (Table 4). Shahrzad and Bitsch (1998) examined the metabolism of gallic acid in human body by developing two methods for the identification and determination of gallic acid and its phenolic metabolites in human plasma and urine after oral administration of 50 mg gallic acid. Determinations were carried out by reversed-phase high-performance liquid chromatography, using UV detection and involving isocratic elution. One of these methods enables the simultaneous separation and determination of gallic acid, 4-O-methylgallic acid, pyrogallol, 2-O-methylpyrogallol and resorcinol in biological fluids with a long analysis time (57 min). The second method was developed to determine gallic acid and 4-O-methylgallic acid in a shorter analysis time (25 min).

However, after oral administration of 50 mg gallic acid, both methods failed to show metabolites other than 4-O-methylgallic acid and gallic acid in plasma and urine.

In 2001, the same research team conducted a study to determine gallic acid pharmacokinetics and relative bioavailability in healthy humans, by employing acidum gallicum tablets that contained 10% gallic acid and 90% glucose or a black tea brew that contained 93% of gallic acid in free form. After the administration of a single oral dose of acidum gallicum tablets or tea (each containing 0.3 mmol gallic acid) to 10 healthy volunteers, gallic acid was rapidly absorbed and eliminated with mean half-lives of 1.19±0.07 and 1.06±0.06 h and mean maximum concentrations of 1.83±0.16 and 2.09±0.22 μmol/L (plasma), respectively.

After oral administration of the tablets or black tea, 36.4±4.5 and 39.6±5.1% of the gallic acid dose were present in urine in the form of gallic acid and of its metabolite 4-O-methylgallic acid, respectively. The relative bioavailability of gallic acid from tea compared with that from the tablets was 1.06±0.26, showing that its bioavailability was independent of the matrix, either tea or tablets. Caccetta et al. (2000) examined whether certain phenolic acids can be detected in the circulation after red wine consumption.

Table 4. Studies of gallic acid bioavailability in humans administrated with different nutritional sources of the phenolic acid

Supplementation	Identified compounds	Biological samples	Method	Reference
Gallic acid (50 mg)	Gallic acid 4-Methyl gallic acid	Plasma Urine	Reversed-phase HPLC-UV detection	Shahrzad and Bitsch, 1998
Acidum gallicum tablets (10% gallic acid and 90% glucose) or black tea	Gallic acid Gallic acid 4-Methyl gallic acid	Plasma Urine	HPLC mobile phase	Shahrzad et al., 2001
Red wine	4-Methyl gallic acid	Plasma	GC-MS	Caccetta et al., 2000
Red wine	Gallic acid 4-Methyl gallic acid 3-O Methyl gallic acid	Plasma	HPLC-MS	Cartron et al., 2003
Polyphenol-rich juice	O-Methylgallic acid-O-sulfates	Plasma, urine	HPLC-MS	Mullen et al., 2010
Concord grape juice	Gallic acid	Ileal effluent	HPLC-MS	Stalmach et al., 2012
Black tea	4-Methyl gallic acid 3-O Methyl gallic acid 3,4-O-Dimethylgallic acid	Urine	GC-MS	Hodgson et al., 2000
Tea	4-Methyl gallic acid	Urine	GC-MS	Hodgson et al., 2004
Six polyphenol-rich beverages	Gallic acid	Urine	HPLC-electrospray ionization-MS	Ito et al., 2005
Black tea and wine	Gallic acid 4-Methyl gallic acid	Urine	HPLC-electrospray ionization-MS-MS	Mennen et al., 2006

Twelve healthy male nonsmokers consumed red wine, phenol-stripped red wine, dealcoholized red wine, or water, each at a separate visit, in random order and 1 week apart, and plasma phenolic acids were measured by gas chromatography-mass spectrometry. The metabolite of gallic acid, 4-O-methylgallic acid, increased significantly ($P<0.025$) after consumption of red wine and dealcoholized red wine compared with water or phenol-stripped red wine. Cartron et al. (2003) sought to evaluate the effect of one single intake (300 mL) of red wine on plasma phenolics over a 24-h time period following the intake. In the first part, blood samples were collected just before and after wine consumption. In the second part, subjects received the 3 types of wine successively, only at the mealtime, over a 3-week periods separated by a 3-week wash out.

Blood samples were drawn in fasting condition before and after each 3-week wine consumption period. The peak of plasma antioxidant capacity appeared at 3-4 h following the single intake of red wine, not coinciding with the peak of plasma gallic acid (earlier to 3-4 h, 1.5 μmol/L), yet coinciding with that of catechin.

In plasma, the predominating form of gallic acid was its 4-O-methylated derivative, but also the 3-O-methyl derivative appeared as minor derivative. Mullen et al. (2010) developed a polyphenol-rich juice drink as a potential approach to increase intake of dietary polyphenols and examined the bioavailability of flavonoids and other phenolic compounds. Ten healthy humans consumed 350 mL of the polyphenol-rich juice drink, after which plasma and urine samples were collected over a 0-24 h period. Applying high-performance liquid chromatography - mass spectrometry analysis resulted in the identification of a total of 13 metabolites in plasma and a total of 20 metabolites in urine, including O-methylgallic acid-O-sulfates as metabolites of gallic acid. Following this study, Stalmach and co-workers (2011) examined the bioavailability of the phenolic compounds in 350 mL of Concord grape juice following acute intake by eight healthy volunteers. Plasma and urine were collected over 0-24 h and analyzed for parent compounds and metabolites. In total, 41 compounds, principally metabolites, were identified; however, gallic acid was not detected in both plasma and urine.

In another study, Stalmach et al. (2012) aimed to compare the *in vitro* gastrointestinal stability of phenolic compounds in Concord grape juice with recoveries in ileal fluid after the ingestion of the juice by ileostomists. Of the 18±1 μmol of gallic acid ingested through the consumption of 350 mL of Concord grape juice, 8.5±1.7 μmol of gallic acid were recovered in ileal effluent, representing 47% of intake. The juice was also ingested by healthy subjects with an intact functioning colon. Peak plasma concentrations of several phenolic compounds were determined, however the authors failed to quantify gallic acid concentration nor in plasma neither in urine.

Apparently, the gallic acid administered with Concord grape juice was absorbed, shown by the recoveries in ileal fluid; however its metabolites were not targeted and detected in plasma and urines. Hodgson et al. (2000) conducted several studies to identify urinary gallic acid metabolites with potential to serve as markers of black tea intake.

In an initial study, the concentrations of nine compounds, assessed by gas chromatography-mass spectrometry, were found to increase in urine after consumption of 3 cups of black tea over 3 h. A subsequent study employed a controlled crossover design in which 10 subjects consumed 5 cups of black tea per day or water for 4 weeks in random order. Twenty-four hour urine samples were collected at the end of each period. Of the 9 candidate compounds identified in the initial study, only 3 were present at higher concentrations in urine of all the 10 subjects during tea-drinking in comparison to water-drinking periods.

These compounds were all identified as methyl ether derivatives of gallic acid, namely 4-O-methylgallic acid, 3-O-methylgallic acid, and 3,4-O-dimethylgallic acid. It is suggested that these compounds have the potential to be used as markers of black tea intake. Another study from Hodgson et al. (2004) explored the relationships of tea intake with 24 h urinary excretion of 4-O-methylgallic acid in human subjects. The relationship of long-term usual (111 participants) and contemporaneously recorded current (344 participants) tea intake with 24 h urinary excretion of 4-O-methylgallic acid was assessed in two populations. 4-Methyl gallic acid was related to usual ($r=0.50$, $P<0.001$) and current ($r=0.57$, $P<0.001$) tea intake, indicating that 4-methyl gallic acid is a good biomarker for black tea-derived polyphenol exposure. Ito et al. (2005) examined a fast method suitable for the analysis of polyphenols in urine, selected as potential biomarkers of intake.

This method was applied to estimate polyphenol recovery after ingestion of six different polyphenol-rich beverages.

Among many other polyphenols, gallic acid was quantified in human urine by high-performance liquid chromatography coupled with electrospray ionisation mass - mass spectrometry with a run time of 6 min per sample after ingestion of green tea or grape-skin extract or cocoa beverage or coffee or grapefruit juice or orange juice. Levels of urinary excretion suggested that gallic acid could be used as specific biomarker to evaluate the consumption of its nutritional sources. Mennen et al. (2006) evaluated the associations between the intake of polyphenol-rich foods and the urinary excretion of several phenolic compounds and examined whether these compounds could be used as biomarkers of intake. Fifty-three participants collected 24 h urine and a spot urine sample and filled a dietary record covering a 2 d period. Thirteen polyphenols and metabolites, including gallic acid and 4-O-methylgallic acid were measured using high-performance liquid chromatography-electrospray ionization- mass spectrometry- mass spectrometry.

In spot samples the combination of fruits and/or fruit juices was positively correlated to gallic acid and 4-O-methylgallic acid ($r=0.24$-0.44, $P<0.05$). Further, black tea and wine consumption were positively correlated with gallic and 4-O-methylgallic acids ($r=0.37$-0.54, $P<0.001$). When Russell et al. (2009) examined the bioavailability of phenolic acids after consumption of 750 g of Scottish strawberries, gallic acid or its metabolites were not detected in the plasma of the four participants.

Most recently, our research team looked for the postprandial effect of raisin administration in plasma antioxidant capacity of ten healthy subjects. Raisins examined were Corinthian Currants, produced exclusively in Greece. They are most widely consumed dried fruits in Greece obtained by black grapes naturally dried without the addition of any substitute. The content of Corinthian raisins in phytochemicals was determined by gas chromatography - mass spectrometry.

A total of 25 phytochemicals were identified and quantified in raisins. Ten healthy volunteers who consumed 144 g of raisins -containing 16.7 μg of gallic acid- were subjected to blood collection 4 hours after consumption. In obtained samples total polyphenols and serum oxidation resistance significantly increased after the first hour of raisin consumption. Increase in serum oxidation resistance 1 h after ingestion was positively correlated to increase in total phenolic compounds in plasma, meaning that increase was due to the absorbed and bioavailable polyphenolic compounds. When quantification of individual phenolic compounds in plasma was carried out, plasma concentration of gallic acid peaked during the first hour after ingestion, while its concentrations ranged from 2.2±0.9 to 9.9±4.6 (SEM) μg/L.

CONCLUSION

Although gallic acid and its derivatives are ubiquitous in food items of plant origin, it's *in vivo* bioavailability in humans has not been studied extensively. Studies carried out so far indicate that gallic acid is well absorbed and in most cases its metabolites together with the parent molecule are detected in body fluids. However, in some surveys gallic acid or its metabolites were not detected either in blood or in urine. Available *in vivo* experimental data for humans indicate that the kinetics of gallic acid uptake results in plasma peak concentrations 1-2 hours after ingestion.

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