Grapes and Gastrointestinal Health: Implications with Intestinal and Systemic Diseases

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Abstract The anti-inflammatory, antioxidant, or antimicrobial properties of phytochemicals found in fruits and vegetables are well documented. Phytoactive compounds and their metabolites have typically been monitored in blood or non-intestinal tissues of animals or human subjects consuming whole foods, extracts, or individual phytochemicals or examined after phytochemical treatment of cells in culture. Much less is known about the influence of polyphenols, in particular those found in grapes (e.g., anthocyanins), on intestinal health and how these polyphenols indirectly influence systemic metabolism. Notably, polyphenols may influence nutrient digestion and absorption, and gut microbiota taxa and their fermentation products, in part, because they are poorly absorbed in the upper gut and thus persist in the colon. Here, they come in direct contact with microbes, influencing microbial growth and metabolism, as well as undergoing enzymatic modification based on the available microbes. Whereas a great deal is known about

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J.M. Pezzuto (ed.), *Grapes and Health*, DOI 10.1007/978-3-319-28995-3_7

the fermentation of fiber, there are gaps in the literature concerning how polyphenols influence microbial metabolism and vice versa. Therefore, this paper will focus on studies examining the influence of polyphenols in general and grape polyphenols in particular, on intestinal health, and subsequent metabolic consequences.

1 Nutrient Content of Grapes

Macronutrient Content Table grapes contain approximately 82 % water, 12–18 % simple sugars (primarily glucose and fructose), and 0.2–0.8 % acid, primarily tartaric and malic acid (California Table Grape Commission website 2015). One serving of table grapes (3/4 cup or 126 g) contains approximately 85 kcals, 20 g carbohydrate, 0.8 g protein, and 0.07 g fat.

Micronutrient One serving of table grapes contains approximately 0.7 g of minerals (ash; e.g., 224 mg potassium, 24 mg phosphorus, 12 mg calcium) and small amounts of vitamins (e.g., 49 IU vitamin A, 0.6 mg vitamin C, 11 μg folic acid) (California Table Grape Commission website 2015).

Phytochemical Content Table grapes are rich in polyphenols including flavonol glycosides (e.g., quercetin, kaempferol, myricetin, laricitrin, isorhamnetin, syringetin), anthocyanins (e.g., malvidin, peonidin, petunidin, cyanidin, delphinidin, pelargonidin), flavan-3-ols (e.g., catechin, epicatechin), phenolic acids (e.g., protocatechuic acid, gallic acid), hydroxycinnamates (e.g., caftaric acid, coutaric acid, fertaric acid), and stilbenes (e.g., *trans*-resveratrol) (Cantos et al. 2002; Castillo-Munoz et al. 2009; Nicoletti et al. 2008; Chuang et al. 2012).

2 Impact of Polyphenols on Nutrient Digestion and Absorption

Influence on Carbohydrate, Fat, or Protein Absorption Polyphenols have been reported to reduce carbohydrate absorption, possibly by interfering with amylase activity, thereby reducing starch digestion and glycemic index (Thompson et al. 1984; Forester et al. 2012). In so doing, they provide carbohydrate for microbial growth in the lower gastrointestinal (GI) tract, particularly saccharolytic bacteria in the human GI tract such as *Bacteroides, Bifidobacterium, Clostridium, Eubacterium, Lactobacillus,* and *Ruminococcus* [reviewed in Maukonen and Saarela (2015a)]. Such an effect would enhance microbial fermentation in the lower GI tract, thereby increasing short-chain fatty acid (SCFA) synthesis and energy harvest and decreasing intestinal pH. Thus, polyphenols have the potential

to influence bacterial diversity and enteric and systemic health status. Polyphenols may also interfere with lipases or proteases, decreasing fat and protein digestion, respectively, thereby increasing their potential to be fermented by intestinal microbes [reviewed in Jakobek (2015)].

Influence on Vitamin or Mineral Absorption Based on their robust antioxidant properties, dietary polyphenols may prevent the oxidation of macro- and micronutrients, thereby preserving their quality. Some polyphenols, however, can interfere with mineral absorption. For example, gallic acid, chlorogenic acids, monomeric flavonoids, and polyphenolic polymerization products inhibit nonheme iron absorption by as much as 50 % [reviewed in Monsen (1988), Smith et al. (2005)]. Moreover, tannins and gallic acid have been reported to bind to zinc and impair its absorption [reviewed in Monsen (1988)].

3 Intestinal Bioaccessibility, Bioavailability, and Metabolism of Polyphenols

Food Components Impact Polyphenol Bioaccessibility and Bioavailability Polyphenol bioaccessibility (i.e., the amount available for absorption in the intestine) and bioavailability (i.e., the rate and extent of absorption and availability for metabolism) are influenced by their own structure (e.g., glycosides versus aglycones), degree of polymerization (e.g., monomers versus polymers), and types of interactions (e.g., covalent or hydrophobic bonding) with food matrices they are associated with (e.g., sugars, fiber, and proteins in the specific berry), dietary status (e.g., fed versus fasting) and diet composition (e.g., protein, fat, carbohydrate, and fiber content), and the intestinal pH and abundance of digestive enzymes, which are influenced mainly by other dietary ingredients [Lila et al. 2012, reviewed in Bohn (2014)]. Conjugated polyphenols require deconjugation in order to diffuse into the enterocyte [reviewed in Rein et al. (2013)]. The brush border of the small intestine contains membrane-bound β-glucosidases which facilitate the process for hydrolyzing gluconated polyphenols into more readily absorbable aglycones [reviewed in van Duynhoven et al. (2001)]. Once within the enterocyte, the aglycone will undergo phase I (e.g., reduction, oxidation, or hydrolysis) or phase II (e.g., conjugation) metabolism, converting them into methyl esters, glucuronides, and sulfates, or be transported as aglycones via the portal system to the liver for similar metabolism [reviewed in Chiou et al. (2014)]. Conjugating aglycones reduces their potential microbial toxicity while also making them easier to transport as biotransformed polyphenols. Additionally, the type and amount of dietary macronutrients can alter the composition of intestinal microbes, which in turn influences polyphenol biotransformation in the GI tract (Fava et al. 2012).

For example, a high-fat meal increases the bioaccessibility of multiple berry anthocyanins, and protein-rich matrices protect berry anthocyanins from degradation in the upper GI tract, thus making them available to the lower GI tract for

microbial metabolism (Ribnicky et al. 2014). In order to demonstrate the potential beneficial effects of protein protection of polyphenols, defatted soybean flour was used to adsorb, concentrate, and stabilize Concord grape juice-derived polyphenols (e.g., particularly anthocyanins, hydroxycinnamic acids, and proanthocyanidins) and exclude polar sugars. Using this method to enhance polyphenol bioavailability, the authors tested the acute, antidiabetic properties of Concord grape juice in C57BL/6J mice. Notably, fasted mice gavaged with a bolus of defatted soybean flour enriched with grape juice polyphenols had lower blood glucose levels compared to control mice (Roopchand et al. 2012). Similarly, fasted mice receiving a single bolus of the polyphenol-rich grape pomace complexed to soy protein isolate had lower blood glucose compared to controls (Roopchand et al. 2013). It is noteworthy that the grape pomace polyphenols in the soy protein isolate complex had a much greater stability compared to those in the non-complexed extract.

In vitro GI systems have provided unique insights into the bioaccessibility and bioavailability of plant polyphenols. For example, using a model mimicking the human GI tract (TIM-1) from the mouth to the ileum, it was demonstrated that most berry anthocyanins were bioaccessible within the 2–3 h post-ingestion, primarily in the jejunum, and thus were potentially available for absorption (Lila et al. 2012). These authors further demonstrated using radiolabeled polyphenols generated in grape cell cultures fed ^{13}C- or ^{14}C-labeled carbohydrate sources and gavaged to rats that grape polyphenols enriched the blood system within 15 min to 4 h post-administration and reached systemic tissues including the brain. Interestingly, grape anthocyanin glycosides (e.g., cyanidins and peonidins) were better absorbed than less polar, grape proanthocyanidins. Consistent with these data, several polyphenols in California table grapes (e.g., quercetin-3-*O*-glucoside, quercetin-3-*O*-glucuronide, and rutin) appeared in the blood stream within the first hour post-gavage (Chuang et al. 2012).

Bacterial Metabolism or Biotransformation of Polyphenols Dietary polyphenols that escape absorption in the upper GI tract are exposed to microbes and intestinal enzymes of the lower GI tract and undergo further metabolism or biotransformations [e.g., deconjugation of the glycosyl or glucuronosyl component on the phenol backbone, cleavage of polymeric proanthocyanidins, hydrolysis of esterified phenolic acids; reviewed in Selma et al. (2009), Kemperman et al. (2010)]. Microbial transformation of polyphenols to more or less bioaccessible and bioactive metabolites can directly affect their influence on intestinal microbial growth and metabolism. Alternatively, biotransformed polyphenols (e.g., aglycones, phenolic acids, monomeric proanthocyanidins) may be directly absorbed into the mucosa or bloodstream, where they may activate local or systemic receptors influencing metabolism. In general, gut microbe enzymes (e.g., glucosidases, glucuronidases, esterases, hydrogenases, dehydroxylases, decarboxylases, demethylases, and isomerases) convert a diverse group of dietary polyphenols into a relatively small group of aromatic metabolites [reviewed in Selma et al. (2009)].

For example, benzoic, hippuric, and vanillic acids are the main microbial metabolites of green tea polyphenols [reviewed in Fang et al. (2008)]. These

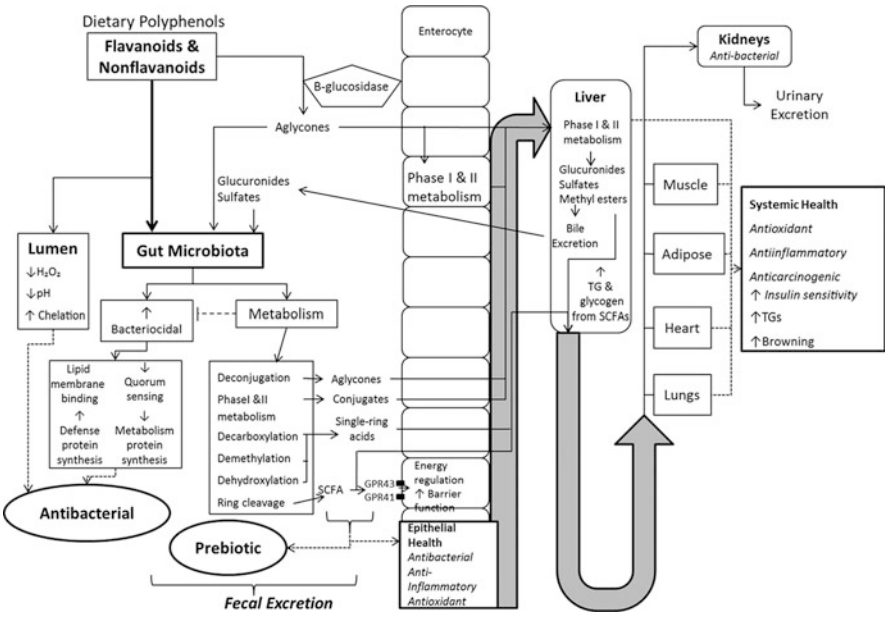

Fig. 1 Polyphenol metabolism and potential intestinal and systemic health benefits. Polyphenols are poorly absorbed and thus come in direct contact with gut microbes in the lower GI tract. Although some polyphenols are deconjugated in the small intestine into aglycones, which may passively diffuse into the enterocyte, the majority travel to the distal small intestine and colon. Within the intestinal lumen, polyphenols can indirectly influence microbial populations by reducing the pH and hydrogen peroxide (H_2O_2) levels. They can also chelate with unabsorbed metal ions, thus negatively influencing the growth of pathogenic bacteria and some Gram-positive bacteria. Polyphenols can be toxic to bacterial cells by disrupting normal cell properties (e.g., binding to cell membranes, proteins, or DNA) or otherwise be metabolized, thereby reducing their potential toxic effects on certain gut microbes. Some microbial metabolites may be used as energy sources (e.g., SCFAs like butyrate), promoting beneficial microbial growth and improving gut barrier function, whereas others interact within the enterocyte or diffuse through enterocytes. Absorbed polyphenol metabolites and aglycones are delivered to the liver via the portal vein before entering the systemic circulation or the bile. Aglycones undergo further metabolism by hepatic phase I and II enzymes, once again becoming conjugated to facilitate their transport systemically or for secretion into the bile for transport back into the intestinal lumen upon release from the gall bladder. As polyphenols and metabolites travel through systemic circulation, they may interact with various tissues or be excreted in the urine [adapted from Kemperman et al. (2010)]

metabolites, in turn, may be absorbed across the intestinal mucosa into the portal blood and sent to the liver for further metabolism (e.g., phase II conjugates such as glucuronidated and sulfated metabolites that can enter the circulation or bile acid pool) by the host, used by intestinal microbes, or excreted in the feces (Fig. 1). For instance, several intestinally derived polyphenol metabolites (i.e., hydrocaffeic, dihydroxyphenylacetic, and hydroferulic acids) suppressed inflammatory prostaglandin production in colon cancer cells and in rodents (Larrosa et al. 2009a). In addition, hydrocaffeic reduced inflammation and DNA damage in a chemically

induced model of ulcerative colitis [i.e., dextran sulfate sodium (DSS) treated; Larrosa et al. 2009a]. Similarly, a microbial metabolite of curcumin (i.e., ferulaldehyde) reduced inflammation and extended lifespan in endotoxin-treated rodents (Radnai et al. 2009). Polyphenols may influence the biotransformation of other phytonutrients [e.g., depolymerization, (de)glycosylation or glucuronidation, (de)methylations, (de)sulfation, or (de)hydroxylation] by selectively altering microbial populations that influence these enzymatic modifications, thereby impacting their solubility and potential for absorption.

4 Prebiotic Properties of Polyphenols

Promicrobial Properties Obesity is associated with intestinal dysbiosis, with an increased ratio of *Firmicutes* to *Bacteroidetes* (Ley et al. 2006). Grape products, extracts, and polyphenols including quercetin, fructo-oligosaccharides, and grape juice, on the other hand, have been shown to positively influence the intestinal microbiota. Fructo-oligosaccharide has also been shown to enhance the growth of health-promoting, butyrate-producing bacteria from *Firmicute* and *Bifidobacterium* families (Scott et al. 2013). Several grape juice varieties have also demonstrated promicrobial effects by increasing the growth of *Lactobacillus acidophilus* and *L. delbrueckii*, two probiotic bacteria, while attenuating growth of *E. coli* in vivo (Agte et al. 2010). Notably, dietary polyphenols have been reported to increase the abundance and diversity of microbial populations [reviewed in Tuohy et al. (2012)], including populations of healthy gut bacteria (e.g., decrease ratio of *Firmicutes*/*Bacteroidetes*; increase *Lactobacilli* and *Bifidobacteria*; increase *Akkermansia muciniphila*, *Roseburia* spp., *Bacteroides* and *Prevotella* spp.) (Selma et al. 2009; Neyrinck et al. 2013; Anhê et al. 2014).

In regard to grape polyphenols, DSS-treated rats consuming the phytoalexin resveratrol had higher levels of *Lactobacilli* and *Bifidobacteria* and improved colon mucosa architecture and inflammatory profile compared to controls (Larrosa et al. 2009b). Inoculation of *L. acidophilus* and *L. plantarum*, two probiotic bacteria, with quercetin plus fructo-oligosaccharides increased their growth in culture compared to normal growth conditions (Yadav et al. 2011). Additionally, grape anthocyanins such as malvidin-3-glucosides increased the growth of *Bifidobacterium* and *Lactobacillus-Enterococcus* bacteria (Hidalgo et al. 2012). Additionally, feeding grape antioxidant dietary fiber, containing the fiber and antioxidant components from grapes, significantly increased *Lactobacillus* spp. within in the cecum of rats compared to controls (Pozuelo et al. 2012). Grape pomace juice given to rats increased fecal abundance of *Lactobacillus* and *Bifidobacterium* and consequently resulted in an increase in the concentration of primary bile acids, cholesterol, and cholesterol metabolites, while decreasing the concentration of secondary bile acids in feces (Sembries et al. 2006). Such alterations in bile acids are associated with a reduced risk of intestinal cancers. Consistent with these data, rats supplemented with red wine polyphenols had lower levels

of *Clostridium* spp. and increased levels of *Lactobacillus* spp. (Dolara et al. 2005). Furthermore, healthy adults consuming red wine had a greater abundance of *Enterococcus, Prevotella, Bacteroides, Bifidobacterium, Bacteroides uniformis, Eggerthella lenta,* and *Blautia coccoides-Eubacterium rectale* groups compared to baseline. Moreover, the wine consumers had improved blood pressure, lower blood cholesterol, and C-reactive protein (CRP) levels, which were positively correlated with *Bifidobacteria* (Queipo-Ortuño et al. 2012). Another potential prebiotic benefit of wine polyphenols is their growth enhancement of specific strains of *L. plantarum* (Barrosa et al. 2014). Adult males given a proanthocyanidin-rich extract had a dramatic shift in fecal microbial populations from *Bacteroides*, *Clostridium*, and *Propionibacterium* phyla to *Bacteroides*, *Lactobacillus*, and *Bifidobacterium* predominance (Cardona et al. 2013).

As such, these phytochemical-mediated alterations in intestinal microbial populations can be considered prebiotic actions, as they can result in an improved health status for the host. Notably, mice consuming a high-fat, high-sugar diet supplemented with two polyphenols found in grapes, *trans*-resveratrol (15 mg/kg BW/day) and/or quercetin (30 mg/kg BW/day), had lower body weights and insulin resistance compared to controls (Etxeberria et al. 2015). Quercetin-mediated improvements in systemic health were associated with a decreased ratio of *Firmicutes*/*Bacteroidetes* and decreased abundance of bacteria induced by the high-fat, high-sucrose diet (e.g., *Erysipelotrichaceae, Bacillus, Eubacterium cylindroides*), thereby attenuating diet-induced dysbiosis. Within the quercetin-mediated increase in the *Bacteroidetes* phylum, the abundance of *Bacteroidaceae* and *Prevotellaceae* families was increased (Etxeberria et al. 2015), which has been previously found to be reduced in high-fat-fed mice (Hildebrandt et al. 2009). Although mice-fed *trans*-resveratrol suppressed intestinal markers of inflammation and enhanced markers of barrier function, it had only a minimal impact on gut microbial profiles.

Antimicrobial Properties Polyphenols have been reported to decrease populations of coliforms and other unhealthy gut bacteria, indicating that they have bacteriostatic or bactericidal activity or prevent adhesion of disease-causing bacteria (Selma et al. 2009). Other antibacterial properties include inhibiting quorum sensing [reviewed in Gonzalez and Keshavan (2006)], disrupting lipid membrane integrity (Kemperman et al. 2010), and DNA polymerase activity [reviewed in Cushnie and Lamb (2005)]. For example, anthocyanin-rich berries have been shown to prevent the growth of several infectious microbial strains (Lee et al. 2003, 2006). Tea polyphenols decreased the growth of *Candida albicans* (Evensen and Braun 2009). Microbial metabolites derived from exposure to phenolic compounds in berries attenuated salmonella growth (Alakomi et al. 2007). Grape seed extract, an oligomeric-rich fraction from grape seed extract, and a grape polyphenol (e.g., gallic acid) demonstrated robust antimicrobial actions against pathogens associated with respiratory diseases (Cueva et al. 2012). Several wine and grape seed polyphenols, specifically flavan-3-ol, exhibited antibacterial activity directed toward specific bacterial strains (e.g., Gram-positive bacteria such as the

Staphylococcus) in human fecal samples cultured with various wine or grape extracts (Cueva et al. 2015). Lastly, resveratrol was shown to be a candidate for decreasing the growth of drug-resistant strains of *Mycobacterium smegmatis* (Lechner et al. 2008).

Influence of Polyphenols on Microbial Fermentation Products By differentially impacting populations of gut microbes, polyphenols can alter the production of the SCFAs acetate, propionate, and butyrate, which are at molar ratios of 60:23:17 under normal feeding conditions (Blaut 2014) and represent approximately 10 % of energy intake in humans (Bergman 1990). These SCFAs attenuated high-fat diet-induced obesity and insulin resistance via increasing AMP kinase (AMPK) activity and oxidative metabolism and inhibiting peroxisome proliferator-activated receptor (PPAR)-γ. Such outcomes demonstrate the ability of SCFAs to decrease body fat by increasing fatty acid and glucose oxidation and decreasing adipogenesis or lipogenesis, respectively (den Besten et al. 2015). In a separate report, SCFAs produced from fructo-oligosaccharides, as well as butyrate and propionate alone, decreased body weight and improved glucose tolerance in mice (De Vadder et al. 2014). This was attributed to SCFA-induced intestinal gluconeogenesis. While butyrate directly induced gluconeogenic gene expression in the small intestine, propionate stimulated intestinal gluconeogenesis through a free fatty acid receptor (FFAR)3-mediated mechanism involving neural circuits between the gut and brain. Interestingly, the beneficial effects of fructo-oligosaccharides and SCFAs were lost in mice deficient in intestinal glucose-6-phosphatase (De Vadder et al. 2014). Other fermentation products include lactate, succinate, isobutyrate, 2-methyl propionate, valerate, isovalerate, hexanoate, and ethanol [reviewed in Blaut (2014), Samuel et al. (2008), Wong et al. (2006)].

Collectively, these fermentation products can regulate energy harvest, depending on the energy density and composition of the diet and subsequent products formed. For example, propionate is a precursor for hepatic gluconeogenesis, propionate and acetate are precursors of cholesterol synthesis, and acetate and butyrate are substrates for hepatic and white adipose tissue (WAT) triglyceride (TG) synthesis. However, butyrate is unique in that it is the preferred energy substrate for colonocyte growth and differentiation, accounting for approximately 70 % of the oxidation of SCFAs (Roediger 1980). Notably, butyrate has been shown to reduce the growth of and stimulate apoptosis in colorectal cancer cells via upregulation of wnt/β-catenin signaling due to butyrate's inhibition of specific histone deacetylases (Lazarova et al. 2014). Butyrate also increases the localization of tight junction proteins on the apical surface of epithelial cells, thereby impeding the translocation of endotoxins (e.g., LPS, bacterial DNA, or peptidoglycans) into the systemic circulation [reviewed in Cox and Blaser (2013)]. Systemically, butyrate has been shown to increase leptin secretion from adipocytes (Samuel et al. 2008). Therefore, phytochemicals that increase butyrate production and proportionately decrease acetate and propionate production decrease energy harvest and vice versa.

Polyphenol-mediated increases in butyrate production could also reduce endotoxemia and subsequent metabolic dysfunction via enhancing goblet cell-

mediated barrier function (Hatayama et al. 2007). Butyrate can also inhibit nuclear factor-κB (NFκB) signaling pathways, thereby reducing inflammatory cytokine synthesis in conjunction with ulcerative colitis or Crohn's disease (Segain et al. 2000; Lührs et al. 2002).

Fermentation Products Influence Intestinal pH Polyphenol-mediated changes in fermentation products by gut microbes influence intestinal pH, which in turn impacts the growth of specific bacteria. The acidic nature of SCFAs reduces luminal pH throughout the lower GI tract, potentially preventing the growth of pathogenic bacteria (i.e., *Enterobacteriaceae*) (Roe et al. 2002; Hirshfield et al. 2003). This effect on pH may also be a determining factor on which a class of fermenters predominates. At more neutral pH (6.5), acetate producers predominate, whereas in a more acidic environment (pH 5.5), butyrate producers predominate (Walker et al. 2005). Indigestible oligosaccharides facilitate a lower pH, allowing butyrate producers to compete for substrates more efficiently than acetate or propionate producers that have slower growth rates (El Oufir et al. 1996). The ring cleavage of flavonoids into SCFAs similar to fermentation of fiber has the same beneficial effects on energy intake, metabolism regulation, and improvements to epithelial health and integrity (Czank et al. 2013).

Fermentation Products May Influence Bile Acid Metabolites Polyphenols may also influence bile acid metabolism, thereby altering the types and abundance of primary and secondary bile acids that have local and systemic effects [reviewed in Maukonen and Saarela (2015b)]. This is particularly relevant during high-fat feeding, because fat increases the secretion of bile acids into the GI tract and fat type and amount influence microbial diversity. For example, consuming a milk/butter fat diet rich in saturated fat (e.g., 37 % kcals from fat, primarily milk/butter fat) for 24 weeks has been shown to increase biliary secretion of taurocholic acid that is metabolized by sulfidogenic bacteria, causing the production of proinflammatory metabolites that impair gut health (Devkota et al. 2012). Consistent with these data, feeding a diet rich in saturated fat (i.e., 60 % kcals from lard) increased the abundance of sulfidogenic bacteria (Zhang et al. 2010; Shen et al. 2014) and compromised gut barrier function (Shen et al. 2014). Consumption of low-carbohydrate, high-fat diets by adult subjects decreased butyrate concentrations and total SCFAs and the abundance of *Bifidobacteria* (Brinkworth et al. 2009).

Fermentation Products Activate Endocrine Cell Signals Polyphenols, their metabolites, or SCFAs may activate intestinal enteroendocrine cells (e.g., L cells) via activation of G-protein receptors (GPRs) including GPR41, GPR43, or GPR119 (aka FFARs). The GPRs are coupled to the secretion of peptides that influence host metabolism. For example, butyrate has been reported to increase glucagon-like-peptide (GLP)-1 secretion (Samuel et al. 2008), and GRP-mediated secretion of GLP-1 and 2 inhibits gastric emptying, enhances insulin secretion and sensitivity, and increases satiety [reviewed in Holst (2007)]. GLP-1 secretion is also influenced by the energy content of the diet and the presence of gut microbes (Wichmann et al. 2013). Similarly, GPR-mediated polypeptide YY (PYY) secretion can protect

against obesity via increasing satiety or energy expenditure, possibly via increasing thermogenesis in BAT or in WAT with beige adipocytes via direct activation of WAT or indirectly via activation of the sympathetic nervous system (Mestdagh et al. 2012). However, GPR41-mediated activation of PYY can paradoxically contribute to obesity via increasing intestinal transit time and thus energy harvest [reviewed in Cox and Blaser (2013)]. Additionally, germ-free mice that lack gut microbiota and thus SCFAs have increased GLP-1 levels, which was associated with decreased intestinal transit time. However, upon monoassociation with the propionate and acetate producer, *Bacteroides thetaiotaomicron*, intestinal transit time, and GLP-1 levels were restored (Wichmann et al. 2013). In spite of these findings, the influence of whole grape consumption on changes in intestinal microbial populations, energy harvest, and barrier function and associations with systemic health has not yet been reported.

5 Antioxidant Properties of Polyphenols and Their Roles in Health Promotion

Polyphenols Quench Prooxidants Polyphenols have been shown to scavenge reactive oxygen (ROS), nitrogen species (RNS), and nitric oxide (NO) radicals that trigger oxidative stress, cytotoxicity, apoptosis, or inflammation due to the their abundance of hydroxyl groups that readily donate a hydrogen atom to or stabilize an unshared electron in electrophiles (Fig. 2). Attenuation of free radicals prevents the activation of proenzymes [e.g., NAPDH oxidase, nitric oxide synthase (NOS)] that generate ROS and NO radicals, respectively, that trigger inflammatory mitogen-activated protein kinases (MAPKs) (e.g., ASK1, JNK, p38, ERK) and transcription factors (e.g., NFκB, AP-1) that induce inflammatory gene expression. Polyphenols also protect against oxidative damage via upregulating the expression of antioxidant genes [e.g., heme oxygenase (HO)-1, glutathione peroxidase (GPX), superoxide dismutase (SOD)-1/2, and γ-glutamate-cysteine ligase catalytic subunit (GCLC)] via activation of the nuclear factor-erythroid 2 (NF-E2)-related factor 2 (Nrf2). By directly neutralizing free radicals and upregulating antioxidant enzymes, polyphenols may enhance glutathione levels and the need for GCLC, the rate-determining enzyme for glutathione synthesis.

Whole grapes, grape products, and grape components have been shown to decrease markers of oxidative stress systemically [reviewed in Chuang et al. (2012)]. However, less is known about the efficacy of grapes in attenuating intestinal prooxidants and disease risk. Red wine polyphenols fed to rats for 16 weeks blocked colon carcinogenesis, which was associated with a decrease in intestinal markers of oxidative stress and an abundance of *Bacteroides, Clostridium,* and *Propionibacterium* spp. (Dolara et al. 2005). Resveratrol supplementation of rats treated with the chemical colon carcinogen 1,2-dimethylhydrazine (DMH) decreased colonic tumor burden, which was associated with reductions in microbial

biotransforming enzymes linked with the development of cancer (e.g., β-glucuronidase, β-glucosidase, β-galactosidase, mucinase, nitroreductase, or sulfatase; Sengottuvelan and Nalinin 2006). Similarly, resveratrol supplementation of rats treated with DMH had decreased colonic DNA damage that correlated with increased activities of antioxidant enzymes (i.e., SOD, catalase, GPX, glutathione reductase) and levels of glutathione *S*-transferase and antioxidants (i.e., reduced glutathione, vitamin C, vitamin E, and β-carotene) and decreased markers of lipid peroxidation compared to non-resveratrol-supplemented mice (Sengottuvelan and Nalini 2009). However, the impact of whole grape consumption of intestinal markers of oxidative stress is unknown.

6 Anti-inflammatory Properties of Polyphenols

Activating PPARγ, an Anti-inflammatory Transcription Factor PPARγ is a transcription factor best known for its role in promoting adipogenesis and glucose uptake. It also has anti-inflammatory properties (Fig. 2). For example, increasing PPARγ activation has been demonstrated to antagonize NFκB and activator protein (AP)-1-mediated inflammatory gene expression, thereby reducing inflammation [reviewed in Ricote and Glass (2007)]. In addition, anti-inflammatory, alternatively activated (i.e., M2) macrophages require PPARγ for their activation (Bouhiel et al. 2007; Odegaard et al. 2007). Consistent with these data, grape feeding increased the expression of PPARγ and δ mRNA, subsequently increasing their DNA-binding activity, and decreased the activity of NFκB in hearts and reduced systemic markers of inflammation in rats (Seymour et al. 2010). Additionally, grape seed procyanidin supplementation reduced WAT mRNA levels of TNFα, IL-6, and CRP and reduced plasma levels of CRP in Zucker rats fed a high-fat diet (Terra et al. 2009). Quercetin and *trans*-resveratrol increased the abundance and activity of PPARγ and the mRNA levels of several PPARγ target genes and quercetin decreased inflammation and insulin resistance in primary cultures of human adipocytes treated with TNFα (Chuang et al. 2010). Similarly, quercetin and kaempferol increased PPARγ activity and decreased LPS-mediated nitric oxide levels and insulin resistance in murine 3T3-L1 (pre)adipocytes (Fang et al. 2008). However, the impact of grape consumption on intestinal PPARγ activity is currently unknown.

Activating Histone Deacetylases that Inhibit NFκB or Activate PGC1 Sirtuins (SIRTs) consist of a family of class III histone deacetylases (HDACs) that removes acetyl groups from lysine residues in histones and nonhistone proteins including transcription factors. This causes an increase or decrease in the activity of the targeted protein, depending on the role that the acetyl group plays in regulating the activity of the respective protein. For example, activation of SIRT1 causes NFκB deacetylation, thereby decreasing NFκB activity and inflammatory signaling. In contrast, deacetylation of PGC1α increases its activity, thereby enhancing mitochondrial biogenesis, activity, substrate oxidation, and energy expenditure.

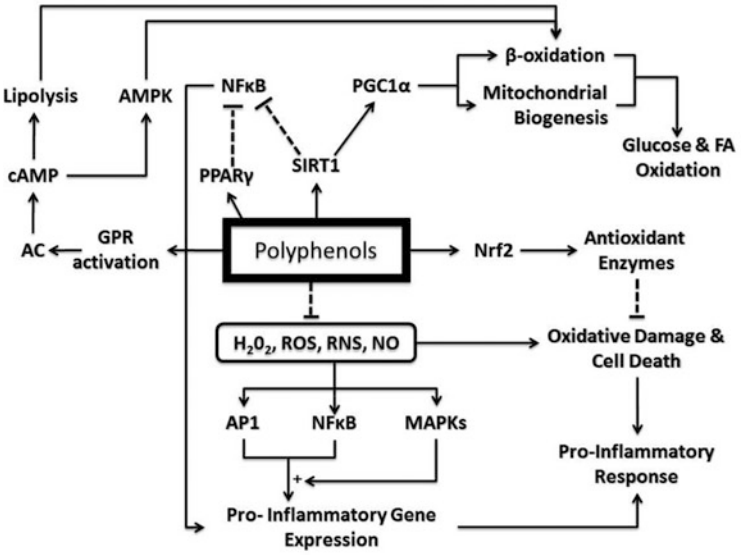

Fig. 2 Anti-inflammatory and antioxidant effects of polyphenols that impact glucose and fatty acid metabolism. Polyphenols have been shown to inhibit the production of prooxidant compounds including hydrogen peroxide (H_2O_2), reactive oxygen species (ROS), reactive nitrogen species (RNS), and nitric oxide (NO), thereby preventing activation of the mitogen-activated protein kinases (MAPKs), nuclear factor κB (NFκB), and activator protein (AP)1 pathways and subsequent proinflammatory response. Additionally, polyphenols have been shown to activate nuclear factor-erythroid 2-related factor 2 (Nrf2), which increases the expression of antioxidant enzymes that inhibit oxidative damage and cell death associated with prooxidants. Polyphenols also may activate peroxisome proliferator-activated receptor gamma (PPARγ) and sirtuin 1 (Sirt1), which also inhibit NFκB and proinflammatory responses via deacetylation. Sirt1 also can activate peroxisome proliferator-activated receptor γ coactivator 1-alpha (PGC1α) which stimulates β-oxidation and mitochondrial biogenesis, leading to glucose and fatty acid (FA) oxidation. Additionally, polyphenols may activate G-protein receptors (GPR) stimulating adenylate cyclase (AC), cyclic adenosine monophosphate (cAMP), and 5′-adenosine monophosphate-activated protein kinase (AMPK) which stimulate lipolysis, β-oxidation, mitochondrial biogenesis, and subsequent glucose and fatty acid oxidation

Notably, several polyphenols found in grapes (i.e., *trans*-resveratrol, quercetin) have been shown to activate SIRT1 (Howitz et al. 2003). Consistent with these data, in vitro or in vivo studies have demonstrated that resveratrol reduced inflammatory signaling and improved insulin sensitivity in a SIRT1-dependent manner by deacetylating NFκB (Fischer-Posovszky et al. 2010; Olholm et al. 2010; Yang et al. 2010; Zhu et al. 2008) and PGC1α, (Lagouge et al. 2006; Sun et al. 2007), leading to an increase in mitochondrial biogenesis, the expression of genes associated with oxidative phosphorylation, and aerobic capacity (Lagouge et al. 2006).

Suppressing Immune Cell Infiltration or Inflammatory Signaling in the Intestines Grape polyphenols such as rutin, glycosides of quercetin, and resveratrol have been reported to reduce intestinal inflammation in rodents (Galvez

et al. 1997; Kwon et al. 2005; Martin et al. 2004, 2006). Similarly, resveratrol attenuated nitric oxide synthase activity and mucosal damage in an experimental necrotizing enterocolitis rat model (Ergun et al. 2007). Intestinal colitis was attenuated by concentrated grape juice in Wistar rats, with the flavonoids being the proposed facilitators of these beneficial changes in gut health (Paiotti et al. 2013). In addition, grape seed extract given to IL-10 deficient mice reduced inflammatory bowel disease inflammatory markers, increased goblet cell number, and decreased myeloperoxidase activity, a marker of neutrophil infiltration (Suwannaphet et al. 2010). Notwithstanding, the impact of whole grape consumption of intestinal markers of inflammation is unknown.

7 Conclusions and Implications

Grapes and their by-products are rich in nutrients and phytochemicals that have anti-inflammatory, antioxidant, and antimicrobial properties that potentially influence intestinal and systemic health. They can have positive and negative effects on nutrient absorption. For example, polyphenols found in grapes have antioxidant properties that protect micro- and macronutrients from oxidative damage, thereby preserving their biological value. However, they can interfere with the digestion and absorption of macro- and micronutrients by interfering with hydrolytic enzymes necessary for digestion and by binding to micronutrients, thereby preventing their absorption. Notably, impaired absorption of nutrients in the upper GI tract allows microbes in the lower GI tract to metabolize them, thereby impacting their growth and the metabolic by-products they produce. Furthermore, the structure of polyphenols, the food matrices they are associated with, and the composition of the diet they are ingested with influence their bioaccessibility and bioavailability.

Dietary polyphenols that escape absorption in the upper GI tract come in contact with microbes in the lower GI tract. These interactions may favorably influence microbial growth (e.g., increased abundance of *Lactobacilli* and *Bifidobacteria*, two types of bacteria positively associated with intestinal health) and their metabolic products (e.g., the SCFA butyrate which enhances colonocyte growth and integrity or GLP-1/2 which enhances systemic insulin secretion and sensitivity and satiety). Furthermore, microbial biotransformation of polyphenols can enhance their absorption into the portal vein, delivering them to the liver, systemic tissues, or back to the gut via bile acid secretion from the gall bladder.

As antimicrobial agents, several polyphenols found in grapes or wine decrease the growth or adherence of disease-causing bacteria, thereby attenuating their virulence. As anticancer or anti-inflammatory bowel disease agents, they may alter bile acid metabolites (e.g., reduce cholic acid metabolism by sulfidogenic bacterial) or neutralize prooxidants (e.g., ROS, NO, RNS, H_2O_2) that damage DNA and proteins. They may also reduce populations of gut microbes that produce these electrophiles. Lastly, polyphenols found in grapes may directly promote local and systemic health of the host by activating HDACs like SIRT1 that activate the anti-

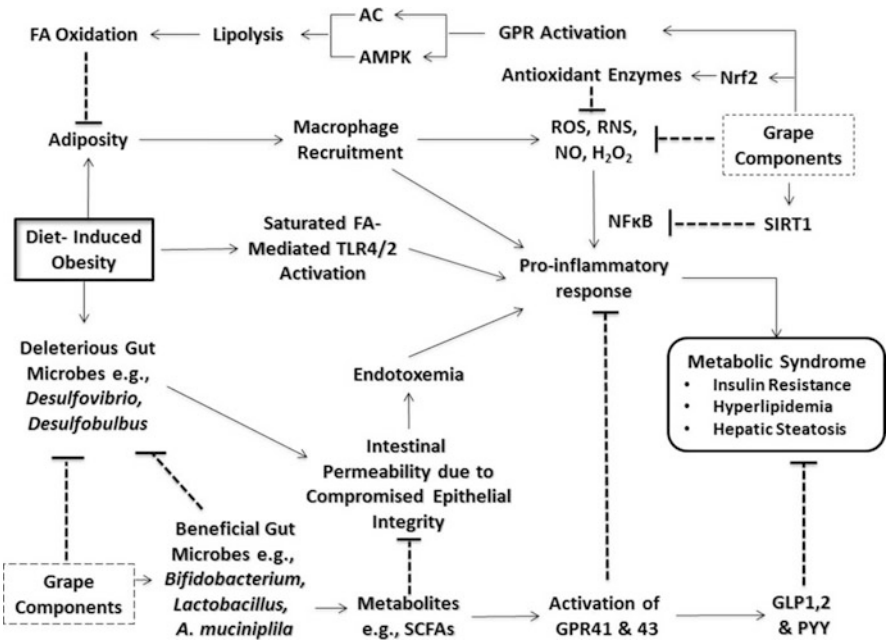

Fig. 3 Proposed working model on how table grapes attenuate intestinal microbes and metabolism, potentially contributing to reductions in diet-induced obesity, inflammatory signaling, and insulin resistance. As prebiotics, grape polyphenols may enhance the abundance of specific types of healthy bacteria (e.g., *Bifidobacterium, Lactobacillus, Akkermansia muciniphila*) that contribute to short-chain fatty acid (SCFA) production and activation of G-protein receptor (GPR)s 41 and 43 resulting in suppression of complications associated with consuming a high-fat diet (i.e., inflammation and metabolic syndrome). Grape polyphenols also decrease the abundance of noxious bacteria (e.g., sulfidogenic bacteria) that impair gut barrier functions (i.e., cause leaky gut). These improvements in barrier function prevent systemic endotoxemia (i.e., increase LPS, peptidoglycan, or bacterial DNA in the bloodstream)-mediated inflammatory gene or protein expression. Alternatively, grape polyphenols reaching the blood stream may directly attenuate saturated fatty acid (SFA)-mediated nutritional toxemia (e.g., SFA-mediated TLR4/2 activation) that triggers white adipose tissue inflammation leading to metabolic syndrome. Grape polyphenols may also activate G-protein receptors (GPRs), thereby activating adenylate cyclase (AC) and 5′-adenosine monophosphate kinase (AMPK), which increase lipolysis and fatty acid (FA) oxidation, thereby attenuating adiposity, subsequent macrophage recruitment and reactive oxidant species (ROS), reactive nitrogen species (RNS), nitric oxide (NO), and hydrogen peroxide (H_2O_2) production associated with high-fat-induced obesity. Alternatively, they may activate nuclear factor-erythroid 2 (NF-E2)-related factor 2 (Nrf2), a transcription factor that induces the expression of antioxidant genes [e.g., heme oxygenase (HO)-1, glutathione peroxidase (GPX), superoxide dismutase (SOD)-1/2, and γ-glutamate-cysteine ligase catalytic subunit (GCLC)] that neutralize free radicals

inflammatory transcription factor PPARγ and deactivate the proinflammatory transcription factor NFκB.

A working model of these potential health-promoting properties of grape phytochemicals is shown in Fig. 3, including the proposed linkage between intestinal

and holistic systems. However, the extent to which whole grapes alter gut microbiota, inflammatory status, and barrier function is hypothetical, as are their contributions to systemic health. Research is needed to determine if feeding whole grapes at levels that are achievable in humans can indeed improve intestinal health and if these proposed beneficial effects in the GI tract are associated with systemic benefits.

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