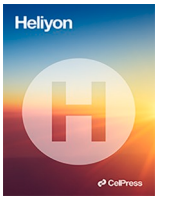
Heliyon 9 (2023) e21431

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Review article

Gut microbiota metabolites, redox status, and the related regulatory effects of probiotics

Jinshan Zhao [1], Fan Zhao [1], Junmeng Yuan, Huawei Liu, Yang Wang [*]

College of Animal Science and Technology, Qingdao Agricultural University, 266109, Qingdao, China

ARTICLE INFO

Keywords:
Oxidative stress
Gut microbiota
Gut microbiota metabolite
Probiotic

ABSTRACT

Oxidative stress is a state of imbalance between oxidation and antioxidation. It is caused by excess levels of free radicals and leads to the damage of DNA, proteins, and lipids. The crucial role of gut microbiota in regulating oxidative stress has been widely demonstrated. Studies have suggested that the redox regulatory effects of gut microbiota are related to gut microbiota metabolites, including fatty acids, lipopolysaccharides, tryptophan metabolites, trimethylamine-*N*-oxide and polyphenolic metabolites. In recent years, the potential benefits of probiotics have been gaining increasing scientific interest owing to their ability to modulate gut microbiota and oxidative stress. In this review, we summarise the adverse health effects of oxidative stress and discuss the role of the gut microbiota and its metabolites in redox regulation. Based on the influence of gut microbiota metabolites, the roles of probiotics in preventing oxidative stress are highlighted.

1. Introduction

Oxidative stress is a stress reaction that occurs when the dynamic equilibrium between oxidants and antioxidants is destroyed. Under normal physiological conditions, free radicals are dynamically balanced. However, under certain conditions, the redox balance of the body is destroyed and the production rate of reactive oxygen species (ROS) exceeds that of the antioxidant system, leading to the accumulation of oxygen free radicals and oxidative stress and ultimately resulting in intestinal damage, metabolic syndrome, cancer, and other diseases [1,2].

The gut microbiota, or the microbial population in the intestines, plays a key role in immune function, digestion, and metabolism. Microbial contact-induced epithelial ROS generation is an extremely conserved phenomenon across different phyla. This mechanism is the general means by which bacterial communities can affect redox homeostasis in the host [3]. In recent years, oxidative stress has been shown to affect the structure and function of the gut microbiota [4] and alter the composition of gut microbiota metabolites [5]. Moreover, the metabolites of the microbiota also play an important role in gut microbiota-mediated redox regulation [6,7]. Specific metabolites, such as fatty acids, lipopolysaccharides (LPS), tryptophan (TRP) metabolites, trimethylamine-*N*-oxide (TMAO) and polyphenolic metabolites, have been reported to regulate oxidative stress [8–11].

Given the above evidence, scientists have begun to believe that targeting the gut microbiota and its metabolites may reveal novel strategies for the prevention and intervention of oxidative stress. Among these strategies, probiotics have received the most attention [12]. In our previous study, we summarised the antioxidant mechanisms of probiotics and found that probiotics may exert the

* Corresponding author.
E-mail address: yangwang@qau.edu.cn (Y. Wang).
[1] The two authors contributed equally to this work.

https://doi.org/10.1016/j.heliyon.2023.e21431
Received 18 July 2023; Received in revised form 29 September 2023; Accepted 20 October 2023
Available online 29 October 2023

antioxidant ability by various mechanisms such as up-regulating the antioxidases of the host, down-regulating the activities of enzymes producing ROS and regulation gut microbiota [13]. Here, we mainly focus on the role of gut microbiota metabolites in redox homeostasis and evaluate the current understanding of the effects of probiotic-related gut microbiota metabolite regulation on oxidative stress. In this review, articles examined in open literature containing the probiotics, oxidative stress, gut microbiota metabolites are reviewed in terms of fatty acids, LPS, TRP metabolites, TMAO and polyphenolic metabolites.

2. Oxidative stress generation and adverse health effects

Oxidative stress is a process by which excess free radicals attack macromolecules and cause tissue damage. Most living organisms can utilise antioxidant enzymes and endogenous antioxidants to remove excess free radicals in a timely manner and maintain the redox balance. However, when stimulated by stressors or pathogens, the antioxidant system is often insufficient at resisting high levels of free radicals, and oxidative stress occurs. ROS are the most active free radicals, and they include superoxide radicals, hydroxyl radicals, and hydrogen peroxide. Excessive ROS can induce DNA hydroxylation, protein denaturation, and lipid peroxidation, leading to apoptosis and tissue damage [14]. Oxidative stress and oxidative damage are ubiquitous. Many factors, such as environmental pollution, infection, cigarette smoking, and excessive exercise, can lead to oxidative stress [15], which consequently contributes to aging [16], intestinal damage [17], heart disease [18], metabolic syndrome [19], diabetes [20], and cancer [21].

2.1. Metabolic diseases

Oxidative stress is related to metabolic diseases, including obesity, type 2 diabetes mellitus (T2DM), and diabetic kidney disease [15]. Oxidative stress has been reported to trigger obesity by increasing preadipocyte proliferation and adipocyte differentiation [22]. In individuals with obesity, chronic oxidative stress and associated inflammation cause insulin resistance, metabolic dysfunction, diabetes, and cardiovascular diseases by disrupting signalling and metabolism [23]. In addition, obesity-associated insulin resistance greatly increases oxidative stress and the risk of hypertension, dyslipidaemia, T2DM, atherosclerosis, and non-alcoholic fatty liver disease [24]. Increasing evidence on the pathophysiology of T2DM has revealed that oxidative stress is the main causative factor responsible for the pathogenesis of insulin resistance, impaired glucose utilisation, and abnormal hepatic glucose production, ultimately leading to T2DM [25]. Additionally, intrarenal oxidative stress plays an important role in the initiation and progression of diabetic kidney disease. Excessive ROS production triggers renal fibrosis and inflammation by promoting lipid peroxidation, DNA damage, protein modification, and mitochondrial dysfunction, leading to significant tissue damage [26,27].

2.2. Cancer

Oxidative stress is closely related to the formation and progression of cancer [21]. Oxidative stress causes DNA strand breakage and incomplete enzymatic repair mechanisms, which ultimately lead to chromosomal changes. In turn, these changes result in genetic amplification, alterations in gene expression, and loss of heterozygosity, leading to carcinogenesis [28]. Breast cancer is the leading type of cancer in women and the leading cause of death among female cancers. An increased level of 8-hydroxy-2 deoxyguanosine (8-OHDG) was found in the DNA of breast cancer tissues compared to that of late-stage cancer tissue [29]. Moreover, the mitochondrial manganese-dependent antioxidant enzyme superoxide dismutase 2 (SOD2) is considered a tumour suppressor gene. The expression of this gene is frequently decreased in human cancers, as its overexpression leads to severe inhibition of cell proliferation for various cell types, including breast cancer cells [30]. SOD2 expression in the breast metastatic tumour cell lines MDA-MB-435 and UACC-893 is 2–3 times lower than that in the non-tumoral epithelial cell line MCF-10 A, suggesting that oxidative stress may play an important role in the early phases of carcinogenesis [31].

Prostate cancer is the most common type of cancer and the second leading cause of cancer-related death in men after lung cancer [32]. Oxidative stress may disrupt the physiologically active proteome of the cell, serve as a stimulus to trigger stress-response signal transduction pathways, and modulate processes favouring cell survival by activating continuous proliferation. Together, these factors enable prostate cancer to progress [33]. In addition to ROS-induced DNA damage, other factors induced by oxidative stress can also lead to prostate cancer. Studies have found that androgens can cause oxidative stress and lead to benign prostatic hyperplasia or prostate cancer if benign prostatic hyperplasia overgrowth occurs [34]. Moreover, the prostate cancer epigenome is characterised by global changes in DNA methylation [35]. Of all the genes known to be methylated in prostate cancer, *glutathione S-transferase P1* (*GSTP1*) is the most frequently methylated. GSTP1 is a detoxifying enzyme that catalyses conjugation reactions between potentially damaging oxidants, electrophiles, and glutathione [36,37]. GSTP1 expression is diminished or absent in prostate cancer, and this absence is tightly regulated by hypermethylation of the CpG island in the promoter [38].

Additionally, exposure to cigarette smoke is a primary risk factor for lung cancer. Many carcinogens and free radicals have been identified in cigarette smoke. Moreover, cigarette smoking leads to the influx and activation of phagocytes, which release ROS [39]. In a study by Gęgotek et al. [40], disturbances in antioxidant capacity and enhanced DNA oxidative modifications were observed in 88 % of adenocarcinoma patients and 81 % of squamous cell lung carcinoma patients. Moreover, the inhibition of oxidative stress has a significant anticancer effect on lung cancer [41,42].

2.3. Impaired reproductive function

Oxidative stress has also been identified to play a key role in the pathogenesis of subfertility in human and animals. Excessive

production of ROS has been associated with impaired sperm motility, concentration, and morphology [43]. A study conducted by du Plessis et al. revealed that H_2O_2 could induce human sperm motility and increase the overall ROS and NO levels [44]. ROS also affect a variety of physiologic functions of the ovary, including ovarian steroid genesis, oocyte maturation, ovulation, leading to polycystic ovary syndrome, endometriosis and preeclampsia [45]. In poultry, oxidized fish oil in feed caused oxidative stress in laying hens, and induced the decreased number of dominant follicles [46]. Dexamethasone injection also elevated the oxidative stress in laying hens and decreased the laying rate, feed-egg ratio, and increased the expressions of apoptosis-related genes in preovulatory follicle, small white follicle, medium white follicle and ovary [47]. In Guinea pigs, cypermthrin treatment led to oxidative stress, and decreased sperm count, mobility, and the percentage of spermatozoa with normal plasma membrane [48].

2.4. Intestinal damage

The gut not only is the main organ for food digestion, absorption, and metabolism, but it also plays an important role in secretion and immunoregulation. The gastrointestinal (GI) tract is the body's largest interface between the internal and external environments. Thus, the external environment, resident immune cells, gut microbiota, and dietary factors make the GI tract prone to ROS attack. The intestinal barrier, which plays a fundamental role in overall health, is composed of four major lines of defence. The first is a mechanical barrier, consisting of lined intestinal epithelial cells and capillary endothelial cells. The epithelial and endothelial cells come into the closest possible contact in the most apical part of the lateral cell membranes at tight junctions, which interconnect the cells and restrict the passage of ions, molecules, and cells through the paracellular space. The second is an immune barrier that consists of gut-associated lymphoid tissue, effector and regulatory T cells, IgA-producing B (plasma) cells, group 3 innate lymphoid cells, resident macrophages, and dendritic cells in the lamina propria. The third line of defence is a chemical barrier, which comprises digestive fluid, antimicrobial peptides, mucin, and other compounds secreted by the intestinal epithelial cells to prevent bacterial adhesion. The final line of defence is a biological barrier, which consists of the gut microbiota responsible for resistance to pathogenic bacteria colonisation [49,50].

Excessive ROS levels can damage the tight junctions of the intestinal epithelial cells and disrupt the GI tract barrier, thereby increasing intestinal permeability. Studies have shown that H_2O_2-induced oxidative stress decreases the expression of tight junctions in porcine intestinal epithelial and Caco-2 cells, leading to systemic endogenous stress syndrome [17,51]. In addition, oxidative stress can cause colitis and increase intestinal permeability [52,53]. The cytoskeleton plays an important role in maintaining the structure and

Table 1
Relationships between gut microbiota metabolites and oxidative stress.

Gut microbiota metabolites		Oxidative stress	Oxidative stress index	References
SCFA		↓	Proinflammatory cytokines↓	[7]
			ROS↓	[7]
			NADPH oxidase/ROS signalling↓	[69]
			antioxidant enzyme activity↑	[64]
MCFA		↓	Cell viability, T-AOC, and expression of antioxidant-related genes↑, ROS production↓	[70]
			H_2O_2 release↓	[71]
			weight gain, cardiovascular disease risk↓	[72]
LCFA		↑	Glutathione depletion in mitochondria↑	[73]
			Apoptosis, oxidative stress, chronic inflammatory responses↑	[74]
			ROS formation↑	[75]
LPS		↑	Nox2↑	[76,77]
			NF-κB pathway↑	[78]
			ROS↑	[61,79]
			8-OHDG↑	[79]
TRP	Kynurenine	↑	formation of H_2O_2↑, ROS↑	[80]
			cell death, ROS pathway↑	[81]
	5-HT	↓	inflammatory cytokines↓	[11]
			ROS↓	[82]
			Nrf2↑	[83]
	Indole and its derivatives	↓	Nrf2, NQO1, GSTA1/2, UGT1A6↑	[84]
	5-MIAA	↓	Nrf2↑	[85]
			free radicals↓	[86]
				[87]
TMAO		↑	ROS-TXNIP-NLRP3 signalling↑	[10]
Polyphenolic metabolites	Luteolin metabolite	↓	NO synthase↓	[88]
	Protocatechuic acid	↓	GPX, CAT, GSH↑, MDA, ROS↓	[89,90]
	5-(3′,4′-dihydroxyphenyl)-γ-valerolactone	↓	antioxidant capacity↑	[91]

Abbreviations: SCFA, short-chain fatty acids; MCFA, medium-chain fatty acids; LCFA, long-chain fatty acids; LPS, lipopolysaccharides; 5-HT, 5-hydroxytryptamine; 5-MIAA, 5-methoxyindoleacetic acid; TRP, tryptophan; TMAO, trimethylamine-*N*-oxide; ROS, reactive oxygen species; NADPH, Nicotinamide Adenine Dinucleotide Phosphate; Nox2, NADPH oxidase 2; NF-κB, nuclear factor kappa B; 8-OHDG, 8-hydroxy-2 deoxyguanosine; Nrf2, erythroid 2-related factor 2; NQO1, NADPH/quinone oxidoreductase; GSTA1/2, glutathione *S*-transferase; UGT1A6, UDP-glucuronosyltransferase 1A6; NO, nitric oxide; GPX, glutathione peroxidase; CAT, catalase; GSH, glutathione; MDA, malondialdehyde.

function of tight junctions in the epithelium. In a previous study, exposure to 0.5 mM H_2O_2 for 30 min almost completely destroyed the connection between the actin cytoskeleton and tight junction proteins in Caco-2 cells, resulting in the destruction of the actin skeleton structure [54,55]. Banan et al. [56] found that oxidants decompose the cytoskeleton and destroy the integrity of the epithelial barrier. Furthermore, excessive ROS levels impair the intestinal immune barrier. Bhattacharyya et al. [57] suggested that oxidative stress stimulates polymorphonuclear neutrophils, contributing to inflammation in a variety of GI diseases. In glucocorticoid-stressed rats, the level of secreted IgA decreased, while intestinal permeability and bacterial adherence to the mucosa increased [58]. Chang et al. [59] demonstrated that trichlorfon exposure decreased the activity of antioxidants and upregulated the levels of the pro-inflammatory cytokines TNF-α and IL-1β. Furthermore, oxidative stress can inhibit mucin synthesis and secretion, which damages the chemical barrier function of the intestine. Zhao et al. [60] reported that bisphenol A causes oxidative stress by significantly increasing the accumulation of ROS and inhibiting the secretion of mucin 2. Cervantes-García et al. [61] found that indomethacin induced enteropathy by elevating intestinal oxidative stress, and it decreased occludin and mucin 2 expression in the intestinal tissue.

Moreover, the gut microbiota constitutes a natural defensive barrier against infection. It is involved in numerous protective, structural, and metabolic roles in the intestinal epithelium and plays a major role in maintaining gut homeostasis [62]. Studies have revealed that increased mitochondrial ROS production decreases intestinal microbial diversity and lowers antimicrobial defences [63,64]. In addition, a long-term high-fat diet (HFD) influences the gut microbiota by changing the redox state. Increased ROS and malondialdehyde (MDA) levels in HFD-induced obese mice showed a strong positive association with *Escherichia coli* and *Enterococcus* but a negative association with *Lactobacillus* [65].

Due to the adverse effects of oxidative stress, it is urgent to clarify the mechanisms and methods for the antioxidation.

3. Gut microbiota influence oxidative stress through metabolites

The gut microbiota protects the host from pathogens by competitive exclusion, particularly by occupying attachment sites, consuming nutrient sources, and producing certain metabolites [66]. When the intestinal microbiota is abnormal, harmful bacteria proliferate excessively, causing significant oxidative stress [3]. Previous studies have reviewed the role of the gut microbiota in oxidative stress [67,68]. In recent decades, an increasing number of studies have shown that gut microbiota metabolites are involved in the regulation of oxidative stress by gut microbiota. The gut microbiota metabolises food into a series of metabolites, including fatty acids, TMAO, and TRP metabolites, and polyphenolic metabolites. Gut bacteria also metabolise and produce bacterial metabolites such as LPS. These gut microbiota metabolites can regulate the redox status and affect the physiological processes of hosts in a variety of ways (Table 1).

3.1. Fatty acids

Short-, medium-, and long-chain fatty acids (SCFA, MCFA, LCFA) are natural compounds in animal and plant tissues that participate in cell metabolism. SCFA are mostly generated by colonic bacteria and are predominantly metabolised by enterocytes and liver. MCFA derive mostly from dietary triglycerides [92]. LCFA, such as myristic acid (14:0), palmitate (16:0), and stearic (18:0) are more abundant. Palmitic acid is the most abundant in human food (average consumption of 20–30 g/day) [93] (Fig. 1).

3.1.1. SCFA

SCFA, particularly acetic acid, propionic acid, and butyric acid, are metabolites produced by beneficial intestinal bacteria through the digestion and fermentation of dietary fibre [94]. The colon is the major site of SCFA formation, where it is also rapidly absorbed as an energy source [95,96]. Studies have shown that SCFA can target the mammalian G protein-coupled receptor pair GPR41 and GPR43

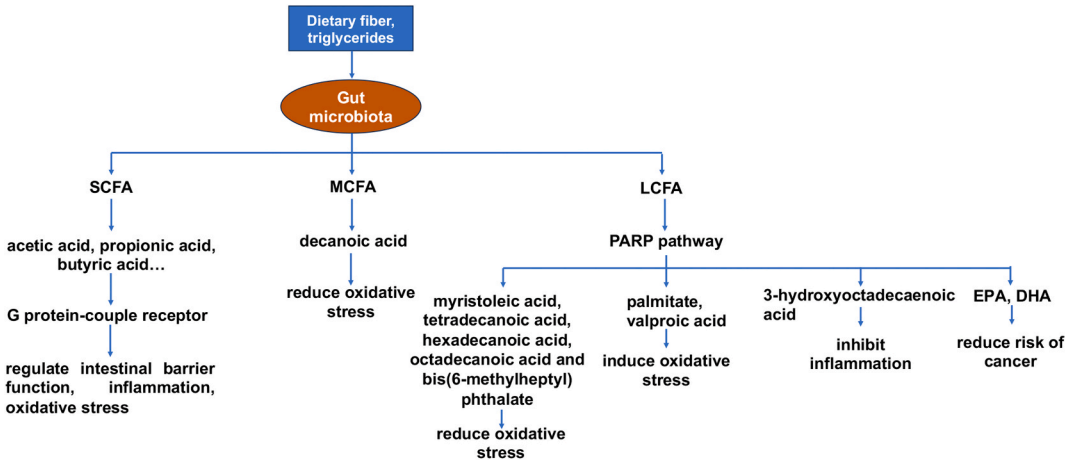


Fig. 1. Mechanisms of gut microbiota producing fatty acids (SCFA, MCFA, LCFA) and their functions.

and inhibit histone deacetylase activity to maintain the gastrointestinal epithelial barrier, regulate insulin secretion, and inhibit inflammation [97]. In clinical investigations and animal models, SCFA administration and an increased intake of dietary fibre have been shown to exert protective effects in patients with inflammatory bowel conditions, allergic airway diseases, obesity, type 1 diabetes, and type 2 diabetes due to the inhibition of proinflammatory cytokines and ROS [7]. The ratio for acetate, propionate, and butyrate to be generated in the intestines is 60:25:15 [98]. These three SCFA have been shown to possess antioxidant capacities. It has been suggested that acetate promotes β-cell survival under stressful conditions [99] and ameliorates sepsis-induced acute kidney injury by inhibiting NADPH oxidase/ROS signalling [69]. Propionate ameliorates colitis in mice and inhibits LPS-induced inflammation by improving the antioxidant system and reducing oxidative stress [100,101]. Butyrate stimulates mitochondrial biogenesis, improves respiratory capacity, and activates antioxidant enzyme activity to improve antioxidant capacity [64].

3.1.2. MCFA

MCFA are fatty acids with 8–12 carbon, including octanoic acid, capric acid and lauric acid. Attention has been paid on MCFA due to its different metabolic pathways and low lipid toxicity compared with LCFA [102]. It is shown that gut microbiota, including Caproiciproducens, Pseudoramibacter, norank_f_Eubacteriaceae, and Oscillibacter catabolised lactate into MCFA [103]. Moreover, MCFA have been reported to have a variety of physiological functions. Bourque et al. found that MCFA could prevent weight gain and decrease cardiovascular disease risk in overweight women [72]. MCFA treatment significantly increased the cell viability, total antioxidant capacity (T-AOC), and expression of antioxidant-related genes in AML12 cells under oxidative stress condition, and reduced ROS production [70]. Mett and Müller (2021) also reported that the saturated MCFA decanoic acid (10:0) reduced the oxidative stress level in neuroblastoma cell lines [71].

3.1.3. LCFA

LCFA are essential molecules in signalling pathways such as peroxisome proliferator-activated receptors (PARPs) [104]. Certain gut bacteria can produce LCFA using the intake lipid, which later is absorbed by the enterocytes. Pujo et al. showed that the LCFA (3-hydroxyoctadecaenoic acid) derived by *Escherichia coli* Nissle 1917 had anti-inflammatory capacities [105]. Research in human have revealed that a high consumption LCFA (DHA, EPA) could reduce the risk of breast, prostate and colon cancer [106]. However, Torres et al. found that he LCFA, such as valproic acid, can induce glutathione depletion in mitochondria, causing mitochondrial dysfunction and oxidative stress [73]. Wang et al. also found that LCFA (palmitate) induced apoptosis, oxidative stress and chronic inflammatory responses in the hepatic cells with steatosis [74]. Using skeletal muscle mitochondria, the study by Seifert et al. demonstrated that even a low supply of LCFA is associated with ROS formation in excess of that generated by NADH-linked substrates [75].

3.2. LPS

LPS, also known as endotoxins, are a major component of the cell wall of gram-negative bacteria. Bacterial LPS typically consist of a hydrophobic domain known as lipid A, a nonrepeating 'core' oligosaccharide, and a distal polysaccharide (or O-antigen) [107,108]. LPS is released during the death and disintegration of gram-negative bacteria, and it is a potent inducer of the innate immune system [109]. This endotoxin is recognised by the interplay of receptor and serum-secreted proteins, such as LPS-binding protein and toll-like receptor 4 (TLR-4) [110]. The stimulation of immune cells by pathogens and LPS produces a variety of molecular species, including ROS, via the respiratory burst as part of the host response to infection [6]. There is much evidence to suggest that LPS can induce oxidative stress both in vitro and in vivo [111]. Gut-derived LPS causes neurodegenerative diseases and increases postprandial oxidative stress by activating NADPH oxidase 2 (Nox2) [76,77]. LPS from *E. coli* contributes to atherosclerotic damage via TLR-4-mediated oxidative stress [112]. Systemically circulating LPS interacts with TLR-4 to activate inflammatory responses and oxidative stress in type 1 cardiorenal syndrome through the nuclear factor kappa B (NF-κB) pathway [78]. Moreover, LPS significantly increases the production of ROS and 8-OHDG in bovine mammary epithelial cells and also reduces the viability of the cells [79].

3.3. TRP metabolites

TRP is the least abundant essential amino acid [113] and the only amino acid that contains an indole structure [114]. Its main functions are to participate in protein synthesis and to be a precursor for a variety of bioactive compounds, such as serotonin, indole, and indole derivatives [115,116]. There are three major metabolic pathways of TRP in the gastrointestinal tract: the kynurenine, 5-hydroxytryptamine (5-HT), and microbial metabolism pathways [117]. TRP metabolites, such as kynurenine, 5-HT, indole, and its derivatives, are related to oxidative stress [8,11,118,119].

3.3.1. Kynurenine

The kynurenine pathway accounts for 90 % of TRP catabolism. Wang et al. showed that the deregulated kynurenine pathway plays a key role in the increased prevalence of cardiovascular disease by regulating inflammation, oxidative stress, and immune activation [81]. Increased levels of kynurenine have been shown to cause cell death through the ROS pathway in nature killer cells [120]. Moreover, kynurenine is also able to photooxidize cysteine, NADH, and ascorbic acid in vitro. These photooxidation processes are responsible for the age-related depletion of reduced glutathione and/or formation of H_2O_2 in the lens [80]. Moreover, a recent study has also unveiled that oxidative stress decreased the fertility and induced gut microbiota dysbiosis by disrupting the kynurenine pathway [121].

3.3.2. 5-HT

5-HT, also known as serotonin, is an indoleamine monoamine produced by TRP metabolism. Tryptophan is metabolised by tryptophan hydroxylase to hydroxytryptophan (5-HTP) and is subsequently metabolised to serotonin by amino acid decarboxylase [122]. Most 5-HT in the body is synthesised, stored, and released from enterochromaffin cells, a subset of enteroendocrine cells, in the intestinal mucosa. 5-HT is an important gastrointestinal signal that mediates many GI functions, including peristalsis, secretion, vasodilation, and perception of pain and nausea, through the activation of 5-HT receptors [123]. The gut microbiota can also metabolise TRP directly to 5-HT and alter the availability of TRP in the host [124]. For instance, a study by Yano et al. demonstrated that indigenous spore-forming microbes directly stimulated intestinal serotonin synthesis and release in mice [125]. Additionally, 5-HT is one of the oldest known neurotransmitters that has been associated with numerous disease states, including depression, social phobia, migraine, irritable bowel syndrome, and pulmonary hypertension [126,127]. Research has shown that 5-HT is an effective antioxidant substance that reduces oxidative stress in murine RAW264.7 macrophages and inhibits the production of inflammatory cytokines [11]. Furthermore, 5-HT can inhibit the production of ROS, thereby reducing oxidative stress in phagocytes [82]. Agonists of 5-HT receptors can improve cellular antioxidant capacity by upregulating the expression of nuclear factor erythroid 2-related factor 2 (Nrf2) in astrocytes [83].

3.3.3. Indole and its derivatives

TRP is largely absorbed in the small intestine, but some of it reaches the colon where it is broken down by intestinal bacteria to produce indole and indole derivatives. Indole is a well-known synthesised signalling molecule [128]. Indole can be used as a signalling molecule and antibacterial agent to regulate intestinal communities of bacteria, fungi, and viruses. Indole derivatives such as indole-3-pyruvic acid, indole-3-acetic acid (IAA), and indole acetaldehyde can be used as ligands for aromatic receptors (AHR), which are widely expressed by cells in the immune system and promote beneficial bacteria over pathogenic bacteria in the gut microbiota to regulate host intestinal and systemic homeostasis. The activated TRP-AHR pathway can induce the expression of downstream cytokines, such as interleukin-22 and interleukin-17, thereby regulating intestinal immune function [129]. One of the best-studied antioxidant responses mediated by AHR is the activation of Nrf2. Evidence suggests that AHR directly activates Nrf2; up-regulates NQO1, GSTA1/2, and/or UGT1A6; and exerts antioxidant effects [84]. Therefore, the activation of the TRP-AHR pathway may also regulate oxidative stress. Additionally, evidence shows that indole can induce antibiotic detoxification by activating the protective mechanisms of antioxidant stress and improving the antibiotic resistance capabilities of the *E. coli* population [8]. IAA, a derivative of indole, has been shown to have anti-inflammatory properties and to alleviate non-alcoholic fatty liver disease in mice by attenuating the effects of hepatic lipogenesis and oxidative and inflammatory stress [118,119]. Furthermore, 5-methoxyindoleacetic acid (5-MIAA), which is produced in the 5-HT metabolic pathway, can scavenge free radicals [86,87]. In a recent study, 5-MIAA activated Nrf2 to reduce hepatic oxidative injury [85].

3.4. TMAO

Choline, a trimethylamine-containing compound and part of the phosphatidylcholine head group, is metabolised by gut microbiota to produce an intermediate compound known as trimethylamine (TMA) [130]. TMA is sequentially absorbed and transported through the portal vein to the liver, where it is oxidized to TMAO by flavin-containing monooxygenase (mainly FMO3) [131]. The gut microbiota is important for TMAO metabolism. Research using gnotobiotic mice suggests that gut bacteria are essential for transforming dietary compounds into TMA [132]. Moreover, some studies performed with antibiotics in rats and humans have revealed that the production of TMA and TMAO is almost completely suppressed by the use of broad-spectrum antibiotics. However, TMAO levels return to normal one month after antibiotic withdrawal [133–135]. TMAO had long been thought to be a choline metabolism waste product that had no function in humans; however, there is now convincing evidence suggesting an association between TMAO and various pathophysiological processes, including endothelial dysfunction, arteriosclerosis, and cardiovascular disease [136,137]. Thus, the harmful effects of TMAO may be related to oxidative stress. Studies suggest that HFD-induced obesity leads to the elevated circulation of gut microbiota-generated TMAO, which contributes to renal interstitial fibrosis and dysfunction by promoting renal oxidative stress and inflammation [138]. Sun et al. reported that TMAO activates ROS-TXNIP-NLRP3 inflammasome signalling in endothelial cells [10]. Additionally, TMAO can lead to endothelial dysfunction in old-aged rats through vascular inflammation and oxidative stress [139], and it can accelerate mouse endothelial cell senescence and vascular aging through oxidative stress [140].

3.5. Polyphenolic metabolites

Dietary polyphenols have beneficial roles in decreasing oxidative stress. The gut microbiota can use the unabsorbed polyphenols as substrates for their enzymatic activities [141]. It is reported that luteolin can be metabolised to luteolin-3-O-β-D-glucuronide and luteolin-3-O-sulfate, and luteolin helps to reduce the NO synthase to maintain the cardiac health by preventing the damage from free radicals. In addition, cyanidin can be metabolised to protocatechuic acid [142,88]. Zhang et al. revealed that protocatechuic acid increased the activities of GPX and CAT and decreased MDA level in aged rats [89]. Moreover, Yip et al. also demonstrated that protocatechuic acid improved the mitochondrial function by reducing ROS level and increasing GSH [90]. Furthermore, 5- (3′, 4′-dihydroxyphenyl)-γ-valerolactone, a metabolite of catechin, also had antioxidant capacity in the intestinal epithelial cells [91].

Taken together, various gut microbiota metabolites are closely associated with oxidative stress. Therefore, regulating these metabolites and related gut bacteria may have antioxidant effects and impove the health of hunman and animals. Since it is well-known that probiotics can regulate gut microbiota, the following focuses on the regulatory effect of probiotics on the gut metabolites to resist

oxidative stress.

4. Antioxidation of probiotics and the regulation of gut microbiota metabolites

Previous studies have shown that probiotics have antioxidant potential. Eating probiotics alone or in foods containing probiotics can reduce oxidative damage, improve the efficiency of free radical scavenging, and alter the activities of key antioxidant enzymes [143]. In particular, lactic acid bacteria have significant functional properties, such as antioxidant and immunoregulatory capacities, and are considered as ideal probiotics [144]. There is evidence that lactic acid bacteria can be used as a supplement to contribute to the

Table 2
Probiotics regulating gut microbiota and related metabolites.

Probiotics	Altered gut microbiota	Gut microbiota metabolites	Functions	References
Mixture of 10 *Lactobacillus* strains and 4 yeast strains	Lactic acid bacteria↑ *Bifidobacterium*↑ *Clostridium leptum*↑ *Roseburia*↑ *Escherichia coli*↓	SCFA↑	Alleviate type 2 diabetes in db/db mice	[157]
Lactobacillus paracasei ssp. *Paracasei BCRC 12188* *Lactobacillus plantarum BCRC 12251* *Streptococcus thermophilus BCRC13869*	*Bifidobacterium*↑ *Lactobacillus*↑ Enterobacteriaceae↓	SCFA↑	Improve the memory of learning abilities in aging mice	[156]
Lactobacillus fermentum 296	*Lactobacillus* sp.↑	SCFA↑	Attenuate cardiometabolic disorders in HFD-treated rats	[158]
DBR (a mixture of 9 probiotics and 10 digestive enzymes)	–	SCFA↑	Decrease LDL and increase HDL levels	[159]
–	*Lactobacillus*↑	SCFA↑	Improve the reproduction performance of laying hens	[157]
multispecies probiotic	–	MCFA↑	Decrease depressive disorder	[162]
Lactobacillus rhamnosus GG	–	MCFA in feces↑	Attenuate alchoholic fatty liver disease	[163]
Enterococcus faecalis	–	LCFA↑	Reduce adiposity and activate beige fat formation in HFD-fed mice	[165]
Enterococcus faecalis AG5	–	LCFA↑	Mitigate HFD induced obesity in Wistar rats	[166,167]
Bifidobacterium infantis *Lactobacillus acidopilus* *Bacillus cereus*	–	LPS↓	Delay the progression of NAFLD	[158]
Lactobacillus subtilis *Streptococcus faecium*	*Escherichia coli*↓	LPS↓	Restore the bowel flore and decrease LPS level in patients with alcoholic hepatitis	[159]
Lactobacillus casei Shirota *Lactobacillus fermentium* *Lactobacillus plantarum* *Lactobacillus salivarius* *Bifidobacterium breve*	–	LPS↓	Modulate the production of cytokines	[171]
Bifidobacterium bifidum *Lactobacillus rhamnosus* *Bifidobacterium longum* *Bifidobacterium longum* subsp. *Infantis*	–	LPS↓	Decrease colonic LPS concentrations amd reduce the proinflammatory tone	[172]
Lactobacillus reuteri	–	Indole derivative↑	–	[160]
Lactobacillus rhamnosus GG	*Lactobacillus*↑	5-MIAA↑	Protect against liver oxidative injury	[85]
Lactobacillus plantarum ZDY04	Lachnospiraceae↑ Erysipelotrichaceae↑ Bacteroidaceae↑ *Mucispirillum*↓	TMAO, TMA↓	Reduce TMAO-induced atherosclerosis	[175]
Lactofermented annurca apple puree	–	TMAO↓	Control of plasma HDL-C and TMAO levels	[176]
Enterobacter aerogenes ZDY01	–	TMAO, TMA↓	Attenuate choline-induced atherosclerosis	[177]
Bifidobacterium animalis subsp. *Lactis* LKM512	–	TMA↓	Reduce the risk of arteriosclerosis development	[178]
Lactobacillus plantarum CLC 17	–	phenolic metabolites↑	–	[182]
Lactobacillus plantarum, *Lactobacillus paraplantarum* and *Lactobacillus pentosus*	–	phenolic acids↑	Regulate glucose metabolism	[183]

Abbreviations: SCFA, short-chain fatty acids; MCFA, medium-chain fatty acids; LCFA, long-chain fatty acids; MCFA, medium-chain fatty acids; LPS, lipopolysaccharides; 5-MIAA, 5-methoxyindoleacetic acid; TMAO, trimethylamine-*N*-oxide; TMA, trimethylamine.

downregulation of ROS-forming enzymes, modulation of Nrf2 and NF-κB transcription factors, and improvement of gastrointestinal inflammation and other chronic diseases caused by oxidative stress [145]. *Lactobacillus plantarum* 9 (LB-9) has been reported to ameliorate dextran sodium sulfate-induced colitis in mice by inhibiting the TNF-α-mediated apoptosis of intestinal epithelial cells and effectively inhibiting oxidative stress responses and inflammation [146]. *Lactobacillus delbrueckii* increases intestinal integrity by improving the intestinal structure and tight junctions, while also enhancing antioxidant functions via activation of the TLR-Btk-Nrf2 signalling pathway [147]. *Bifidobacterium* is an extensively studied probiotic that is an important member of the gut microbiota of humans and animals. Supplementation of *Bifidobacterium animal* can increase the jejunal T-AOC level and decreased the jejunal MDA level in pigs [148], also increased the SOD, catalase (CAT), and gluthathione peroxidase (GPX) activites and decreased the MDA in the plasma and livers of D-galactose-treated rats [149]; these effects exemplify the potent antioxidant properties of these probiotics. Moreover, the culture supernatant, intact cells, and intracellular cell-free extracts of *Bifidobacterium animalis* can effectively scavenge free radicals, significantly enhance the activities of antioxidative enzymes, and reduce the MDA content, lipofuscin level, and monoamine oxidase activity in mice [150]. *Bacillus* is widely used as feed additive, as it can grow under harsh environmental conditions (e.g., acidic, alkaline, or high-temperature environments) due to the formation of spores. Dietary supplementation with different concentrations of *Bacillus subtilis* has been reported to enhance the antioxidative status and digestive enzyme activities of quails [151]. Tang et al. [152] showed that *Bacillus amyloliquefaciens* SC06 induced AKT-FOXO signalling pathway-mediated autophagy to alleviate oxidation-induced apoptosis and cell damage in IPEC-J2 cells. *Bacillus amyloliquefaciens* SC06 can also alleviate IPEC-1-induced oxidative stress by modulating the Nrf2-Keap 1 signalling pathway and decreasing ROS production [153]. Furthermore, *Bacillus amyloliquefaciens* SC06 increased the hepatic capacity of HFD-induced obese mice by regulating the Nrf2-Keap1 signalling pathway, decreasing the Firmicutes/Bacteroidetes ratio, and increasing *TM7* abundance to reduce HFD-related lipid accumulation and liver injury [154]. The antioxidant capacity of probiotics is determined based on numerous processes, including the chelating of metal ions, production of antioxidases and antioxidant metabolites, increases in the antioxidase activities and antioxidant metabolites of the host, the mediation of antioxidant signalling pathways, and the reduction of ROS-producing enzyme activities [13]. Moreover, studies have shown that probiotics can regulate the oxidative status of hosts by affecting their gut microbiota [155]. Additionally, recent reports have indicated that the antioxidant role of probiotics in the gut microbiota is closely related to gut microbiota metabolites [156]. The regulations of gut microbiota metabolites by probiotics are discussed below and summarised in Table 2.

4.1. Regulation of fatty acids by probiotics

Many studies have indicated that probiotics may resist oxidative damage by regulating SCFA levels. Wang et al. [161] reported that composite probiotics (specifically a mixture of ten *Lactobacillus* strains and four yeast strains) can improve gut barrier function by increasing the abundance of SCFA-producing bacteria, the SCFA levels, and the expression of Claudin-1 and Mucin-2, while also decreasing the levels of *E. coli* and LPS. A probiotic mixture (PM-1) containing *Lactobacillus paracasei* subsp. *Paracasei* BCRC 12188, *Lactobacillus plantarum* BCRC 12251, and *Streptococcus thermophilus* BCRC13869 increased SCFA production and Nrf2 expression in D-galactose-treated aging mice, and its possible antioxidant effect may have been triggered by SCFA [156]. Acid-producing probiotics modulate vasodilatation and hypotension by increasing SCFA levels [162]. Ichim et al. reported that DBR, a mixture of nine probiotics and 10 digestive enzymes, reduced serum cholesterol and cardiovascular risk by increasing propionic acid levels [163]. Moreover, EUBIO-BPSG is a phytogenic formulation composed of *B. pilosa* phytochemicals which has antioxidant capacity [164]. Tran Nguyen Minh et al. revealed that EUBIO-BPSG could promote the growth of *Lactobacillus* to produce SCFA in the in vitro co-culture experiments, and also improve the egg production of laying hens and increased fecal *Lactobacillus* in vivo, implying the SCFA induced by EUBIO-BPSG may elevate the antioxidant capacity of laying hens to improve the reproductive performance [157].

It is reported that MCFA can also be regulated by probiotics. Capric acid, an MCFA, was elevated after 28 days of the multispecies probiotic intake in individuals with major depressive disorder compared with the placebo group [165]. Besides, compared with the alcohol-treated mice, MCFA were increased in feces, but decreased in liver when the mice were co-exposed to *Lactobacillus rhamnosus* GG [166]. Although it is known that alcohol treatmen can lead to oxidative stress [167], there is a lack of direct evidence for probiotics improving antioxidant capacity by regulating MCFA.

In addition, Quan et al. demonstrated that *Enterococcus faecalis*, a probiotic, produced an unsaturated LCFA (myristoleic acid). *Enterococcus faecalis* and its metabolite myristoleic acid can reduce adiposity by brown adipose tissue activation and beige fat formation in HFD-fed mice [168]. Mishara et al. also found that *Enterococcus faecalis* AG5 produced several LCFA such as tetradecanoic acid, hexadecanoic acid, octadecanoic acid and bis(6-methylheptyl) phthalate, and mitigated HFD induced obesity in Wistar rats [169]. As the changes in intestinal microbiota following HFD could promote metabolic endotoxemia and trigger metabolic disorders, including obesity and oxidative stress [170]. Therefore, the above findings imply that *Enterococcus faecalis* may alleviate obesity and oxidative stress by the production of LCFA.

4.2. Regulation of LPS by probiotics

Probiotics can combat LPS to reduce oxidative stress. A probiotic mixture of *Bifidobacterium infantis*, *Lactobacillus acidopilus*, and *Bacillus cereus* has been shown to downregulate serum LPS and liver TLR-4 levels through the LPS/TLR-4 signalling pathway and delay the progression of non-alcoholic fatty liver disease [158]. *Lactobacillus subtilis* and *Streptococcus faecium* can reduce gut-derived microbial LPS by restoring the gut microbiota of patients with alcoholic hepatitis [159]. Furthermore, selected probiotics can inhibit the binding of LPS to the CD14 receptor, thereby reducing the overall activation of NF-κB and the production of proinflammatory cytokines

[171]. Rodes et al. revealed that specific probiotic strains, such as *Lactobacillus rhamnosus*, *Bifidobacterium bifidum* and *Bifidobacterium longum* subsp. *Infantis*, can decrease colonic LPS concentrations, which might further reduce the secretion of inflammatory cytokines in macrophages [172].

4.3. Regulation of TRP metabolites by probiotics

As for TRP metabolites, gut microbe-related SCFA promote colonic serotonin production through their effects on enterochromaffin cells [173]. There is evidence that a reduction in gut *Bifidobacterium* species is associated with deficient TRP metabolism in the intestine and marked gastrointestinal dysfunction in mice with autism spectrum disorder [174]. *Lactobacillus reuteri* provides indole derivatives of dietary L-TRP, such as indole-3-lactic acid, which activates AHR and leads to the downregulation of Thpok and the reprogramming of $CD4^+$ intraepithelial lymphocytes into $CD4^+CD8\alpha\alpha+$ double-positive intraepithelial lymphocytes. This reprogramming may be useful for treating disorders that may be sensitive to double-positive intraepithelial lymphocytes, such as inflammatory bowel diseases [160]. Additionally, a recent study has shown that the *Lactobacillus*-derived molecule 5-MIAA can activate hepatic Nrf2, promote the transcription of genes involved in the cellular antioxidant response, and improve the hepatic antioxidant capacity of mice [85].

4.4. Regulation of TMAO by probiotics

Lactobacillus plantarum ZDY04 has been reported to significantly reduce serum TMAO and caecal TMA levels by modulating the relative abundance of Lachnospiraceae, Erysipelotrichaceae, Bacteroidaceae, and *Mucispirillum* in mice, and it can also reduce the development of atherosclerosis [175]. Tenore et al. reported a reduction in TMAO levels in subjects with a risk of cardiovascular disease following the consumption of lactofermented Annurca apple puree [176]. *Enterobacter aerogenes* ZDY01 can decrease caecal TMA and serum TMAO levels by utilising caecal TMA as a nutrient [177]. Additionally, *Bifidobacterium animalis* subsp. *Lactis* LKM512 may decrease TMA levels in healthy individuals [178]. However, other studies have reported contradictory results. Tripolt et al. found that *Lactobacillus casei* supplementation had no significant effect on the TMAO levels in subjects with metabolic syndrome [179]. Malik et al. also noted that *Lactobacillus plantarum* 299v did not significantly alter plasma TMAO levels in 20 men with stable coronary artery disease [180].

4.5. Regulation of polyphenolic metabolites by probiotics

It is reported that polyphenols exert their beneficial effects by elevating the abundance of probiotic bacterial such as *Bifidobacteriaceae* and *Lactobacillaceae* and inhibiting pathogenic bacteria such as *E. coli*, *Clostridium perfringens* and *Helicobacter pylori* [181]. In turn, probiotic bacteria promote the metabolite of polyphenols. Gil-Sánchez et al. revealed that inclusion of *Lactobacillus plantarum* CLC 17 to a Dynamic Gastronitestinal Simulator (simgi®) led to a greater formation of phenolic metabolites [182]. Ueda et al. demonstrated that probiotics, such as *Lactobacillus plantarum*, *Lactobacillus paraplantarum* and *Lactobacillus pentosus*, express tannin metabolising enzymes like tannase and gallate decarboxylase to produce phenolic acids that may play an essential role in glucose metabolism and thus affect the development and treatment of obesity [183].

5. Conclusions

In conclusion, this review describes how the disruption of redox homeostasis may lead to gastrointestinal and systemic diseases. The recent surge in gut microbiota studies due to advancements in sequencing techniques and metabolomics has enriched our

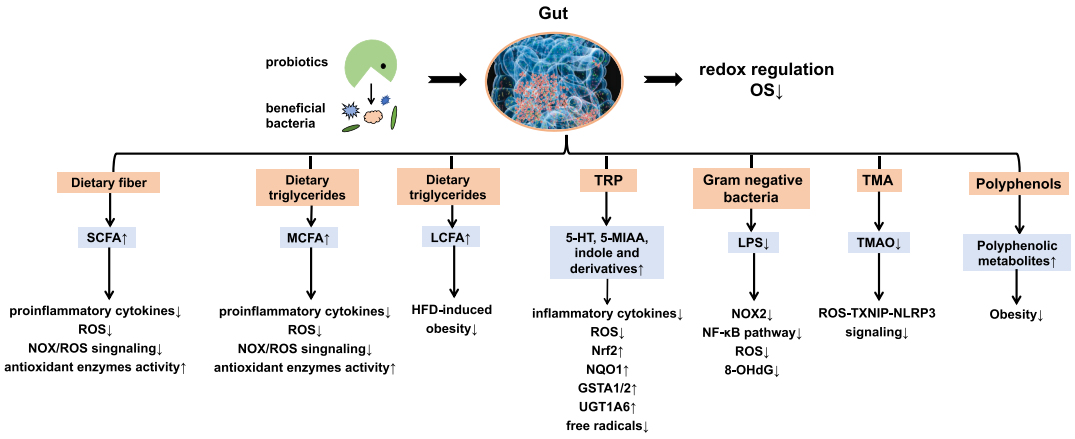


Fig. 2. Probiotics modulate oxidative stress through gut microbiota metabolites.

knowledge of the role of gut microbiota and related metabolites in oxidative stress. A subset of gut microbiota metabolites, such as fatty acids, LPS, TRP metabolites, TMAO and polyphenolic metabolites have been shown to be relevant to redox regulation. Moreover, the use of probiotics appears to be a reasonable approach for modulating gut microbiota metabolites, thereby preventing or avoiding oxidative stress and related diseases (Fig. 2). However, studies on this topic have been limited and further research is required. In future studies, the combination of microbiome analysis with other omics, such as proteomics and metabolomics, will help us clarify the interactions between gut microbiota metabolites and host redox status and will illuminate the mechanisms of probiotics in regulating oxidative stress through gut microbiota metabolites.

Funding statement

This study was supported by the National Natural Science Foundation of China (Grant No. 32102586), the Shandong Provincial Natural Science Foundation (Grant No. ZR2020QC183) and the State Key Laboratory of Animal Nutrition.

Data availability statement

Not applicable.

Additional information

No additional information is available for this paper.

CRediT authorship contribution statement

Jinshan Zhao: Conceptualization, Resources, Writing – original draft. **Fan Zhao:** Investigation, Writing – original draft. **Junmeng Yuan:** Formal analysis, Investigation. **Huawei Liu:** Investigation. **Yang Wang:** Conceptualization, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] M. Valko, D. Leibfritz, J. Moncol, M.T. Cronin, M. Mazur, J. Telser, Free radicals and antioxidants in normal physiological functions and human disease, Int. J. Biochem. Cell Biol. 39 (2007) 44–84, https://doi.org/10.1016/j.biocel.2006.07.001.
[2] Z. Ďuračková, Some current insights into oxidative stress, Physiol. Res. 59 (2010) 459–469, https://doi.org/10.33549/physiolres.931844.
[3] R.M. Jones, A.S. Neish, Redox signaling mediated by the gut microbiota, Free Radic. Biol. Med. 105 (2017) 41–47, https://doi.org/10.1016/j.freeradbiomed.2016.10.495.
[4] L. Hao, Y. Cheng, W. Su, C. Wang, Z. Lu, M. Jin, F. Wang, Y. Wang, Pediococcus pentosaceus ZJUAF-4 relieves oxidative stress and restores the gut microbiota in diquat-induced intestinal injury, Appl. Microbiol. Biotechnol. 105 (2021) 1657–1668, https://doi.org/10.1007/s00253-021-11111-6.
[5] L. Sun, H. Jia, J. Li, M. Yu, Y. Yang, D. Tian, H. Zhang, Z. Zou, Cecal gut microbiota and metabolites might contribute to the severity of acute myocardial ischemia by impacting the intestinal permeability, oxidative stress, and energy metabolism, Front. Microbiol. 10 (2019) 1745, https://doi.org/10.3389/fmicb.2019.01745.
[6] V. Houde, D. Grenier, F. Chandad, Protective effects of grape seed proanthocyanidins against oxidative stress induced by lipopolysaccharides of periodontopathogens, J. Periodontol. 77 (2006) 1371–1379, https://doi.org/10.1902/jop.2006.050419.
[7] M. Spiljar, D. Merkler, M. Trajkovski, The immune system bridges the gut microbiota with systemic energy homeostasis: focus on TLRs, mucosal barrier, and SCFAs, Front. Immunol. 8 (2017) 1353, https://doi.org/10.3389/fimmu.2017.01353.
[8] H.H. Lee, M.N. Molla, C.R. Cantor, J.J. Collins, Bacterial charity work leads to population-wide resistance, Nature 467 (2010) 82–85, https://doi.org/10.1038/nature09354.
[9] M. Han, P. Song, C. Huang, A. Rezaei, S. Farrar, M.A. Brown, X. Ma, Dietary grape seed proanthocyanidins (GSPs) improve weaned intestinal microbiota and mucosal barrier using a piglet model, Oncotarget 7 (2016) 80313–80326, https://doi.org/10.18632/oncotarget.13450.
[10] X. Sun, X. Jiao, Y. Ma, Y. Liu, L. Zhang, Y. He, Y. Chen, Trimethylamine N-oxide induces inflammation and endothelial dysfunction in human umbilical vein endothelial cells via activating ROS-TXNIP-NLRP3 inflammasome, Biochem. Biophys. Res. Commun. 481 (2016) 63–70, https://doi.org/10.1016/j.bbrc.2016.11.017.
[11] O. Vašíček, A. Lojek, M. Číž, Serotonin and its metabolites reduce oxidative stress in murine RAW264.7 macrophages and prevent inflammation, J. Physiol. Biochem. 76 (2020) 49–60, https://doi.org/10.1007/s13105-019-00714-3.
[12] A. Oniszczuk, T. Oniszczuk, M. Gancarz, J. Szymańska, Role of gut microbiota, probiotics and prebiotics in the cardiovascular diseases, Molecules 26 (2021) 1172, https://doi.org/10.3390/molecules26041172.
[13] Y. Wang, Y. Wu, Y. Wang, H. Xu, X. Mei, D. Yu, Y. Wang, W. Li, Antioxidant properties of probiotic bacteria, Nutrients 9 (2017) 521, https://doi.org/10.3390/nu9050521.
[14] T. Finkel, N.J. Holbrook, Oxidants, Oxidative stress and the biology of ageing, Nature 408 (2000) 239–247, https://doi.org/10.1038/35041687.
[15] M.L. Ávila-Escalante, F. Coop-Gamas, M. Cervantes-Rodríguez, D. Méndez-Iturbide, I.I. Aranda-González, The effect of diet on oxidative stress and metabolic diseases-Clinically controlled trials, J. Food Biochem. 44 (2020), e13191, https://doi.org/10.1111/jfbc.13191.
[16] D. Liu, Y. Xu, p53, oxidative stress, and aging, Antioxidants Redox Signal. 15 (2011) 1669–1678, https://doi.org/10.1089/ars.2010.3644.
[17] D. Liang, Y. Zhuo, Z. Guo, L. He, X. Wang, Y. He, L. Li, H. Dai, SIRT1/PGC-1 pathway activation triggers autophagy/mitophagy and attenuates oxidative damage in intestinal epithelial cells, Biochimie 170 (2020) 10–20, https://doi.org/10.1016/j.biochi.2019.12.001.
[18] J.N. Peoples, A. Saraf, N. Ghazal, T.T. Pham, J.Q. Kwong, Mitochondrial dysfunction and oxidative stress in heart disease, Exp. Mol. Med. 51 (2019) 1–13, https://doi.org/10.1038/s12276-019-0355-7.

[19] C. Tian, L. Hao, W. Yi, S. Ding, F. Xu, Polyphenols, oxidative stress, and metabolic syndrome, Oxid. Med. Cell. Longev. 2020 (2020), 7398453, https://doi.org/10.1155/2020/7398453.

[20] B.S. Karam, A. Chavez-Moreno, W. Koh, J.G. Akar, F.G. Akar, Oxidative stress and inflammation as central mediators of atrial fibrillation in obesity and diabetes, Cardiovasc. Diabetol. 16 (2017) 120, https://doi.org/10.1186/s12933-017-0604-9.

[21] M.D. Jelic, A.D. Mandic, S.M. Maricic, B.U. Srdjenovic, Oxidative stress and its role in cancer, J. Cancer Res. Therapeut. 17 (2021) 22–28, https://doi.org/10.4103/jcrt.JCRT_862_16.

[22] M. Higuchi, G.J. Dusting, H. Peshavariya, F. Jiang, S.T. Hsiao, E.C. Chan, G.S. Liu, Differentiation of human adipose-derived stem cells into fat involves reactive oxygen species and Forkhead box O1 mediated upregulation of antioxidant enzymes, Stem Cell. Dev. 22 (2013) 878–888, https://doi.org/10.1089/scd.2012.0306.

[23] S. Jiang, H. Liu, C. Li, Dietary regulation of oxidative stress in chronic metabolic diseases, Foods 10 (2021) 1854, https://doi.org/10.3390/foods10081854.

[24] G. Boden, C. Homko, C.A. Barrero, T.P. Stein, X. Chen, P. Cheung, C. Fecchio, S. Koller, S. Merali, Excessive caloric intake acutely causes oxidative stress, GLUT4 carbonylation, and insulin resistance in healthy men, Sci. Transl. Med. 7 (2015) 304re7, https://doi.org/10.1126/scitranslmed.aac4765.

[25] K. Rehman, M.S.H. Akash, Mechanism of generation of oxidative stress and pathophysiology of type 2 diabetes mellitus: how are they interlinked? J. Cell. Biochem. 118 (2017) 3577–3585, https://doi.org/10.1002/jcb.26097.

[26] J.C. Jha, C. Banal, B.S. Chow, M.E. Cooper, K. Jandeleit-Dahm, Diabetes and kidney disease: role of oxidative stress, Antioxidants Redox Signal. 25 (2016) 657–684, https://doi.org/10.1089/ars.2016.6664.

[27] M. Sakashita, T. Tanaka, R. Inagi, Metabolic changes and oxidative stress in diabetic kidney disease, Antioxidants 10 (2021) 1143, https://doi.org/10.3390/antiox10071143.

[28] A. Valavanidis, T. Vlachogianni, K. Fiotakis, S. Loridas, Pulmonary oxidative stress, inflammation and cancer: respirable particulate matter, fibrous dusts and ozone as major causes of lung carcinogenesis through reactive oxygen species mechanisms, Int. J. Environ. Res. Publ. Health 10 (2013) 3886–3907, https://doi.org/10.3390/ijerph10093886.

[29] F. Hecht, C.F. Pessoa, L.B. Gentile, D. Rosenthal, D.P. Carvalho, R.S. Fortunato, The role of oxidative stress on breast cancer development and therapy, Tumour Biol 37 (2016) 4281–4291, https://doi.org/10.1007/s13277-016-4873-9.

[30] C.J. Weydert, T.A. Waugh, J.M. Ritchie, K.S. Iyer, J.L. Smith, L. Li, D.R. Spitz, L.W. Oberley, Overexpression of manganese or copper–zinc superoxide dismutase inhibits breast cancer growth, Free Radic. Biol. Med. 41 (2006) 226–237, https://doi.org/10.1016/j.freeradbiomed.2006.03.015.

[31] M.J. Hitchler, K. Wikainapakul, L. Yu, K. Powers, W. Attatippaholkun, F.E. Domann, Epigenetic regulation of manganese superoxide dismutase expression in human breast cancer cells, Epigenetics 1 (2006) 163–171, https://doi.org/10.4161/epi.1.4.3401.

[32] A. Jemal, R. Siegel, J. Xu, E. Ward, Cancer statistics, CA A Cancer J. Clin. 60 (2010) (2010) 277–300, https://doi.org/10.3322/caac.20073.

[33] A. Paschos, R. Pandya, W.C. Duivenvoorden, J.H. Pinthus, Oxidative stress in prostate cancer: changing research concepts towards a novel paradigm for prevention and therapeutics, Prostate Cancer Prostatic Dis. 16 (2013) 217–225, https://doi.org/10.1038/pcan.2013.13.

[34] J.H. Pinthus, I. Bryskin, J. Trachtenberg, J.P. Lu, G. Singh, E. Fridman, B.C. Wilson, Androgen induces adaptation to oxidative stress in prostate cancer: implications for treatment with radiation therapy, Neoplasia 9 (2007) 68–80, https://doi.org/10.1593/neo.06739.

[35] K.V. Donkena, C.Y. Young, D.J. Tindall, Oxidative stress and DNA methylation in prostate cancer, Obstet. Gynecol. Int. 2010 (2010), 302051, https://doi.org/10.1155/2010/302051.

[36] J.D. Hayes, J.U. Flanagan, I.R. Jowsey, Glutathione transferases, Annu. Rev. Pharmacol. Toxicol. 45 (2005) 51–88, https://doi.org/10.1146/annurev.pharmtox.45.120403.095857.

[37] A.C. Blackburn, K.I. Matthaei, C. Lim, M.C. Taylor, J.Y. Cappello, J.D. Hayes, M.W. Anders, P.G. Board, Deficiency of glutathione transferase zeta causes oxidative stress and activation of antioxidant response pathways, Mol. Pharmacol. 69 (2006) 650–657, https://doi.org/10.1124/mol.105.018911.

[38] D.K. Vanaja, M. Ehrich, D. Van den Boom, J.C. Cheville, R.J. Karnes, D.J. Tindall, C.R. Cantor, C.Y. Young, Hypermethylation of genes for diagnosis and risk stratification of prostate cancer, Cancer Invest. 27 (2009) 549–560, https://doi.org/10.1080/07357900802620794.

[39] H. Esme, M. Cemek, M. Sezer, H. Saglam, A. Demir, H. Melek, M. Unlu, High levels of oxidative stress in patients with advanced lung cancer, Respirology 13 (2008) 112–116, https://doi.org/10.1111/j.1440-1843.2007.01212.x.

[40] A. Gęgotek, J. Nikliński, N. Žarković, K. Žarković, G. Waeg, W. Łuczaj, R. Charkiewicz, E. Skrzydlewska, Lipid mediators involved in the oxidative stress and antioxidant defence of human lung cancer cells, Redox Biol. 9 (2016) 210–219, https://doi.org/10.1016/j.redox.2016.08.010.

[41] K. Jaakkola, P. Lähteenmäki, J. Laakso, E. Harju, H. Tykkä, K. Mahlberg, Treatment with antioxidant and other nutrients in combination with chemotherapy and irradiation in patients with small-cell lung cancer, Anticancer Res. 12 (1992) 599–606. https://europepmc.org/article/med/1320355.

[42] J. Wang, J.Z. Li, A.X. Lu, K.F. Zhang, B.J. Li, Anticancer effect of salidroside on A549 lung cancer cells through inhibition of oxidative stress and phospho-p38 expression, Oncol. Lett. 7 (2014) 1159–1164, https://doi.org/10.3892/ol.2014.1863.

[43] A. Agarwal, G. Virk, C. Ong, S.S. Du Plessis, Effect of oxidative stress on male reproduction, World J. Mens Health 32 (2014) 1–17, https://doi.org/10.5534/wjmh.2014.32.1.1.

[44] S.S. Du Plessis, D.A. McAllister, A. Luu, J. Savia, A. Agarwal, F. Lampiao, Effects of H_2O_2 exposure on human sperm motility parameters, reactive oxygen species levels and nitric oxide levels, Andrologia 42 (2010) 206–210, https://doi.org/10.1111/j.1439-0272.2009.00980.x.

[45] J. Lu, Z. Wang, J. Cao, Y. Chen, Y.L. Dong, A novel and compact review on the role of oxidative stress in female reproduction, Reprod. Biol. Endocrinol. 16 (2018) 1–18, https://doi.org/10.1186/s12958-018-0391-5.

[46] Q. Liu, W. Li, J. Zhang, L. Zhao, C. Ji, J. Zhang, S. Huang, Q. Ma, Lipoamide alleviates oxidized fish oil-induced host inflammatory response and oxidative damage in the oviduct of laying hens, Front. Vet. Sci. 9 (2022), 875769, https://doi.org/10.3389/fvets.2022.875769.

[47] K. Bai, E. Hao, C. Huang, Q. Yue, D. Wan, L. Shi, Y. Chen, H. Chen, R. Huang, Melatonin alleviates ovarian function damage and oxidative stress induced by dexamethasone in the laying hens through FOXO1 signaling pathway, Poultry Sci. 102 (2023), 102745, https://doi.org/10.1016/j.psj.2023.102745.

[48] B.N. Vemo, A. Kenfack, F. Ngoula, E.A. Nantia, N. Kodjio, A.J.N. Guiekep, A.M.M. Tsambou, A. Teguia, Effects of ethanol extract of Bersama engleriana leaves on oxidative stress and reproductive parameters in male Guinea pig (Cavia porcellus) exposed to cypermethrin, Int. J. Biol. Chem. 11 (2017) 2243–2253, https://doi.org/10.4314/ijbcs.v11i5.23.

[49] S.F. Assimakopoulos, C. Triantos, I. Maroulis, C. Gogos, The role of the gut barrier function in health and disease, Gastroenterol. Res. 11 (2018) 261–263, https://doi.org/10.14740/gr1053w.

[50] J. Huo, Z. Wu, W. Sun, Z. Wang, J. Wu, M. Huang, B. Wang, B. Sun, Protective effects of natural polysaccharides on intestinal barrier injury: a review, J. Agric. Food Chem. 70 (2022) 711–735, https://doi.org/10.1021/acs.jafc.1c05966.

[51] T. Hasegawa, A. Mizugaki, Y. Inoue, H. Kato, H. Murakami, Cystine reduces tight junction permeability and intestinal inflammation induced by oxidative stress in Caco-2 cells, Amino Acids 53 (2021) 1021–1032, https://doi.org/10.1007/s00726-021-03001-y.

[52] K.F. Castro-Ochoa, H. Vargas-Robles, S. Chánez-Paredes, A. Felipe-López, R.I. Cabrera-Silva, M. Shibayama, A. Betanzos, P. Nava, E.A. Galinski, M. Schnoor, Homoectoine protects against colitis by preventing a Claudin switch in epithelial tight junctions, Dig. Dis. Sci. 64 (2019) 409–420, https://doi.org/10.1007/s10620-018-5309-8.

[53] H. Li, P. Wang, L. Huang, P. Li, D. Zhang, Effects of regulating gut microbiota on the serotonin metabolism in the chronic unpredictable mild stress rat model, Neuro Gastroenterol. Motil. 31 (2019), e13677, https://doi.org/10.1111/nmo.13677.

[54] A. Banan, J.Z. Fields, Y. Zhang, A. Keshavarzian, Phospholipase C-gamma inhibition prevents EGF protection of intestinal cytoskeleton and barrier against oxidants, Am. J. Physiol. Gastrointest. Liver Physiol. 281 (2001) G412–G423, https://doi.org/10.1152/ajpgi.2001.281.2.G412.

[55] R.K. Rao, S. Basuroy, V.U. Rao, K.J. Karnaky Jr., A. Gupta, Tyrosine phosphorylation and dissociation of occludin-ZO-1 and E-cadherin-beta-catenin complexes from the cytoskeleton by oxidative stress, Biochem. J. 368 (2002) 471–481, https://doi.org/10.1042/BJ20011804.

[56] A. Banan, J.Z. Fields, A. Farhadi, D.A. Talmage, L. Zhang, A. Keshavarzian, Activation of delta-isoform of protein kinase C is required for oxidant-induced disruption of both the microtubule cytoskeleton and permeability barrier of intestinal epithelia, J. Pharmacol. Exp. Therapeut. 303 (2002) 17–28, https://doi.org/10.1124/jpet.102.037218.

[57] A. Bhattacharyya, R. Chattopadhyay, S. Mitra, S.E. Crowe, Oxidative stress: an essential factor in the pathogenesis of gastrointestinal mucosal diseases, Physiol. Rev. 94 (2014) 329–354, https://doi.org/10.1152/physrev.00040.2012.

[58] A. Farhadi, A. Banan, J. Fields, A. Keshavarzian, Intestinal barrier: an interface between health and disease, J. Gastroenterol. Hepatol. 18 (2003) 479–497, https://doi.org/10.1046/j.1440-1746.2003.03032.x.

[59] X. Chang, X. Wang, J. Feng, X. Su, J. Liang, H. Li, J. Zhang, Impact of chronic exposure to trichlorfon on intestinal barrier, oxidative stress, inflammatory response and intestinal microbiome in common carp (Cyprinus carpio L.), Environ. Pollut. 259 (2020), 113846, https://doi.org/10.1016/j.envpol.2019.113846.

[60] Z. Zhao, W. Qu, K. Wang, S. Chen, L. Zhang, D. Wu, Z. Chen, Bisphenol A inhibits mucin 2 secretion in intestinal goblet cells through mitochondrial dysfunction and oxidative stress, Biomed. Pharmacother. 111 (2019) 901–908, https://doi.org/10.1016/j.biopha.2019.01.007.

[61] D. Cervantes-García, A.I. Bahena-Delgado, M. Jiménez, L.E. Córdova-Dávalos, V. Ruiz-Esparza Palacios, E. Sánchez-Alemán, M.C. Martínez-Saldaña, E. Salinas, Glycomacropeptide ameliorates indomethacin-induced enteropathy in rats by modifying intestinal inflammation and oxidative stress, Molecules 25 (2020) 2351, https://doi.org/10.3390/molecules25102351.

[62] J. Gagnière, J. Raisch, J. Veziant, N. Barnich, R. Bonnet, E. Buc, M.A. Bringer, D. Pezet, M. Bonnet, Gut microbiota imbalance and colorectal cancer, World J. Gastroenterol. 22 (2016) 501–518, https://doi.org/10.3748/wjg.v22.i2.501.

[63] T. Yardeni, C.E. Tanes, K. Bittinger, L.M. Mattei, P.M. Schaefer, L.N. Singh, G.D. Wu, D.G. Murdock, D.C. Wallace, Host mitochondria influence gut microbiome diversity: a role for ROS, Sci. Signal. 12 (2019), https://doi.org/10.1126/scisignal.aaw3159 eaaw3159.

[64] J.W.O. Ballard, S.G. Towarnicki, Mitochondria, the gut microbiome and ROS, Cell. Signal. 75 (2020), 109737, https://doi.org/10.1016/j.cellsig.2020.109737.

[65] Y. Qiao, J. Sun, Y. Ding, G. Le, Y. Shi, Alterations of the gut microbiota in high-fat diet mice is strongly linked to oxidative stress, Appl. Microbiol. Biotechnol. 97 (2013) 1689–1697, https://doi.org/10.1007/s00253-012-4323-6.

[66] I. Sekirov, S.L. Russell, L.C. Antunes, B.B. Finlay, Gut microbiota in health and disease, Physiol. Rev. 90 (2010) 859–904, https://doi.org/10.1152/physrev.00045.2009.

[67] F. Marciano, P. Vajro, Oxidative stress and gut microbiota, in: Gastrointestinal Tissue, Academic Press, 2017, pp. 113–123.

[68] B. Dam, A. Misra, S. Banerjee, Role of gut microbiota in combating oxidative stress, in: Oxidative Stress in Microbial Diseases, Springer, Singapore, 2019, pp. 43–82.

[69] N.O. Al-Harbi, A. Nadeem, S.F. Ahmad, M.R. Alotaibi, A.F. AlAsmari, W.A. Alanazi, M.M. Al-Harbi, A.M. El-Sherbeeny, K.E. Ibrahim, Short chain fatty acid, acetate ameliorates sepsis-induced acute kidney injury by inhibition of NADPH oxidase signaling in T cells, Int. Immunopharm. 58 (2018) 24–31, https://doi.org/10.1016/j.intimp.2018.02.023.

[70] D. Wang, J. Chen, H. Sun, W. Chen, X. Yang, MCFA alleviate H_2O_2-induced oxidative stress in AML12 cells via the ERK1/2/Nrf2 pathway, Lipids 57 (2022) 153–162, https://doi.org/10.1002/lipd.12339.

[71] J. Mett, U. Müller, The medium-chain fatty acid decanoic acid reduces oxidative stress levels in neuroblastoma cells, Sci. Rep. 11 (2021) 6135, https://doi.org/10.1038/s41598-021-85523-9.

[72] C. Bourque, M.P. St-Onge, A.A. Papamandjaris, J.S. Cohn, P.J. Jones, Consumption of an oil composed of medium chain triacyglycerols, phytosterols and N-3 fatty acids improves cardiovascular risk profile in overweight women, Metabolism 52 (2003) 771–777, https://doi.org/10.1016/s0026-0495(03)00070-2.

[73] S. Torres, A. Baulies, N. Insausti-Urkia, C. Alarcón-Vila, R. Fucho, E. Solsona-Vilarrasa, S. Núñez, D. Robles, V. Ribas, L. Wakefield, M. Grompe, M.I. Lucena, R. J. Andrade, S. Win, T.A. Aung, N. Kaplowitz, C. García-Ruiz, J.C. Fernández-Checa, Endoplasmic reticulum stress-induced upregulation of STARD1 promotes acetaminophen-induced acute liver failure, Gastroenterology 157 (2019) 552–568, https://doi.org/10.1053/j.gastro.2019.04.023.

[74] B. Wang, L. Li, J. Fu, P. Yu, D. Gong, C. Zeng, P. Yu, D. Gong, C. Zeng, Z. Zeng, Effects of long-chain and medium-chain fatty acids on apoptosis and oxidative stress in human liver cells with steatosis, J. Food Sci. 81 (2016) H794–H800, https://doi.org/10.1111/1750-3841.13210.

[75] E.L. Seifert, C. Estey, J.Y. Xuan, M.E. Harper, Electron transport chain-dependent and-independent mechanisms of mitochondrial H_2O_2 emission during long-chain fatty acid oxidation, J. Biol. Chem. 285 (2010) 5748–5758, https://doi.org/10.1074/jbc.m109.026203.

[76] R. Carnevale, D. Pastori, C. Nocella, V. Cammisotto, S. Bartimoccia, M. Novo, M. Del Ben, A. Farcomeni, F. Angelico, F. Violi, Gut-derived lipopolysaccharides increase post-prandial oxidative stress via Nox2 activation in patients with impaired fasting glucose tolerance: effect of extra-virgin olive oil, Eur. J. Nutr. 58 (2019) 843–851, https://doi.org/10.1007/s00394-018-1718-x.

[77] L. Loffredo, E. Ettorre, A.M. Zicari, M. Inghilleri, C. Nocella, L. Perri, A. Spalice, C. Fossati, M.C. De Lucia, F. Pigozzi, M. Cacciafesta, F. Violi, R. Carnevale, Neurodegenerative Disease study group, Oxidative stress and gut-derived lipopolysaccharides in neurodegenerative disease: role of NOX2, Oxid. Med. Cell. Longev. (2020) (2020), 8630275, https://doi.org/10.1155/2020/8630275.

[78] G.M. Virzì, A. Breglia, C. Castellani, G. Ankawi, C. Bolin, M. de Cal, V. Cianci, A. Angelini, G. Vescovo, C. Ronco, Lipopolysaccharide in systemic circulation induces activation of inflammatory response and oxidative stress in cardiorenal syndrome type 1, J. Nephrol. 32 (2019) 803–810, https://doi.org/10.1007/s40620-019-00613-2.

[79] S. Qi, L. Wang, X. Chang, Y. Zhang, Y. Zhang, M.Q. Gao, MCPIP1 mediates inflammatory responses induced by lipopolysaccharide and lipoteichoic acid in bovine mammary epithelial cells, Acta Biochim. Biophys. Sin. 51 (2019) 150–158, https://doi.org/10.1093/abbs/gmy163.

[80] K.J. Reszka, P. Bilski, C.F. Chignell, J. Dillon, Free radical reactions photosensitized by the human lens component, kynurenine: an EPR and spin trapping investigation, Free Radic. Biol. Med. 20 (1996) 23–34, https://doi.org/10.1016/0891-5849(95)02018-7.

[81] Q. Wang, D. Liu, P. Song, M.H. Zou, Deregulated tryptophan-kynurenine pathway is linked to inflammation, oxidative stress, and immune activation pathway in cardiovascular diseases, Front. Biosci. 20 (2015) 1116–1143, https://doi.org/10.2741/4363.

[82] M. Cíz, D. Komrsková, L. Pracharová, K. Okénková, H. Cízová, A. Moravcová, V. Jancinová, M. Petríková, A. Lojek, R. Nosál, Serotonin modulates the oxidative burst of human phagocytes via various mechanisms, Platelets 18 (2007) 583–590, https://doi.org/10.1080/09537100701471865.

[83] I. Miyazaki, M. Asanuma, S. Murakami, M. Takeshima, N. Torigoe, Y. Kitamura, K. Miyoshi, Targeting 5-HT(1A) receptors in astrocytes to protect dopaminergic neurons in Parkinsonian models, Neurobiol. Dis. 59 (2013) 244–256, https://doi.org/10.1016/j.nbd.2013.08.003.

[84] C. Dietrich, Antioxidant functions of the aryl hydrocarbon receptor, Stem Cell. Int. (2016) (2016), 7943495, https://doi.org/10.1155/2016/7943495.

[85] B.J. Saeedi, K.H. Liu, J.A. Owens, S. Hunter-Chang, M.C. Camacho, R.U. Eboka, B. Chandrasekharan, N.F. Baker, T.M. Darby, B.S. Robinson, R.M. Jones, D. P. Jones, A.S. Neish, Gut-resident lactobacilli activate hepatic Nrf2 and protect against oxidative liver injury, Cell Metabol. 31 (2020) 956–968.e5, https://doi.org/10.1016/j.cmet.2020.03.006.

[86] B. Poeggeler, R.J. Reiter, R. Hardeland, D.X. Tan, L.R. Barlow-Walden, Melatonin and structurally related, endogenous indoles act as potent electron donors and radical scavengers in vitro, Redox Rep. 2 (1996) 179–184, https://doi.org/10.1080/13510002.1996.11747046.

[87] T.B. Ng, F. Liu, L. Zhao, Antioxidative and free radical scavenging activities of pineal indoles, J. Neural. Transm. 107 (2000) 1243–1251, https://doi.org/10.1007/s007020070014.

[88] Y. Luo, P. Shang, D. Li, Luteolin: a flavonoid that has multiple cardio-protective effects and its molecular mechanisms, Front. Pharmacol. 8 (2017) 692, https://doi.org/10.3389/fphar.2017.00692.

[89] S. Zhang, Z. Gai, T. Gui, J. Chen, Q. Chen, Y. Li, Antioxidant effects of protocatechuic acid and protocatechuic aldehyde: old wine in a new bottle, Evid. Based. Complementary. Altern. Med. 2021 (2021), 6139308, https://doi.org/10.1155/2021/6139308.

[90] E.C.H. Yip, A.S.L. Chan, H. Pang, Y.K. Tam, Y.H. Wong, Protocatechuic acid induces cell death in HepG2 hepatocellular carcinoma cells through a c-Jun N-terminal kinase-dependent mechanism, Cell Biol. Toxicol. 22 (2006) 293–302, https://doi.org/10.1007/s10565-006-9000-z.

[91] T. Grimm, A. Schäfer, P. Högger, Antioxidant activity and inhibition of matrix metalloproteinases by metabolites of maritime pine bark extract (pycnogenol), Free Radic. Biol. Med. 36 (2004) 811–822, https://doi.org/10.1016/j.freeradbiomed.2003.12.017.

[92] P. Schönfeld, L. Wojtczak, Short-and medium-chain fatty acids in energy metabolism: the cellular perspective, J. Lipid Res. 57 (2016) 943–954, https://doi.org/10.1194/jlr.r067629.

[93] G. Jamar, L.P. Pisani, Inflammatory crosstalk between saturated fatty acids and gut microbiota–white adipose tissue axis, Eur. J. Nutr. 62 (2023) 1077–1091, https://doi.org/10.1007/s00394-022-03062-z.

[94] C. Martin-Gallausiaux, L. Marinelli, H.M. Blottière, P. Larraufie, N. Lapaque, SCFA: mechanisms and functional importance in the gut, Proc. Nutr. Soc. 80 (2021) 37–49, https://doi.org/10.1017/S0029665120006916.

[95] T. Yang, S.M. Mbadinga, L. Zhou, S.Z. Yang, J.F. Liu, J.D. Gu, B.Z. Mu, Propionate metabolism and diversity of relevant functional genes by in silico analysis and detection in subsurface petroleum reservoirs, World J. Microbiol. Biotechnol. 33 (2017) 182, https://doi.org/10.1007/s11274-017-2350-2.

[96] C.B. Christiansen, M.B.N. Gabe, B. Svendsen, L.O. Dragsted, M.M. Rosenkilde, J.J. Holst, The impact of short-chain fatty acids on GLP-1 and PYY secretion from the isolated perfused rat colon, Am. J. Physiol. Gastrointest. Liver Physiol. 315 (2018), https://doi.org/10.1152/ajpgi.00346.2017. G53–65.

[97] W. Huang, Y. Man, C. Gao, L. Zhou, J. Gu, H. Xu, Q. Wan, Y. Long, L. Chai, Y. Xu, Y. Xu, Short-chain fatty acids ameliorate diabetic nephropathy via GPR43-mediated inhibition of oxidative stress and NF-κB signaling, Oxid. Med. Cell. Longev. (2020) (2020), 4074832, https://doi.org/10.1155/2020/4074832.

[98] T.J. Yeo, I.S. Choi, K.K. Cho, Use of cellulose and recent research into butyrate, J. Life Sci. 22 (2012) 1571–1586, https://doi.org/10.5352/JLS.2012.22.11.1571.

[99] S. Hu, R. Kuwabara, B.J. de Haan, A.M. Smink, P. de Vos, Acetate and butyrate improve β-cell metabolism and mitochondrial respiration under oxidative stress, Int. J. Mol. Sci. 21 (2020) 1542, https://doi.org/10.3390/ijms21041542.

[100] L.C. Tong, Y. Wang, Z.B. Wang, W.Y. Liu, S. Sun, L. Li, D.F. Su, L.C. Zhang, Propionate ameliorates dextran sodium sulfate-induced colitis by improving intestinal barrier function and reducing inflammation and oxidative stress, Front. Pharmacol. 7 (2016) 253, https://doi.org/10.3389/fphar.2016.00253.

[101] D. Chen, Z.Q. Gao, Y.Y. Wang, B.B. Wan, G. Liu, J.L. Chen, Y.X. Wu, Q. Zhou, S.Y. Jiang, R.Q. Yu, Q. Pang, Sodium propionate enhances Nrf2-mediated protective defense against oxidative stress and inflammation in lipopolysaccharide-induced neonatal mice, J. Inflamm. Res. 14 (2021) 803–816, https://doi.org/10.2147/JIR.S303105.

[102] M. St-Onge, A. Bosarge, L.L.T. Goree, B. Darnell, Medium chain triglyceride oil consumption as part of a weight loss diet does not lead to an adverse metabolicprofile when compared to olive oil, J. Am. Coll. Nutr. 27 (2008) 547–552, https://doi.org/10.1080/07315724.2008.10719737.

[103] W. Ren, Q. Wu, L. Deng, Y. Hu, W. Guo, N. Ren, Simultaneous medium-chain fatty acids production and process carbon emissions reduction in a continuous-flow reactor: re-understanding of carbon flow distribution, Environ. Res. 212 (2022), 113294, https://doi.org/10.1016/j.envres.2022.113294.

[104] P.G. Roopashree, S.S. Shetty, N.S. Kumari, Effect of medium chain fatty acid in human health and disease, J. Funct.Foods 87 (2021), 104724, https://doi.org/10.1016/j.jff.2021.104724.

[105] J. Pujo, C. Petitfils, P. Le Faouder, V. Eeckhaut, G. Payros, S. Maurel, T. Perez-Berezo, M. Van Hul, F. Barreau, C. Blanpied, S. Chavanas, F. Van Immerseel, J. Bertrand-Michel, E. Oswald, C. Knauf, G. Dietrich, P.D. Cani, N. Cenac, Bacteria-derived long chain fatty acid exhibits anti-inflammatory properties in colitis, Gut 70 (2021) 1088–1097, https://doi.org/10.1136/gutjnl-2020-321173.

[106] M. Xue, Y. Ge, C. Yu, Z. Zheng, X. He, J. Zhao, Apoptosis is induced by docosahexaenoic acid in breast cancer cells via death receptor and mitochondria-mediated pathways, Mol. Med. Rep. 16 (2017) 978–982, https://doi.org/10.3892/mmr.2017.6678.

[107] C.R. Raetz, C. Whitfield, Lipopolysaccharide endotoxins, Annu. Rev. Biochem. 71 (2002) 635–700, https://doi.org/10.1146/annurev.biochem.71.110601.135414.

[108] B. Bertani, N. Ruiz, Function and biogenesis of lipopolysaccharides, EcoSal Plus 8 (2018), https://doi.org/10.1128/ecosalplus.ESP-0001-2018.

[109] S.I. Miller, R.K. Ernst, M.W. Bader, LPS, TLR4 and infectious disease diversity, Nat. Rev. Microbiol. 3 (2005) 36–46, https://doi.org/10.1038/nrmicro1068.

[110] C. Giangrande, L. Colarusso, R. Lanzetta, A. Molinaro, P. Pucci, A. Amoresano, Innate immunity probed by lipopolysaccharides affinity strategy and proteomics, Anal. Bioanal. Chem. 405 (2013) 775–784, https://doi.org/10.1007/s00216-012-6204-3.

[111] S.A. Shah, M. Khan, M.H. Jo, M.G. Jo, F.U. Amin, M.O. Kim, Melatonin stimulates the SIRT1/Nrf2 signaling pathway counteracting lipopolysaccharide (LPS)-induced oxidative stress to rescue postnatal rat brain, CNS Neurosci. Ther. 23 (2017) 33–44, https://doi.org/10.1111/cns.12588.

[112] R. Carnevale, C. Nocella, V. Petrozza, V. Cammisotto, L. Pacini, V. Sorrentino, O. Martinelli, L. Irace, S. Sciarretta, G. Frati, et al., Localization of lipopolysaccharide from Escherichia coli into human atherosclerotic plaque, Sci. Rep. 8 (2018) 3598, https://doi.org/10.1038/s41598-018-22076-4.

[113] Q. Wang, D. Liu, P. Song, M.H. Zou, Tryptophan-kynurenine pathway is dysregulated in inflammation, and immune activation, Front. Biosci (Landmark Ed) 20 (2015) 1116–1143, https://doi.org/10.2741/4363.

[114] M. Borghi, M. Puccetti, M. Pariano, G. Renga, C. Stincardini, M. Ricci, S. Giovagnoli, C. Costantini, L. Romani, Tryptophan as a central hub for host/microbial symbiosis, Int. J. Tryptophan Res. 13 (2020), 1178646920919755, https://doi.org/10.1177/1178646920919755.

[115] L.M. Alkhalaf, K.S. Ryan, Biosynthetic manipulation of tryptophan in bacteria: pathways and mechanisms, Chem. Biol. 22 (2015) 317–328, https://doi.org/10.1016/j.chembiol.2015.02.005.

[116] S. Cussotto, I. Delgado, A. Anesi, S. Dexpert, A. Aubert, C. Beau, D. Forestier, P. Ledaguenel, E. Magne, F. Mattivi, L. Capuron, Tryptophan metabolic pathways are altered in obesity and are associated with systemic inflammation, Front. Immunol. 11 (2020) 557, https://doi.org/10.3389/fimmu.2020.00557.

[117] P.J. Kennedy, J.F. Cryan, T.G. Dinan, G. Clarke, Kynurenine pathway metabolism and the microbiota-gut-brain axis, Neuropharmacology 112 (2017) 399–412, https://doi.org/10.1016/j.neuropharm.2016.07.002.

[118] W.R. Wikoff, A.T. Anfora, J. Liu, P.G. Schultz, S.A. Lesley, E.C. Peters, G. Siuzdak, Metabolomics analysis reveals large effects of gut microflora on mammalian blood metabolites, Proc. Natl. Acad. Sci. U.S.A. 106 (2009) 3698–3703, https://doi.org/10.1073/pnas.0812874106.

[119] Y. Ji, Y. Gao, H. Chen, Y. Yin, W. Zhang, Indole-3-acetic acid alleviates nonalcoholic fatty liver disease in mice via attenuation of hepatic lipogenesis, and oxidative and inflammatory stress, Nutrients 11 (2019) 2062, https://doi.org/10.3390/nu11092062.

[120] H. Song, H. Park, Y.S. Kim, K.D. Kim, H.K. Lee, D.H. Cho, J.W. Yang, D.Y. Hur, L-kynurenine-induced apoptosis in human NK cells is mediated by reactive oxygen species, Int. Immunopharm. 11 (2011) 932–938, https://doi.org/10.1016/j.intimp.2011.02.005.

[121] J. Wang, R. Jia, P. Celi, Y. Zhuo, X. Ding, Q. Zeng, S. Bai, S. Xu, H. Yin, L. Lv, K. Zhang, Resveratrol alleviating the ovarian function under oxidative stress by alternating microbiota related tryptophan-kynurenine pathway, Front. Immunol. 13 (2022), 911381, https://doi.org/10.3389/fimmu.2022.911381.

[122] J.M. Yabut, J.D. Crane, A.E. Green, D.J. Keating, W.I. Khan, G.R. Steinberg, Emerging roles for serotonin in regulating metabolism: new implications for an ancient molecule, Endocr. Rev. 40 (2019) 1092–1107, https://doi.org/10.1210/er.2018-00283.

[123] G.M. Mawe, J.M. Hoffman, Serotonin signalling in the gut—functions, dysfunctions and therapeutic targets, Nat. Rev. Gastroenterol. Hepatol. 10 (2013) 473–486, https://doi.org/10.1038/nrgastro.2013.105.

[124] H.M. Grifka-Walk, B.R. Jenkins, D.J. Kominsky, Amino acid Trp: the far out impacts of host and commensal tryptophan metabolism, Front. Immunol. 12 (2021), 653208, https://doi.org/10.3389/fimmu.2021.653208.

[125] J.M. Yano, K. Yu, G.P. Donaldson, G.G. Shastri, P. Ann, L. Ma, C.R. Nagler, R.F. Ismagilov, S.K. Mazmanian, E.Y. Hsiao, Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis, Cell 161 (2015) 264–276, https://doi.org/10.1016/j.cell.2015.02.047.

[126] D. Hoyer, J.P. Hannon, G.R. Martin, Molecular, pharmacological and functional diversity of 5-HT receptors, Pharmacol. Biochem. Behav. 71 (2002) 533–554, https://doi.org/10.1016/s0091-3057(01)00746-8.

[127] M. Manocha, W.I. Khan, Serotonin and GI disorders: an update on clinical and experimental studies, Clin. Transl. Gastroenterol. 3 (2012) e13, https://doi.org/10.1038/ctg.2012.8.

[128] J.H. Lee, T.K. Wood, J. Lee, Roles of indole as an interspecies and interkingdom signaling molecule, Trends Microbiol. 23 (2015) 707–718, https://doi.org/10.1016/j.tim.2015.08.001.

[129] M. Sun, N. Ma, T. He, L.J. Johnston, X. Ma, Tryptophan (Trp) modulates gut homeostasis via aryl hydrocarbon receptor (AhR), Crit. Rev. Food Sci. Nutr. 60 (2020) 1760–1768, https://doi.org/10.1080/10408398.2019.1598334.

[130] A. Wilson, C. McLean, R.B. Kim, Trimethylamine-N-oxide: a link between the gut microbiome, bile acid metabolism, and atherosclerosis, Curr. Opin. Lipidol. 27 (2016) 148–154, https://doi.org/10.1097/MOL.0000000000000274.

[131] R. Spector, New insight into the dietary cause of atherosclerosis: implications for pharmacology, J. Pharmacol. Exp. Therapeut. 358 (2016) 103–108, https://doi.org/10.1124/jpet.116.233296.

[132] S.H. Zeisel, M. Warrier, Trimethylamine N-oxide, the microbiome, and heart and kidney disease, Annu. Rev. Nutr. 37 (2017) 157–181, https://doi.org/10.1146/annurev-nutr-071816-064732.

[133] Z. Wang, E. Klipfell, B.J. Bennett, R. Koeth, B.S. Levison, B. Dugar, A.E. Feldstein, E.B. Britt, X. Fu, Y.M. Chung, Y. Wu, P. Schauer, J.D. Smith, H. Allayee, W. H. Wilson Tang, J.A. DiDonato, A.J. Lusis, S.L. Hazen, Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease, Nature 472 (2011) 57–63, https://doi.org/10.1038/nature09922.

[134] W.H. Tang, Z. Wang, B.S. Levison, R.A. Koeth, E.B. Britt, X. Fu, Y. Wu, S.L. Hazen, Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk, N. Engl. J. Med. 368 (2013) 1575–1584, https://doi.org/10.1056/NEJMoa1109400.

[135] M.H. Janeiro, M.J. Ramírez, F.I. Milagro, J.A. Martínez, M. Solas, Implication of trimethylamine N-oxide (TMAO) in disease: potential biomarker or new therapeutic target, Nutrients 10 (2018) 1398, https://doi.org/10.3390/nu10101398.

[136] C.L. Organ, H. Otsuka, S. Bhushan, Z. Wang, J. Bradley, R. Trivedi, D.J. Polhemus, W.H. Tang, Y. Wu, S.L. Hazen, D.J. Lefer, Choline diet and its gut microbe-derived metabolite, trimethylamine N-oxide, exacerbate pressure overload-induced heart failure, Circ. Heart Fail. 9 (2016), e002314, https://doi.org/10.1161/CIRCHEARTFAILURE.115.002314.

[137] Y. Zhu, Q. Li, H. Jiang, Gut microbiota in atherosclerosis: focus on trimethylamine N-oxide, APMIS 128 (2020) 353–366, https://doi.org/10.1111/apm.13038.

[138] G. Sun, Z. Yin, N. Liu, X. Bian, R. Yu, X. Su, B. Zhang, Y. Wang, Gut microbial metabolite TMAO contributes to renal dysfunction in a mouse model of diet-induced obesity, Biochem. Biophys. Res. Commun. 493 (2017) 964–970, https://doi.org/10.1016/j.bbrc.2017.09.108.

[139] T. Li, Y. Chen, C. Gua, X. Li, Elevated circulating trimethylamine N-oxide levels contribute to endothelial dysfunction in aged rats through vascular inflammation and oxidative stress, Front. Physiol. 8 (2017) 350, https://doi.org/10.3389/fphys.2017.00350.

[140] Y. Ke, D. Li, M. Zhao, C. Liu, J. Liu, A. Zeng, X. Shi, S. Cheng, B. Pan, L. Zheng, H. Hong, Gut flora-dependent metabolite trimethylamine-N-oxide accelerates endothelial cell senescence and vascular aging through oxidative stress, Free Radic. Biol. Med. 116 (2018) 88–100, https://doi.org/10.1016/j.freeradbiomed.2018.01.007.

[141] S.M. Aravind, S. Wichienchot, R. Tsao, S. Ramakrishnan, S. Chakkaravarthi, Role of dietary polyphenols on gut microbiota, their metabolites and health benefits, Food Res. Int. 142 (2021), 110189, https://doi.org/10.1016/j.foodres.2021.110189.

[142] N. Hayasaka, N. Shimizu, T. Komoda, S. Mohri, T. Tsushida, T. Eitsuka, T. Miyazawa, K. Nakagawa, Absorption and metabolism of luteolin in rats and humans in relation to in vitro anti-inflammatory effects, J. Agric. Food Chem. 66 (2018) 11320–11329.

[143] V. Mishra, C. Shah, N. Mokashe, R. Chavan, H. Yadav, J. Prajapati, Probiotics as potential antioxidants: a systematic review, J. Agric. Food Chem. 63 (2015) 3615–3626, https://doi.org/10.1021/jf506326t.

[144] R.C. Reuben, P.C. Roy, S.L. Sarkar, R.U. Alam, I.K. Jahid, Isolation, characterization, and assessment of lactic acid bacteria toward their selection as poultry probiotics, BMC Microbiol. 19 (2019) 253, https://doi.org/10.1186/s12866-019-1626-0.

[145] Y. Kong, K.J. Olejar, S.L.W. On, V. Chelikani, The potential of Lactobacillus spp. for modulating oxidative stress in the gastrointestinal tract, Antioxidants 9 (2020) 610, https://doi.org/10.3390/antiox9070610.

[146] J.M. Chae, M.H. Chang, W. Heo, H.T. Cho, D.H. Lee, B.B. Hwang, J.W. Kim, S.M. Yoon, S. Yang, J.H. Lee, Y.J. Kim, LB-9, novel probiotic lactic acid bacteria, ameliorates dextran sodium sulfate-induced colitis in mice by inhibiting TNF-α-mediated apoptosis of intestinal epithelial cells, J. Med. Food 22 (2019) 271–276, https://doi.org/10.1089/jmf.2018.4236.

[147] F. Chen, J. Chen, Q. Chen, L. Yang, J. Yin, Y. Li, X. Huang, Lactobacillus delbrueckii protected intestinal integrity alleviated intestinal oxidative damage and activated toll-like receptor–Bruton's tyrosine kinase–nuclear factor erythroid 2-related Factor 2 pathway in weaned piglets challenged with lipopolysaccharide, Antioxidants 10 (2021) 468, https://doi.org/10.3390/antiox10030468.

[148] J. Pang, Y. Liu, L. Kang, H. Ye, J. Zang, J. Wang, D. Han, Bifidobacterium animalis promotes the growth of weaning piglets by improving intestinal development, enhancing antioxidant capacity, and modulating gut microbiota, J. Appl. Environ Microbiol. 88 (2022), e01296-22, https://doi.org/10.1128/aem.01296-22.

[149] P. Vitheejongjaroen, A. Kasorn, N. Puttarat, F. Loison, M. Taweechotipatr, Bifidobacterium animalis MSMC83 improves oxidative stress and gut microbiota in D-galactose-induced rats, Antioxidants 11 (2022) 2146, https://doi.org/10.3390/antiox11112146.

[150] Q. Shen, N. Shang, P. Li, In vitro and in vivo antioxidant activity of Bifidobacterium animalis 01 isolated from centenarians, Curr. Microbiol. 62 (2011) 1097–1103, https://doi.org/10.1007/s00284-010-9827-7.

[151] A.E. Abdel-Moneim, D.A. Selim, H.A. Basuony, E.M. Sabic, A.A. Saleh, T.A. Ebeid, Effect of dietary supplementation of Bacillus subtilis spores on growth performance, oxidative status, and digestive enzyme activities in Japanese quail birds, Trop. Anim. Health Prod. 52 (2020) 671–680, https://doi.org/10.1007/s11250-019-02055-1.

[152] L. Tang, Z. Zeng, Y. Zhou, B. Wang, P. Zou, Q. Wang, J. Ying, F. Wang, X. Li, S. Xu, P. Zhao, W. Li, Bacillus amyloliquefaciens SC06 induced AKT–FOXO signaling pathway-mediated autophagy to alleviate oxidative stress in IPEC-J2 cells, Antioxidants 10 (2021) 1545, https://doi.org/10.3390/antiox10101545.

[153] Y. Wang, Y. Wu, Y. Wang, A. Fu, L. Gong, W. Li, Y. Li, Bacillus amyloliquefaciens SC06 alleviates the oxidative stress of IPEC-1 via modulating Nrf2/Keap 1 signaling pathway and decreasing ROS production, Appl. Microbiol. Biotechnol. 101 (2017) 3015–3026, https://doi.org/10.1007/s00253-016-8032-4.

[154] Y. Wang, Y. Wu, B. Wang, H. Xu, X. Mei, X. Xu, X. Zhang, J. Ni, W. Li, Bacillus amyloliquefaciens SC06 protects mice against high-fat diet-induced obesity and liver injury via regulating host metabolism and gut microbiota, Front. Microbiol. 10 (2019) 1161, https://doi.org/10.3389/fmicb.2019.01161.

[155] S. Westfall, N. Lomis, I. Kahouli, S.Y. Dia, S.P. Singh, S. Prakash, Microbiome, probiotics and neurodegenerative diseases: deciphering the gut brain axis, Cell. Mol. Life Sci. 74 (2017) 3769–3787, https://doi.org/10.1007/s00018-017-2550-9.

[156] S.T. Ho, Y.T. Hsieh, S.Y. Wang, M.J. Chen, Improving effect of a probiotic mixture on memory and learning abilities in d-galactose-treated aging mice, J. Dairy Sci. 102 (2019) 1901–1909, https://doi.org/10.3168/jds.2018-15811.

[157] H. Tran Nguyen Minh, T.F. Kuo, W.Y. Lin, T.C. Peng, G. Yang, C.Y. Lin, T.H. Chang, Y.L. Yang, C.H. Ho, B.R. Ou, C.W. Yang, Y.C. Liang, W.C. Yang, A novel phytogenic formulation, EUBIO-BPSG, as a promising one health approach to replace antibiotics and promote reproduction performance in laying hens, Bioengineering 10 (2023) 346, https://doi.org/10.3390/bioengineering10060633.

[158] L. Xue, J. He, N. Gao, X. Lu, M. Li, X. Wu, Z. Liu, Y. Jin, J. Liu, J. Xu, et al., Probiotics may delay the progression of nonalcoholic fatty liver disease by restoring the gut microbiota structure and improving intestinal endotoxemia, Sci. Rep. 7 (2017), 45176, https://doi.org/10.1038/srep45176.

[159] S.H. Han, K.T. Suk, D.J. Kim, M.Y. Kim, S.K. Baik, Y.D. Kim, G.J. Cheon, D.H. Choi, Y.L. Ham, D.H. Shin, E.J. Kim, Effects of probiotics (cultured Lactobacillus subtilis/Streptococcus faecium) in the treatment of alcoholic hepatitis: randomized-controlled multicenter study, Eur. J. Gastroenterol. Hepatol. 27 (2015) 1300–1306, https://doi.org/10.1097/MEG.0000000000000458.

[160] L. Cervantes-Barragan, J.N. Chai, M.D. Tianero, B. Di Luccia, P.P. Ahern, J. Merriman, V.S. Cortez, M.G. Caparon, M.S. Donia, S. Gilfillan, M. Cella, J.I. Gordon, C.S. Hsieh, M. Colonna, Lactobacillus reuteri induces gut intraepithelial CD4+CD8αα+ T cells, Science 357 (2017) 806–810, https://doi.org/10.1126/science.aah5825.

[161] Y. Wang, D. Dilidaxi, Y. Wu, J. Sailike, X. Sun, X.H. Nabi, Composite probiotics alleviate type 2 diabetes by regulating intestinal microbiota and inducing GLP-1 secretion in db/db mice, Biomed. Pharmacother. 125 (2020), 109914, https://doi.org/10.1016/j.biopha.2020.109914.

[162] R.G.S. Cavalcante, T.M.R. de Albuquerque, M.O. de Luna Freire, G.A.H. Ferreira, L.A. Carneiro Dos Santos, M. Magnani, J.C. Cruz, V.A. Braga, E.L. de Souza, J. L. de Brito Alves, The probiotic Lactobacillus fermentum 296 attenuates cardiometabolic disorders in high fat diet-treated rats, Nutr. Metabol. Cardiovasc. Dis. 29 (2019) 1408–1417, https://doi.org/10.1016/j.numecd.2019.08.003.

[163] T.E. Ichim, A.N. Patel, K.A. Shafer, Experimental support for the effects of a probiotic/digestive enzyme supplement on serum cholesterol concentrations and the intestinal microbiome, J. Transl. Med. 14 (2016) 184, https://doi.org/10.1186/s12967-016-0945-2.

[164] A. Adedapo, F. Jimoh, A. Afolayan, Comparison of the nutritive value and biological activities of the acetone, methanol and water extracts of the leaves of Bidens pilosa and Chenopodium album, Acta Pol. Pharm. 68 (2011) 83–92, https://doi.org/10.1038/aps.2010.180.

[165] K. Kreuzer, A. Reiter, A.M. Birkl-Töglhofer, N. Dalkner, S. Mörkl, M. Mairinger, E. Fleischmann, F. Fellendorf, M. Platzer, M. Lenger, T. Färber, M. Seidl, A. Birner, R. Queissner, L. Mendel, A. Maget, A. Kohlhammer-Dohr, A. Häussl, J. Wagner-Skacel, H. Schöggl, D. Amberger-Otti, A. Painold, T. Lahousen-Luxenberger, B. Leitner-Afschar, J. Haybaeck, H. Habisch, T. Madl, E. Reininghaus, S. Bengesser, The PROVIT study—effects of multispecies probiotic add-on treatment on metabolomics in major depressive disorder—a randomized, placebo-controlled trial, Metabolites 12 (2022) 770, https://doi.org/10.3390/metabo12080770.

[166] X. Shi, X. Wei, X. Yin, Y. Wang, M. Zhang, C. Zhao, H. Zhao, C.J. McClain, W. Feng, X. Zhang, Hepatic and fecal metabolomic analysis of the effects of Lactobacillus rhamnosus GG on alcoholic fatty liver disease in mice, J. Proteome Res. 14 (2015) 1174–1182, https://doi.org/10.1021/pr501121c.
[167] D. Wu, A.I. Cederbaum, Alcohol, oxidative stress, and free radical damage, Alcohol Res. Health 27 (2003) 277–284, https://doi.org/10.1079/PNS2006496.
[168] L.H. Quan, C. Zhang, M. Dong, J. Jiang, H. Xu, C. Yan, X. Liu, H. Zhou, H. Zhang, L. Chen, F.L. Zhong, Z.B. Luo, S.M. Lam, G. Shui, D. Li, W. Jin, Myristoleic acid produced by enterococci reduces obesity through brown adipose tissue activation, Gut 67 (2020) 1239–1247, https://doi.org/10.1136/gutjnl-2019-319114.
[169] A.K. Mishra, S.S. Kumar, A.R. Ghosh, Probiotic Enterococcus faecalis AG5 effectively assimilates cholesterol and produces fatty acids including propionate, FEMS Microbiol. Lett. 366 (2019), https://doi.org/10.1093/femsle/fnz039 fnz039.
[170] P.D. Cani, N.M. Delzenne, Interplay between obesity and associated metabolic disorders: new insights into the gut microbiota, Curr. Opin. Pharmacol. 9 (2009) 737–743, https://doi.org/10.1016/j.coph.2009.06.016.
[171] B. Yousefi, M. Eslami, A. Ghasemian, P. Kokhaei, A. Salek Farrokhi, N. Darabi, Probiotics importance and their immunomodulatory properties, J. Cell. Physiol. 234 (2019) 8008–8018, https://doi.org/10.1002/jcp.27559.
[172] L. Rodes, A. Khan, A. Paul, M. Coussa-Charley, D. Marinescu, C. Tomaro-Duchesneau, W. Shao, I. Kahouli, S. Prakash, Effect of probiotics Lactobacillus and Bifidobacterium on gut-derived lipopolysaccharides and inflammatory cytokines: an in vitro study using a human colonic microbiota model, J. Microbiol. Biotechnol. 23 (2013) 518–526, https://doi.org/10.4014/jmb.1205.05018.
[173] C.S. Reigstad, C.E. Salmonson, J.F. Rainey, J.H. Szurszewski, D.R. Linden, J.L. Sonnenburg, G. Farrugia, P.C. Kashyap, Gut microbes promote colonic serotonin production through an effect of short-chain fatty acids on enterochromaffin cells, Faseb. J. 29 (2015) 1395–1403, https://doi.org/10.1096/fj.14-259598.
[174] A.V. Golubeva, S.A. Joyce, G. Moloney, A. Burokas, E. Sherwin, S. Arboleya, I. Flynn, D. Khochanskiy, A. Moya-Pérez, V. Peterson, K. Rea, K. Murohy, O. Makarova, S. Buravkow, N.P. Hyland, C. Stanton, G. Clarke, C.G.M. Gahan, T.G. Dian, J.F. Cryan, Microbiota related changes in bile acid & tryptophan metabolism are associated with gastrointestinal dysfunction in a mouse mode of autism, EBioMedicine 24 (2017) 166–178, https://doi.org/10.1016/j.ebiom.2017.09.020.
[175] L. Qiu, X. Tao, H. Xiong, J. Yu, H. Wei, Lactobacillus plantarum ZDY04 exhibits a strain-specific property of lowering TMAO via the modulation of gut microbiota in mice, Food Funct. 9 (2018) 4299–4309, https://doi.org/10.1039/c8fo00349a.
[176] G.C. Tenore, D. Caruso, G. Buonomo, M. D'Avino, R. Ciampaglia, M. Maisto, C. Schisano, B. Bocchino, E. Novellino, Lactofermented Annurca apple puree as a functional food indicated for the control of plasma lipid and oxidative amine levels: results from a randomised clinical trial, Nutrients 11 (2019) 122, https://doi.org/10.3390/nu11010122.
[177] J. Tang, M. Qin, L. Tang, D. Shan, C. Zhang, Y. Zhang, H. Wei, L. Qiu, J. Yu, Enterobacter aerogenes ZDY01 inhibits choline-induced atherosclerosis through CDCA-FXR-FGF15 axis, Food Funct. 12 (2021) 9932–9946, https://doi.org/10.1039/d1fo02021h.
[178] M. Matsumoto, Y. Kitada, Y. Shimomura, Y. Naito, Bifidobacterium animalis subsp. lactis LKM512 reduces levels of intestinal trimethylamine produced by intestinal microbiota in healthy volunteers: a double-blind, placebo-controlled study, J. Funct.Foods 36 (2017) 94–101, https://doi.org/10.1016/j.jff.2017.06.032.
[179] N.J. Tripolt, B. Leber, A. Triebl, H. Köfeler, V. Stadlbauer, H. Sourij, Effect of Lactobacillus casei Shirota supplementation on trimethylamine-N-oxide levels in patients with metabolic syndrome: an open-label, randomized study, Atherosclerosis 242 (2015) 141–144, https://doi.org/10.1016/j.atherosclerosis.2015.05.005.
[180] M. Malik, T.M. Suboc, S. Tyagi, N. Salzman, J. Wang, R. Ying, M.J. Tanner, M. Kakarla, J.E. Baker, M.E. Widlansky, Lactobacillus plantarum 299v supplementation improves vascular endothelial function and reduces inflammatory biomarkers in men with stable coronary artery disease, Circ. Res. 123 (2018) 1091–1102, https://doi.org/10.1161/CIRCRESAHA.118.313565.
[181] C.A. Morais, V.V. de Rosso, D. Estadella, L.P. Pisani, Anthocyanins as inflammatory modulators and the role of the gut microbiota, J. Nutr. Biochem. 33 (2016) 1–7, https://doi.org/10.1016/j.jnutbio.2015.11.008.
[182] I. Gil-Sánchez, C. Cueva, A. Tamargo, J.C. Quintela, E. de la Fuente, A.W. Walker, M.V. Moreno-Arribas, B. Bartolomé, Application of the dynamic gastrointestinal simulator (simgi®) to assess the impact of probiotic supplementation in the metabolism of grape polyphenols, Food Res. Int. 129 (2020), 108790, https://doi.org/10.1016/j.foodres.2019.108790.
[183] S. Ueda, R. Nomoto, K.I. Yoshida, R. Osawa, Comparison of three tannases cloned from closely related lactobacillus species: L. Plantarum, L. Paraplantarum, and L. Pentosus, BMC Microbiol. 14 (2014) 87, https://doi.org/10.1186/1471-2180-14-87.