Trends in Food Science & Technology 81 (2018) 232–236

Contents lists available at ScienceDirect

Trends in Food Science & Technology

journal homepage: www.elsevier.com/locate/tifs

Review

Reciprocal interactions between resveratrol and gut microbiota deepen our understanding of molecular mechanisms underlying its health benefits

Liang Shen[a,b,**], Hong-Fang Ji[a,b,*]

[a] Institute of Biomedical Research, Shandong University of Technology, Zibo, Shandong, People's Republic of China
[b] Zibo Key Laboratory for Neurodegenerative Diseases Drug Development, Shandong Provincial Research Center for Bioinformatic Engineering and Technique, School of Life Sciences, Shandong University of Technology, Zibo, Shandong, People's Republic of China

ARTICLE INFO

Keywords:
Resveratrol
Gut microbiota
Modulation
Bioconversion

ABSTRACT

Background: Resveratrol is a stilbene-based phytochemical, which possesses multiple pharmacological activities. However, the low bioavalibility of resveratrol mystifies its pharmacology.
Scope and approach: We discussed the reciprocal interactions of resveratrol with gut microbiota as investigated by *in vitro*, animal models as well as humans studies.
Key findings and conclusions: The first part described the current *in vitro* and *in vivo* evidence concerning the modulative effect of resveratrol on gut microbiota composition, particularly focusing on the involvement of gut microbiota modulation in the anti-diabetic, anti-obesity, and anti-atherosclerosis effects of resveratrol. The second part summarized the bioconversion of resveratrol by gut microbiota, and the identification of metabolites along with bacterial species as generators of these metabolites. This may not only help reconcile the bioavailability conundrum of resveratrol, but also provide directions to expedite its medical applications.

1. Introduction

Resveratrol (3,5,4′-trihydroxy-*trans*-stilbene) is a polyphenolic compound present in many traditional herbs and in several kinds of fruits like grapes and berries, and food products, particularly red wine (Burns, Yokota, Ashihara, Lean, & Crozier, 2002; Stervbo, Vang, & Bonnesen, 2007). Resveratrol has been one of the most intensively investigated phytochemical ever as indicated by thousands of publications, which is not only for its cardioprotective effect to interpret the French paradox of correlation between red wine intake and low mortality due to coronary heart diseases (Biagi & Bertelli, 2015; Renaud & de Lorgeril, 1992), but also because of its multiple biological and pharmacological effects. Numerous cellular and animal models studies as well as clinical trials indicate the diverse beneficial effects of resveratrol including reducing oxidative damage and inflammation, and acting as a neuroprotective, chemo-preventive, anti-obesity and anti-aging agent (Ahmed et al., 2017; Bath, Kosmeder, & Pezzuto, 2001; Baur et al., 2006; Delmas, Jannin, & Latruffe, 2005; Fernández-Quintela, Milton-Laskibar, González, & Portillo, 2017; Jang et al., 1997; Lee, Wendorff, & Berger, 2017; Liu et al., 2018; Rauf et al., 2017; Smoliga, Baur, & Hausenblas, 2011; Szkudelski & Szkudelska, 2015; Ur Rasheed, Tripathi, Mishra, Shukla, & Singh, 2016).

2. The conundrum of resveratrol and gut microbiota

Although resveratrol possesses multiple biological effects, resveratrol exhibits very low bioavalibility as demonstrated by many human and animal models studies (Amri et al., 2012; Cottart, Nivet-Antoine, Laguillier-Morizot, & Beaudeux, 2010; Cottart, Nivet-Antoine, Laguillier-Morizot, & Beaudeux, 2014; Walle, 2011; Wenzel & Somoza, 2005). For instance, upon oral dose of 25 mg of resveratrol to human volunteers, only trace amounts of resveratrol (< 5 ng/ml) could be detected in plasma (Walle, Hsieh, DeLegge, Oatis, & Walle, 2004). As the resveratrol concentrations used in *in vitro* experiments can not be achieved *in vivo* after administration, low oral bioavailability but high bioactivity represents a conundrum remained to be reconciled. Interestingly, after oral administration, in contrast to the poor levels in other tissues, the concentrations of resveratrol is much high in gut tract (Patel et al., 2010; Walle et al., 2004). It was reported that oral administration of resveratrol at daily doses of 0.5 and 1.0 g in colorectal cancer patients can achieve sufficient levels in the gastrointestinal tract to elicit pharmacological activities (Patel et al., 2010).

The gut microbiome is a complicated ecosystem hosting about trillion microbiota. In recent years, a wealth of evidence is emerging about the associations between gut microbiota dysbiosis and development of

* Corresponding author. Institute of Biomedical Research, Shandong University of Technology, Zibo, Shandong, People's Republic of China.
** Corresponding author. Institute of Biomedical Research, Shandong University of Technology, Zibo, Shandong, People's Republic of China.
E-mail addresses: shen@sdut.edu.cn (L. Shen), jhf@sdut.edu.cn (H.-F. Ji).

https://doi.org/10.1016/j.tifs.2018.09.026
Received 24 January 2018; Received in revised form 11 September 2018; Accepted 25 September 2018
Available online 27 September 2018

Table 1
Summary of studies concerning the modulation of gut microbiota by resveratrol.

References	Model	Supplementation	Microbial analysis methods	Alerted bacterial taxa
Most et al., 2017	overweight and obese men and women	epigallocatechin-3-gallate and resveratrol, 282 and 80 mg/d for 12 weeks	real-time PCR assays	decrease Bacteroidetes and *Faecalibacterium prausnitzii* abundances in men
Dao et al., 2011	C57Bl/6J wild type mice and $Glp1r^{-/-}$ mice	60 mg/kg/d for 5 weeks.	real-time PCR assays	alterations in abundances *of Parabacteroides jonsonii*, *Alistipes putredinis*, and *Bacteroides vulgatus*
Qiao et al., 2014	Kunming mice	200 mg/kg/d for 12 weeks.	16S rRNA gene sequence	increase Bacteroidetes-to-Firmicutes ratio, decrease *Enterococcus faecalis*, and increase Lactobacillus and Bifidobacterium abundances
Sung, Byrne, et al., 2017, Sung, Kim, et al., 2017	C57Bl/6N mice	chow with 0.4% resveratrol for 8 weeks	16S rRNA gene sequence	reduce Turicibacteraceae, *Moryella*, Lachnospiraceae, and *Akkermansia*, and increase Bacteroides, Parabacteroides abundances.
Zhao et al., 2017	Wistar rats	combination of quercetin 30 mg/kg/d and resveratrol 15 mg/kg/d for 10 weeks	16S rRNA gene sequence	reduce Firmicutes to Bacteroidetes ratio, decrease abundances of *Firmicutes*, *Desulfovibrionaceae*, *Acidaminococcaceae*, *Coriobacteriaceae*, *Bilophila*, *Lachnospiraceae* and its genus *Lachnoclostridium*; increase abundance of *Bacteroidales_S24-7_group*, *Christensenellaceae*, *Akkermansia*, *Ruminococcaceae* and its genera *Ruminococcaceae_UCG-014*, and *Ruminococcaceae_UCG-005*
Jung et al., 2016	C57BL/6J mice	200 mg/kg/d for 8 weeks	16S rRNA gene sequence	attenuate increase of *Lactococcus*, *Clostridium XI*, *Oscillibacter*, and *Hydrogenoanaerobacterium* abundances
Sung, Byrne, et al., 2017, Sung, Kim, et al., 2017	C57Bl/6N mice	~ 450 mg/kg/d for 2 weeks	16S rRNA gene sequence	increase Bacteriodetes to Firmicutes ratio, and *Parabacteroides*, *Bilophila*, *Akkermansia* abundances, and decrease *Lachnospiraceae* abundance
Chen et al., 2016	$ApoE^{-/-}$ mice	chow with 0.4% resveratrol	16S rRNA gene sequence	increase Bacteroidetes and decrease Firmicutes abundances
Larrosa et al., 2009	Fischer F344 rats	1 mg/kg/d for 25 days	–	increase *Lactobacilli* and *Bifidobacteria*, and decrease *Enterobacteria* abundances
Jung et al., 2009	*in vitro*	resveratrol	minimum inhibitory concentrations	inhibit growth rates of most of 43 animal-associated bacterial strains
Giuliani et al., 2016	*in vitro*	resveratrol	16S rRNA gene sequence	increase *Enterobacteriales* and decrease *Bacteroidales* abundances

various types of human diseases, which include diabetes, several types of cancers, neurodegenerative diseases, cardiovascular diseases, *etc.* (Brown & Hazen, 2018; Karlsson et al., 2013; Marques, Mackay, & Kaye, 2018; Nash et al., 2017; Shen, Liu, & Ji, 2017; Tang, Kitai, & Hazen, 2017). Therefore, targeting gut microbiota has been considered to be a novel potential therapy avenue for these diseases. In view of the above aspects, this review described the reciprocal interactions of resveratrol with gut microbiota, which are, resveratrol modulates gut microbiota composition, and gut microbiota metabolize resveratrol. The current knowledge may help elucidate the action mechanisms of this phytochemical underlying its wide spectrum of pharmacological effects and provide important pharmacological implications.

3. Mechanism 1: resveratrol modulates gut microbiota

The modulative effects of resveratrol on gut microbiota have been revealed by many human, animal models, along with *in vitro* studies. The main information extracted from these studies, including experimental models, supplementation dose and period, and alerted bacterial taxa, are summarized in Table 1.

3.1. Human study

Most et al. explored the effects of combined epigallocatechin-3-gallate and resveratrol supplementation on the composition of human gut microbiota. They found that combined epigallocatechin-3-gallate and resveratrol supplementation for 12 weeks could significantly reduce the abundance of *Bacteroidetes* and tended to decrease the abundance of *Faecalibacterium prausnitzii* in overweight men, but the trends were not observed in women (Most, Penders, Lucchesi, Goossens, & Blaak, 2017).

3.2. Animal models study

Many animal models studies explored the involvement of gut microbiota modulation in the anti-diabetic, anti-obesity and anti-atherosclerosis effects of resveratrol. There are 6 studies focused on anti-diabetic or anti-obesity effects, and 2 on cardioprotective effect of resveratrol.

Dao et al. explored the mechanism underlying the anti-diabetic effect of resveratrol (Dao et al., 2011). They revealed that resveratrol directly targeted the intestine and resveratrol administration for 5 weeks could normalize the modified composition of caecal bacterial taxa of mice induced by a high-fat diet. The directly affected bacteria in abundance were identified to be *Parabacteroides jonsonii*, *Alistipes putredinis*, and *Bacteroides vulgatus* through denaturing gradient gel electrophoresis analyses (Dao et al., 2011). A similar study by Qiao et al. also supported the gut microbiota modulation as a acting pathway of resveratrol underlying its anti-diabetic effect (Qiao et al., 2014). It was found that resveratrol normalized the gut microbiota dysbiosis induced by a high-fat diet in mice, as indicated by the increase in Bacteroidetes to Firmicutes ratio, decrease in the abundance of *Enterococcus faecalis*, and increase in the abundances of *Lactobacillus* and *Bifidobacterium*. Further analysis indicated that resveratrol could significantly increase the expression of a circulating lipoprotein lipase inhibitor, fasting-induced adipose factor (Qiao et al., 2014). Another recent study by Sung and coworkers indicated that resveratrol administration to obese mice could reduce the relative abundances of Turicibacteraceae, *Moryella*, Lachnospiraceae, and *Akkermansia*, and increase those of *Bacteroides* and *Parabacteroides* (Sung, Byrne, et al., 2017, Sung, Kim, et al., 2017). The contribution of gut microbiota modulation to its anti-diabetic effects was further supported by the improved glucose homeostasis through fecal transfer from healthy resveratrol-administrated donor mice (Sung, Byrne, et al., 2017, Sung, Kim, et al., 2017).

A recent study by Zhao et al. confirmed that gut microbiota acted as a target for the anti-obesity effects of a combination of quercetin and