

REVIEW ARTICLE

The roles of gut microbiota and circadian rhythm in the cardiovascular protective effects of polyphenols

Andy W.C. Man¹ | Ning Xia¹ | Andreas Daiber^{2,3} | Huige Li¹ 

¹Department of Pharmacology, Johannes Gutenberg University Medical Center, Mainz, Germany

²Center of Cardiology 1, Molecular Cardiology, Johannes Gutenberg University Medical Center, Mainz, Germany

³Partner Site Rhine-Main, German Center for Cardiovascular Research (DZHK), Mainz, Germany

Correspondence

Professor Huige Li, Department of Pharmacology, Johannes Gutenberg University Medical Center, Langenbeckstraße 1, Mainz 55131, Germany.
Email: huigeli@uni-mainz.de

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Polyphenols are secondary metabolites of plants that have been widely studied for their health benefits as antioxidants. In the last decade, several clinical trials and epidemiological studies have shown that long-term consumption of polyphenol-rich diet protects against chronic diseases such as cancers and cardiovascular diseases. Current cardiovascular studies have also suggested an important role of gut microbiota and circadian rhythm in the pathogenesis metabolic and cardiovascular diseases. It is known that polyphenols can modulate the composition of core gut microbiota and interact with circadian clocks. In this article, we summarize recent findings, review the molecular mechanisms and the potential of polyphenols as dietary supplements for regulating gut microbiota and circadian rhythms, and discuss future research directions.

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1 | INTRODUCTION

Polyphenols are secondary metabolites of plants that are generally involved in defence against UV radiation or invading pathogens. Phenolic compounds are highly variable in their structure and occurrence but generally contain at least one or more benzene rings linked to a hydroxyl group (Puupponen-Pimiä et al., 2002; Tomas-Barberan & Espin, 2001). Polyphenols are water-soluble phenolic compounds and are categorized into several types including flavonoids, phenolic acids, and phenolic amides according to their chemical structure (Tsao, 2010). Polyphenols can be found in a wide range of fruits, vegetables, and beverages, while fruits like grapes and berries contain more than

2-mg polyphenol per gram fresh weight (Puupponen-Pimiä et al., 2002). For humans, common sources of polyphenols include tea, red wine, and other fruit and herbal products. Polyphenols in these dietary supplements have been extensively studied for their potential health benefits, as antioxidants. However, polyphenols are recognized as xenobiotics and have relatively low bioavailability in our body. Polyphenols may be readily absorbed in the small intestine or remain almost unchanged in colon depending on the structural complexity and polymerization (Pandey & Rizvi, 2009). In general, less than 10% of total polyphenol intake is absorbed in the small intestine while the remainder may accumulate in the large intestine and be subjected to enzymic attack by the gut microbiota to form smaller, low molecular weight phenolic metabolites which may then be absorbed into the body (Espin, González-Sarriás, & Tomás-Barberán, 2017; Pandey & Rizvi, 2009).

Abbreviations: CVD, cardiovascular disease; EGCG, epigallocatechin-3-gallate; HFD, high-fat diet; Namp1, nicotinamide phosphoribosyltransferase; TMAO, trimethylamine-*N*-oxide

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Cardiovascular diseases (CVDs) are a major contributor to morbidity and mortality in developed countries (Organization, 2009). Towards the end of the 20th century, a large number of clinical trials and epigenetics studies have strongly correlated the long-term consumption of a polyphenol-rich diet with protection against chronic diseases such as cancers and CVDs (Arts & Hollman, 2005; Mitjavila & Moreno, 2012; Pounis et al., 2018). The risk of CVD was reduced by 46% in individuals with a diet rich in polyphenols (Tresserra-Rimbau et al., 2014). Also, polyphenols can affect the composition of core gut microbiota, while gut microbiota also determines the health effect of polyphenols, and this reciprocal interaction between polyphenol and gut microbiota has been well established (Anhê et al., 2015; Selma, Espin, & Tomas-Barberan, 2009). On the other hand, recent researches have shown that many plant compounds, including polyphenols, interact with circadian clocks by modulating the amplitude and period of the transcription and expression of clock genes (Miranda et al., 2013; Qi et al., 2017; Ribas-Latre et al., 2015b). Current cardiovascular researches have suggested a strong correlation on the gut microbiota and circadian rhythm with metabolic and CVDs (Reinke & Asher, 2019; Tang, Kitai, & Hazen, 2017). These suggest that polyphenols could be good candidates in targeting CVDs via modulating gut microbiota and circadian rhythm. Among the beneficial effect of polyphenol in chronic health and disease, the current review focuses on the present understanding of the biological effect and importance of polyphenols in the interaction with gut microbiota and circadian rhythm in animal models of CVD.

2 | GUT MICROBIOTA AND CARDIOVASCULAR HEALTH

Gut microbiota is a complex ecosystem consisting of numerous species of microbes that are highly interactive with the host organisms from birth. This interaction forms a symbiotic signalling system in which the host environment affects the composition gut microbiota while gut microbiota also produce metabolites that influence the host (Cardona, Andrés-Lacueva, Tulipani, Tinahones, & Queipo-Ortuño, 2013). Therefore, gut microbiota have been considered as a virtual endocrine system with their metabolites communicating with distal organs and affecting organ functions. Currently, the majority of the gut microbiota identified consist of five phyla: *Bacteroidetes*, *Firmicutes*, *Actinobacteria*, *Proteobacteria*, and *Verrucomicrobia*. Their relative abundance and diversity of species are highly variable but, usually, anaerobic *Bacteroidetes* and *Firmicutes* contribute more than 90% of the total gut microbiota population (Castaner et al., 2018; Qin et al., 2010). The ratio of the *Firmicutes* to *Bacteroidetes* varies across individuals, and the variations are mainly caused by differences in host genomes and environmental factors, such as usage of antibiotic and probiotics, lifestyle, hygiene status, and diet (Qin et al., 2010). The *Firmicutes* to *Bacteroidetes* ratio is significantly increased in obese mice (Ley et al., 2005). Due to advances in genome sequencing technologies, bioinformatics has become an excellent research tool to identify and characterize the composition of microbiota. Similarities between the microbiota in the placenta and the infant meconium were detected, suggesting a

pioneer microbial gut colonization process, initiated before birth (Collado, Rautava, Aakko, Isolauri, & Salminen, 2016).

Significant interest has been focused on gut microbiota due to accumulating evidence that microbiota play an important role in health and diseases (Cardona et al., 2013; Espin et al., 2017). Changes in the composition of gut microbiota are associated with pathologies of the cardiovascular system. In addition, not only the composition of gut microbiota but their changes in metabolic profile has also been identified as a major contributing factor in the development of CVDs. A number of clinical and animal studies have provided strong evidence that links different species of microbiota with the development of CVDs and thrombosis (Kiouptsi & Reinhardt, 2018). Gut microbiota also regulates the hepatic synthesis and plasma level of von Willebrand factor (VWF) via toll-like receptor 2 (TLR2) and leads to defective thrombus growth in mice (Jäckel et al., 2017). Moreover, clinical studies have suggested an involvement of innate immune pathways in gut microbiota-mediated CVDs (Ridker et al., 2017). However, the underlying mechanism on how individual species trigger the progression of CVDs is largely unresolved.

Trimethylamine-*N*-oxide (TMAO), a compound that is generated by a two-step process by both the host and by gut microbiota, is implicated in the development of atherosclerosis. Dietary **L-carnitine**, **choline**, and **lecithin** are converted to **trimethylamine** by the TMA-generating lyase (CutC/D) of gut microbiota, especially *Firmicutes* and *Proteobacteria*, then host flavin-containing monoamine oxidases (FMO) are responsible for the conversion to TMAO (Rath, Heidrich, Pieper, & Vital, 2017; Velasquez, Ramezani, Manal, & Raj, 2016). Plasma TMAO concentration is positively correlated to the mortality risk in patients with stable coronary artery disease, carotid intima-media thickness in obese individuals or patients with thrombosis risk (Kiouptsi & Reinhardt, 2018; Randrianarisoa et al., 2016; Senthong et al., 2016; Wang et al., 2011; Zhu et al., 2016). TMAO has been shown to exacerbate atherosclerosis in apolipoprotein E (ApoE) knockout mouse model (Wang et al., 2011) while Jonsson et al. found no correlation between plasma TMAO concentrations and atherosclerotic lesion size (Lindskog Jonsson et al., 2018). This discrepancy could be due to the difference in experimental design. Jonsson et al. supplemented choline at 8-week-old mice when the atherosclerotic disease already started to develop (Coleman, Hayek, Keidar, & Aviram, 2006). These may suggest that gut microbiota is critical in modulating dietary choline-associated early-stage atherosclerosis development. Inhibition of host FMO was beneficial in reducing atherosclerosis, although it is also accompanied by several serious side effects including hepatic inflammation (Shih et al., 2015; Warriar et al., 2015). Therefore, reduction of TMAO level by non-lethal inhibition of gut microbial enzyme activities may become a novel therapeutic strategy to prevent the development of CVD and arterial thrombosis (Wang et al., 2015).

3 | EFFECTS OF POLYPHENOLS IN MODULATING GUT MICROBIOTA

Some reports have shown that the effects of dietary polyphenols are limited due to their poor bioavailability, which is a major concern for their development as therapeutic agents (Subramanian et al., 2010).

However, growing studies support the hypothesis that polyphenols with poor bioavailability, such as **resveratrol** (3,5,4'-trihydroxy-*trans*-stilbene), are possibly acting primarily through the gut microbiota remodelling (Anhê et al., 2015). Polyphenols that are not absorbed in the small intestine reach the colon where they interact with gut microbiota and affect the microbial composition and function. The majority of previous polyphenol researches focused on the effects on their antimicrobial activity. The newly emerging concept of polyphenol supplementations is to assess them as potential prebiotics which shape the composition of gut microbiota (Etxeberria et al., 2013). Current researches suggested that either shaping the gut microbiota to favour specific species or lowering the *Firmicutes/Bacteroidetes* ratio can provide beneficial effects to the host (Espín et al., 2017). Recent publications on the effect of polyphenol in modulation of gut microbiota in metabolic diseases and animal models of CVD are summarized in Table 1.

Resveratrol inhibited TMAO-induced atherosclerosis in *ApoE*^{-/-} mice (Chen et al., 2016) and it also increased the relative abundance of *Bacteroidetes*, *Lactobacillus*, *Bifidobacterium*, and *Akkermansia* and a reduction in the *Firmicutes/Bacteroidetes* ratio in mice. Chen et al. suggest that resveratrol attenuates TMAO-induced atherosclerosis by decreasing TMAO levels via gut microbiota remodelling (Chen et al., 2016). Resveratrol treatment also increases the fasting-induced adipose factor (*Fiaf*), a key gene for the deposition of triglycerides, which may be associated with the prebiotic effect of resveratrol on gut microbiota (Qiao et al., 2014). Other polyphenols, such as **quercetin** and apple procyanidins, have also been reported to reduce *Firmicutes/Bacteroidetes* ratio in rat and mouse models (Lyu et al., 2017). Thus, polyphenols can play critical roles in shaping the gut microbiota composition, especially under CVD conditions.

Akkermasia muciniphila belongs to the *Verrucomicrobia* phylum which is a mucin-degrading microbe. Recent studies demonstrate that levels of *A. muciniphila* inversely correlated with body weight in human and rodent models. The abundance of *A. muciniphila* was decreased in obese and Type 2 diabetic mice (Everard et al., 2013). Recently, 16S rRNA metagenomic analysis suggests that *A. muciniphila* can stimulate the gut microbial richness and a reduction in the *Firmicutes/Bacteroidetes* ratio, leading to an anti-inflammatory action in the intestinal tract and the enhancement of the intestinal barrier (Naito, Uchiyama, & Takagi, 2018; Wu et al., 2017). Oral administration of *A. Po* in western diet-fed *ApoE*^{-/-} mice attenuates atherosclerotic lesions by ameliorating endotoxemia-induced inflammation (Li, Lin, Vanhoutte, Woo, & Xu, 2016). Grape and cranberry extracts are reported to increase the abundance of *A. muciniphila* and help to suppress obesity and insulin resistance (Anhê & Marette, 2017; Roopchand et al., 2015). The procyanidin fraction separated from apple is also shown to induce *Akkermasia* populations and has anti-inflammatory effects in mice fed with high-fat, high-sucrose diet (Masumoto et al., 2016). These results suggest that the enrichment of this particular microbe by polyphenol supplements could be used for the probiotic treatment of obesity-related CVDs.

Another polyphenol, quercetin, which is found in onion, has a differential effect on the growth of gut microbiota. Chronic dietary

intake of quercetin (0.08% in diet) ameliorated hyperglycaemia and dyslipidaemia and reduced the risk for cardiovascular complication in db/db mice (Jeong, Kang, Choi, Kim, & Kim, 2012). However, the mechanisms underlying the prevention of cardiovascular complication by quercetin remains uncertain. A reduction in *Firmicutes/Bacteroidetes* ratio was observed with quercetin in an ex vivo simulation of the human colon (Parker, Trower, & Stevenson, 2013). Quercetin was reported to have minimum inhibitory concentrations (MIC) much lower for *Ruminococcus gausvreauii*, compared to *Bifidobacterium catenulatum* and *Enterococcus caccae* (Firman et al., 2016). *Ruminococcus* produce **butyrate** as the end product metabolite, which can adjust the phase of the hepatic circadian clocks in mice (Leone et al., 2015). These data suggest that polyphenols may also affect circadian rhythm, partly by altering the gut microbiota populations. Rutin, also known as quercetin-3-*O*-rutoside, is a glycosylated quercetin and has been identified as the most potent protein disulphide isomerase (PDI) inhibitor which inhibits thrombus formation (Jasuja et al., 2012; Zwicker et al., 2019). Interestingly, rutin had no inhibitory influence on most gut microbiota but enhanced the adherence of probiotic *Lactobacillus rhamnosus* (Duda-Chodak, 2012). However, the direct mechanisms underlying the promotion of cardiovascular health by rutin, through the modulation of gut microbiota, have still to be defined.

4 | GUT MICROBIOTA-DERIVED ACTIVE METABOLITES OF POLYPHENOLS

Gut microbiota possesses innate metabolic pathways that generate de novo and potentially bioactive compounds from dietary polyphenols. Gut microbiota is critically important in turning ingested polyphenols into bioavailable products as most of polyphenol are not well absorbed by our body. As mentioned, 90% of ingested polyphenols are not absorbed in the small intestine and reach the large intestine. They are then metabolized by gut microbiota into bioavailable products. In general, the glycosylated forms of polyphenol compounds are ingested, and the gut microbiota metabolizes these dietary polyphenols to lower molecular weight phenolic compounds, such as small phenolic acids (Bode et al., 2013). These gut microbiota-derived metabolites of polyphenols sometimes provide essential, bioavailable polyphenolic acids. Polyphenols are substrates for a variety of enzymic processes by gut microbiota that provide polyphenol derivatives in a form capable of being absorbed (Marín, Miguélez, Villar, & Lombó, 2015; Pasinetti et al., 2018). Thus, the beneficial effects of polyphenols are also based on how the gut microbiota metabolizes these compounds.

There is growing evidence that the metabolism of polyphenols by gut microbiota can influence their bioactivity. The importance of the presence of gut microbiota for metabolizing polyphenol have been demonstrated in models either treated with antibiotics or germ-free animal. For example, grape seed extract is shown to produce 3-hydroxybenzoic acid (3-HBA), 3-(3'-hydroxyphenyl)propionic acid (3-HPP), and 3-(3'-hydroxyphenyl)propionic acid (3-HPPA) through enzymatic processing by either *Lactobacillus plantarum*, *Lactobacillus*

TABLE 1 Effect of polyphenol on the microbiota in animal models of cardiovascular or metabolic diseases

Polyphenol	Dose	Animal model	Changes in microbiota	Metabolic or functional consequence	Reference
Resveratrol	0.4% in diet 0.4% in diet	WT mice ApoE ^{-/-} mice	<ul style="list-style-type: none"> ↑ <i>Bacteroides</i>, <i>Lactobacillus</i>, <i>Bifidobacterium</i>, and <i>Akkermansia</i> ↓ <i>Prevotella</i>, uncultured <i>Ruminococcaceae</i> (<i>Ruminococcaceae_uncultured</i>), <i>Anaerotruncus</i>, <i>Alistipes</i>, <i>Helicobacter</i>, and uncultured <i>Peptococcaceae</i> (<i>Peptococcaceae_uncultured</i>) ↑ <i>Bacteroidetes</i> (35.1% to 44.1%), ↓ <i>Firmicutes</i> (50.3% to 35.4%) 	↓ Plasma TMA and/or TMAO levels	(Chen et al., 2016)
			<ul style="list-style-type: none"> ↑ <i>Bacteroides</i>, <i>Lactobacillus</i>, <i>Bifidobacterium</i>, and <i>Akkermansia</i> ↓ <i>Prevotella</i>, <i>Ruminococcaceae_undefined</i>, and <i>Biophila</i> ↑ <i>Bacteroidetes</i> (20.6% to 34.0%), ↓ <i>Firmicutes</i> (60.1% to 50.1%) 	↓ Plasma TMA and/or TMAO levels Attenuate atherosclerosis	(Chen et al., 2016)
	200 mg·kg ⁻¹ ·day ⁻¹	HF-diet mice	<ul style="list-style-type: none"> ↑ <i>Lactobacillus</i> and <i>Bifidobacterium</i> ↓ <i>Enterococcus faecalis</i> 	↑ Fasting-induced adipose factor (<i>Fiaf</i>) ↓ Obesity	(Qiao et al., 2014)
	15 mg·kg ⁻¹	HFFS-diet rat	No change in <i>Bacteroidetes</i> and <i>Firmicutes</i>	No profound effects	(Etxeberria et al., 2015)
Pomegranate peel extract (PPE; containing 8% punicalagin and 5% ellagic acid)	0.2% in drinking water (6 mg·day ⁻¹ per mouse)	HF-diet mice	<ul style="list-style-type: none"> ↑ <i>Bifidobacterium</i> spp. <i>Lactobacillus</i> spp., <i>acteroides-Prevotella</i> spp. 	↓ Inflammation ↓ Hypercholesterolaemia	(Neyrinck et al., 2013)
Quercetin	30 mg·kg ⁻¹ ·day ⁻¹	HFFS-diet rat	<ul style="list-style-type: none"> ↑ <i>Bacteroidetes</i> (10.8% to 27.3%), ↓ <i>Firmicutes</i> (85.0% to 56.0%) ↑ <i>Bacteroidaceae</i> 	Amelioration of insulin resistance ↓ Body weight gain	(Etxeberria et al., 2015)
Cranberry powdered extract (37% flavonols, 39% proanthocyanidins, 12% phenolic acids, and 13% anthocyanins)	40 mg·ml ⁻¹ of water	HFFS-diet mice	↑ <i>Akkermansia</i> (30% increase)	↓ Visceral obesity and liver steatosis ↑ Insulin sensitivity ↓ Circulating LPS	(Anhê, Roy, et al., 2015)
Apple polyphenol fraction (30% Procyanidin)	Not specify	HFFS-diet mice	<ul style="list-style-type: none"> ↓ <i>Firmicutes</i> ↑ <i>Akkermansia</i> genera ↓ <i>Clostridium</i>, <i>Lachnospiraceae</i>, and <i>Bifidobacterium</i> 	↓ Obesity ↓ Circulating LPS	(Masumoto et al., 2016)

casei, *Lactobacillus acidophilus*, or *Bifidobacterium lactis* (Chen et al., 2012; Marín et al., 2015; Wang et al., 2014). Studies using germ-free or antibiotic-treated mice also support the importance of gut microbes for the conversion of these polyphenols into bioactive and bioavailable metabolites in vivo (Gross et al., 2010; Sánchez-Patán et al., 2012; Stalmach, Edwards, Wightman, & Crozier, 2013). Antibiotic-treated mice or germ-free mice can also be used for faecal transplantation experiments to examine the effect of the reconstitution of gut microbiota. For example, Anhê et al. suggested that germ-free mice reconstituted with the gut microbiota of camu camu extract-treated mice gained less weight and displayed higher energy expenditure than those colonized with the high-fat, high-sucrose control (Anhê et al., 2019). Wang et al. showed that both antibiotics-treated mice and germ-free mice lack protocatechuic acid (PCA), a metabolite of cyanidin-3 to 0- β -glucoside (Cy-3-G) in the plasma (Wang et al., 2012). However, interpretation of results from such antibiotic-based studies may be confounded by incomplete elimination of particular microbial species or the selection of resistant species (Kennedy, King, & Baldrige, 2018).

Daidzein, an isoflavone found in soy, is metabolized by the gut microbiota to equol (Yuan, Wang, & Liu, 2007). Equol is more bioactive than daidzein in terms of anti-oestrogenic activity, antioxidant capacity, and anti-cancer effects (Arques, Rodriguez, Langa, Landete, & Medina, 2015). Equol treatment in ApoE^{-/-} mice fed with high-fat diet (HFD) reduces atherosclerotic lesions in the aorta, reduces triglycerides, total cholesterol, and LDL cholesterol, and increases HDL cholesterol (Zhang et al., 2016).

Gut microbiota affects the pattern of resveratrol metabolites produced. Resveratrol is modified by glucuronidation and sulfation reactions in the liver and intestine (Margherita Springer et al., 2019). One of the most studied metabolites of resveratrol is piceid (or polydatin), which has higher bioavailability than resveratrol (Wang et al., 2015) and *Bacillus cereus* in the gut microbiota was responsible for the transformation of resveratrol into piceid (Cichewicz & Kouzi, 1998). Piceid also shows antioxidant and anti-inflammatory activities and its molecular targets, including **SIRT1** and NF- κ B, are similar to those of resveratrol. Interestingly, its antioxidant activity is higher than that of resveratrol (Fabris, Momo, Ravagnan, & Stevanato, 2008). The gut microbiota plays a very important part in resveratrol metabolism by increasing its availability from precursors and producing resveratrol-derived metabolites (Fabris et al., 2008).

Anthocyanins, polyphenols that are found in plants, have beneficial effects on targeting obesity and CVD (Tsuda, 2012). The beneficial effects of some anthocyanins are mediated by metabolism by the gut microbiota. A large proportion of dietary anthocyanins consumed is degraded by gut microbiota as free anthocyanidins, protocatechuic acid (PCA), and gallic acid (GA; Aura et al., 2005). PCA exerts its cardioprotective effects and restores cardiac function in Type 1 diabetic rats by reducing oxidative stress (Semaming, Kumfu, Pannangpetch, Chattipakorn, & Chattipakorn, 2014). GA also increased NO levels by increasing phosphorylation of endothelial NOS (Radtke, Kiderlen, Kayser, & Kolodziej, 2004). GA reduced blood pressure in spontaneously hypertensive rats (SHR) by inhibiting **ACE**

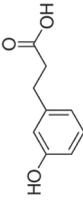
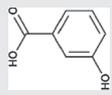
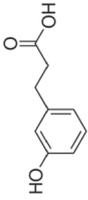
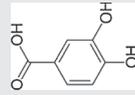
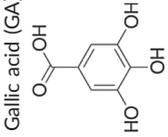
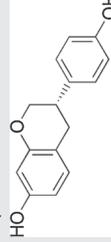
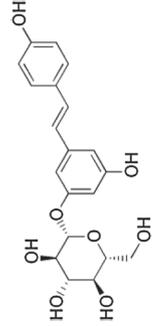
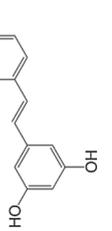
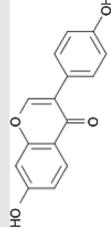
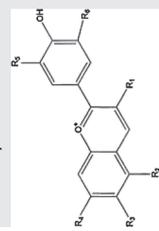
(Kang et al., 2015). Gut microbiota is also important in metabolizing anthocyanins from blackcurrants, to PCA and GA which confers protective effects against obesity and insulin resistance (Esposito et al., 2015). These suggest that the metabolism of polyphenol by gut microbiota is important in producing important bioactive compounds (Table 2). However, most of these compounds are not well studied and more work is needed on the detailed mechanisms used by the specific microbe populations metabolizing the polyphenols and how these bioactive compounds directly affect cardiovascular health.

5 | CIRCADIAN REGULATION AND CVD

Every organism has a core biological rhythm that orchestrates biological process in adjusting to daily environmental changes, which is also known as circadian. Circadian rhythm, originally from Latin “*circa*” meaning around and “*diem*” meaning a day, generally oscillates with a cycle around 24-hr light and dark period in response to daily cycles of abiotic and biotic factors (Bass & Takahashi, 2010). The circadian system is composed by networks of molecular clocks throughout the core and peripheral tissues, including blood vessels and perivascular adipose tissues (Reppert & Weaver, 2002). While circadian rhythms are autonomous and self-sustaining, the system has remarkable plasticity, and there are internal or external factors that can modify circadian rhythms from the molecular to behavioural level (Monk, 2010; Potter, Cade, Grant, & Hardie, 2016). These factors are called “zeitgeber” or a cue to adjust the endogenous circadian cycle. Desynchronization of the circadian system, or the misalignment between circadian rhythms and metabolisms (e.g., for night-shift workers), is thought to contribute to the development of certain chronic diseases, including obesity and CVDs (Mukherji et al., 2015).

A normal day-night blood pressure difference is essential in maintaining a robust cardiovascular system. Circadian blood pressure is controlled by the orchestration of exogenous cue of day-night alterations and the endogenous changes in the circadian of neurohormonal levels mediated by clock genes (Paschos & FitzGerald, 2010). Clinical studies have reported the circadian pattern of physiological and pathological cardiovascular events. These suggest the attribution of diurnal variation to cardiovascular variables such as heart rate, blood pressure, and endothelial functions (Kawano et al., 2002; Otto et al., 2004; Panza, Epstein, & Quyyumi, 1991; Singh et al., 2003; Walters, Skene, Hampton, & Ferns, 2003). A “non-dipping” blood pressure may exhibit a night/day ratio more than 0.9 (Muxfeldt, Cardoso, & Salles, 2009). Various vascular and metabolic dysfunctions are associated with the non-dipping phenotype (Ayala et al., 2013). The non-dipping hypertensive patients exhibit endothelial dysfunction, manifested by a reduction in NO release and a compromised endothelium-dependent vasodilation (Anea et al., 2009; Viswambharan et al., 2007). More than 75% of patients with symptomatic heart failure are “non-dippers” (Mallion et al., 2008). Abnormal sympathetic activation among non-dippers is also observed with inappropriate release of **noradrenaline** at rest, a blunted nocturnal fall in noradrenaline and **adrenaline** excretion rates, as well as an enhanced responsiveness of α_1

TABLE 2 Polyphenol-derived gut microbiota metabolites in animal models of cardiovascular or metabolic diseases

Polyphenol	Possible microbial responsible for metabolism	Metabolite	Protective effect	Reference
Grape seed extract (Proanthocyanidins)	<i>Lactobacillus plantarum</i>	3-(3'-hydroxyphenyl)propionic acid (3-HPPA)	<ul style="list-style-type: none"> • Reduce blood pressure • Vasodilatory activity 	(Wang et al., 2014) (Najmanová et al., 2016)
				
	<i>Lactobacillus plantarum</i> , <i>Lactobacillus casei</i> , <i>Lactobacillus acidophilus</i> , and <i>Bifidobacterium lactis</i>	3-hydroxybenzoic acid (3-HBA)	<ul style="list-style-type: none"> • Anti-inflammatory activity • Prevent venous constriction 	(Marín et al., 2015) (Wang et al., 2014) (Northover, 1967)
				
	<i>Enterococcus casseliflavus</i> , <i>Clostridium coccooides</i> , and <i>Clostridium orbiscindens</i>	3-(3'-hydroxyphenyl)propionic acid (3-HPPP)	<ul style="list-style-type: none"> • Evokes aortic relaxation • Preserves insulin-stimulated eNOS phosphorylation and NO production 	(Marín et al., 2015) (Wang et al., 2014) (Najmanová et al., 2016; Qian, Babu, Symons, & Jalili, 2017)
				
	<i>Lactobacillus spp.</i> and <i>Bifidobacterium spp.</i>	Protocatechuic acid (PCA)	<ul style="list-style-type: none"> • Antiatherogenic effect • Cardioprotective effect • Anti-obesity 	(Wang et al., 2012) (Semaming et al., 2014) (Esposito et al., 2015)
				
	<i>Lactobacillus plantarum</i> 299v and <i>Bacillus subtilis</i>	Gallic acid (GA)	<ul style="list-style-type: none"> • Increase NO • Reduce blood pressure 	(Kang et al., 2015) (Radtke et al., 2004) (Hidalgo et al., 2012) (Chen et al., 2012)
				
	<i>Bacteroides Ovatius spp.</i> , <i>Streptococcus intermedius spp.</i> , and <i>Ruminococcus productus spp.</i>	Equol	<ul style="list-style-type: none"> • Reduces atherosclerotic lesions • Improve metabolic profiles 	(Yuan et al., 2007) (Zhang et al., 2016)
				
	<i>Bacillus cereus</i>	Piceid	<ul style="list-style-type: none"> • Similar to resveratrol, but higher bioavailability than resveratrol 	(Cichewicz & Kouzi, 1998) (Fabris et al., 2008)
				
				
				
				

adrenoceptors (Agarwal, 2010; Nielsen et al., 1999; Uzu, Takeji, Yamauchi, & Kimura, 2001).

The disruption of circadian rhythm also plays a critical role in the pathogenesis of vascular remodelling (Anea, Sullivan, & Rudic, 2009; Anea, Zhang, et al., 2009). Throughout aging, the intrinsic circadian clock mechanism decays (Farajnia, Deboer, Rohling, Meijer, & Michel, 2014) and disrupted circadian clocks may result in impairment of vascular remodelling and premature vascular aging and associated with diseases including hypertension, stenotic atherosclerotic lesions, vascular graft failure, and diabetic vasculopathies (Bunger et al., 2005; Kondratov, Kondratova, Gorbacheva, Vykhovanets, & Antoch, 2006). Disruption of circadian rhythm leads to endothelial dysfunction (Anea, Zhang, et al., 2009) as well as smooth muscle cellularity and extracellular matrix reformation which is highly correlated to the onset of hypertension and CVD (Sutton-Tyrrell et al., 2005). Moreover, the co-existence of arterial stiffening and non-dipping status could exacerbate the adverse cardiovascular effects including augmented nocturnal cardiac outputs (Celik, Yilmaz, & Esmen, 2015).

Circadian clock genes are critical in maintaining the robust relationship between circadian and cardiovascular system. For example, deficiency of *Bmal1* impairs adaptive vascular remodelling and increases collagen deposition in the medial layer (Anea, Zhang, et al., 2009). **CLOCK** and **BMAL** are also critical in maintaining glucose homeostasis, while *Clock* mutant mice show phenotypes of cardiovascular and metabolic diseases such as obesity and hypertension (Rudic et al., 2004; Turek et al., 2005). Mice with functional loss of *Per2* show vascular senescence and endothelial dysfunctions with reduced PGs, elevated vasoconstrictor **COX-1** expression, and significant reduction in the endothelium-dependent relaxation response to ATP-stimulated endothelial NO release (Viswambaran et al., 2007). More importantly, growing evidence has pointed towards a potential interaction between gut microbiota with the host circadian-metabolic axis. Gut microbiota may interfere with the host circadian via microbial metabolites such as butyrate, polyphenolic derivatives, vitamins, and amines, while disruption of host circadian system may also influence the gut microbiota (Parker, Kalsbeek, & Cheeseman, 2019). These suggest that circadian clock genes are important in maintaining the robust relationship between circadian rhythm and cardiovascular health.

6 | POLYPHENOL AND CIRCADIAN REGULATION

Food consumption is a major “zeitgeber”, especially to the peripheral tissue clock. The two major aspects of how nutrition affects the circadian clock include the composition of the diet and the timing of food intake. Appropriate nutrition is believed to help maintain robust circadian rhythms and metabolic and cardiovascular health (Potter et al., 2016). Apart from essential dietary compounds such as fatty acids, non-essential dietary compounds including **alcohol** and **caffeine** are well known to influence the circadian system (Brager, Ruby, Prosser, & Glass, 2010; Sherman et al., 2011). Recent studies also show that plant compounds including polyphenols can interact with circadian

clock genes and impact the amplitude or period of the transcription of the genes. Several polyphenols have been reported to have a direct effect on the core clock gene expression.

Polyphenols interact with the circadian rhythm by affecting the expression of the core and peripheral circadian clock gene expressions. Two major factors that need to be considered in the effect of the polyphenol are the bioavailability of the compounds and the timing of the administration. A compound (not just limited to polyphenol) could positively affect the clock at certain time of a day while possibly be negative at other times. Specifically, the major polyphenols reported capable of modulating the molecular clock to date are resveratrol and the proanthocyanidins. Here, we will be discussing the recent findings on the effect of these polyphenols on circadian rhythm related to obesity and cardiovascular complications.

6.1 | Resveratrol and SIRT1 interaction in orchestrating circadian rhythms

Resveratrol is a polyphenol phytoalexin present in a variety of plant species and in red wine. Preclinical studies have demonstrated the protective effects of resveratrol in CVD, diabetes, cancer, and neurodegenerative diseases (Xia, Daiber, Förstermann, & Li, 2017). In 2008, the first study showed that the expression of circadian clock genes *Per1*, *Per2*, and *Bmal1* was altered by resveratrol, in cultured rat fibroblast cells (Oike & Kobori, 2008). HFD can cause phase delay in the circadian rhythm of **adiponectin** and results in obesity and CVDs (Barnea, Madar, & Froy, 2008), while resveratrol treatment ($30 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$) normalized the adipose tissue-specific clock in mice via targeting the clock-related gene **Rev-Erba** (Miranda et al., 2013). Moreover, resveratrol feeding (0.1% in diet) also attenuated HFD-induced obesity and weight gain in mice models by normalizing the nearly flat daily circadian rhythms of *Per2*, *Clock*, and *Bmal1* gene expression (Sun et al., 2015). These studies confirm that the circadian rhythm is one of the targets of the beneficial effect of resveratrol. Resveratrol has many potential targets and the most studied is the histone deacetylase, SIRT1 (Li, Xia, & Förstermann, 2012; Xia et al., 2017; Xia, Förstermann, & Li, 2014). As both calorie restriction and resveratrol strongly affect both circadian rhythm and lifespan, it had been suggested that the SIRT1/**PGC-1 α** axis may be involved in this resveratrol-mediated beneficial effect (Oike & Kobori, 2008).

SIRT1 has been extensively investigated in terms of its vasoprotective effects, preventing endothelial senescence and vascular remodelling, promoting angiogenesis, enhancing endothelium-dependent vasodilatation, and suppressing vascular inflammation (Bai, Vanhoutte, & Wang, 2014; Man et al., 2016; Stein & Matter, 2011). SIRT1 is also expressed in a circadian manner (Asher et al., 2008), with a high oscillating rhythm in young animals, which is nearly flattened in aged animals (Chang & Guarente, 2013). Circadian transcription of core circadian genes including *Clock*, *Bmal1*, *Cry*, and *Per* is also related to SIRT1 (Asher et al., 2008). SIRT1 directly activates the transcription of *Bmal1*, the major circadian clock gene, and, via **PGC-1 α** , increases the amplitude of other circadian clock genes (Chang & Guarente, 2013). SIRT1 also deacetylates BMAL1 to affect

its circadian regulatory activity (Belden & Dunlap, 2008). The SIRT1/PGC-1 α axis is involved in the crosstalk between the circadian clock and energy metabolism (Masri, Orozco-Solis, Aguilar-Arnal, Cervantes, & Sassone-Corsi, 2015). PGC-1 α , a target of SIRT1, is a strong transcription factor and the key regulator of energy metabolism and intimately involved in obesity and obesity-related cardiovascular disorders (Liang & Ward, 2006). On the other hand, one of the transcriptional targets of CLOCK-BMAL1 is nicotinamide phosphoribosyltransferase (Nampt), an enzyme required for the biosynthesis of NAD⁺, which ensures the rhythmic regulation of SIRT1 activity (Nakahata, Sahar, Astarita, Kaluzova, & Sassone-Corsi, 2009; Ramsey et al., 2009). NAD⁺ plays a pivotal role in circadian epigenomic regulation and shows robust diurnal rhythms in synchronized cells and mice (Bellet et al., 2013). While NAD⁺ levels affect the activity of SIRT1, the deacetylase function of SIRT1 also affects circadian levels of metabolites NAD⁺ and acetyl-CoA (Nakahata & Bessho, 2016). The components of this amplifying loop, including SIRT1 and PGC-1 α and the NAD⁺ synthetic enzyme Nampt, are critical in the intrinsic circadian regulation (Chang & Guarente, 2013). These findings raise the possibility that resveratrol modulates circadian rhythm in preventing obesity and related cardiovascular complications via SIRT1-mediated metabolic axis (Figure 1).

Interestingly, Gadacha et al. have also suggested that the timing of resveratrol consumption is critical for its positive health effect (Gadacha et al., 2009). Resveratrol, well known as an antioxidant, also exhibits pro-oxidant properties and increases oxidative stress in a dose-dependent manner when administered during the inactive period in rat models (Gadacha et al., 2009). It is highly possible that the time of consumption of resveratrol may strongly affect its function to the circadian rhythm and cardiovascular system (Figure 1). As cardiovascular complications in humans most often occur in the morning, researches in resveratrol effect should be focused in this time point to maximize the beneficial effect.

6.2 | Effects of proanthocyanidins on circadian rhythms and metabolic diseases

Proanthocyanidins are oligomeric flavonoids found in high amounts in grape seeds. Grape seed extract has been widely used to study the health effects of proanthocyanidins. Proanthocyanidin consumption leads to a varied range of beneficial effects including improvement in insulin resistance (Montagut et al., 2010), reduction of CVDs, and obesity (Rasmussen, Frederiksen, Struntze Krogholm, & Poulsen, 2005).

Proanthocyanidins could modulate circadian rhythms by maintaining high levels of melatonin during the light cycle. Grape seed proanthocyanidin extract (250 mg·kg⁻¹) altered the pattern of expression of clock genes, in the rat hypothalamus and modulated the serum melatonin level when it was administered during the light cycle, but not during the dark. This indicates that modulation of clock genes expression by proanthocyanidins is highly dependent on the time of administration (Ribas-Latre et al., 2015).

Also, *Bmal1* is reported to be a target of proanthocyanidin along with *Nampt* and NAD⁺. Grape seed proanthocyanidin extract

(250 mg·kg⁻¹) modulated BMAL1 acetylation, Nampt expression, and NAD⁺ level in rat liver depending on the time of administration (Ribas-Latre et al., 2015a). Proanthocyanidins are shown to increase BMAL1 acetylation, Nampt expression, and NAD⁺ level in the dark cycle while the effect is opposite in light cycle in rat (Ribas-Latre, Baselga-Escudero, et al., 2015a). Also, expression of *Clock* and *Per2* genes and Nampt is also increased by proanthocyanidins in white adipose tissue in mice (Ribas-Latre, Baselga-Escudero, et al., 2015a). Grape seed proanthocyanidin extract is also shown to increase endothelial NOS, 5'-AMP-activated protein kinase (AMPK), and SIRT1 expression critically by the induction of Krüppel-like factors (KLFs) in the light cycle of rats (Cui, Liu, Feng, Zhao, & Gao, 2012). Recent studies have demonstrated that these KLFs, a family of evolutionarily conserved zinc-finger transcription factors, are highly linked to circadian clocks (Fan, Hsieh, Sweet, & Jain, 2018; Guillaumond et al., 2010; Spörl et al., 2012). This evidence suggest that the SIRT1-KLFs axis could also be an important modulator of the health benefits of proanthocyanidins. These reports also suggest that proanthocyanidins may regulate lipid and glucose metabolism by adjusting the circadian rhythm and depend largely on the time of administration.

6.3 | Tea polyphenol epigallocatechin-3-gallate and circadian rhythm

Dietary tea polyphenols have been shown to ameliorate CVDs, metabolic syndrome, and memory impairment via circadian-related mechanisms. Epigallocatechin-3-gallate (EGCG) is a major catechin found in green tea with antioxidant, anti-inflammatory, and cardioprotective effects (Tipoe, Leung, Hung, & Fung, 2007). In mice fed a high-fat, high-fructose diet-, circadian rhythm is desynchronized, and the circadian clock gene and clock-controlled genes are expressed with poor oscillation (Hatori et al., 2012). EGCG treatment (2 g·L⁻¹ in drinking water) ameliorates the diet-induced decline of circadian function and normalizes the circadian expression of *Clock*, *Bmal1*, and *Cry1* by regulating the level of SIRT1-PGC-1 α loop (Mi et al., 2017). Also, EGCG treatment reduces fatty acid synthesis and elevates β -oxidation in mice fed with a high-fat, high-fructose diet (Mi et al., 2017). This prevents adipocyte hypertrophy and fat accumulations in both brown and white adipose tissues. These results suggest that EGCG is beneficial to cardiovascular health by regulating the circadian rhythm in the liver and fat tissue. Interestingly, this beneficial effect of EGCG was only demonstrated in the dark cycle of mice.

6.4 | Other polyphenol studies in modulating circadian rhythms

Recently, He et al. reported that treatment with nobiletin increased the amplitude of the expression of circadian clock genes and attenuated the effect of metabolic decreases, in a circadian-related manner (He et al., 2016). In db/db mice fed with HFD (a model of diabetes and diet-induced obesity), nobiletin (200 mg·kg⁻¹) prevented HFD-induced weight gain and fat mass increase. Deletion of clock genes abolished the beneficial effects of nobiletin, reinforcing the importance

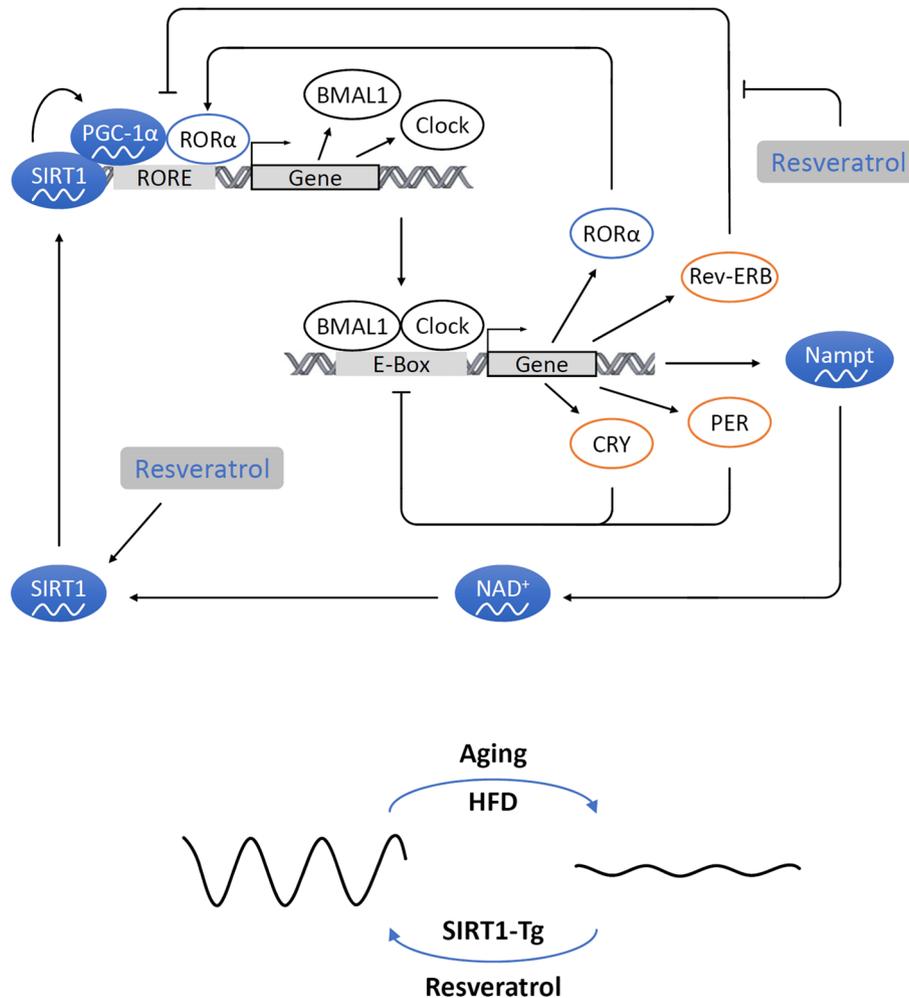


FIGURE 1 Resveratrol and SIRT1 interaction in orchestrating circadian rhythms. The circadian rhythm is governed by transcriptional autoregulatory mechanisms. BMAL1 and CLOCK form a heterodimer to positively regulate the expression of target genes. PER and CRY proteins repress the transcription activity of CLOCK-BMAL1, representing a negative feedback loop. Orphan nuclear receptors REV-ERBa and REV-ERBβ and RORα proteins also contribute to the transcriptional control of the *Bmal1* and *Clock* genes. RORα activation of *Bmal1* transcription requires the SIRT1 substrate PGC-1α. Nampt, SIRT1, and PGC-1α form an amplifying regulatory loop driving the expression of circadian genes. *Nampt*, *Sirt1*, and *Pgc-1α* are expressed in a phased, circadian manner. In addition, the circadian transcription of the NAD⁺ biosynthetic enzyme Nampt renders SIRT1 activity circadian. SIRT1 functions as a positive regulator of BMAL1 and circadian components: (a) SIRT1 deacetylates PER2 thereby facilitating its ubiquitination and degradation by the proteasome. (b) SIRT1 stimulates *Pgc-1α* transcription. (c) SIRT1 deacetylates and thereby activates PGC-1α. (d) SIRT1 and PGC-1α cooperatively bind to the *Bmal1* promoter to activate transcription. In this way, SIRT1 and PGC-1α function together to regulate *Bmal1* gene expression and the amplitude of the circadian machinery. Central circadian control declines with aging. Aged mice show decreased levels of SIRT1 and other circadian regulatory proteins and an inability to adjust to abrupt light re-entrainment. Brain-specific overexpression of SIRT1 in aged mice improves circadian function. Disruption of the circadian expression of SIRT1 and clock genes leads to metabolic and cardiovascular diseases. High-fat diet disrupts the circadian expression pattern of *Per2*, *Clock*, and *Bmal1*. This nearly flat daily circadian rhythms can be largely normalized by resveratrol treatment. Mechanistically, resveratrol reversed the HFD-induced expression of Rev-ERBa. Moreover, resveratrol also increases the expression and activity of SIRT1. However, resveratrol treatment in the inactive period may also increase oxidative stress which increases the risk of metabolic and cardiovascular diseases. HFD, high-fat diet; NAD⁺, nicotinamide adenine dinucleotide; Nampt, nicotinamide phosphoribosyltransferase; SIRT1-Tg, SIRT1 overexpression

of circadian rhythms (He et al., 2016). Other polyphenols, such as homoorientin (in passion flower extract), also increased the amplitude of *Per1*, *Per2*, and *Cry1* gene expression as well as corticosterone circadian rhythm (Toda, Hitoie, Takeda, Shimizu, & Shimoda, 2017). Gut microbiota-derived polyphenol metabolites also affect circadian rhythms. Secoisolaricylresinol diglucoside, a polyphenol from sunflower, is metabolized by *Firmicutes* to enterolactone which modulated the expression of clock genes (Damdimopoulou et al., 2011). However,

the detailed mechanisms on how these polyphenols benefit cardiovascular health in a circadian-dependent manner remain unclear.

7 | SUMMARY AND FUTURE DIRECTIONS

The gut microbiota provide the first line of interaction with polyphenols. The effect of polyphenols on manipulating the gut microbiota

species and the metabolites of polyphenols produced by the gut microbiota are important to determine the effects and bioavailability of polyphenols. On the other hand, the effects of polyphenols on entraining circadian rhythms is very clear. Currently, there is no strong evidence for a causal relationship between the effects of polyphenols on circadian rhythm and the gut microbiota, in terms of their benefit for CVD. The scattered evidence from different studies on polyphenols, circadian rhythm, or gut microbiota suggests that the beneficial effect of polyphenols is highly dependent on the crosstalk between circadian rhythm and gut microbiota. This review has highlighted the importance of a robust circadian rhythm and gut microbiota in the beneficial response to polyphenols, in CVD models.

The effects of polyphenols, especially resveratrol, in CVDs are well studied and reported. The controversy of the effect of polyphenols in metabolic complications and CVD in both experimental and clinical studies may be explained in part by the personalized gut microbiota populations, as well as the differences in the time of consumption. Therefore, with the advances in microbiota sequencing techniques, studies of polyphenols should pay particular attention to the population of the gut microbiota in the experimental model. Also, there are many differences found between different studies, in terms of formulation, dose, source, and identity of the polyphenol under investigation, which should be taken into account very carefully (Potì, Santi, Spaggiari, Zimetti, & Zanotti, 2019). Consensus in the source and dose of polyphenol should be considered in future studies. New studies of polyphenols and circadian rhythms should note that the timing of polyphenol administration is critical for the beneficial effects. For example, resveratrol supplement studies may show different results depending on the time of day that the participants took the supplement in clinical studies. Therefore, future researches on polyphenols should also be more informative by studying different administration time points that could increase their protective effects against metabolic disorders, also associated with circadian rhythm disruption.

Currently, most of the studies on the effects of polyphenols on gut microbiota and circadian rhythm are based on correlations. So far, there is no clear causal relationship found, and the interaction between polyphenols, the microbiota, and circadian rhythms should be further examined. Because most polyphenols actually have low bioavailability, the mechanisms identified in cell lines or animal models are not readily translatable to clinical studies. It is possible that the actions of polyphenols in vivo are highly dependent on gut microbiota. For example, Nohr et al. proposed that the beneficial effect of resveratrol in anti-inflammation and preventing CVDs could be due to the inhibition of Gram-negative bacteria-derived LPSs in the gut (Nohr et al., 2016). Therefore, changes in the microbiota composition (e.g., *Firmicutes/Bacteroidetes* ratio) or specific species (e.g., *A. muciniphila*) should be carefully described in further studies. The use of humanized rodent model may be a good solution to address further questions in the dynamics of microbiota and polyphenols (Bowey, Adlercreutz, & Rowland, 2003). Humanized (gnotobiotic) rodents are germ-free animals inoculated with human fecal microbiota. So far, no studies have reported the composition of the gut microbiota in humanized rodents fed with polyphenol-rich diets.

At this stage, and considering the observations made in different models, we would suggest that the SIRT1/PGC-1 α signalling loop is a critical component of the effects of polyphenols on circadian rhythm which mediates cardiovascular health. SIRT1 is an important regulator for cardiovascular health (Bai et al., 2014; Man et al., 2016; Stein & Matter, 2011), while PGC-1 α is the key regulator of energy metabolism and crucially involved in obesity and related cardiovascular disorders (Liang & Ward, 2006). The SIRT1/PGC-1 α loop is thereby highly important in studying the crosstalk between circadian rhythm, metabolism, and the cardiovascular system. This may also suggest that mitochondria play an important role in polyphenol-mediated circadian clock regulation. Moreover, other polyphenols may also act on the SIRT1/PGC-1 α loop by up-regulating Nampt and NAD⁺. Therefore, further experiments may focus on how these different polyphenols stimulate the up-regulation of Nampt and NAD⁺ and act on the SIRT1/PGC-1 α loop to normalize circadian rhythm. Such studies may also help to explain the discrepancy of in vitro and in vivo studies.

At last, although most of the results on polyphenols studies are so far promising, further studies are warranted in both animals and humans. As there is a growing evidence for the interrelationship between gut microbiota and host circadian rhythms, understanding the effects of polyphenols on both gut microbiota and host circadian rhythms is crucial. The use of models with clock genes knockouts, may give more insights on the dependence of the intrinsic clocks for polyphenol actions. Supplementation of polyphenols together with specific probiotic may also enhance the bioavailability and effect of the treatment. One may consider that as the rodents in animal models are nocturnal animals, the evaluation of the results from the light/dark treatment may be very different in humans. The detailed assessment of the beneficial effect of polyphenols in humans will be necessary. The researches in personalized approaches in polyphenol supplement, including specific times of consumption, to maximize the beneficial effects and administration with specific probiotics to remodel the gut microbiota, may be a new strategy for nutritional interventions to target CVDs.

7.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Harding et al., 2018), and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18 (Alexander et al., 2017a; Alexander et al., 2017b; Alexander, Christopoulos et al., 2017; Alexander, Cidlowski et al., 2017).

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ORCID

Huige Li  <https://orcid.org/0000-0003-3458-7391>

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