REVIEW

# Cardiovascular and Antiobesity Effects of Resveratrol Mediated through the Gut Microbiota

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**ABSTRACT**

Encouraging scientific research into the health effects of dietary bioactive resveratrol has been confounded by its rapid first-pass metabolism, which leads to low in vivo bioavailability. Preliminary studies have shown that resveratrol can modulate gut microbiota composition, undergo biotransformation to active metabolites via the intestinal microbiota, or affect gut barrier function. In rodents, resveratrol can modify the relative Bacteroidetes:Firmicutes ratio and reverse the gut microbial dysbiosis caused by a high-fat diet. By upregulating the expression of genes involved in maintaining tight junctions between intestinal cells, resveratrol contributes to gut barrier integrity. The composition of the gut microbiome and rapid metabolism of resveratrol determines the production of resveratrol metabolites, which are found at greater concentrations in humans after ingestion than their parent molecule and can have similar biological effects. Resveratrol may affect cardiovascular risk factors such as elevated blood cholesterol or trimethylamine *N*-oxide concentrations. Modulating the composition of the gut microbiota by resveratrol may affect central energy metabolism and modify concentrations of satiety hormones to produce antiobesity effects. Encouraging research from animal models could be tested in humans. *Adv Nutr* 2017;8:839–49.

Keywords: resveratrol, microbiome, obesity, cardiovascular disease, inflammation, gut barrier integrity

## Introduction

Resveratrol is a plant-derived stilbenoid with antifungal and antibacterial properties. It is found in the human diet from various foods such as grapes and the wine produced therefrom, berries such as cranberries and red currants, and peanut skins (1). Interest in the health-promoting properties of resveratrol has been greatly influenced by experiments that have shown an increase in the lifespan of simple organisms by *1*) stimulating the activity of enzymes such as AMP-activated protein kinase and the sirtuins that are also activated by calorie restriction (2) and *2*) putatively affecting metabolic pathways that modulate molecular damage (3). Interestingly, resveratrol has also been shown to protect against metabolic disturbances induced by a high-fat diet and shows potential in reversing the negative effects of the metabolic syndrome in rodent models (4, 5). A series of landmark studies has also shown strong cancer chemopreventive activity through the inhibition of cyclooxygenase and anti-inflammatory actions (6–8). The latter has been postulated as the mechanism whereby moderate wine consumption is associated with cardioprotection and other beneficial effects on health, commonly known as the French paradox, a term that refers to the relatively low incidence of coronary artery disease in France despite a high consumption of saturated fats (9, 10).

Resveratrol intakes from the diet are low compared with other polyphenols (11). A study that pooled resveratrol intakes from France, Germany, Greece, and Italy estimated median intakes of resveratrol and its main glucoside to be 100 μg/d (12), which is similar to median intakes estimated in an older population in the Netherlands [123 μg/d (13)] and somewhat lower than was found in another older population located in a wine-growing municipality in Chianti, Italy [500 μg/d (14)]. In addition to these low dietary intakes, resveratrol is poorly bioavailable, either when imbibed as red wine (15) or consumed as food or a dietary supplement (16). In fact, when administered orally, only ~1–8% of free resveratrol is found in serum samples, whereas 25% is excreted without absorption, and the rest (generally

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Abbreviations used: EGCG, epigallocatechin gallate; GLP-1, glucagon-like peptide 1; HFS, high-fat and high-sucrose; mTOR, mechanistic target of rapamycin; TMAO, trimethylamine *N*-oxide.

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>70%) is extensively metabolized by the liver, intestinal tract, and gut microbiota (16). A schematic description of the metabolism and disposition of resveratrol is shown in **Figure 1**. Hence, plasma concentrations of free resveratrol are considerably lower than its metabolites, which calls into question whether results obtained from in vitro experiments with the use of resveratrol can be used to elucidate the mechanisms behind improvements in human health.

With the increased interest in the role of the gut microbiome in the maintenance of human health and the pathogenesis of many diseases, several mechanisms have been proposed by which resveratrol can exert its health effects through modulating the composition of the gut microbiota (17, 18). In addition, direct effects of resveratrol and its metabolites on gut integrity and barrier function have been suggested (17). Broad-spectrum antibacterial activity of resveratrol has been found in several clinically important bacterial species, including opportunistic pathogens of the digestive tract: *Escherichia coli*, *Enterococcus faecalis*, and *Salmonella enterica* subsp. *enterica* (19). The bactericidal effect of resveratrol is, however, differential, with much lower activity seen against commensal bacterial species such as *Lactobacillus* spp. (20). Resveratrol may thus be able to affect the composition of bacterial species in the gut to one that is conducive to human health. In addition, whereas high intersubject variability of resveratrol absorption, metabolism, and excretion determines the pharmacokinetic characteristics of resveratrol (21), the gut microbiota that is capable of metabolizing resveratrol further modulates the fate and physiologic effects of resveratrol. Preliminary studies have shown that gut microorganisms affect the pattern of resveratrol metabolites produced; for example, the Coriobacteriaceae family of Actinobacteria is capable of metabolizing resveratrol to dihydroresveratrol, as may *Bacteroides* spp. (21). The complex metabolic activity of microbes in the large intestine may thus be responsible for the variation in resveratrol metabolite concentrations between individuals and ultimately for its effects on clinically important endpoints, because potent antioxidant and proliferative effects similar to those found with resveratrol have also been seen with its major metabolites (22).

The aim of this review is to briefly summarize the current evidence for the cardiovascular and antiobesity effects of resveratrol that are mediated through the gut microbiome. As a basis for our review, we searched the PubMed database with the use of the keywords "resveratrol gut microbiota" to identify primary research articles that have investigated the effect of resveratrol on the gut microbiome, and we support these articles with relevant background citations. We focus on preclinical and clinical evidence and discuss the mechanisms by which an interaction between resveratrol and the gut microbiome may affect clinically relevant outcomes.

## Current Status of Knowledge

### Metabolism and disposition of resveratrol in humans

Poor water solubility is likely responsible for the low oral bioavailability of resveratrol in vivo (23). Walle et al. (24) showed that >70% of an oral dose of 25 mg was absorbed, but only 1–8% of total resveratrol in plasma was found as free resveratrol because of the rapid metabolism of resveratrol, mainly to glucoronides and sulfate conjugates (24–26). There is a trend to a higher proportion of free resveratrol in plasma as doses increase (25, 26). The recovery of ingested resveratrol has been shown to be highly variable: 55–85% of the 25-mg oral dose in Walle et al. (24) was recovered in the urine and 0–40% in the feces. Interestingly, ~10% of an intravenous dose was also recovered in the feces, indicating that resveratrol metabolites in the circulation are excreted back into the intestines (24), presumably via biliary secretion (23). In vitro fecal fermentation experiments have confirmed that 18.3 mg resveratrol/L, a much higher concentration than obtainable by the diet, can be almost completely degraded to metabolites by the gut microbiome of healthy volunteers within 24 h, with the main metabolites, including lunularin, dihydroresveratrol, and 3,4-dihydroxy-*trans*-stilbene, produced by the gut (21).

### Proposed mechanisms of action of resveratrol on the gut microbiome

***Modulation of the composition of the gut microbiota.*** Resveratrol has the potential to affect the growth of species within the gut microbiota and alter its composition, as shown by changes caused by resveratrol to bacterial monocultures or to the relative abundance of particular microorganisms within complex communities (**Table 1**). In vitro bacterial growth has been shown to be slowed by the addition of resveratrol at concentrations of 50 mg/L for most of a panel of 43 human- and animal-origin bacteria, whereas growth was stimulated for one strain of *Lactobacillus acidophilus* (27). In the same series of experiments, the motility of the human pathogen *Proteus mirabilis* was inhibited, which potentially curtailed its swarming behavior, and 25% of the strains were able to transform resveratrol to several metabolites, including resveratroloside, piceid, and dihydroresveratrol (27). The doses used in this study were several orders of magnitude higher than normal dietary intakes; however, the exposure of the gut microbiome to the concentration used is possible with dietary supplementation. In an in vitro fermentation model, a stilbene extract from grapes containing resveratrol affected microbial metabolism and composition. The stilbene extract containing 0.76 and 1.0 g resveratrol/L, a pharmacologic dose, decreased the production of $NH_4^+$ and SCFAs; Enterobacteriaceae numbers increased, whereas *Bacteroides* decreased, and there was no apparent effect on lactobacilli or clostridia (28). Taken together, the in vitro studies indicate that resveratrol has a broad antibacterial activity at concentrations that can be reached with dietary supplements. Moreover, it appears that stilbenes inhibit bacteria involved in saccharolytic and proteolytic activities, whereas gram-negative species are less sensitive to the antimicrobial effects of stilbenes.

In vivo work in experimental mouse and rat models has also demonstrated shifts in microbial populations in

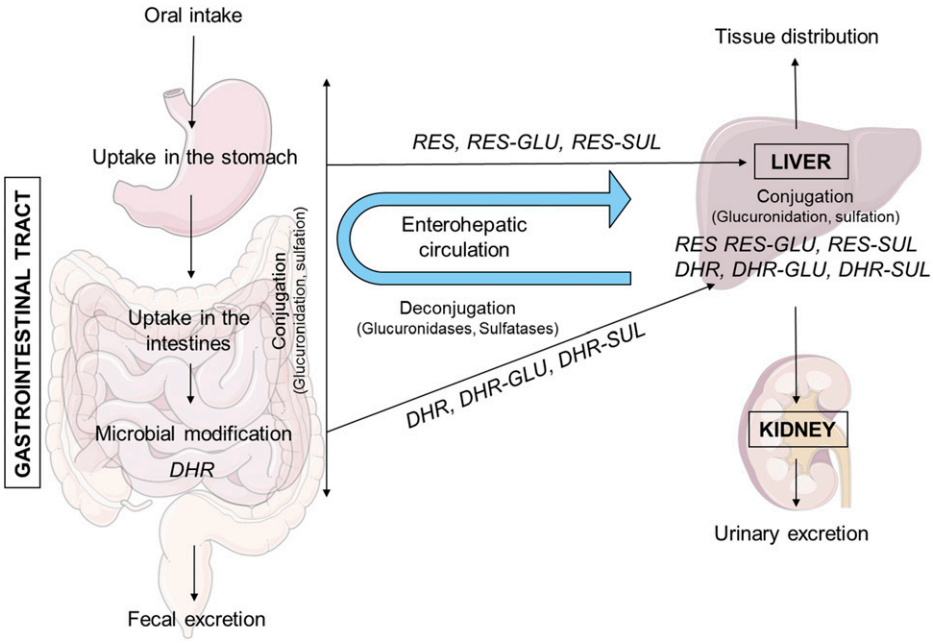


**FIGURE 1** The metabolism and disposition of RES. RES is mainly absorbed in the small intestine after oral intake. It is then quickly and extensively metabolized to RES-GLU and RES-SUL forms in the intestine and the liver. The RES-GLU and RES-SUL forms are excreted by the kidney in the urine. In the human body, sulfatases and glucuronidases can convert the conjugated forms of RES back to the free RES form. Enterohepatic recycling also occurs by biliary excretion and intestinal reabsorption. Moreover, in the intestine, unabsorbed RES is converted to microbial metabolites—for example, DHR—which can also be further metabolized to DHR-GLU and DHR-SUL derivatives. Finally, the unabsorbed RES and its metabolites are excreted in the feces. DHR, dihydroresveratrol; GLU, glucuronide; RES, resveratrol; SUL, sulfate.

response to resveratrol supplementation (Table 1). A study conducted in outbred mice showed that 4 g resveratrol/kg caused gut microbiota remodeling with an increase in the relative abundance of *Bacteroides*, *Lactobacillus*, *Bifidobacterium*, and *Akkermansia*, and decreases in *Prevotella*, Ruminococcaceae, *Anaerotruncus*, *Alistipes*, *Helicobacter*, and Peptococcaceae (29). Moreover, at the phylum level, resveratrol substantially increased Bacteroidetes:Firmicutes ratios in both C57BL/6J and apoE$^{-/-}$ mice. Similarly, in mice with surgically induced heart failure, 4 g resveratrol/kg increased the relative abundance of *Parabacteroides*, *Bilophila*, and *Akkermansia*, and decreased the relative abundance of Lachnospiraceae; moreover, the Bacteroidetes:Firmicutes ratio increased (30). In several studies in mice, the combined effect of an obesogenic diet and resveratrol has been investigated. The combination of a high-fat diet and resveratrol on the Bacteroidetes:Firmicutes ratio [decreases that are associated with obesity development (38, 39) and occur in response to a high-fat diet] was intermediate between the high-fat diet and the control diet in one study: 200 mg resveratrol $\cdot$ kg$^{-1}$ $\cdot$ d$^{-1}$ could partly mitigate the effects of a high-fat diet on this ratio (31). Substantial changes in the composition of the gut microbiota upon 60 mg resveratrol $\cdot$ kg$^{-1}$ $\cdot$ d$^{-1}$ supplementation were also observed in mice fed a high-fat diet compared with a control diet, and resveratrol normalized changes in the microbiota induced by the high-fat diet, although in this case resveratrol inhibited the growth of *Bacteroides vulgatus* as well as *Parabacteroides johnsonii* and *Alistipes putredinis* to the extent that these species were no longer detectable by denaturing gradient gel electrophoresis after supplementation (32). In one study in mice with the use of a 2 $\times$ 2 factorial design [standard diet, standard diet and resveratrol, high-fat and high-sucrose (HFS) diet, and HFS diet and resveratrol], 4 g resveratrol/kg affected the gut microbiome only in mice fed the obesogenic diet; resveratrol had no effect in mice fed the standard diet (34). In particular, resveratrol treatment increased the Bacteroidetes:Firmicutes ratio, decreased the relative abundance of Turicibacteraceae, *Moryella*, Lachnospiraceae, and *Akkermansia*, and increased *Bacteroides* and *Parabacteroides* in the HFS diet group only (34). In yet another mouse study, similar results were found: 200 mg resveratrol $\cdot$ kg$^{-1}$ $\cdot$ d$^{-1}$ had marked effects on the composition of the gut microbiota and ameliorated changes caused by a high-fat diet (33). The increase in *Lactococcus*, *Clostridium*, *Oscillibacter*, *Hydrogenoanaerobacterium*, and *Flavonifractor* induced by a high-fat diet was partially attenuated by resveratrol treatment in this study.

These results were also confirmed in experiments in rats, in which 1 mg resveratrol $\cdot$ kg$^{-1}$ $\cdot$ d$^{-1}$ increased *Lactobacillus* and *Bifidobacterium* while diminishing the increase of Enterobacteriaceae upon dextran sulfate sodium–induced colitis (35). On the other hand, a study in rats fed an HFS diet showed no phylum-level changes caused by 15 mg resveratrol $\cdot$ kg$^{-1}$ $\cdot$ d$^{-1}$, but Gracilibacteraceae (Firmicutes) concentrations were lower than in HFS-only rats, and *Parabacteroides* and various *Clostridium* spp. as well as *Gracilibacter thermotolerans* and *Parabacteroides distasonis* were also suppressed by resveratrol compared with the control diet (36).

Some preliminary research on changes in urinary metabolites derived from the gut microbiota after resveratrol supplementation has been conducted in humans (40). Specifically, concentrations of tryptamine and tyramine from amino acid metabolism were lower after 1000 mg resveratrol/d supplementation in 24 middle-aged men with metabolic syndrome. Lower concentrations of tryptamine may reflect

**TABLE 1** Effect of resveratrol on gut microbial populations in in vitro and in rodent models[1]

| Model/system | Treatment | Effect relative to control | | | | | | | | Reference |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Lactic acid bacteria | *Bifidobacteria* | *Enterococcus faecalis* | *Bacteroides* spp. | *Akkermansia* spp. | *Prevotella* spp. | Ruminococcaceae | Firmicutes | |
| In vitro monoculture panel | Control: liquid culture medium | | | | | | | | | 27 |
| | Intervention: 50 mg resveratrol/L | ↑↓[2] | — | ↓ | ↓ | — | — | ↓ | ↓ | |
| In vitro mixed-culture fermentation model | Control: liquid culture medium | | | | | | | | | 28 |
| | Intervention 1: 0.76 g resveratrol/L (stilbenes: 1.5 g/L) | ↔ | — | — | ↓ | — | — | — | ↔ | |
| | Intervention 2: 1.0 g resveratrol/L (stilbenes: 2 g/L) | ↔ | — | — | ↓ | — | — | — | ↔ | |
| Mouse | Control: standard diet | | | | | | | | | 29 |
| | Intervention 1: 4 g resveratrol/kg in C57BL/6J mice | ↑ | ↑ | — | ↑ | ↑ | ↓ | ↓ | ↓ | |
| | Intervention 2: 4 g resveratrol/kg in apoE$^{-/-}$ mice | ↑ | ↑ | — | ↑ | ↑ | ↓ | ↓ | ↓ | |
| Mouse | Control: standard diet | | | | | | | | | 30 |
| | Intervention: 450 mg resveratrol · kg$^{-1}$ · d$^{-1}$ | — | — | — | ↑ | ↑ | — | — | ↓ | |
| Mouse | Control: standard diet | | | | | | | | | 31 |
| | Intervention 1: high-fat diet | ↓ | ↓↓ | ↑ | ↓ | | | | | |
| | Intervention 2: resveratrol and high-fat diet (200 mg · kg$^{-1}$ · d$^{-1}$) | ↔ | — | ↔ | ↔ | — | — | — | — | |
| Mouse | Control: high-fat diet | | | | | | | | | 32 |
| | Intervention: resveratrol and high-fat diet (60 mg · kg$^{-1}$ · d$^{-1}$) | — | — | — | ↓ | — | — | — | — | |
| Mouse | Control 1: standard diet | | | | | | | | | 33 |
| | Intervention 1: 200 mg resveratrol · kg$^{-1}$ · d$^{-1}$ | ↔ | — | — | — | — | — | ↔ | ↔ | |
| | Control 2: high-fat diet | | | | | | | | | |
| | Intervention 2: resveratrol and high-fat diet (200 mg · kg$^{-1}$ · d$^{-1}$) | ↓ | — | — | — | — | — | ↔ | ↓ | |
| Mouse | Control 1: standard diet | | | | | | | | | 34 |
| | Intervention 1: 4 g resveratrol/kg | — | — | — | ↔ | ↔ | — | — | ↔ | |
| | Control 2: HFS diet | — | — | — | ↔ | ↔ | — | — | ↔ | |
| | Intervention 3: HFS and resveratrol (diet containing 4 g/kg) | — | — | — | ↑ | ↓ | — | — | ↓ | |
| Rat | Control: standard diet | | | | | | | | | 35 |
| | Intervention 1: DSS-induced colitis model | — | — | ↑ | — | — | — | — | — | |
| | Intervention 2: DSS-induced colitis model and 1 mg resveratrol · kg$^{-1}$ · d$^{-1}$ | ↑ | ↑ | ↔ | — | — | — | — | — | |

*(Continued)*

**TABLE 1** (*Continued*)

| Model/system | Treatment | Effect relative to control | | | | | | | | Reference |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Lactic acid bacteria | *Bifidobacteria* | *Enterococcus faecalis* | *Bacteroides* spp. | *Akkermansia* spp. | *Prevotella* spp. | Ruminococcaceae | Firmicutes | |
| Rat | Control: high-fat sucrose diet | | | | | | | | | 36 |
| | Intervention: HFS and resveratrol (diet containing 15 mg · kg$^{-1}$ · d$^{-1}$) | ↔ | — | — | — | ↔ | ↔ | ↔ | ↓ | |
| Human | Control: placebo (microcrystalline cellulose) | | | | | | | | | 37 |
| | Intervention: 282 mg EGCG and 80 mg resveratrol/d | — | — | — | ↓[3] | ↔ | — | — | ↔ | |

[1] DSS, dextran sulfate sodium; EGCG, epigallocatechin gallate; HFS, high-fat and high-sucrose; ↑, significant increase; ↓, significant decrease; ↔, no significant difference compared with control.
[2] Several strains were tested with divergent results.
[3] Men only.

a relative decrease in Firmicutes and therefore a reduction in the functional ability of the gut microbiome to produce tryptophan decarboxylases (41). Likewise, resveratrol treatment may inhibit the increase in *E. faecalis* occurring during a high-fat diet or in inflammatory states in rodent models, thereby reducing the activity of tyrosine decarboxylase in producing tyramine (42). Although the composition of the gut microbiome was not measured directly in the human study, substantial changes in the production of microbiome-associated metabolites mirrored trends found in animal studies in which resveratrol was found to modulate the gut microbiota (40).

The effect of a resveratrol supplement in combination with the dietary polyphenol epigallocatechin gallate (EGCG) on the gut microbiota has been investigated in a single clinical trial conducted in 37 healthy untrained overweight and obese adults (37). Dietary supplements containing 141 mg EGCG and 40 mg resveratrol were consumed twice daily for 12 wk. At baseline, there were significant differences in the microbiome of men compared with women, which indicates that sex should be controlled for in future human studies in this area. The intervention substantially reduced the abundance of Bacteroidetes in men but not in women. The abundance of other bacterial phyla and species, including Firmicutes, Actinobacteria, γ-Proteobacteria, *Akkermansia muciniphila* (phylum Verrucomicrobiae), sulfate-reducing bacteria, acetogenic bacteria, and the archeon *Methanobrevibacter smithii* was unchanged. Because resveratrol and EGCG were tested together, however, it is difficult to speculate on the role each of these compounds would have had if dosed separately.

In conclusion, there is good evidence that based on both in vitro and rodent studies, resveratrol directly modifies the composition of the gut microbiota either by inhibiting the growth of individual microbial species or causing population shifts. In some experiments, resveratrol appeared to reverse dysbiosis arising from an obesogenic diet, for example by increasing the Bacteroidetes:Firmicutes ratio. However, the most robust results have been limited to studies in rodents, and their clinical significance for humans is therefore unclear. In most rodent studies, doses used were considerably higher than the 450-mg acceptable daily intake established for humans, and although there was good concordance in the pharmacologic response between species (43), doses used in animal models cannot be directly translated to humans. Further experiments establishing efficacy at appropriate doses in humans are warranted.

***Beneficial effects of resveratrol metabolites produced by the gut microbiota.*** Resveratrol undergoes rapid and extensive glucuronidation and sulfation reactions in the host liver and duodenum (44, 45). Moreover, the gut microbiota can metabolize resveratrol, as found in both in vitro fermentation experiments with human fecal cultures and controlled intervention studies with healthy volunteers, although with pronounced interindividual differences (21). One study of 73 men and women at high cardiovascular disease

risk found 21 different urinary resveratrol metabolites, including glucuronide and sulfate conjugates of dihydroresveratrol formed by the intestinal microbiota after the chronic consumption of 272 mL red wine or dealcoholized red wine/d for 4 wk, as determined with the use of ultra-HPLC–mass spectrometry (46). There was no difference in resveratrol bioavailability because of the alcohol content of the wine. In a secondary study by the same research group in 10 healthy men who consumed either grape extract or red wine, the metabolic fate of resveratrol was examined (47). Seventeen metabolites were identified in plasma and urine. The dietary supplement formulation released resveratrol more slowly into the digestive tract than wine and showed a delayed absorption, leading to 2- to 4-fold higher urinary concentrations of microbial metabolites (47).

Dihydroresveratrol, 3,4′-dihydroxy-*trans*-stilbene, and 3,4′-dihydroxybibenzyl (lunularin) have been identified both in vitro and in vivo as the main microbiota-derived metabolites formed from resveratrol (48). However, resveratrol metabolism by the gut microbiota has shown pronounced interindividual differences, both in terms of the proportion of ingested resveratrol metabolized and the pattern of metabolites formed (21). Two strains out of a battery of 31 intestinal-origin bacterial strains, *Slackia equolifaciens* and *Adlercreutzia equolifaciens*, were identified as producers of dihydroresveratrol (21); interestingly, these strains are also capable of bioconverting other plant-derived polyphenols such as isoflavones and various catechins (49, 50). Dihydroresveratrol plasma concentrations have been found, however, to vary considerably between individuals after resveratrol supplementation, although one study found that it was produced in all 12 volunteers after daily supplementation with 150 mg resveratrol (51).

Although microbiota-derived resveratrol metabolites have not been researched as intensively as resveratrol, several studies point to their biological effects. The NO synthase inhibition activity of dihydroresveratrol is similar to resveratrol itself (52), and it displays comparable antioxidant activity and effects on cell proliferation and cycling (24, 53). Interestingly, the glucose-lowering drug metformin appears to affect dihydroresveratrol formation: there is an apparent shift toward higher concentrations of dihydroresveratrol with an increasing dose of metformin without a change in the circulating concentrations of resveratrol (54), suggesting the production of other metabolites is reduced. Taken with other results that have shown that metformin attenuated favorable effects from resveratrol supplementation on glucose control and the blood lipid profile (55), the production of metabolites other than dihydroresveratrol by the gut microbiota may be responsible for its cardiovascular benefits.

The resveratrol metabolite lunularin, also found in plants such as the common cow wheat and common celery, has bioactive properties, including reducing the secretion of proinflammatory mediators after an LPS challenge (56). Moreover, it showed moderately cytotoxic effects against liver carcinoma cells and mildly antibacterial activity against the gram-negative bacterium *Pseudomonas aeruginosa* (57). Likewise, several studies have identified in vitro effects of 3,4′-dihydroxy-*trans*-stilbene: chemopreventive effects via the nuclear factor erythroid-2–related factor 2 pathway (58) were found, it was more effective than resveratrol in ameliorating insulin resistance (59), and it appeared to have cytogenetic activity comparable to resveratrol (60). The current limited research base shows that similar to resveratrol, its gut-derived metabolites have anti-inflammatory properties, may be mildly chemopreventive, and could improve glucose control or insulin sensitivity.

***Improved gut barrier function.*** Resveratrol may influence the crosstalk between the gut microbiome and the immune system via its effects on barrier function and integrity. The integrity of proteins in the junction of cells is important in maintaining the intestinal barrier function, and tight junction protein upregulation has been associated with improved intestinal cell integrity (61). Several studies have shown that resveratrol can improve cell junction integrity by upregulating the expression of intestinal tight junction proteins such as tight junction protein 2 (36) and occludin (62). Moreover, the increase in gut permeability caused by the common mycotoxin deoxynivaenol could be arrested by resveratrol, which has been shown to promote the assembly of tight junction protein claudin 4 (63). Considering the importance of the gut barrier function for immunity and in the pathophysiology of several disease processes ("leaky gut"), the role of resveratrol in contributing to the maintenance of an intact intestinal barrier clearly warrants further investigation.

## Health effects of resveratrol mediated through the gut microbiota

Research into the health effects of resveratrol or its metabolites that are mediated by the gut microbiota are limited to experimental animal models. The focus of the research is on cardiovascular effects and the metabolic syndrome, although these areas overlap into immunity and other areas of health.

***Cardiovascular disease.*** A major contributor to the progression of cardiovascular disease is the process of atherosclerosis. Trimethylamine-*N*-oxide (TMAO) is a metabolite produced by a 2-step process whereby dietary L-carnitine, choline, and lecithin are converted to trimethylamine by the gut microbiota, and host flavin-containing monoamine oxidases are responsible for the conversion to TMAO, which is implicated in the development of atherosclerosis (64). In a 5-y follow-up cohort study, a higher plasma TMAO concentration was associated with a 4-fold increase in mortality risk in patients with stable coronary artery disease (65). Circulating TMAO concentrations have been shown to predict increases in carotid intima-media thickness, an early marker of atherosclerosis, in healthy overweight individuals with a family history of

type 2 diabetes participating in a recent longitudinal cross-sectional study (66).

Bacteria from several families commonly found in the gut are capable of producing trimethylamine, although strains within one species may differ in their ability to produce trimethylamine (67). Overall, studies in rodents have indicated that resveratrol reduces the increase in bacteria of Firmicutes (25, 26, 32, 38, 39), which partially modulates the catabolism of choline and carnitine to trimethylamine (68). In a series of experiments with the use of both standard and atherosclerosis-prone mice, resveratrol treatment (0.4%) inhibited the synthesis of trimethylamine and its further conversion to TMAO through gut microbiota remodeling, which was associated with an increase in the Bacteroides:Firmicutes ratio, and potentially through the inhibition of microbial trimethylamine lyase activity (29, 69). Moreover, increases in the proportion of *Lactobacillus* and *Bifidobacterium* appeared to increase the activity of bile salt hydrolase, which increased bile acid excretion and thus lowered cholesterol by increased endogenous bile acid production via repression of the enterohepatic farnesoid X receptor fibroblast growth factor 15 (29). In atherosclerosis-prone apoE$^{-/-}$ mice, 4 g resveratrol/kg attenuated atherosclerosis both in the presence and absence of dietary choline. Moreover, the improvement in atherosclerosis induced by resveratrol in choline-fed mice was inhibited by antibiotic treatment. The latter results suggest that mechanisms other than the inhibition of the gut microbial trimethylamine production are involved in the antiatherosclerotic effects of resveratrol in this murine model of atherosclerosis (29). Thus, beyond shifting the microbiome's composition toward a healthier pattern, it could be modulated by resveratrol to specifically target the production of secondary metabolites (70).

***Obesity.*** There is a complex relation between obesity, diet, and the composition and functionality of the gut microbiome (18, 71). Studies in mice have suggested that resveratrol can influence this relation in several ways, either by directly modulating the gut microbiome to one associated with a healthy weight (31, 34) or by changing the expression and activity of genes involved in weight maintenance, such as fasting-induced adipose factor or the mechanistic target of rapamycin (mTOR), known regulators of peripheral lipid and glucose metabolism as well as central energy metabolism (31, 33, 72). Changes in gene expression related to inflammation, apoptosis, and mitochondrial FA oxidation by resveratrol may also mitigate metabolic disturbances caused by obesity (35).

One study involved C57BL/6N mice in a 2 × 2 factorial design, with resveratrol and the control compared with a standard diet and an HFS diet (45% of calories from fat, 17% of calories from sucrose) (34). Resveratrol treatment (4 g/kg) reduced fat mass in mice fed the HFS diet only, and there was a nonsignificant decrease in body weight in both resveratrol-treated groups. Resveratrol also improved glucose homeostasis in mice fed the obesogenic diet. Fecal microbiota transplantations from mice fed resveratrol or a control diet were used to determine whether these changes could arise from changes in the gut microbiome that were seen. Glucose homeostasis (glucose AUC) improved considerably in obese mice that received fecal microbiota transplantations from resveratrol-treated mice, but there was no change from the baseline in mice receiving a fecal microbiota transplantation from mice fed the control diet, which suggests that the glucose homeostasis improvements were caused by changes in the gut microbiota or metabolites remaining in the feces rather than resveratrol itself.

In a similar study conducted in mice fed with a high-fat diet (50% of calories from fat), a high-fat diet with 200 mg resveratrol · kg$^{-1}$ · d$^{-1}$, or a control diet (10% of calories from fat), resveratrol prevented weight gain caused by the high-fat diet (31). Several changes in the composition of the gut microbiota were noted; most importantly, it prevented a high-fat diet-induced gut microbiota dysbiosis, namely by increasing the Bacteroidetes:Firmicutes ratio. Bacteria from Firmicutes, which are relatively more prevalent in the obese (71), produce greater amounts of energy from dietary fiber than the other major gut bacterial phylum, Bacteroidetes (18), by increasing the production of SCFAs (73). Thus, the available energy content of the diet is augmented by increasing the amount of harvestable energy available from otherwise indigestible carbohydrates (74). In addition, a greater abundance of Bacteroidetes in humans may also increase postprandial fat oxidation (37). However, the relation is complex. SCFA production also stimulates the secretion of the satiety-related hormones leptin, glucagon-like peptide 1 (GLP-1), and pancreatic peptide $YY_{3-36}$, which are known to reduce ad libitum eating and thus lower body weight (75–79). In addition, the expression of fasting-induced adipose factor, which normally has to be suppressed in ileal cells to enable the microbiota-induced deposition of TGs in adipocytes (80), was promoted in both the control and high-fat resveratrol diets, suggesting that resveratrol affected how gut microbes enabled lipid transport in the body (31).

Resveratrol may have marked effects on the signaling activity of mTOR (33), a central regulator of energy storage and consumption (81). A study performed in mice exposed to a high-fat or control diet found that high-fat diet-related microbial dysbiosis correlated with increased body weight and biomarkers of the metabolic syndrome such as elevated blood glucose concentrations and insulin resistance. The specific inhibition of the mTOR1 signaling pathway, which reduces fat deposition and impairs adipocyte maintenance (82), with 200 mg resveratrol · kg$^{-1}$ · d$^{-1}$ may have caused the reductions in body weight and improvements in markers of glucose homeostasis in the resveratrol-treated group (33). Moreover, the activation of the mTOR2 signaling pathway followed by mTOR1 inhibition with resveratrol has been speculated to directly suppress the growth of obesity-associated gut microorganisms such as *Lactococcus*, *Clostridium* cluster XI, *Oscillibacter*, and *Hydrogenoanaerobacterium* (33).

Impaired GLP-1 signaling is also thought to play a role in obesity and type 2 diabetes development (83). Modifications of the gut microbiota that are derived from the diet may affect secreted GLP-1 concentrations and the consequences of the metabolic syndrome (84). In mice, gut microbiota composition changes were concurrent with increases in circulating GLP-1 concentrations in resveratrol-treated mice maintained on a high-fat diet compared with the control and high-fat diets. These changes were associated with improved glucose control, specifically reducing the glucose AUC compared with mice that consumed a high-fat diet, corresponding to an increase in insulin secretion (32). In addition, this study showed that resveratrol induced beneficial changes in markers of inflammation: TNF-α was suppressed in many tissues, whereas anti-inflammatory cytokine IL-10 was enhanced (32). In contrast, however, 500 mg resveratrol 2 times/d in a pilot study in humans had no effect on GLP-1 secretion, glycemic control, gastric emptying, body weight, or energy intake (85).

## Future Research Directions

The current state of the research on resveratrol and its effects on human health via the microbiota has several limitations that hamper its development. The composition of the gut microbiome is complex, with a common set of microbial species present in all individuals, although the relative proportions may vary widely within a much larger set of bacteria, fungi, and archaea that make up the human gut microbiome (86). Commonly used methods to analyze gut microbial composition include isolating bacteria on selective media (35), quantitative real-time PCR, fluorescence in situ hybridization combined with flow cytometry (31), and the main metagenomic approaches, 16S ribosomal RNA–based amplicon sequencing and whole shotgun sequencing (21). In the literature that describes the effects of resveratrol, gut microbiota diversity was investigated according to taxonomic classification levels that varied from strain to phylum. Clear inconsistencies in how specific compositional changes have been compared exist between studies. The translatability of results between research groups is reduced by both the use of different methods of characterizing the gut microbiota and the taxonomic level used to compare microbial composition between groups. The use of standard methodologies and reference genomes could be beneficial in comparing research results with the effect of resveratrol on the composition of the gut microbiota (87–89). Moreover, the gut microbiota is affected by the composition of the diet, and variations in the composition of nondefined animal diets used add a potential source of random error to experimental work. Purified diets could improve reproducibility between animal experiments.

An inherent difficulty in conducting research into the effects of dietary components via the modulation of the gut microbiota is that microbiota-modulating effects may be extraneous to direct biological effects—or result from them. Gnotobiotic rodent models offer the opportunity to show that biological effects are mediated through effects on the microbiome. Therefore, germ-free models should be further used in resveratrol research. For example, a landmark paper recently showed that improvements in insulin sensitivity from resistant starch occurred independent of the gut microbiome with the use of a germ-free mouse model (90).

A few studies have reported encouraging health effects in animals; however, human studies that link resveratrol's health effects with its modulation of the human microbiome are sparse. The most reproducible outcomes of resveratrol supplementation in rodent models appear to involve the attenuation of the negative health effects of a high-fat diet. Considering the effect of certain metabolite-producing types and links to the composition of the gut, pre- and probiotics should be examined to determine whether they can amplify the effects of resveratrol. Moreover, the results showing that resveratrol can improve gut barrier functioning have applications that overlap with cardiovascular health and obesity, such as immunity and gastrointestinal health. The use of in vitro techniques, particularly at physiologic rather than pharmacologic doses, would be beneficial in identifying relevant mechanisms by which resveratrol affects the microbiome. Further research should aim to determine whether modulating the gut microbiota with the use of resveratrol could modify metabolic factors associated with obesity.

In conclusion, resveratrol is capable of affecting the composition of the gut microbiome. It can preferentially slow the growth of certain microbes, which results in a more favorable microbial profile, particularly under obesity-promoting dietary conditions. In addition, resveratrol metabolites produced by gut bacteria have distinct biological effects: it may be possible to steer the production of these metabolites through the concurrent use of pre- or probiotics. Resveratrol or its metabolites can also influence the production of appetite hormones and metabolic byproducts of certain dietary components and the integrity of the intestinal epithelium, which may have antiobesity or cardioprotective effects. Further elucidation of the biological effects of resveratrol mediated via the gut microbiota in humans is warranted.

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