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Metabolites Are Key to Understanding Health Effects of Wine Polyphenolics[1–3]

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Abstract

Phenolic compounds in grapes and wine are grouped within the following major classes: stilbenes, phenolic acids, ellagitannins, flavan-3-ols, anthocyanins, flavonols, and proanthocyanidins. Consumption of foods containing phenolic substances has been linked to beneficial effects toward chronic diseases such as coronary heart disease and colorectal cancer. However, such correlations need to be supported by in vivo testing and bioavailability studies are the first step in establishing cause and effect. Class members from all phenolic groups can be glucuronidated, sulfated, and/or methylated and detected at low concentrations in the bloodstream and in urine. But the majority of phenolic compounds from grapes and wine are metabolized in the gastrointestinal tract, where they are broken down by gut microflora. This typically involves deglycosylation, followed by breakdown of ring structures to produce phenolic acids and aldehydes. These metabolites can be detected in bloodstream, urine, and fecal samples by using sophisticated instrumentation methods for quantitation and identification at low concentrations. The health effects related to grape and wine consumption may well be due to these poorly understood phenolic acid metabolites. This review discusses the known metabolism of each major class of wine and grape phenolics, the means to measure them, and ideas for future investigations. J. Nutr. 138: 1824S–1831S, 2009.

Introduction

The U.S. daily intake of flavonoids in 1999–2002 was estimated at 189.7 mg/d, with the majority (83.5%) accounted for by flavan-3-ols, and wine contributing only 4 mg (1). For the year 2000, Americans consumed 20 mL of wine per day on average compared with 226 mL and 13 mL of beer and spirits, respectively (2). If consumption was 1 180-mL glass of red wine per day, this would contribute roughly 36.5 mg/(d · person) of flavan-3-ols and 46.8 mg/(d · person) of procyanidin dimers (B1, B2, B3, and B4) (3), greatly increasing flavonoid intake. Actual amounts would depend upon the wine varietal.

Consumers of alcohol that include moderate wine intake have reduced mortality compared with those that do not consume wine, due to a lower incidence of coronary heart disease and cancer (4). Wine consumption has been reported to have an inverse association with colorectal cancers (5,6) and light wine intake could protect against nonalcoholic liver disease (7). Evidence exists for an inverse correlation between wine intake and coronary heart disease and could be the basis of the French paradox (8).

Polyphenols in wine (**Fig. 1**) may be responsible for the effects in these epidemiological studies. The majority of these potentially bioactive compounds are also found in grapes. For instance, anthocyanins found in cabernet sauvignon, merlot, and syrah grapes are effectively extracted into their wines (9). It is not clear, however, if the bioavailabilities of these anthocyanins are the same if consumed from grapes or wine. Matrix effects may be present for the absorption and metabolism of grape and wine phenolics.

To determine which compounds in grapes and wine are the most bioactive, their effects in disease models must be known, including absorption and metabolism. Rats that consume a red wine extract have elevated levels of the microbial phenolic acid metabolites 3-hydroxyphenylpropionic, 3-hydroxybenzoic, 3-hydroxyhippuric, hippuric, p-coumaric, vanillic, 4-hydroxybenzoic, and 3-hydroxyphenylacetic acids in urine. These urine metabolites account for roughly 10% of the administered red wine polyphenols (10). Most grape and wine flavonoids and others

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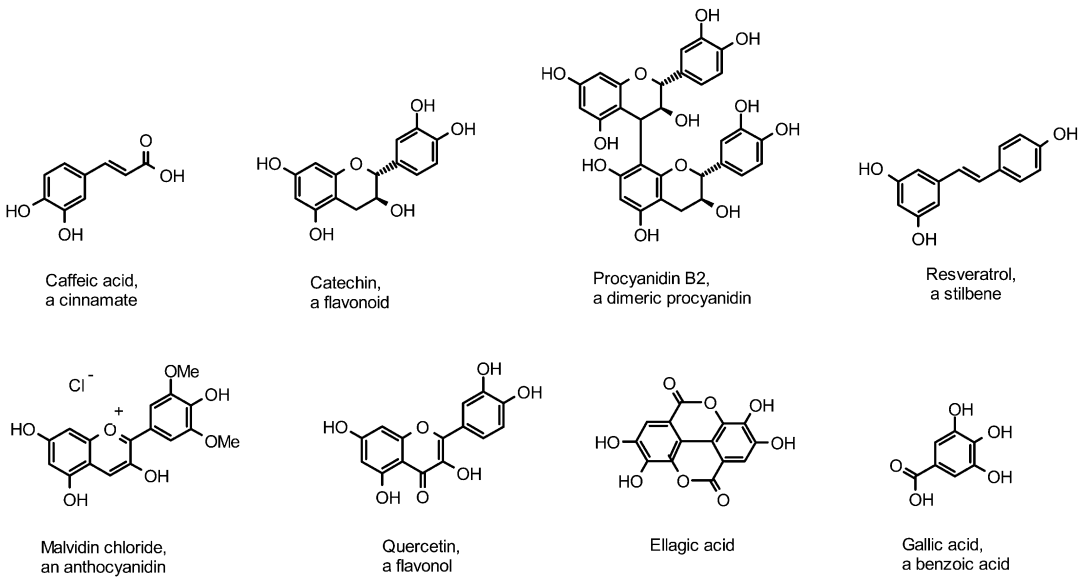

FIGURE 1 Phenolic compounds in grapes and wine.

are rapidly metabolized in the human body, making it difficult to determine whether these compounds are effective against disease. The metabolites gallic acid, 4-*O*-methylgallic acid, and 3-*O*-methylgallic acid are detected in the plasma of human subjects who consume 300 mL of red wine (11). In fact, the metabolites gallic acid and 4-*O*-methylgallic acid are well correlated with wine consumption and may be used as urinary biomarkers for wine intake in health-related studies (12). Phenolic acid metabolites are mainly formed from gut microfloral metabolism and could be responsible for much of the disease reduction associated with consuming wine and grape phenolics.

Gut flora that could participate in metabolism of flavonoids are *Bacteroides*, *Clostridium*, *Eubacterium*, *Ruminococcus*, *Eggertheilla* (13), *Streptococcus*, *Lactobacillus*, and *Bifidobacterium* genera (14). An individual's microfloral profile will likely determine gut metabolites from wine polyphenols and secondarily affect the activity of phase I and II enzymes, in turn determining the formation of human enzymatic metabolites that are absorbed into the bloodstream (15–18). Specific human metabolites include various combinations of glucuronidated, sulfated, and methylated compounds, which will be discussed in detail within this review. Individuals suffering from diseases such as inflammatory bowel disease may have altered gut flora profiles (19), which could alter their gut metabolite profiles along with liver metabolism products. Wine phenolics also have the ability to either suppress or enhance the presence of specific gut flora. Epicatechin, catechin, 3-*O*-methylgallic acid, gallic acid, and caffeic acid can all suppress populations of certain pathogenic bacteria while supporting the growth of beneficial gut bacteria (20).

Due to the multitude of grape and wine phenolic metabolites (**Fig. 2**) produced in vivo, it is important to both identify and quantify them in biological samples such as plasma, urine, and feces. Metabolomics can be used to detect metabolites of wine polyphenols but also changes in an individual's entire metabolic profile, induced by these potentially bioactive compounds. Mass spectrometer detectors capable of enhanced mass accuracy are particularly useful in searching for unknown phenolic metabolites. Specific analytical techniques used in studying phenolic metabolism are presented within each section of this paper.

Stilbenes

Stilbene concentrations can range from roughly 50 to 100 $mg \cdot kg^{-1}$ in dry red grape skin and ~20 mg/L in finished wine (21). The most important stilbene with respect to health is

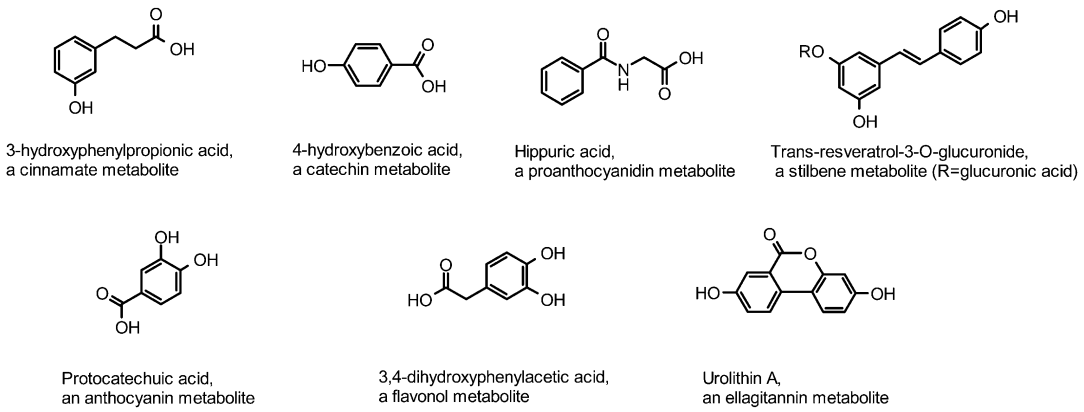

FIGURE 2 Representative metabolites for each phenolic class.

resveratrol, which is the focus of numerous health-related articles in the literature. Mice fed a high-energy diet and given resveratrol were found to live longer (22). Taking into account the body surface area of humans, the dose used in this study would be roughly equivalent to a human consuming 5 L/d of finished wine (23), suggesting wine consumption might not be the preferred source of resveratrol.

Resveratrol is rapidly metabolized when given to rats orally. The blood concentration of resveratrol peaks only 10 min after ingestion (24). In humans, native resveratrol is excreted in higher amounts over a 24-h period than either catechin or quercetin (25), indicating that it may be metabolized to a lower extent. Resveratrol is sulfated in both the small intestine and liver, which may minimize its health effects in vivo. This sulfation has been shown to be inhibited by many flavonols, yet not catechin (26). Resveratrol is also heavily glucuronidated in vivo and detected in the plasma of rats. Over time this glucuronide metabolite appears to be converted back to native resveratrol in the major organs. In addition, no microfloral metabolites of resveratrol appear to be produced (27).

Cis- and *trans*-resveratrol are both found in grapes and wine (28,29) and are glucuronidated to 3-*O* and 4-*O*-glucuronide metabolites in the gastrointestinal tract. Caco-2 cells can glucuronidate *cis*-resveratrol and low amounts of *trans*-resveratrol to the 3-*O*-glucuronide metabolites (30). Stilbenes can also be glucuronidated in vitro by human liver microsomes (31).

After moderate consumption of red wine, *trans*-resveratrol-3-*O*-glucuronide, *cis*-resveratrol-3-*O*-glucuronide, *cis*-resveratrol-3-*O*-glucoside, and *trans*-resveratrol were observed in LDL and urine. *Cis*- and *trans*-resveratrol glucuronide and sulfate metabolites were also detected in human LDL and urine after consumption of red wine (32). This could minimize oxidation of LDL and perhaps explain in part the beneficial effects of moderate wine consumption on the heart, yet the health effects of metabolites are still widely unknown.

Metabolism of resveratrol has also been studied by positron emission tomography, where F-18 radiolabeled resveratrol was injected i.v. into rats. Less than 1% of radioactivity was found in the plasma, but amounts in the kidney, lung, liver, intestine, and urine were 9.50, 2.27, 25.26, 4.79, and 28.81%, respectively, 5 min after injection. Levels in the kidney, lung, and liver were lower after 60 min, and 31.05 and 37.87% were found in the intestine and urine, respectively (33). Positron emission tomography allows investigators to monitor in vivo metabolism over time and dramatically reduces the numbers of animals required for a study. Quantitation of *trans*-resveratrol is normally achieved by HPLC and has been optimized for plasma analysis (34). HPLC combined with tandem MS detection (LC-MS/MS) is a powerful tool for identification of resveratrol and its conjugated metabolites in biological samples such as human urine and LDL (32,35).

Phenolic acids

Phenolic acids are found in the pulp of *Vitis vinifera* grapes and are divided into benzoic and hydroxycinnamic acids. Caftaric and gallic acids are probably the most important of these acids in grapes (36), with caffeic and gallic acids being dominant in wines (37). Gallic and caffeic acids could be important anticancer agents (38–40), highlighting the importance in determining their bioavailability in vivo.

When consumed, these compounds can be absorbed but are also subject to considerable bacterial metabolism in the gut. After 2 h of incubation of caffeic acid with human fecal microflora, 3-hydroxyphenylpropionic and benzoic acids are produced and none of the parent compound is detected (41). Phenolic acids are also subject to human cell metabolism and transportation. When various hydroxycinnamic acids are incubated with Caco-2 cells, methyl hydroxycinnamates may be hydrolyzed to their aglycones outside of the cells. Methyl hydroxycinnamates that are not hydrolyzed and are transported inside the cells can be sulfated or glucuronidated by sulfotransferases or UDP-glucuronosyltransferases. If aglycones are transported into Caco-2 cells, they will only be sulfated, with the exception of caffeic acid, which is methylated by only *O*-methyltransferases (42).

Evidence shows that intestinal cell transport can be somewhat selective. *p*-Coumaric acid is better absorbed than gallic acid when given to rats orally (43), which could be due to the fact that gallic acid is not transported by the monocarboxylic acid transporter (MCT) in cells like Caco-2 but rather by paracellular diffusion (44). *m*-Coumaric acid and *m*-hydroxyphenylpropionic acid are transported by the MCT in Caco-2 cells (45), but *ρ*-coumaric acid is not transported by MCT-1 (46), indicating that isomers have different absorption characteristics. Caffeic acid is somewhat transported by the MCT in Caco-2 cells, but mostly by paracellular diffusion (47).

Quantification of phenolic acids is essential to improving our understanding and it can be achieved by using HPLC (48). Identification of many metabolites is possible when coupled to MS/MS (49). Metabolomic methods that involve GC with time-of-flight mass spectrometric detection can measure phenolic acid metabolites in plasma, urine, and feces samples, with run-times well under 30 min (50).

Ellagitannins

Ellagitannins are found in wine due to their extraction from barrels or oak chips (51). They can reduce cell proliferation of colon cancer cells, possibly by inhibiting activity of the epidermal growth factor receptor (52). Ellagitannins ingested by rats are rapidly metabolized in the stomach and metabolites do not appear to include ellagic acid (53). In the Iberian pig model, ellagic acid is formed in the small intestine from ellagitannins plus 25 urolithin metabolites and 6 ellagic acid-derived compounds, all of which can all be analyzed by LC-MS/MS. These results are different from those found in rats, probably due to differences in microbial profiles. Many of these ellagitannin metabolites are highly absorbed into the bloodstream, including urolithin A, a major metabolite in urine along with its glucuronide. Urolithin A is also the only metabolite passed through the gastrointestinal tract to the feces (54). In humans, ellagitannin metabolites such as urolithin B and its conjugates are found in concentrations that vary greatly between individuals depending on their gut microflora (55).

Monomeric flavan-3-ols

Red wine contains roughly 100 mg/L of catechin and 75 mg/L of epicatechin. White and rosé wine have minimal amounts of catechin and epicatechin (<10 mg/L on average) (56), because flavan-3-ols are found in the skins and seeds of grapes. Diets high in flavan-3-ols reduce the risk of coronary heart disease (57). Evidence that catechins and procyanidins bind to apolipoprotein A-1 and transferrin proteins in humans and rats, respectively (58), may help explain such an epidemiological result. In human subjects, the highest levels of plasma (+)-catechin (2.2 μmol/L) can be achieved when fruit, vegetables, and wine are consumed (59).

Catechin appears to be metabolized only if absorbed from the small intestinal lumen. Both 3′-*O*-methylcatechin-glucuronide and catechin-glucuronide are produced in intestinal cells and methylation and sulfation of catechin metabolites are produced in the liver (60). Catechin is mainly found as the glucuronide metabolite in plasma after rats are fed catechin, yet glucuronidated 3′-*O*-methylcatechin is also found in relative abundance (60,61). Large amounts of the 3′-*O*-methyl metabolite are also found to be glucuronidated and sulfated on the same compound, presumably produced in the liver, and are only detected in the bile (60). In humans, between 3.0 and 10.3% of ingested catechin from red wine is accounted for in urine, mostly as catechin and its 3′-*O*-methyl-glucuronide and sulfate metabolites (62). Catechin can also be conjugated with glutathione with the assistance of enzymes such as tyrosinase, peroxidase, and cytochrome p450 (63).

Epicatechin is found as glucuronide and sulfoglucuronide metabolites in plasma. Its 3′-*O*-methyl metabolite is also sulfated. Evidence points to a competitive absorption of catechin and epicatechin from rat intestines (61). When (+)-catechin is administered orally to rats, the metabolite (+)-catechin 5-*O*-β-glucuronide is found in the plasma, bile, and urine. Similarly, when (−)-epicatechin is fed to rats, the metabolite (−)-epicatechin 5-*O*-β-glucuronide is detected in the same biological samples (64).

(+)-Catechin and (−)-epicatechin are absorbed from the small intestine by both passive and facilitated diffusion (65). In rats, (+)-catechin in wine has been shown to be absorbed better than (−)-catechin, which is found in cocoa (66). This could be partially due to facilitated diffusion of (+)-catechin into intestinal cells. Ethanol does not appear to increase plasma absorption of catechin in humans but does increase the rate of elimination from plasma (67). One study reported increased absorption of catechin when ethanol was also consumed, yet this difference was not significant ($P = 0.06$) (62).

Aside from metabolism that occurs in intestinal cells and liver, catechin can also be metabolized by gut microflora to produce phenolic acid metabolites. In rats, these metabolites can be found in urine, with 3-hydroxyphenylpropionic acid, 3-hydroxybenzoic acid, and 3-hydroxyhippuric acid present in the highest concentrations (10). When catechin is incubated with human gut microflora, it is metabolized to 4-hydroxybenzoic acid, 2,4,6-trihydroxybenzaldehyde, phloroglucinol, and 4-methoxysalicylic acid (14), again emphasizing the effects of individual microfloral profiles on gut metabolism.

LC-MS/MS is a common tool for identification of flavan-3-ols (68) in biological samples. A metabolomic approach would be chosen if looking for changes in an organism's metabolome, after having consumed a compound such as catechin. Quadrupole/time-of-flight mass analyzers combined with HPLC are best for searching for known and unknown compounds, enabling the detection of catechin metabolites and metabolic biomarkers that are altered by catechin ingestion (69).

Anthocyanins

Anthocyanins can average ~500 mg/L in finished young red wines (70), making them potentially important bioactive compounds. Based on 2001–2002 information from NHANES, the daily intake of anthocyanins in the US was 12.53 mg/(person·d). Of these anthocyanins, only 0.66 mg was from wine and 0.93 mg from grape juice (71). Wine is the main contributor of anthocyanins in the diets of Australians, likely due to higher wine intake, and also a slight contributor of flavan-3-ols and flavonols (72). Anthocyanins are promising candidates in the prevention of colon cancer (73,74), yet it is not clear whether the parent compounds or metabolites are responsible in vivo.

In humans, nanomolar plasma concentrations of anthocyanins are found after they are consumed. Most of the absorbed anthocyanins are found in urine within the first 3 h (75) and between 1.5 and 5.1% of ingested anthocyanins are detected in urine after 12 h (76). Small amounts of anthocyanins can be found in the lower gastrointestinal tract of rats and none in the liver, kidneys, or brain organs (53). Rats that consume grape anthocyanins also have detectable amounts of anthocyanins in their feces (77). Anthocyanins are also glucuronidated and methylated in mice, which are found in the intestine and urine samples (73). When malvidin-3-glucoside is consumed, however, only the unmetabolized form is detected in human plasma and urine (78). As with other phenolic classes, analysis of anthocyanins and their conjugated metabolites in biological samples is best performed with liquid chromatography combined with MS/MS detection (79).

Absorbed cyanidin-3-glucoside in rats is either conjugated or unconjugated and, as with catechin, ethanol does not appear to increase the absorption of cyanidin-3-glucoside from the small intestine (80). In fact, anthocyanins from grape juices are better absorbed than anthocyanins in wine, as examined in humans. It was suggested that this finding is due to the higher sugar content of grape juice (81), yet in rats, cyanidin-3-glucoside absorption was not influenced by the presence of glucose (82). After rats are fed cyanidin-3-glucoside, the aglycone is only found in the small intestine, cyanidin-3-glucoside is found in the plasma, and methylated cyanidin-3-glucoside is found in the liver and kidney organs (83,84).

Anthocyanins are metabolized by gut microflora via glycosylation and ring fission of C-ring to produce phenolic acids and aldehydes (85). This accounts for the majority of anthocyanin metabolism in vivo. After rats consume anthocyanins, the phenolic acids in urine far exceed the ingested anthocyanins (53), indicating that anthocyanin consumption may increase baseline catabolism. Keppler and Humpf (86) studied 6 anthocyanin standards in pig cecum and found protocatechuic acid, syringic acid, vanillic acid, phloroglucinol acid, gallic acid, and phloroglucinol aldehyde. Similarly, a cabernet sauvignon anthocyanin extract was metabolized to 3-*O*-methylgallic acid, syringic acid, and 2,4,6-trihydroxybenzaldehyde (phloroglucinol aldehyde) using pig gut microflora (87).

When rats were fed cyanidin-3-glucoside, protocatechuic acid was produced and the plasma concentration was 8 times higher than the absorbed cyanidin-3-glucoside (83,84). After human consumption of cyanidin-3-glucoside, 0.02% of the substance was absorbed into the bloodstream in total. Protocatechuic acid was formed as a metabolite and the total absorbed amount in the bloodstream accounted for 44% of the consumed cyanidin-3-glucoside. The amount of protocatechuic acid recovered in the feces was 28%. Small amounts of cyanidin-3-glucoside and its metabolites were detected in the urine but not protocatechuic acid (88).

Flavonols

Flavonols can average up to ~50 mg/L in finished red wines, with white wines having essentially no flavonol content. Specific flavonols found in wine are quercetin-3-galactoside, quercetin-3-glucuronide, syringetin-3-glucoside, myricetin, quercetin, laricitrin, kaempferol, isorhamnetin, and isorhamnetin-3-hexoside (89). Individuals who consume more flavonols were found to have a lower risk of developing pancreatic cancer (90). When humans consumed 100 mL of grape juice, small amounts of

quercetin were absorbed into the blood (91). After female humans were fed rutin for 6 wk, quercetin, kaempherol, and isorhamnetin were found in the plasma samples (92). This is presumably due to deglycosylation of rutin and further metabolism of quercetin. Flavonols and their metabolites can be identified and quantified by HPLC-electrospray ionization-MS/MS (*68*).

Unlike catechin, quercetin and quercetin-3-glucoside are both absorbed much higher in rat intestines when ethanol is present (93). Quercetin appears to be better absorbed than catechin in rats and is found as glucuronide and sulfated metabolites (94). In humans quercetin is found as sulfate and glucuronide metabolites in both plasma and urine after 30 min, but less so than catechin or resveratrol (25). Lactase phlorizin hydrolase is a glucosidase found in the small intestinal lumen and is able to hydrolyze 2 quercetin glycosides (95). Quercetin is also methylated in the rat intestine to produce isorhamnetin and tamarixetin (93) and is methylated by human liver methyltransferase (96).

In an in vitro study utilizing the flora from pig cecum, rutin was shown to by deglycosylated to quercetin and it could be further metabolized to phloroglucinol and 3,4-dihydroxyphenylacetic acid (97). The result was different when human gut microflora was used, where quercetin was metabolized to 4-hydroxybenzoic acid, 3,4-dihydroxybenzoic acid, and 3,4-dihydroxyphenylacetic acid (14).

Proanthocyanidins

Red wines can have ~370 mg/L of procyanidin dimers (B1, B2, B3, and B4) and trimers (C1 and C2) and are not found in white and rose wines (56). When rats were fed grape seed procyanidins, levels of LDL decreased and cholesterol elimination with bile acids increased (98). Compared with catechin, procyanidins are not absorbed from the gut in rats (99), yet synthesized (−)-epicatechin dimers linked with an ethyl bridge are absorbed in rats and rapidly methylated. These synthesized (−)-epicatechin dimers peak in plasma concentrations after 2 h of oral administration and small amounts are detected in the liver (100). Procyanidin dimers and trimers can be quantified by reverse-phase HPLC (100,101), yet procyanidins with greater degrees of polymerization need to be analyzed by normal-phase HPLC (101). Synthesis of radiolabeled phenolic compounds for feeding studies and metabolite standards for quantitation will continue to be essential in establishing in vivo metabolism pathways (102,103).

Procyanidins, like many other phenolic classes, are metabolized by gut flora in rats to produce phenolic acids that can be detected in urine. These metabolites include 3-hydroxyphenylvaleric, 3,4-dihydroxyphenylpropionic, 3-hydroxyphenylpropionic, *m*-coumaric, *p*-coumaric, 3,4-dihydroxyphenylacetic, 3-hydroxyphenylacetic, protocatechuic, 3-hydroxybenzoic, 4-hydroxybenzoic, vanillic, 3-hydroxyhippuric, 4-hydroxyhippuric, and hippuric acids. Procyanidin dimer B_3 is metabolized to all of these metabolites, yet procyanidins of increased polymerization produce fewer phenolic acid metabolites (104).

In conclusion, it is clear that consideration of wine and grape metabolites is essential to understanding their biological impact, because most phenolic compounds in grapes and wine are heavily metabolized when ingested. Absorbed compounds are detected in the plasma as glucuronide, sulfate, and methyl metabolites. The percentage of absorbed native compounds, however, is usually quite low, but large quantities of metabolites are observed as a number of simple phenolic acids and some aldehydes. It appears that the origin of these substances is bacterial and that these gut metabolites could potentially be well absorbed into the bloodstream. Thus, the production of these metabolites formed by specific bacteria in the gut needs to be investigated further, including levels of metabolites in feces. It is also clear that much more needs to be known about how an individual's gut microfloral ecology affects metabolism of phenolic compounds and the complementary question of how dietary phenolics alter the gut ecology. As analytical methods develop increasingly lower limits of quantitation, it may also be possible to conduct more human metabolism studies involving radiolabeled parent compounds at safe dose levels.

Other articles in this supplement include (105–111).

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