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REVIEW

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Gut microbiota-derived metabolites: implications for metabolic syndrome and therapeutic interventions

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Abstract

Background The gut microbiota (GM) and their metabolites have garnered significant attention for their roles in metabolic syndrome (MetS) and associated conditions. MetS, characterized by a cluster of metabolic abnormalities, significantly increases the risk of cardiovascular disease (CVD), obesity, insulin resistance, and type 2 diabetes mellitus (T2DM). The dysbiosis of gut microbiota, marked by changes in microbial composition and function, has been implicated in the pathogenesis of MetS.

Main body This review synthesizes recent findings elucidating the influence of GM composition and microbiota-derived metabolites on MetS pathogenesis and progression. Notably, alterations in GM composition and dysregulation of metabolites such as short-chain fatty acids (SCFAs), trimethylamine N-oxide (TMAO), polyamines, amino acids, and indole derivatives have been implicated in MetS development. These metabolites play crucial roles in metabolic processes, and their imbalance can trigger or exacerbate metabolic disturbances associated with MetS. Various therapeutic approaches, including dietary interventions, probiotics, prebiotics, and precision medicine targeting specific metabolites, offer promising strategies for managing MetS. These interventions aim to restore a healthy GM balance and regulate the production of beneficial metabolites.

Conclusion The complexity of GM interactions and their systemic effects necessitate more standardized research methodologies. Future investigations focusing on personalized therapeutic interventions and non-invasive diagnostic tools are warranted to address the complexities of MetS management. Advancing our understanding of the GM-metabolite-MetS axis will be crucial for developing effective, targeted treatments and improving patient outcomes in MetS.

Keywords Gut microbiota, Metabolic syndrome, Dysbiosis, Microbiota-derived metabolites, Therapeutic interventions

Introduction

Metabolic syndrome (MetS) comprises a cluster of metabolic disorders that significantly increase the risk of cardiovascular disease (CVD), obesity, insulin resistance, and type 2 diabetes mellitus (T2DM). The prevalence of MetS demonstrates considerable variability worldwide, influenced by factors such as geographical location, diagnostic criteria, age, gender, and associated health conditions [1–15]. For instance, while Africa reports an overall prevalence of 32.4%,

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Pakistan exhibits a prevalence of 28.8%, with noteworthy regional variations [1, 4]. In contrast, the USA witnesses an escalating trend in MetS prevalence, particularly among individuals with lower educational attainment [9]. Gender disparities are evident, with higher prevalence observed among females in various regions such as Pakistan and India [1, 8]. Similarly, studies in China, Brazil, Finland, Mexico, Iran, and Zahedan highlight the global burden of MetS [2, 6, 7, 10–12, 15].

Recent research has underscored the intricate interplay between gut microbiota (GM), microbiota-derived metabolites, and host physiology in MetS pathogenesis [16]. Understanding these relationships is vital for developing effective therapeutic strategies for MetS management. The gut microbiota, comprising trillions of microorganisms, plays a crucial role in host metabolism by fermenting dietary substrates and producing various metabolites that can impact systemic health [17]. Among these metabolites, short-chain fatty acids (SCFAs), such as acetate, propionate, and butyrate, have garnered significant attention due to their pleiotropic effects on metabolic processes, inflammation, and gut barrier function [18–20]. Alterations in the composition and function of the gut microbiota, known as dysbiosis, have been linked to the development of MetS, partly through perturbations in SCFA production and signaling [21–23]. Additionally, trimethylamine N-oxide (TMAO), a metabolite derived from gut microbial metabolism of dietary nutrients like choline and carnitine, has emerged as a biomarker and mediator in MetS, influencing various metabolic pathways and contributing to cardiovascular risk [24–26].

Furthermore, polyamines, tryptophan and indole derivatives derived from gut microbial metabolism exhibit intricate relationships with MetS, affecting polyamine synthesis, amino acid utilization, and signaling pathways implicated in metabolic regulation [27–29]. Additionally, dysregulated bile acid metabolism plays a significant role in the development of metabolic syndrome [30]. Alterations in gut microbiota composition and function can perturb the balance of these metabolites, contributing to metabolic dysregulation and MetS pathophysiology [31–33].

This review aims to synthesize recent findings on the relevance of GM composition and microbiota-derived metabolites in MetS and seeks to outline clear directions for future research, suggesting that a deeper exploration into the causative links between microbiota-derived metabolites and metabolic dysfunctions could lead to more targeted therapeutic interventions.

Gut microbiota metabolites in metabolic syndrome

The pivotal role of the gut microbiota (GM) in metabolic syndrome (MetS) and related disorders has been extensively studied in recent years as highlighted in Table 1. Gradisteanu et al. examined microbiome patterns in MetS patients, revealing significant alterations correlated with metabolic abnormalities [16]. Several studies highlight the crucial role of gut microbiota in the development and progression of metabolic syndrome (MetS). The gut microbiome composition can be influenced by various factors such as diet, antibiotics, and maternal microbiota, which in turn affects disease susceptibility and metabolic health [21–23]. Alterations in the gut microbial community have been associated with obesity-related metabolic syndrome, insulin resistance, dyslipidemia, and inflammation by gut microbial metabolites [34–36].

The pathogenetic mechanisms through which these metabolites contribute to the development of metabolic syndrome (MetS) are multifaceted. Short-chain fatty acids (SCFAs), such as acetate and butyrate, exert regulatory effects on glucose and lipid metabolism, inflammation, and intestinal barrier function, all critical factors in MetS pathology [18–20, 37–40]. Trimethylamine N-oxide (TMAO) serves as both a biomarker and a mediator in MetS, exacerbating metabolic dysfunction by triggering inflammatory responses and oxidative stress pathways [24–26, 41–46]. Bile acids, by activating receptors like FXR and GPBAR1, influence glucose homeostasis and modulate gut microbial composition and energy metabolism, contributing significantly to MetS progression [47–50].

Additionally, polyamines, including spermine, spermidine, and putrescine, synthesized by gut microbiota such as Lactobacillus and Clostridium, are integral to cellular processes like growth and proliferation. Dysregulated levels of polyamines contribute to oxidative stress and inflammation, impacting gut barrier integrity and immune function, thereby exacerbating insulin resistance and dyslipidemia observed in metabolic syndrome (MetS) [29, 33, 51–54]. Tryptophan derivatives, such as indole-3-aldehyde (3-IAld) and indole-3-acetic acid (IAA), produced by bacterial metabolism of dietary tryptophan, activate pathways like the aryl hydrocarbon receptor (AhR), influencing immune responses and adipose tissue metabolism. Disrupted tryptophan metabolism by gut microbiota may thus promote systemic inflammation, insulin resistance, and dyslipidemia, pivotal aspects of MetS [27, 55–58].

Xavier-Santos et al. highlighted the impact of GM on metabolic processes and proposed interventions like probiotics and prebiotics for managing MetS [59]. Therapeutic interventions targeting GM and microbiota-derived

Table 1 The relevance of gut microbiota metabolites in metabolism and metabolic syndrome

Gut microbiota metabolites	Typical metabolite example(s)	Substrate	Microbiota involved in acting on substrate	Contribution of metabolite to overall metabolism	Role in metabolic syndrome	Mechanism of pathogenesis of metabolic syndrome	Therapeutic approaches	References
Short chain fatty acids	Acetate, propionate, butyrate, hexanoate, isovalerate, isobutyrate, 2-methylpropionate, valerate	Dietary fibers, various dietary carbohydrates	*Firmicutes: Clostridium* spp., *Eubacterium* spp., *Roseburia* spp., *Lactobacillus* spp., Faecalibacterium prausnitzii, Faecalibacterium prausnitzii *Bacteroidetes: Bacteroides* spp., *Prevotella* spp.,	Regulate metabolic processes including glucose and lipid metabolism, inflammation, and gut barrier integrity	Implicated in the pathogenesis of MetS, associated with obesity-related MetS, insulin resistance, dyslipidemia, and inflammation	Dysregulation of SCFA levels	Probiotics, prebiotics, synbiotics, FMT, and dietary interventions	[18–20, 37–40]
Amine oxides	Trimethylamine N-oxide	Phosphatidylcholine, choline, betaine, and l-carnitine, which are abundant in seafoods, dairy products, egg yolks, muscle, and organ meats	*Firmicutes: Clostridia species, Staphylococcus species Proteobacteria: Proteus species, Shigella species, Aerobacter species, Members of the Enterobacteriaceae family*	Biomarker and mediator in MetS	Potential as a predictive marker for MetS	TMAO may induce metabolic through inflammation and oxidative stress, characterized by increased reactive oxygen species (ROS) production and upregulation of cytokines and adhesion molecules	Dietary interventions	[24–26, 41–46]
Bile acids	Cholate, hyocholate, deoxycholate, taurohyocholate, ursodeoxycholate, taurocholate, glycocholate, hyodeoxycholate. Lithocholate, taurodeoxycholate, etc	Cholesterols	*Firmicutes: Clostridium* spp., *Eubacterium* spp., *Faecalibacterium prausnitzii, Lactobacillus* spp., *Enterococcus* spp. Bacteriodetes: *Bacteroides* spp, *Prevotella* spp.	Regulation of lipid and glucose metabolism, facilitation of nutrient absorption	influence glucose homeostasis through the activation of various signaling pathways, including the farnesoid X receptor (FXR), G protein bile acid receptor (GPBAR1), and the Takeda G-protein-coupled receptor 5 (TGR5); activation of bile acid-activated receptors (BARs), including FXR and GPBAR1; modulation of gut microbial balance enhanced BA excretion; inhibition of B. intestinalis growth	Modulation of FXR, GPBAR1, and TGR5 expression; inhibition of energy and BA metabolism enzymes	Bile acid sequestrants, FMT, modulation of gut microbiota	[47–50]

Table 1 (continued)

Gut microbiota metabolites	Typical metabolite example(s)	Substrate	Microbiota involved in acting on substrate	Contribution of metabolite to overall metabolism	Role in metabolic syndrome	Mechanism of pathogenesis of metabolic syndrome	Therapeutic approaches	References
Polyamines and metabolic syndrome	Spermine, Spermidine, Putrescine	Generally dietary proteins	Firmicutes: Lactobacillus spp., Clostridium spp., Enterococcus spp. Bacteriodetes: Bacteroides spp. Proteobacteria: *Escherichia coli*	Biomarkers and mediators in MetS	Potential targets for metabolic syndrome management	Polyamine metabolism dysregulation may contribute to metabolic dysfunction	Dietary interventions, spermidine supplementation, and gut microbiota modulation	[29, 33, 51–54]
Tryptophan and indole derivatives in metabolic syndrome	Indole-3-aldehyde (3-IAld), indole-3-acetic acid (IAA), indole-3-aldehyde (IAA), indole-3-lactic acid (ILA) and indole-3-propionic acid (IPA)	Trytophan	Firmicutes: *Lactobacillus* spp., *Clostridium* spp., *Enterococcus* spp., Faecalibacterium prausnitzii, Bacteriodetes: *Bacteroides* spp., *Prevotella* spp., Actinobacteria: *Bifidobacterium* spp.,	Involved in regulating metabolic processes	Implications in metabolic syndrome development and treatment	Complex signaling pathways involving indole derivatives contribute to MetS	Dietary interventions, and novel therapeutic agents targeting indole metabolism	[27, 55–58]

metabolites have shown promise in managing MetS. These include probiotics, prebiotics, synbiotics, fecal microbiota transplantation (FMT], dietary interventions, and precision medicine approaches [37, 39, 60, 61]. For example, dietary adjustments and supplementation with specific nutrients have been proposed to modulate GM composition and metabolite production [62, 63].

Short-chain fatty acids in metabolic syndrome

Short-chain fatty acids (SCFAs), particularly acetate, propionate, and butyrate, are metabolites produced by gut microbiota fermentation of dietary fiber. SCFAs play a vital role in regulating metabolic processes, including glucose and lipid metabolism, inflammation, and gut barrier integrity [18–20]. Dysregulation of SCFA levels has been implicated in the pathogenesis of metabolic syndrome. Ganesan et al. and Zhang et al. both emphasize the dysregulation of SCFAs in metabolic disorders [64, 65]. Ganesan et al. found decreased SCFA levels, particularly acetate and butyrate, in NAFLD patients, while Zhang et al. observed decreased propionic acid levels in Cushing's syndrome patients. These findings suggest a potential link between SCFAs and metabolic syndrome severity.

Nogal et al. examined the relationships between circulating acetate levels, gut microbiome composition, and visceral fat in a large population-based cohort [66]. They found that acetate levels were positively correlated with gut microbiota diversity and negatively associated with visceral fat. This study suggests that gut microbiota composition and SCFA production could influence cardiometabolic health by modulating visceral fat accumulation. Various dietary components, including fiber, dairy products, anthocyanins, and betaine, have been studied for their effects on gut microbiota composition and metabolic syndrome.

Impact of dietary intervention on metabolic syndrome targeting SCFA

Consumption of fiber-rich diets promotes the growth of beneficial bacteria and SCFA production, thereby attenuating metabolic syndrome risk [39, 67, 68]. Dairy product consumption, particularly low-fat options, has been associated with beneficial alterations in plasma metabolome profiles and mitigation of metabolic syndrome [34]. Additionally, dietary supplements like betaine have shown promise in improving gut microbiota dysbiosis and metabolic syndrome parameters via the gut microbiota-derived miR-378a/YY1 regulatory axis [69].

Li et al. explored the effects of different types of dietary fiber (DF) on the growth and development of Magang geese [70]. They observed that low-, medium-, and high-viscosity DFs reduced lipid levels in geese by promoting the production of SCFAs and activating the AMPK pathway-related genes. This study emphasizes the beneficial effects of DFs on lipid metabolism through SCFA production, providing insights into dietary interventions for metabolic syndrome. He et al. and Maurer et al. investigated dietary interventions with mulberry leaf extract (MLE) and citrus extract, respectively [71, 72]. Both studies found that these extracts positively influenced SCFA production, contributing to improved metabolic profiles in MetS subjects. He et al. demonstrated that MLE modulated SCFA production through the AMPK signaling pathway, while Maurer et al. observed increased butyrate production with citrus extract supplementation.

Wang et al. and Li et al. focused on the effects of dietary interventions on SCFA production by gut microbiota modulation [73, 74]. Wang et al. found that Lactobacillus administration increased SCFA production, particularly acetic acid, contributing to improved metabolic parameters. Li et al. demonstrated that dietary butyrate reduced weight gain and improved insulin resistance in mice, with the effects mediated by gut microbiota, particularly Lachnospiraceae bacterium 28–4.

Trimethylamine N-oxide (TMAO) in metabolic syndrome (MetS)

Emerging research suggests that gut microbiome-derived metabolites, particularly trimethylamine N-oxide (TMAO), may play a pivotal role in the pathogenesis of MetS and its associated complications. Several studies investigate the relationship between TMAO and metabolic syndrome (MetS), emphasizing its potential as a biomarker and its role in the pathogenesis of MetS. Kuo et al. found a positive association between serum TMAO levels and MetS in patients with coronary artery disease (CAD) [24]. Similarly, Mirzababaei et al. reported a significant correlation between elevated TMAO levels and MetS, indicating its potential as a predictive marker for MetS [25]. Moreover, Sun et al. highlighted the association between TMAO levels and the severity of psoriasis, suggesting its role as an indicator of disease severity in psoriatic patients with MetS [26].

Metabolomics studies reveal a distinctive urinary metabolite signature associated with metabolic syndrome progression. Bruzzone et al. identified TMAO and sixteen other metabolites that evolve with MetS progression, providing insights into the molecular basis of the syndrome and offering potential biomarkers for early detection and monitoring [60]. Nurwanti and Bai found that both TMAO and BMI were independently associated with an increased risk of metabolic syndrome [44]. TMAO exhibited a higher odds ratio for metabolic syndrome compared to BMI, suggesting its potential as a

more sensitive biomarker for metabolic syndrome risk in middle-aged and elderly adults.

While TMAO is associated with MetS, its role in atherosclerotic cardiovascular disease (ASCVD) remains under discussion. Ringel et al. found no independent association between TMAO plasma levels and stable ASCVD but identified associations with obesity and diabetes mellitus (DM), indicating a potential functional role in metabolic syndrome [45]. Additionally, Hoyles et al. demonstrated the direct interaction of microbiome-associated methylamines, including TMAO, with the blood–brain barrier (BBB), influencing cerebrovascular and cognitive function [75]. This highlights the intricate relationship between gut microbiota-derived metabolites and brain health, with implications for neurological disorders associated with metabolic syndrome.

Effects of dietary intervention on TMAO levels

The gut microbiota plays a crucial role in metabolic syndrome, influencing TMAO production and other metabolic pathways. Gao et al. demonstrated that L-carnitine supplementation modulated gut microbiota composition and attenuated high-fat diet-induced metabolic syndrome in mice, providing evidence for the therapeutic potential of L-carnitine in metabolic syndrome [76].

Thomas et al. compared the effects of egg intake and choline supplementation on TMAO formation and gut microbiota in MetS individuals, observing an increase in plasma carotenoids with no significant effect on TMAO levels but noting correlations between microbiota diversity and metabolic parameters [61]. Additionally, Franck et al. investigated the effects of red raspberry consumption on metabolic parameters and trimethylamine N-oxide (TMAO) levels [77]. Despite changes in gene expression and metabolomic profiles, raspberry supplementation did not lead to significant metabolic improvements, emphasizing the complexity of dietary interventions. Collectively, these studies underscore the role of dietary interventions and gut microbiota modulation in influencing MetS and associated complications, with TMAO emerging as a potential mediator whose precise mechanisms warrant further investigation for developing targeted therapeutic strategies.

Role of bile acids in metabolic syndrome

Bile acids, synthesized from cholesterol in the liver, undergo further modification by the gut microbiota, leading to the generation of a diverse pool of bile acid species. Dysregulated bile acid metabolism has been implicated in the pathogenesis of metabolic syndrome. Children with MetS exhibit elevated levels of total, secondary, and 12α-hydroxylated bile acids, along with deoxycholic acid, which correlates with dyslipidemia and insulin resistance markers [30]. Moreover, dysregulated bile acid profiles negatively correlate with gut bacterial diversity, potentially contributing to gut microbial dysbiosis in MetS [30].

Studies have elucidated the role of bile acid-activated receptors (BARs), such as the farnesoid-x-receptor (FXR) and G protein Bile Acid Receptor (GPBAR1), in metabolic regulation. Activation of these receptors modulates inflammatory responses and metabolic pathways, suggesting therapeutic potential in addressing metabolic disorders [78].

Interventions on bile acids for treating metabolic syndrome

Various interventions targeting bile acid metabolism have shown promise in ameliorating metabolic syndrome. For instance, dietary supplementation with xanthohumol derivatives leads to improvements in obesity and MetS parameters, partly mediated by alterations in gut microbiota composition and bile acid metabolism [79]. Similarly, caffeine treatment improves metabolic syndrome in high-fat diet-induced obese mice by alleviating insulin resistance and serum lipid disorders [80]. The underlying mechanisms involve alterations in gut microbiota composition and bile acid metabolism. Additionally, synbiotic interventions, combining beneficial bacteria like Akkermansia muciniphila with antioxidants, demonstrate efficacy in modulating gut microbiota and bile acid profiles, thereby attenuating obesity and NAFLD progression [81].

Polyamines in metabolic syndrome

Polyamines, such as putrescine, spermidine, and spermine, are organic compounds that occur naturally in many foods and are also synthesized within the human body. Although not directly produced by the gut microbiota, these compounds are influenced by microbial activities within the gut. For instance, a study demonstrated that polyamines like putrescine, derived from the gut microbiota, help promote colonic epithelial proliferation and regulate macrophage differentiation [53]. This suggests a vital role for microbial polyamines in maintaining mucosal homeostasis. Similarly, Ma et al. found that spermidine supplementation led to weight loss and improved insulin resistance in diet-induced obese mice, with these effects linked to enhanced intestinal barrier function and significant changes in the gut microbiota composition, including an increase in the SCFA-producing bacterium Lachnospiraceae NK4A136 group [51].

Further exploring the impact of gut microbiota on polyamine metabolism, Sheng et al. investigated men with metabolic syndrome and discovered alterations in gut microbial species, coupled with increased polyamine metabolism pathways. This activity was associated with elevated levels of gamma-glutamyl transpeptidase

(GGT), a marker often linked with metabolic dysfunction. By modulating glutathione levels and maintaining cellular oxidative balance, GGT indirectly supports the enzymatic processes involved in polyamine synthesis and degradation in the gut [33]. Additionally, Tari Selcuk et al. conducted a study that found correlations between dietary polyamine intake and various metabolic risk parameters in postmenopausal women [54]. The intake of spermidine was found to be positively associated with increased waist circumference, systolic and diastolic blood pressure, body mass index (BMI), and waist-to-height ratio (WHtR). In contrast, the intake of spermine was negatively associated with waist circumference, systolic blood pressure, BMI, and WHtR, underscoring the significant impact of dietary sources of polyamines. These findings collectively highlight the complex interplay between dietary polyamines, gut microbiota, and the host's metabolic health, emphasizing the indirect but profound influence that gut microbiota have on polyamine levels and their broader systemic effects.

Effect of bariatric surgery on polyamine levels and metabolic syndrome improvement

Ocaña-Wilhelmi et al. investigated the impact of bariatric surgery on serum polyamine levels in morbidly obese patients with metabolic syndrome [29]. They observed a significant increase in polyamine metabolites after surgery, particularly putrescine and acetyl derivatives of spermidine and spermine. Moreover, changes in putrescine and acetyl putrescine levels were associated with the resolution of metabolic syndrome post-surgery.

Understanding the complex mechanisms involving polyamines and gut microbiota could pave the way for novel interventions targeting metabolic disorders. However, further research is warranted to elucidate underlying mechanisms and optimize therapeutic strategies.

Impact of dietary intervention on metabolic syndrome targeting polyamines

Dietary intake of polyamines, which are abundant in foods such as soy, legumes, and mushrooms, has been shown to enhance gut microbiota composition and function. A study by Vasquez et al. suggests that dietary intervention can modulate the gut microbiome and subsequently influence polyamine levels, which could improve gut health and reduce inflammation [82]. Similarly, Xiao et al. demonstrated that dietary fibers and polyamines could enrich short-chain fatty acid (SCFA)-producing bacteria and genes involved in tryptophan metabolism, further supporting the notion that diet significantly affects gut microbiota and metabolite production [83].

Tryptophan and indole derivatives in metabolic syndrome

Indole and its derivatives are metabolites produced by the gut microbiota from the amino acid tryptophan. Tryptophan metabolism produces several bioactive compounds, including indole-3-aldehyde (3-IAId), indole-3-acetic acid, indole-3-aldehyde (IAA), indole-3-lactic acid, and indole-3-propionic acid (IPA), which have shown significant cardiometabolic effects. Several studies underscore the therapeutic potential of indole derivatives.

The interplay between tryptophan metabolism and cardiovascular disease (CVD) is notable. Melhem and Taleb discussed the intricate relationship between tryptophan metabolites, particularly kynurenine pathway intermediates, and CVD pathogenesis, suggesting avenues for tailored therapeutic interventions [84]. Furthermore, indole derivatives, particularly those from gut microbiota metabolism, play crucial signaling roles. Shatova and Shestopalov elucidated the signaling functions of indole derivatives, emphasizing their role in gut-microbiota crosstalk and metabolic syndrome [85]. Su et al. highlighted the immunomodulatory effects of gut microbiota-derived tryptophan metabolites, offering insights into potential immunotherapeutic strategies [86].

Indole derivatives, such as Indole-3-aldehyde (3-IAId) and indole-3-propionic acid (IPA), play significant roles in the context of metabolic syndrome, particularly in relation to metabolic dysfunction-associated steatotic liver disease (MASLD). Studies have indicated a close relationship between MASLD and gut microbiota-derived metabolites, including indole derivatives. A study by Min et al. demonstrated that patients with hepatic steatosis exhibited decreased levels of IPA and indole-3-acetic acid (IAA) in their feces compared to healthy controls [57]. This finding is significant as it indicates a potential link between indole derivatives and the development of hepatic steatosis.

Moreover, research has shown that the administration of IPA and IAA can ameliorate hepatic steatosis and inflammation in animal models of MASLD induced by a Western diet (WD). This effect is achieved through the suppression of the NF-κB signaling pathway, which is associated with a reduction in endotoxin levels and the inactivation of macrophages [57]. Specifically, Bifidobacterium bifidum, a gut bacterium, metabolizes tryptophan to produce IAA, which effectively prevents hepatic steatosis and inflammation. Also, Alam et al. investigated the efficacy of Lysimachia candida Lindl. extract in mitigating metabolic syndrome phenotypes in rats, highlighting its ability to restore metabolic pathways crucial for glucose homeostasis and insulin sensitivity [27]. This suggests a potential therapeutic role for indole derivatives derived from the gut microbiota in the treatment of MASLD.

Effects of dietary intervention on tryptophan and indole derivatives

Dietary tryptophan, found in foods like turkey, eggs, and cheese, can be modulated through specific dietary interventions. Selective nourishment of gut microbiota with amino acids, including tryptophan, could serve as a novel prebiotic approach to improve gut health [87]. Dietary interventions with specific lipids, such as phosphatidylcholine and sphingomyelin, can modulate endogenous tryptophan metabolism and gut microbiota composition, with phosphatidylcholine showing more promise in reducing colitis symptoms and inflammation in preclinical models [88].

A polyphenol-rich diet can influence GM and enhance the production of bioactive metabolites, specifically indole derivatives from dietary tryptophan, which are linked to maintaining intestinal barrier integrity. In a randomized controlled trial with older adults, a polyphenol-rich diet significantly increased serum levels of IPA in participants with normal renal function, but not in those with impaired RF. The study found that IPA variations were associated with changes in C-reactive protein and shifts in GM composition, particularly within the Clostridiales and Enterobacteriales orders [89]. These results suggest that a polyphenol-rich diet may be beneficial for older adults with normal renal function, highlighting the importance of considering renal function when defining dietary interventions aimed at improving gut health and metabolic outcomes.

Dietary interventions and gut microbiota in metabolic syndrome

Wang et al. and Zeng et al. explore dietary interventions and their effects on metabolism and gut microbiota. Wang et al. focus on kelp-resistant starch (KRS) and its impact on intestinal morphology and function, highlighting changes in amino acid metabolism among other pathways [90, 91]. Zeng et al. investigate a citrus polymethoxyflavone-rich extract (PMFE) and its ability to alleviate metabolic syndrome through modulation of gut microbiota and regulation of branched-chain amino acid (BCAA) metabolism. Both studies underscore the intricate relationship between dietary interventions, gut microbiota, and metabolic pathways. Li and Song utilized Mendelian randomization to investigate the causal relationship between antioxidants, minerals, and vitamins with MetS traits [92]. They found associations between specific vitamins and minerals with components of MetS, providing insights into potential causal relationships.

Association between vitamins and metabolic syndrome

Several studies have investigated the association between various vitamins and metabolic syndrome (MetS) as highlighted in Table 2. Nguyen et al. found that lower intakes of vitamins B1, B2, B3, C, and A were associated with MetS, while higher serum levels of heavy metals (Pb, Hg, Cd), vitamin A, E, and hs-CRP were observed in subjects with MetS [101]. Pei et al. explored water-soluble vitamins (VC, VB9, VB12) and found negative associations with MetS, with higher quartiles of VC associated with lower MetS risk [103]. Nguyen and Kim found that vitamin B2 intake and high curry consumption were associated with reduced MetS risk in postmenopausal women [102].

Zhang et al. investigated the effects of diet-induced gut microbiota dysbiosis on spermatogenesis in a MetS sheep model. They found a notable reduction in bile acid levels, affecting vitamin A absorption, which contributed to abnormal spermatogenesis [105]. This study highlights the intricate relationship between gut microbiota, vitamin absorption, and MetS-related outcomes. Boughanem et al. explored the modulation of gut microbiota and serum vitamin D levels by a Mediterranean diet (MedDiet) intervention in obese patients with MetS [97]. They observed differences in gut microbiota composition and functionality between groups with optimal and low vitamin D levels. The study suggests a potential link between gut microbiota, vitamin D status, and metabolic pathways, emphasizing the role of dietary interventions in managing MetS. Zhang et al. investigated the effects of vitamin D supplementation on high-fat diet-induced NAFLD in rats [100]. They found that vitamin D treatment improved NAFLD by modulating gut microbiota composition and metabolites. This study suggests a potential therapeutic role for vitamin D in NAFLD through gut microbiota regulation.

Zhu et al. conducted a prospective study in a US cohort and found inverse associations between folate, vitamin B6, and vitamin B12 intakes or serum concentrations with incident MetS [96]. This study underscores the importance of B vitamin status in MetS risk reduction. Soto-Martin et al. investigated the growth requirements of butyrate-producing gut bacteria, emphasizing their dependence on dietary vitamins [106]. The study highlights the role of vitamins, particularly thiamine and folate, in supporting the growth and function of beneficial gut bacteria associated with metabolic health. Villatoro-Santos et al. explored the associations between vitamins B6, B12, and folate with MetS prevalence in Mesoamerican children and adults [107]. Their findings suggest differential associations between vitamins and MetS across age groups.

HighliKim and Kang found a dose-dependent association between high serum retinol (vitamin A) and α-tocopherol (vitamin E) levels with increased MetS risk among Korean adults [95]. Barzegar-Amini et al.

Table 2 Role of vitamin intake in metabolic syndrome

Role of the nutrient/diet in metabolic syndrome	Therapeutic approaches	Future considerations	Reference(s)
Plant-sourced nutrients associated with lower MetS risk; animal- and mixed-sourced nutrients linked to higher odds of MetS	Dietary adjustments, education on nutrient-rich foods	Further exploration of nutrient patterns and their impact on MetS development	[63, 93]
Association between high serum retinol and α-tocopherol levels with increased MetS risk	Monitoring and supplementation of deficient vitamins	Investigating the role of serum vitamins as potential biomarkers of MetS	[94, 95]
Association between higher folate intake and a lower MetS score; inverse associations between folate, vitamin B6, and vitamin B12 intakes or serum concentrations with incident MetS	Dietary folate, vitamin B6, and B12 supplementation	Assessing the potential of folate supplementation in MetS management	[62, 96]
Impact of vitamin D deficiency on higher prevalence of MetS; Mediterranean diet (MedDiet) intervention modulates gut microbiota and serum vitamin D levels in obese patients with MetS; vitamin D supplementation improves NAFLD in rats by modulating gut microbiota composition and metabolites	Vitamin D supplementation, sunlight exposure	Investigating the efficacy of vitamin D supplementation in MetS prevention	[97–100]
Combined intake of multiple vitamins is negatively associated with obesity risk; lower intakes of vitamins B1, B2, B3, C, and A associated with MetS; negative association between water-soluble vitamins (VC, VB9, VB12) and MetS; higher quartiles of VC linked to lower MetS risk; vitamin B2 intake and high curry consumption associated with reduced MetS risk in postmenopausal women	Encouraging a balanced intake of multiple vitamins, including supplementation with water-soluble vitamins and B2	Exploring specific water-soluble vitamins' role in reducing MetS risk and the impact of diet-based interventions on MetS	[101–104]
Diet-induced gut microbiota dysbiosis impacts vitamin A absorption, affecting spermatogenesis in MetS sheep model	Modulation of gut microbiota through diet	Research on gut microbiota's role in vitamin absorption and MetS outcomes	[105]
Growth of butyrate-producing gut bacteria depends on dietary vitamins, particularly thiamine and folate	Dietary interventions to support beneficial gut bacteria	Exploring the role of dietary vitamins in gut microbiota and metabolic health	[106]
Differential associations between vitamins B6, B12, and folate with MetS prevalence across age groups in Mesoamerican children and adults	Age-specific vitamin supplementation	Investigating age-related differences in vitamin-MetS associations	[107]

reported lower serum vitamin E levels in individuals with MetS, suggesting an inverse association between vitamin E status and MetS presence [94]. Overall, these studies demonstrate the complex and varied relationships between vitamin intake, serum levels, gut microbiota, and metabolic syndrome (MetS).

Role of dietary supplements

Interventions targeting the gut microbiota and circulating metabolites offer promising avenues for metabolic syndrome management. Gholami et al. investigated the association between dietary supplement intake and MetS, while initial findings indicated significant differences in supplement consumption among those with MetS, the relationship was not significant after adjusting for covariates in the multivariate regression model [108]. Cano-Ibáñez et al. found that despite being overweight, participants with MetS exhibited suboptimal nutrient intake, particularly among men, with nutrient density positively associated with female sex, higher education, better Mediterranean diet adherence, non-smoking, and active lifestyles [109]. Qiu et al. and Zhang et al. demonstrated the therapeutic potential of traditional Chinese herbal medicine and prebiotic supplementation in ameliorating metabolic disorders [110, 111]. Additionally, Alhamoud et al. highlighted the anti-obesity effects of 6-gingerol through microbiota modulation and lipid metabolism alterations [112].

These studies collectively underscore the complex interplay between dietary nutrients, serum vitamin levels, and metabolic health outcomes like MetS and obesity. While some nutrients demonstrate protective effects against MetS, others may increase risk factors. Understanding these associations can inform dietary recommendations and intervention strategies for improving metabolic health.

Metformin's role in gut health and metabolic syndrome management

Metformin plays a pivotal role in managing metabolic syndrome, demonstrating its crucial importance in improving not only glucose metabolism but also broader aspects of metabolic health. Metformin positively impacts gut microbiota, enhancing its therapeutic effects in treating metabolic syndrome (MetS). It promotes the growth of short-chain fatty acid (SCFA) producing bacteria, including Blautia, Bacteroides, Butyricoccus, Bifidobacterium, Prevotella, Megasphaera, and Butyrivibrio, leading to increased fecal concentrations of lactate and succinate [113, 114]. Metformin also boosts mucin-degrading bacteria like Akkermansia muciniphila, which improves glucose metabolism by regulating gut permeability, reducing lipopolysaccharides (LPS), and enhancing postprandial insulin secretion through GLP-1 interactions [114, 115].

Further studies highlight metformin's influence on the gut microbiome and its role in improving metabolic health. Metformin administration impacts metabolic syndrome by modulating the gut microbiota, leading to changes in microbial communities such as Prevotellaceae, Rikenellaceae, and Clostridiales, which may influence glucose metabolism, lipid profiles, and overall gut health, helping to distinguish MetS from type 2 diabetes mellitus (T2DM) and highlighting the unique microbiome signatures associated with each condition [116]. In accordance with the findings of Lee et al., metformin regulates metabolic syndrome by modulating the gut microbiome, which enhances glucose metabolism, increases short-chain fatty acids, strengthens intestinal permeability against lipopolysaccharides, modulates the immune response, and interacts with bile acids [117].

Additionally, metformin may offer cardiovascular benefits by reducing trimethylamine N-oxide (TMAO) concentrations and its precursor metabolites, which are linked to cardiovascular diseases [118]. Overall, metformin enhances gut and cardiovascular health by modulating the gut microbiota, increasing beneficial bacterial species, and reducing harmful metabolites. Furthermore, Ahmadi et al. provide evidence that metformin reduces aging-related microbiome dysbiosis and improves cognitive function by modulating the gut microbiome/goblet cell/mucin axis [119]. This multifaceted influence underscores metformin's potential beyond glucose regulation, suggesting it can also play a significant role in overall metabolic health, inflammation reduction, and the maintenance of gut integrity. These findings highlight the importance of understanding the gut microbiome's role in therapeutic interventions and open avenues for future research on metformin's broader health benefits.

Therapeutic potential of probiotics, prebiotics, and synbiotics in metabolic syndrome and associated metabolic disorders

The complex interplay between the composition of gut microbiota, the metabolites they produce, and the body's physiological processes significantly influences the development of metabolic syndrome (MetS). Among the array of therapeutic strategies, probiotics, prebiotics, and synbiotics have emerged as promising interventions for modulating gut microbiota and improving metabolic health.

Probiotics, live microorganisms with health benefits when consumed adequately, play a pivotal role in managing MetS. They foster the growth of beneficial bacteria to restore microbial balance. This restoration of microbial balance has been linked to reductions in obesity-related

MetS, insulin resistance, dyslipidemia, and inflammation. Notably, probiotics exert their effects by influencing various metabolic pathways beyond SCFA production. They modulate bile acid composition, polyamine metabolism, amino acid metabolism, and indole derivative production, thereby impacting metabolic function [53, 120, 121].

Recent studies have expanded on these findings, exploring the potential of fecal microbiota transplantation (FMT) as an innovative approach to treating metabolic syndrome and associated metabolic disorders. For instance, a randomized controlled trial demonstrated that FMT combined with low-fermentable fiber supplementation significantly improved insulin sensitivity in patients with severe obesity and metabolic syndrome [122]. Similarly, another study found that FMT capsules derived from lean donors led to sustained changes in the gut microbiome of obese patients, although it did not result in significant weight loss [123]. Moreover, in adolescents with obesity, FMT did not affect BMI but showed promising reductions in abdominal adiposity [124]. Further emphasizing the potential of FMT, a trial in obese subjects with type 2 diabetes demonstrated enhanced microbiota engraftment and improved metabolic parameters following repeated FMT treatments [125].

Prebiotics, non-digestible fibers that selectively nourish beneficial gut bacteria, offer another avenue for MetS management. By serving as substrates for SCFA production, prebiotics regulate glucose and lipid metabolism while modulating gut microbiota composition [19]. Dietary interventions enriched with prebiotics have demonstrated efficacy in improving metabolic parameters associated with MetS [37]. Furthermore, prebiotics contribute to metabolic health by promoting bile acid homeostasis, polyamine balance, amino acid metabolism, and indole production through their influence on gut microbiota [51, 58, 126, 127].

Synbiotics, which combine probiotics and prebiotics, offer an integrated approach to enhancing gut microbiota and metabolic health. By providing a conducive environment for probiotic proliferation, prebiotics augment the efficacy of probiotic supplementation in MetS management [39]. This synergistic effect addresses dysbiosis-induced metabolic dysfunction comprehensively. For instance, research by Ouyang et al. underscores the therapeutic potential of synbiotics in alleviating small intestinal bacterial overgrowth and improving lipid metabolism, particularly in pregnant women with subclinical hypothyroidism [128].

Probiotics, prebiotics, and synbiotics represent promising strategies for managing MetS by modulating gut microbiota composition and influencing various metabolic pathways. Their multifaceted effects underscore their potential as holistic approaches to metabolic health.

Conclusion and future directions

In conclusion, the gut microbiota and microbiota-derived metabolites represent key players in the pathogenesis of metabolic syndrome and associated disorders. Understanding the complex interplay between GM composition, microbial metabolites, and host physiology holds promise for the development of personalized therapeutic interventions and non-invasive diagnostic tools for metabolic disorders. However, addressing challenges such as methodological heterogeneity and the need for translational research is essential for advancing our understanding and clinical management of MetS.

Probiotics, prebiotics, and synbiotics represent promising therapeutic approaches for managing metabolic syndrome by modulating gut microbiota composition and microbial metabolite production. These interventions target the underlying dysbiosis and metabolic dysfunction associated with MetS, offering potential avenues for personalized therapy. Future research should focus on elucidating the mechanistic links between gut microbiota, metabolites, and MetS pathogenesis to optimize therapeutic strategies and develop non-invasive diagnostic tools.

Future research efforts should focus on elucidating the specific mechanisms by which gut microbiota and microbiota-derived metabolites influence MetS development and progression. Additionally, well-designed, controlled trials are needed to evaluate the efficacy of therapeutic interventions targeting GM composition and metabolite profiles in MetS management. Translational research aiming to leverage stool metabolites for non-invasive diagnostics and personalized therapeutic interventions represents a promising avenue for future investigation. Moreover, integrating omics technologies and systems biology approaches may provide deeper insights into the complex interplay between diet, microbiome, and cardiometabolic diseases, paving the way for precision medicine in MetS management.

Abbreviations

MetS	Metabolic syndrome
CVD	Cardiovascular disease
T2DM	Type 2 diabetes mellitus
GM	Gut microbiota
SCFA	Short-chain fatty acid
TMAO	Trimethylamine N-oxide
FMT	Fecal microbiota transplantation
DF	Dietary fiber
MLE	Mulberry leaf extract
AMPK	AMP-Activated protein kinase
ASCVD	Atherosclerotic cardiovascular disease
DM	Diabetes mellitus
BBB	Blood-brain barrier
FXR	Farnesoid X receptor
GPBAR1	G protein bile acid receptor 1
TGR5	Takeda G-protein-coupled receptor 5
NAFLD	Non-alcoholic fatty liver disease
BMI	Body mass index

BCAA	Branched-chain amino acid
GGT	Gamma-glutamyl transpeptidase
IAA	Indole-3-acetic acid
IPA	Indole-3-propionic acid
KRS	Kelp-resistant starch
MASLD	Metabolic dysfunction-associated steatotic liver disease
MedDiet	Mediterranean diet
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
PMFE	Polymethoxyflavone-rich extract
3-IAld	Indole-3-aldehyde
WD	Western diet
WHtR	Waist-to-height ratio

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SOO conceived and designed the study. SOO wrote the initial version of the manuscript. OOB, IOO, and ASF reviewed the initial version of the manuscript. SOO, OOB, IOO, ASF, BOA, and ENE wrote the final draft of the manuscript. All authors read and approved the final manuscript.

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