

Gut bacteria-derived molecules as mediators and markers in cardiovascular diseases. The role of the gut-blood barrier

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GUT BACTERIA IN HUMAN HOMEOSTASIS

It has been found that the number of gut bacteria is at least equal to the number of human body cells. The most common bacterial phyla in the human gut include Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria. The mammalian gut is colonised early after birth by bacteria and fungi; however, some animal model studies suggest that even foetal guts may contain some bacterial species [1]. The composition of the gut microflora depends on diet, age, and geography. The gut bacteria composition is affected also by the mode of delivery and postnatal feeding. It has been found that breastfeeding and vaginal birth are associated with more enriched microflora than formula-feeding and caesarean birth, respectively [2, 3].

Accumulating evidence shows that human homeostasis depends on a reciprocal relationship with gut microbiota. On the one hand, gut bacteria produce numerous vital nutrients for human homeostasis, such as vitamins K and B and short chain fatty acids (SCFA), and contribute to the transformation and degradation of bile acids, steroids, and xenobiotics. On the other hand, gut microbiota may use nutrients, such as tryptophan, an essential amino acid, thereby reducing the supply of substrates for endogenous synthesis of vital compounds to the host.

Several studies showed dysbiosis in gut microbiota in cardiovascular diseases (CVD) in humans and in animal models of CVD [4]. Moreover, experimental faecal transplantation in an animal model of CVD suggests that the manipulation of the gut microbiota may have therapeutic potential [5].

Finally, increasing research implies that gut bacteria metabolites, such as hydrogen sulphide (H₂S), SCFA, indoles, or

trimethylamines, affect the circulatory system homeostasis, acting on its humoral and nervous control [6–11].

MECHANISMS OF INTERACTION BETWEEN GUT BACTERIA METABOLITES AND THE CIRCULATORY SYSTEM

The mechanisms of interaction between gut bacteria and the circulatory system are not clear. Based on available research, it may be speculated that at least two potential pathways are possible (Fig. 1). Firstly, gut bacteria and/or their metabolites may stimulate sensory fibres of the enteric nervous system, which communicate with the brain centres involved in the control of the autonomic nervous system. Such a pattern of communication between the gut and the brain was described for the regulation of emotional behaviour in a mouse [12]. Secondly, gut bacteria metabolites enter the circulation and, as blood-borne compounds, may reach virtually all organs and tissues that contribute to the circulatory system homeostasis. Since the majority of gut-derived compounds first enter the liver, systemic effects may also be exerted by liver metabolites of gut bacteria-derived compounds, or by changes in the liver metabolism.

To access the circulation, gut bacteria-derived molecules need to cross the gut-blood barrier (GBB). The GBB is a complex system of several biological layers, which prevents the free passage of compounds between the gut and blood (Fig. 2) [13].

THE GUT-BLOOD BARRIER

The GBB controls the transport of nutrients from the gut to the bloodstream. Substances are transported across the GBB via various pathways, depending on physicochemical prop-

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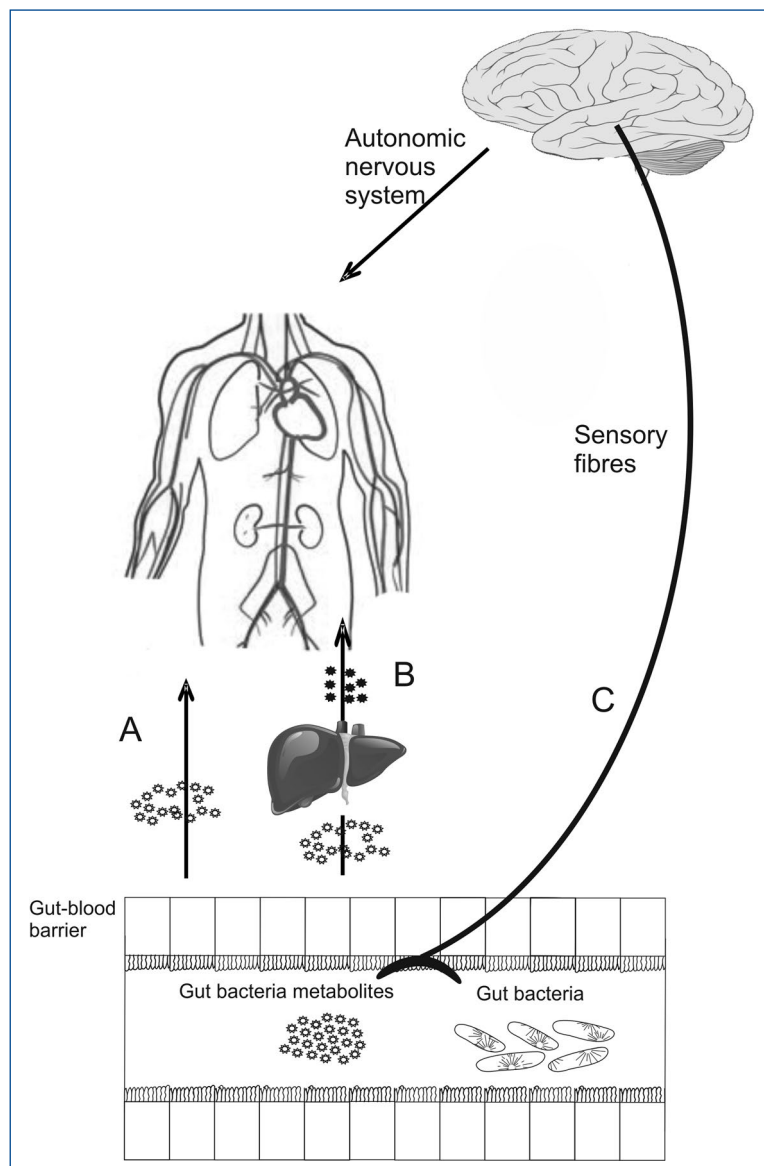


Figure 1. Postulated pathways of cardiovascular actions of gut-bacteria and their metabolites. **A.** Gut-bacteria metabolites cross the gut-blood barrier, bypass the liver (rectal plexuses), and target tissues; **B.** Gut bacteria metabolites cross the gut-blood barrier and are converted to other compounds with a cardiovascular potential; **C.** Gut bacteria and/or their metabolites stimulate sensory fibres of the enteric nervous system that project to the brain centres controlling the circulatory system via the autonomic nervous system

erties of the particles, i.e. lipophilic and small hydrophilic compounds are transported transcellularly, bigger hydrophilic compounds paracellularly, whereas amino acids and vitamins by means of active transport. The GBB consists of several layers, including vascular endothelium, epithelial cell lining, and mucus layer. Paracellular spaces between epithelial cells are sealed with tight junction proteins, adherent junction proteins, and desmosomes, which serve as a mechanical linkage between the cells and control water and ion permeability, as well as absorption of proteins and bacterial antigens. The integrity and proper functioning of the GBB depend on many, not fully

understood factors, which include gut bacteria composition and adequate blood perfusion [13, 14].

Interestingly, there is some clinical and experimental evidence that CVD may affect the GBB function and that the GBB permeability may be a new marker in CVD [13]. In this case, a key factor for proper functioning of the GBB is appropriate blood perfusion through the intestines. Therefore, CVD, such as atherosclerosis or heart failure, may have a negative impact on the GBB functions by affecting the intestinal blood flow. For example, an impaired GBB has been shown in patients with heart failure [15].

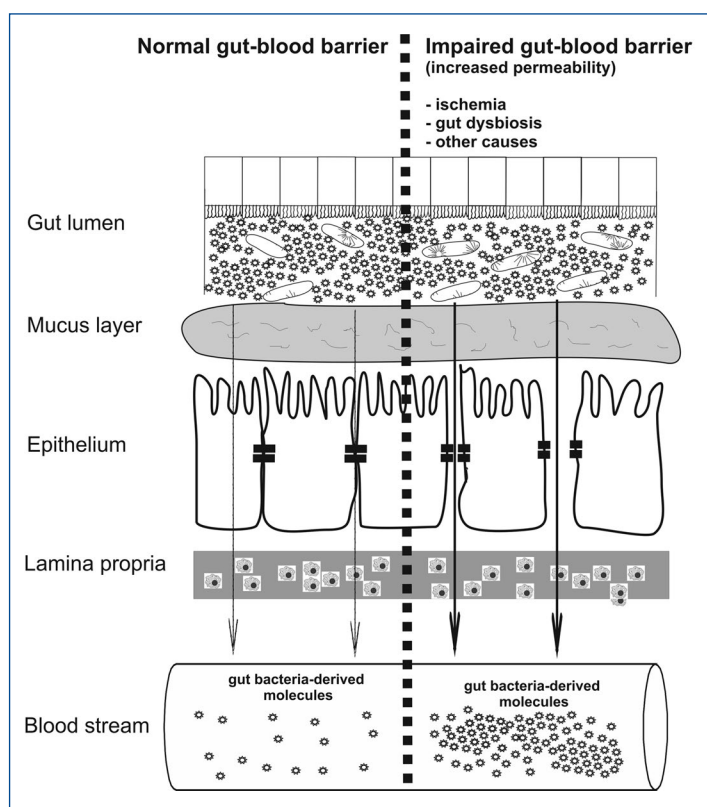


Figure 2. The gut-blood barrier (GBB). To access the circulation, gut bacteria-derived molecules need to cross the GBB. The GBB is a complex system of several biological layers, including mucus layer, epithelium and lamina propria. The GBB separates the gut lumen from the bloodstream and prevents the passage of harmful compounds, while allowing the absorption of nutrients. Various pathological processes, including ischaemia and gut dysbiosis, may disturb the GBB, which may increase the passage of gut bacteria-derived molecules from the intestine

An increased permeability of the GBB in CVD was also found in animal models of CVD. For instance, recently we have found that hypertension in rats is accompanied by morphological and haemodynamic alterations in the colon, and increased permeability of the colon to trimethylamine (TMA), a gut bacteria metabolite. Interestingly, the antihypertensive treatment with enalapril normalised the changes. Similarly, Santisteban et al. [16] found that hypertensive rats showed morphological changes in the small intestine and higher blood level of orally administered 4 kDa dextran, suggesting altered GBB permeability in hypertension.

GUT BACTERIA-DERIVED MOLECULES AS MEDIATORS IN THE CIRCULATORY SYSTEM TRIMETHYLAMINE N-OXIDE

Trimethylamine N-oxide (TMAO) is a small organic molecule belonging to the class of amine oxides with the formula $(\text{CH}_3)_3\text{NO}$, and is a common compound found in animals, but also present in plants and fungi. TMAO plasma level in humans, rats, and mice is within the range $0.5\text{--}10\ \mu\text{mol/L}$ whereas in deep-sea animals it ranges from 100 to $300\ \mu\text{mol/L}$.

TMAO plasma level increases after ingesting dietary L-carnitine and choline that are processed to TMA by gut bacteria including *Clostridium*, *Collinsella*, *Desulfovibrio*, *Lactobacillus*, and *Proteus*. TMA is absorbed from the large bowel and carried by portal blood to the liver in which most of the TMA is oxidised to TMAO by flavin-containing monooxygenase-3 (FMO3). TMA and TMAO are excreted mainly with the urine.

So far, clinicians have focused mainly on the role of TMA and TMAO in trimethylaminuria, or fish-odour syndrome, a rare, autosomal recessive disease. Trimethylaminuria is characterised by FMO3 deficiency, which results in the accumulation of TMA in the body fluids, producing the characteristic smell of urine, breath, and sweat.

Recently, a number of clinical studies point to a positive correlation between an elevated plasma TMAO and an increased risk of CVD. TMAO, as a metabolite of dietary compounds that are present in red meat and egg yolks, has been proposed to be a link between the diet and CVD. Likewise, some experimental evidence suggests that TMAO may contribute to the aetiology of CVD, including hyperten-

sion, atherosclerosis and coronary artery disease (CAD). For example, Koeth et al. [17] showed that TMAO modulates cholesterol and sterol metabolism, promoting the progression of atherosclerosis. In our laboratory, we found that in rats TMAO prolonged the hypertensive effects of chronically infused angiotensin II, a crucial hormone in the circulatory system homeostasis [18]. It has also been reported that TMAO exacerbates inflammatory reactions of vascular wall, activating NLRP3 inflammasome and inducing reactive oxygen species production [19]. Furthermore, TMAO has been found to inhibit the substrate-dependent respiration, thereby decreasing beta-oxidation of fatty acids by heart muscle cells [20]. It has also been reported that TMAO directly contributes to platelet hyperreactivity, leading to augmented intracellular Ca(2+) release and enhanced thrombotic potential, independently predicting incident thrombosis risk [21]. Finally, it has been suggested that TMAO plays a role in the aetiology of diabetes, a key risk factor of CVD [22].

However, numerous biochemical studies highlight the protective functions of TMAO, including the stabilisation of protein folded state and nucleic acids, and protection of cells from osmotic and hydrostatic stresses by counteracting the effects of denaturants, such as urea, osmotic, and hydrostatic pressures. Furthermore, there are some observational and experimental data implying that TMAO may have a beneficial effect in CVD. Therefore, it may be speculated that the accumulation of TMAO is a mechanism of adaptation to pathological conditions associated with CVD, such as alterations in hydrostatic pressure or water-electrolyte balance. This notion may be supported by the following premises. Firstly, a seafood diet, rich in TMAO, is an important component of the Mediterranean diet that is thought to have a beneficial effect on the circulatory system. In this regard TMAO plasma concentration increases significantly after consumption of fish, reaching a concentration even several-fold higher than after consumption of red meat or eggs [23]. Secondly, some experimental studies provide evidence of a possible protective effect of TMAO. It has been reported that TMAO may slow formation of aortic lesion in the mouse model [24], and that TMAO neutralises endoplasmic reticulum stress in diabetic rats [25]. We have found that an experimental 100-fold increase in blood TMAO level had no effect on haemodynamic parameters and motor activity in rats [18]. Finally, TMAO acts as an osmolyte in marine animals, particularly in deep-sea and salt water fishes. Osmolytes maintain cell volume, protecting cells from hydrostatic and osmotic stress. Interestingly, the TMAO blood level in marine animals is approximately 50 times higher than the concentration associated with an increased cardiovascular risk in humans. Therefore, currently it is unclear if TMAO is a causative factor, a protecting factor, or merely a marker of disrupted cardiovascular homeostasis, or a marker of increased permeability of the GBB [8].

Hydrogen sulphide

H₂S is a colourless, flammable, water-soluble gas with a characteristic smell of rotten eggs. In medicine, H₂S has been considered a toxic gas for three centuries, dating from the book *De Morbis Artificum Diatriba* published in 1713 by the Italian physician Bernardino Ramazzini, who described toxic effects of the gas in sewage workers. Even though the evidence that H₂S is synthesised in animal tissue was published in 1930, the physiological functions of H₂S have been widely investigated for the last two decades only. H₂S is synthesised in the majority of tissues from sulphur amino acids by several enzymes including cystathionine beta-synthase and cystathionine gamma-lyase [7].

A plethora of studies prove that H₂S and/or the products of its oxidation contribute to the regulation of the circulatory system. Interestingly, the size and characteristics of haemodynamic effects of H₂S are similar to those of another well-established gaseous transmitter in the circulatory system, i.e. nitric oxide [7, 26].

In short, H₂S donors decrease arterial blood pressure, which depends mostly on vasodilation. However, similarly to epinephrine, H₂S may act as a vasoconstrictor or as a vasorelaxant, depending on the concentration, vascular bed, and animal species [27]. The mechanisms responsible for the H₂S-dependent vasodilation are not clear; however, an opening of ATP sensitive potassium channels seems to be one of the most likely mechanisms. Haemodynamic effects of H₂S may also depend on its interaction with nitric oxide, and formation of new compounds such as S-nitrosothiols. H₂S is also oxidised into thiosulfates and other products, which have been shown to exert significant biological effects. Furthermore, H₂S was found to act as a cardioprotective, proangiogenic, and cytoprotective molecule. It has been suggested that decreased synthesis of endogenous H₂S contributes to the development of hypertension. Yang et al. [28] showed that genetic deletion of cystathionine γ -lyase, an enzyme synthesising H₂S, produced hypertension in mice.

Thus far, the research has focused on cardiovascular effects of H₂S produced enzymatically by the vasculature, the heart, and the kidneys. However, recent studies indicate that the circulatory system may also be influenced by gut bacteria-derived H₂S [6]. In this case, H₂S is produced by sulphate-reducing bacteria, which are ubiquitous in the mammalian colon [6].

In our laboratory, we found that intracolonic administration of H₂S exerts a potent, long-lasting hypotensive effect, which persists several times longer than previously reported for parenteral infusions of H₂S donors. Moreover, rats treated with neomycin, an antibiotic, showed significantly decreased portal blood levels of thiosulfate and sulphane sulphur, the products of H₂S oxidation, and a greater hypotensive response to H₂S. These findings suggest that the gut-derived H₂S may exert systemic hypotensive effects, and that changes in colonic H₂S homeostasis may be associated with hypertension [6].

Indoles

Indoles are abundant products of gut bacteria metabolism, and currently their role in many physiological and pathological processes is under investigation. Indoles including indole, indole-3-acetic acid, indole-3-propionic acid, skatole, and others, are gut bacteria-derived metabolites of tryptophan. In humans, tryptophan, an essential amino acid, is also the precursor of endogenous synthesis of several important mediators, such as tryptamine, serotonin, and melatonin [29].

Indole exerts diverse effects on gut bacteria and host homeostasis. Research suggests that indole may be involved in intracellular signalling, biofilm formation, and antibiotic resistance in bacteria [30]. However, its role in the circulatory system has not yet been elucidated.

The absorption of indole through the colonic mucosa epithelium is followed by 3-hydroxylation and O-sulphation, which forms indoxyl sulphate (indoxyl). Indoxyl is excreted by the kidneys, and its plasma concentration increases in kidney diseases. In fact, there is some evidence that indoxyl may not only be a marker of kidney failure, but may also contribute to the progression of chronic kidney disease (CKD). Indoxyl sulphate has been found to impair antioxidant mechanisms in cells and promote free radical formation in renal tubular cells and glomerular mesangial cells. Orally administered probiotics containing non-indole-producing bacteria as well as AST-120, an indole absorbing compound, were found to be beneficial in the treatment of patients with kidney disease [31].

Furthermore, indoxyl is thought to link CKD with an increased risk of CVD. In vitro studies show that indoxyl sulphate promotes senescence of endothelium, decreases production of nitric oxide, and increases production of reactive oxygen species in cultured human vascular endothelial cells. In addition, indoxyl was found to stimulate hypertrophy of neonatal rat cardiac myocytes, and production of collagen by neonatal cardiac fibroblasts. In CKD patients, a positive correlation between an increased serum indoxyl sulphate and aortic calcification and vascular stiffness was reported [9, 32].

Short-chain fatty acids

Short chain fatty acids, including acetic, propionic, butyric, and valeric acids, are formed by bacterial fermentation from complex carbohydrates. The rate and amount of SCFA production depends on gut bacteria composition, diet, and gut transit time. SCFA play a role locally in intestines as an energy source for intestinal cells and suppress the growth of pathogens by reducing pH in the gut. Furthermore, several studies suggest that SCFA affect the circulatory system locally in the guts and in the systemic circulation.

Mortensen et al. [33] reported vasorelaxant effects of SCFA in colonic resistance arteries, suggesting that SCFA improve the colonic microcirculation, thereby providing an explanation for their trophic effect on intestinal mucosa. Likewise, the vasodilatory effect and an increase in blood flow after the treatment with SCFA was shown in the coronary cir-

ulation; however, long-chain and medium-chain fatty acids were found to be more potent vasodilators than SCFA [34]. The vasodilatory effect of SCFA was also demonstrated in rat caudal artery [35] and rat mesenteric resistance artery [36].

Bauer et al. [37] showed hypotensive and vasodilatory effects of SCFA in cats and dogs. Furthermore, it was found that the infusion of sodium butyrate into the kidney medulla in rats lowered the angiotensin II-induced hypertension by inhibiting renal (pro)renin receptor and intrarenal renin-angiotensin system [38].

There is also some evidence that gut bacteria-derived SCFA may affect arterial blood pressure in humans. Namely, Gomez-Arango et al. [10] showed that in overweight pregnant women the abundance of butyrate-producing bacteria and butyrate production in the gut was negatively associated with blood pressure, suggesting that gut-derived butyrate may contribute to maintenance of normal blood pressure in pregnant women.

The biological effects of SCFA seem to be mediated by GPR41 and GPR43 receptors, as well as by Olfr78, specialised chemosensors — olfactory receptors that are expressed in various tissues, including vasculature and juxtaglomerular apparatus in the kidneys.

GUT BACTERIA-DERIVED MOLECULES AS MARKERS AND THERAPEUTIC TARGETS IN CVD

From among the gut bacteria-derived molecules discussed in the above paragraphs, TMAO seems to have the greatest clinical importance established so far.

There is evidence suggesting a positive correlation between high plasma TMAO concentration and mortality in patients with CAD or peripheral atherosclerosis [39, 40]. A recent meta-analysis performed by Heianza et al. [41] suggests a positive correlation between plasma levels of TMAO and its precursors and all-cause mortality and major adverse cardiovascular events. In clinical studies, the sub-group of patients undergoing coronary angioplasty due to acute coronary syndrome, who have elevated TMAO levels, is characterised by poor prognosis [42]. It has also been shown that TMAO plasma concentration may be used in secondary risk assessment in patients presenting with acute myocardial infarction. The concentration may serve as an independent predictor of increased mortality in this group of patients, and thus be helpful in secondary risk stratification [43]. What is more, TMAO plasma concentration is increased in patients with CKD and is connected with all-cause mortality in CKD patients' sub-population. Therefore, TMAO may be considered as an independent risk factor of cardiovascular complications and CAD progress [44, 45]. TMAO can also be used as an independent marker of early atherosclerosis, expressed as carotid intima-media complex thickness [46].

Whereas H₂S-rich water balneotherapy has been practiced for centuries, and a number of experimental data suggest that H₂S has protective and therapeutic potential in CVD,

Table 1. Gut bacteria-derived molecules in the circulatory system and cardiovascular diseases

Gut bacteria metabolites	Biological/cardiovascular actions	Potential clinical importance
Trimethylamine N-oxide (TMAO)	Sterol metabolism, modulation and promotion of atherosclerosis [17] Augmentation of angiotensin II effects [18] Intravascular inflammation [19] Inhibition of beta-oxidation in heart muscle cells [20] Increased platelet reactivity [21] Diabetes development [22]	Increased mortality in CAD and peripheral atherosclerosis [39, 40] Correlation with all-cause mortality and MACE [41] Poor prognosis in ACS [42] Secondary risk stratification in ACS [43] CAD progression and higher CV risk in CKD [44, 45] Increased rate of CV complications of diabetes [50]
Hydrogen sulphide	Vasoconstriction or vasorelaxation [27, 38] Blood pressure regulation — hypotensive action [6, 28] Cytoprotection, proangiogenic action (experimental models)	Heart failure development [48]
Indoles	Intracellular signalling, biofilm formation, antibiotic resistance in bacteria [30] Accumulation in patients with CKD [9] Impairment of antioxidation and promotion of free radical formation [9] Promotion of endothelium dysfunction: decreased production of nitric oxide, increased production of reactive oxygen species [9] Hypertrophy of cardiac myocytes and production of collagen by cardiac fibroblasts [32]	Decrease of indole concentration is beneficial in CKD [31] Correlation of high concentration of indoxyl sulphate with aortic lesion formation and mortality in CKD [9] Pro-arrhythmogenic potential [9] Association with CV events and mortality in CKD [49]
Short-chain fatty acids	Energy source of colonic cells and pH regulating agents Vasorelaxation and improvement of colonic microcirculation [33] Dilatation of coronary and resistance arteries [34–36] Hypotensive potential and inhibition of angiotensin II effect [37, 38]	Anti-hypertensive action [10]

ACS — acute coronary syndrome; CAD — coronary artery disease; CKD — chronic kidney disease; CV — cardiovascular; MACE — major adverse cardiovascular events

there is still no evidence to support the use of H₂S donors in clinical practice. Clinical research on H₂S is thwarted by the lack of a reliable slow-releasing H₂S-donor. The available slow-releasing H₂S-donors are poorly soluble in water and their ability to release H₂S in biologically relevant amounts under physiological conditions is feeble [47]. Interestingly, recently it has been suggested that a decreased clearance of sulphates, products of H₂S oxidation, may be involved in the pathophysiology of heart failure [48].

Indole and its metabolites are thought to be harmful, linked to development of diseases or their progression. Increased plasma indole levels were associated with higher mortality in patients with CKD [9], progression of cardiac fibrosis [32], pro-arrhythmogenic, and prothrombotic effects [9]

and were predictive of increased risk of cardiovascular events in CKD [49]. In contrast, SCFA seem to be cardioprotective compounds, with vasodilating and hypotensive potential. Just recently, it has been shown that abundant butyrate production in the gut is negatively associated with blood pressure in pregnant women [10].

CONCLUSIONS

In conclusion, clinical and experimental research indicates that gut bacteria-derived metabolites enter the circulation and exert numerous biological effects (Table 1). Whether they have toxic, beneficial, or diagnostic significance in CVD requires further studies. Nevertheless, new therapeutic options in CVD may include compounds releasing gut bacteria metabolites or

their antagonists, as well as administration of selected bacterial strains (probiotics) with the capacity to produce a desired gut bacteria metabolite.

Conflict of interest: none declared

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