Exploring the relationship between berberine and the gut microbiome: A closer look at recent studies

Berberin ve bağırsak mikrobiyomu arasındaki ilişkinin araştırılması: Son çalışmalara yakından bir bakış

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Abstract

Aim: Berberine, known for regulating blood glucose and reducing inflammation, also enhances gut microbiota diversity and repairs microbial profiles. However, comprehensive reviews on its disease-specific impacts are limited. This study aims to explore berberine's influence on microbiota diversity in various diseases, offering a novel perspective.

Methods: A literature review was conducted using PubMed, Web of Science, ScienceDirect, and Google Scholar, focusing on studies from 2018-2023. Keywords related to berberine and gut microbiota were used, excluding irrelevant topics. A total of 84 titles and abstracts were screened, with 33 articles meeting inclusion criteria for detailed review.

Results: Berberine promotes beneficial species like Bacteroidetes and Akkermansia, shows antimicrobial properties, and targets specific pathogens. Studies, particularly in obese and Type 2 diabetic mice, suggest it can improve gut microbiota and diversity. However, the optimal dosage remains unclear, and individual microbial responses can vary, sometimes leading to dysbiotic profiles.

Conclusion: Berberine shows promise in enhancing gut microbiota diversity and combating pathogens. Nevertheless, further studies are needed to confirm its therapeutic potential and establish optimal treatment protocols with long-term clinical outcomes.

Keywords: Berberine; microbiota; microbial; microbiome

Öz

Amaç: Berberin, kan şekeri düzenleme ve iltihap azaltma özellikleriyle bilinir ve ayrıca bağırsak mikrobiyota çeşitliliğini artırır ve mikrobiyal profilleri onarır. Ancak, hastalıklara özgü etkileri üzerine kapsamlı incelemeler sınırlıdır. Bu çalışma, berberinin çeşitli hastalıklardaki mikrobiyota çeşitliliği üzerindeki etkisini araştırmayı ve bu konuda yeni bir bakış açısı sunmayı amaçlamaktadır.

Yöntem: 2018-2023 yılları arasında PubMed, Web of Science, ScienceDirect ve Google Scholar gibi veritabanlarında, berberin ve bağırsak mikrobiyotası ile ilgili anahtar kelimeler kullanılarak bir literatür taraması yapılmıştır. İlgisiz konular hariç tutularak 84 başlık ve özet incelenmiş, 33 makale belirlenen kriterlere göre detaylı olarak gözden geçirilmiştir.

Bulgular: Berberin, Bacteroidetes ve Akkermansia gibi yararlı türleri destekler, antimikrobiyal özellikler gösterir ve belirli patojenleri hedef alır. Özellikle obez ve Tip 2 diyabetik farelerde yapılan çalışmalar, bağırsak mikrobiyotası ve çeşitliliğinde iyileşme potansiyeline işaret etmektedir. Ancak, optimal dozaj belirsizdir ve bireysel mikrobiyal yanıtlar farklılık gösterebilir, bazen disbiyotik profillere yol açabilir.

Sonuç: Berberin, bağırsak mikrobiyota çeşitliliğini artırma ve patojenlerle mücadelede umut vadetmektedir. Bununla birlikte, terapötik potansiyelini doğrulamak ve uzun vadeli klinik sonuçlar elde etmek için daha fazla araştırma gereklidir.

Anahtar Sözcükler: Berberin; mikrobiyota; mikrobiyal; mikrobiyom

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INTRODUCTION

Berberine (BBR) is a distinctive molecule belonging to the protoberberine group of isoquinoline alkaloids. Classified as a quaternary ammonium salt, it is characterized by the molecular formula $C_{20}H_{18}NO_4$ (1, 2). It is a bioactive compound found in many plants such as *B. Petiolaris*, *B. aristate*, *B. darwinii*, and *B. vulgaris* (3-6) (Figure 1). The stems and roots of *Berberis aristata, B. darwinii, B. petiolaris,* and *B. vulgaris* have been extensively studied for their high berberine content. Additionally, many other medicinal plants with high berberine content have been reported, including *Coptis chinensis* (Chinese goldthread) and *Hydrastis canadensis* (goldenseal) (7). Berberine is found in various plant families, such as *Annonaceae, Berberidaceae, Menispermaceae, Papaveraceae, Ranunculaceae,* and *Rutaceae.* Within the genus *Berberis, B. vulgaris* is particularly significant, with its bark containing over 8% alkaloids, of which approximately 5% is berberine. This compound is prevalent in the barks, leaves, twigs, rhizomes, roots, and stems of numerous medicinal plants like *Argemone mexicana, Berberis aristata,* and *Hydrastis canadensis*. Research indicates that the highest concentrations of berberine are typically found in the bark and roots of these plants (8).

Berberine, with its multi-target mechanism, has demonstrated positive pharmacological effects in diverse diseases, including inflammation, atherosclerosis, hyperlipidemia, mental disorders, liver diseases, intestinal diseases, autoimmune and cardiovascular diseases, and non-alcoholic fatty liver disease (NAFLD), notably reducing blood lipids and glucose in health issues like Type 2 diabetes and hyperlipidemia (9-14). Berberine supplementation significantly reduced the levels of polysaccharide lyases and carbohydrate esterases compared to the control group, while stimulating key pathways from the Kyoto Encyclopedia of Genes and Genomes (KEGG), including carbohydrate metabolism and microbial metabolism, by altering microbial enzyme activities. In vivo studies further demonstrated that while berberine did not affect *Enterobacteriaceae*, it inhibited some butyrate-producing bacteria and, at high doses, improved chicken gut morphology and reduced inflammation independently of gut microbiota changes (15).

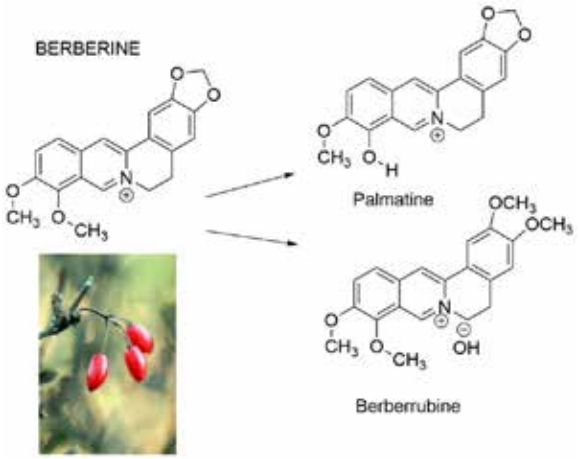

Figure 1. Molecular structures of berberine, berberrubine and palmatine

The intestinal microbiota, consisting of trillions of microorganisms, serves as the primary endocrine organ and plays a crucial role in essential physiological processes, including macronutrient digestion and vitamin synthesis, contributing to the preservation of host homeostasis. Therefore, it is evident that alterations in the balance of the intestinal flora can potentially contribute to the onset of various chronic and autoimmune diseases, such as obesity, diabetes, and other metabolic syndromes (16). It has also been discussed in previous studies that the low oral bioavailability of berberine and its effects may be due to intestinal microbiota interaction (10, 17). Studies have suggested that berberine may improve insulin resistance by modulating the gut microbiota and may also help treat cardiovascular diseases that accompany dyslipidemia and obesity (18). Although there has been increasing evidence in recent years that berberine can regulate the dysbiotic intestinal microbiome composition, there are also studies showing that it reduces the overall intestinal microbial diversity (19-21). While some studies suggest that berberine contributes to microbial balance by replacing dominant gut bacteria, other studies have emphasized the importance of berberine dosage and have shown that high doses taken as a dietary supplement may lead to dysbiosis-like changes in the intestinal microbiota (22). However, it's worth noting that, despite various studies addressing and discussing BBR and gut microbiota interactions from different perspectives, there has not yet been a com-

prehensive discussion regarding berberine's effects on the overall diversity of the gut microbiota, including both the positive and negative aspects of these effects (1, 2, 10, 23).

METHODS

In this narrative review article, a comprehensive literature search was conducted to evaluate the effects of berberine on the gut microbiota. Scientific studies published between 2018 and 2023 were sourced from various electronic databases, including PubMed, Web of Science, Science Direct, and Google Scholar (Figure 2). The search strategy employed the following keywords and combinations: ("Berberine" OR "Gut Microbiota" OR "Gut Microbiome") OR ("Gut Bacteria and Berberine" OR "Berberine and SCFA (short chain fatty acid)" OR "Gut Microbiota Richness" OR "Gut Microbiota Diversity" OR "Berberine and diseases") AND NOT ("review" [Title/Abstract] OR "Berberine and Cancer" OR "Berberine and Neurology"). This extensive search yielded a total of 84 titles and abstracts for initial screening, out of which 33 articles were thoroughly reviewed based on the inclusion criteria.

The selected studies prioritized those involving 16S rRNA and metagenomic analyses. The included articles comprised review articles, clinical and experimental intervention studies, observational studies, and systematic reviews. These studies commonly explored berberine's impact on gut microbiota alterations, microbial diversity and richness, short-chain fatty acids (SCFA), and berberine's potential therapeutic effects mediated by gut microbiota on various diseases. Additionally, studies investigating the effects of berberine on health issues such as metabolic diseases, inflammatory bowel diseases, and obesity were included.

This methodological approach facilitated a comprehensive evaluation of the existing literature, enabling a better understanding of the interactions between berberine and gut microbiota.

RESULTS

Berberine and gut microbiota interaction

While berberine is known to have beneficial health effects, its significantly low bioavailability has attracted attention and has been extensively investigated. Studies suggest that the interaction of berberine with the gut microbiota may contribute to potential health benefits. BBR has poor oral bioavailability; therefore, the ability to regulate gut microbiota and gut metabolites may be present (24). It has the potential to contribute to disease management. In human pharmacokinetic studies, less than 5% of orally administered berberine enters systemic circulation. Berberine is rapidly distributed and filtered by the liver, resulting in low circulation levels, and undergoes phase I demethylation followed by phase II conjugation processes. Its accu-

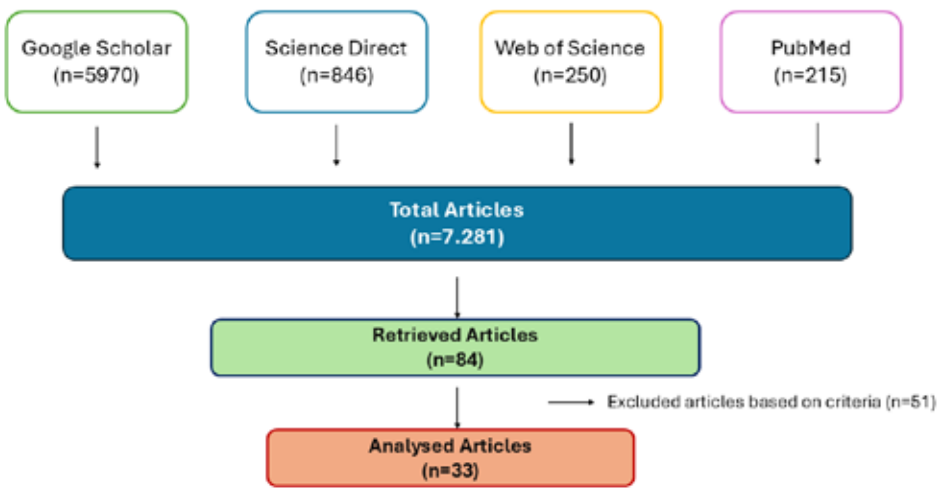

Figure 2. Flow diagram

mulation in tissues (e.g., liver, kidneys, muscle, brain) explains the pharmacological effects observed in clinical studies (e.g., cholesterol and blood glucose reduction) despite low plasma levels (25). Several studies have shown that berberine exhibits positive effects on various diseases such as cancer, inflammation, bacterial infections, and non-alcoholic fatty liver disease. In a study conducted in rats, the absolute bioavailability of orally administered 100 mg/kg berberine was measured at 0.68%. In dogs, the maximum concentration of berberine in the blood was found to be 36.88 ng/mL when administered at a dose of 50 mg/kg. This discrepancy between the low bioavailability and the potent pharmacological effects of berberine has puzzled researchers for some time (2, 23). It has been proposed that the bioavailability of berberine, which is markedly below 1%, is estimated to result in a peak plasma concentration of around 0.4 ng/ml following the administration of a 400 mg oral dose, thus reinforcing this suggestion (23). Additionally, a report highlights a specific finding on the interaction between berberine and the gut microbiota, indicating that approximately 43.5% of berberine undergoes metabolism in the intestines. Furthermore, nitroreductases within the gut microbiota have been documented to transform berberine into dihydroberberine (dhBBR), a more readily absorbable form that boasts a fivefold increase in intestinal absorption compared to berberine (26). Moreover, recent research has revealed that berberine modulates the gut microbiota, promoting microbial balance in rats subjected to a high-fat diet, and manifests therapeutic effects in metabolic diseases, particularly impacting the phylum-level composition (11, 27).

Health effects of berberine on intestinal microbiota

Berberine takes center stage as a potential adjunct in the management of various diseases, particularly by revealing its biological effects through interactions with the intestinal microbiota. Its ability to modulate the balance of gut microbiota positions berberine as a promising compound for therapeutic research, emphasizing its significance in promoting overall health. The antidepressant effect of BBR is linked to its regulation of the brain-gut axis via gut microbiota and SCFAs, increasing levels of serotonin, norepinephrine, dopamine, and BDNF. This mechanism alleviates depression-like behaviors (28). In a study, the effects of Diane-35, probiotics, and berberine were compared in a dihydrotestosterone (DHT)-induced polycystic ovary syndrome (PCOS) rat model. Diane-35 and probiotics improved reproductive and metabolic functions in PCOS rats by restoring gut microbiota diversity (29). It has been observed that berberine intervention significantly alters the gut microbiota in mice with glucose and lipid metabolism disorders, enriching bacteria such as *Akkermansia, Eubacterium*, and *Ruminococcus* (30). The use of berberine for therapeutic purposes has been observed to significantly increase the richness and diversity of the microbial community, alleviating symptoms of Type 2 diabetes in diabetic rats (24). Additionally, in another study aiming to compare the effects of berberine in combination with probiotics and berberine alone in Type 2 diabetes (T2D) patients, it was observed that they shared similar changes in terms of microbial alterations and functions. As a result of the study, the use of berberine for correcting intestinal microbiota dysbiosis in T2D patients was recommended (31). In other research evaluating the combination of BBR with a probiotic, it was found that the combination did not provide any additional benefit in improving postprandial plasma triglycerides (pTG) compared to berberine alone (32). In a study conducted on chickens, the impact of low (0.1 g/kg feed), medium (0.5 g/kg feed), and high (1 g/kg feed) doses of berberine intervention on the microbiome composition was investigated. Analysis of 16S rRNA gene sequences revealed that low and medium doses of berberine promoted beneficial bacteria from the *Lachnospiraceae* family in the chicken's cecum, while medium and high doses tended to increase villus length in the small intestine. The highest concentration of berberine significantly increased microbial diversity in the ileum. These findings suggest that berberine dosages can influence microbiome composition, with effects varying depending on the dose (33). However, berberine has been shown to have beneficial effects, like probiotics and antibiotics, in creating the microbial composition targeting the increase in *lactobacilli* and *bifidobacteria* in inflammatory bowel disease (IBD) patients (34). It can also be seen that the cholesterol-lowering effect of berberine is due to its

Table 1. Berberine's interactions with gut microbiota.

Animal/ human models	Dosage of BBR	Key findings	Refs.
Healthy Sprague-Dawley rats	150 mg/kg daily for 4 weeks	Hepatic inflammation↑ *Bacteroidetes*↑ *Firmicutes*↓ Diversity↓	(20)
Sprague-Dawley rat	200 mg/kg daily for 6 weeks	T2D symptoms↓ The community richness↑ Diversity↑ *Lactobacillaceae*↑ *Bacteroidetes*↓ *Proteobacteria*¯ *Verrucomicrobia*↓	(24)
Human, diagnosed with T2D	BBR; 0.6 g (6 pills) twice daily before meals Probiotics; 4 g (2 strips of powder) once daily at bedtime for 12 weeks	78 species changed BBR alone or in combination with probiotics altered the gut microbiome	(31)
Human, diagnosed with T2D	BBR; 0.6 g (6 pills) twice daily before meals Probiotics;4 g (2 strips of powder) once daily at bedtime for 12 weeks	Prob + BBR group did not show added benefits in improving pTG compared to BBR alone.	(32)
Hyperlipidemic human patient	0.5 g twice daily for 3 months	*Blautia*↑ *Akkermansia*↑ *Clostridium XI*↑ *Robinsoniella*↑ *Cronobacter*↑ *Anaerostipes*↑ *Coprobacillus*↑ *Alistipes*↓ *Helicobacter*↓ *Enterorhabdus*↓ *Desulfovibrio*↓	(35)
C57BL/6 mice	200 mg/kg daily for 56 days	Anti-hyperlipidemic effect of BBR *Blautia producta*↑ *Clostridiales*↑ *Akkermansia muciniphila*↑ In the HFD + BBR group; Blautia↑	(36)
Specific pathogen-free ICR mice	100-200-300 mg/kg daily for 5 weeks	*Akkermansia*↑ Too high dose of BBR may act as a weak antibiotic.	(38)
Sprague-Dawley and hamsters	100 mg/kg daily 10 days	Treatment of HFD-hamsters with BBR increased the butyrate content	(37)
Apoe −/− mice (SPF class)	0.5 g/L in water daily for 14 weeks	Berberine in HFD-fed Apoe −/− mice; Restored intestinal barrier HFD-induced inflammation↓ Akkermansia spp. ↑	(40)
BKS-Leprdb (*db/db*, T2DM model) and C57BLKS/JNju mice	136.5 mg/kg BRB 113.75 mg/kg metformin daily 19 weeks	In the berberine and metformin groups; *Butyricimonas*↑ *Lactobacilli*↑ *Coprococcus*↑ *Ruminococcus*↑ *Akkermansia*↑ *Prevotella*↓ *Proteus*↓	(41)
Sprague-Dawley rats	150 mg/kg berberine chloride daily for 4 months	HDF-induced metabolic disorders ameliorated *Bactriodetes* phylum↑	(42)

Human, diagnosed with hyperglycemia	0.5 g oral BBR tablets twice daily 0.70 g live *Bifidobacterium* capsules twice daily for 16 weeks	HbA1c↓ Bifidobacterium enhances the hypoglycemic effect of berberine	(43)
db/db mice and wild type mice	6 groups of *db/db* mice (*db*, M250, B250, B125, B250 + M250, and B125 + M250) with wild type (WT) as control for 14 days	Combination metformin and berberine; *Proteobacteria*↑ *Verrucomicrobia*↑ B125 + M250; insulin sensitivity↑ distinct changes in intestinal microbial communities	(44)
Specific pathogen-free (SPF) Wistar rat	200 mg/kg BBR 100 mg/kg BBR 200 mg/kg MET once a day for 18 weeks	Metformin more dominant effect on Lactobacillus and Klebsiella↑ Berberine more dominant effect on Allobaculum, Blautia, Bacteroides and Butyricicoccus↑ HDF-induced changes were reversed in both	(45)
HDF- Sprague Dawley rats	150 mg/kg daily for 4 weeks	BBR altered the intestinal microbiota in rats with MS. *A. muciniphila*↑ *Bacteroides*↑ *Ruminococcus*↑ *Candidatus arthromitus*↓ *Prevotella*↓ *Phascolarctobacterium*↓	(46)
Male apoE-/- mice; Mice are coprophagic (feces-eating)	Intragastric administration twice a week 50 mg/kg for 12 weeks	BBR may ameliorate HFD-induced atherosclerosis via gut microbiota modulation. BBR-treated gut microbiota transferred between mice.	(47)
C57BL/6J mice	100 mg/kg oral daily for 4 weeks	HDF-induced intestinal dysbiosis↓ Bacteroidetes↑ Clostridiales↑ Lactobacillaceae↑ Bacteroidale↑	(48)
Sprague-Dawley rats	150 mg/kg via gavage daily for 6 weeks	Inhibit the synthesis of trimethylamine N-oxide remodeled the intestinal microbiota Lactobacillus genus↑	(49)
C57BL/6J mice	100 μg/kg/d for 15 weeks	It may improve chronic HFD-induced metabolic syndrome. Its combination with antibiotics is no different from its effect alone in preventing HDF-induced weight gain.	(50)
Goto-Kakizaki (GK) rats	200 mg/kg BBR 100 mg/kg Metformine intragastricly once daily for 8 weeks	In two groups; *Bacteroidetes*↓ *Bacteroidetes/Firmicutes*↓ *Muribaculaceae*↓ *Allobaculum*↑ Berberine can modulate gut microbiota in T2DM rats	(51)
C57BL/6J-Apc min/+ mice and wild-type C57BL/6	500 ppm berberine for 12 weeks	Restored the enteric microbiome community in HFD-fed mice. Verrucomicrobia↓ Akkermansia↓ SCFA↑	(52)
C57BL/6 J mice	150 mg/kg/day BBR chloride via intragastric for 4 weeks	Protective effect in hypertension *Firmicutes/Bacteroidetes*↓ *Lactobacillus*↑	(53)
Balb/c mice	40 mg/kg BBR, once a day for 10 days	The results showed that BBR could modulate the intestinal microbiota composition in ulcerative colitis model mice.	(54)

Syrian golden hamsters	HFD group, LB group (HFD+75 mg/kg/day BBR), HB group (HFD+150 mg/kg/day BBR), LM group (HFD+75 mg/kg/day MTF), HM group (HFD+150 mg/kg/day MTF	The α-diversity of the gut microbiota, which was for 8 weeks significantly reduced by HFD nutrition, was significantly reversed by MTF and BBR; A relatively milder effect of berberine than MTF was detected on bacterial diversity.	(55)

* BBR: Berberine, T2D: Type 2 Diabetes, Prob: Probiotic, HDF: High fat diet, MS: Metabolic syndrome

Table 2. Effect of berberine on intestinal diversity.

Animal/ human models	Dosage of BBR	Key findings	Refs.
Broiler Chickens	1 g berberine/kg supplemented diet for 21 days	*Proteobacteria*↑ *Firmicutes*↓ High doses of BBR have dysbiosis-like effects.	(15)
C57BL/6J mice	10 mg/kg BBR 50 mg/kg BBR 100 mg/kg BBR for 33 days	There is no significant dose-response relationship for BBR between 10 – 100 mg/kg. Richness and diversity↓ A. muciniphila It may reduce alcoholic fatty liver.	(21)
Healthy Duorc × (Landrace × Large White) weaned piglet	0.1% for 21 days	Beneficial bacteria like; *S. variabile*↑ *L. johnsonii*↑ *P. distasonis*↑ Richness and diversity↑	(22)
Sprague-Dawley rat	150 mg/kg oral daily for 6 weeks	Richness↑ Alleviated HFD-induced hepatic steatosis and damage.	(27)
Wistar rats	50 mg/kg BBR 100 mg/kg BBR intragastrically once daily for 14 consecutive days	Richness↓ BBR can reduce depression in rats.	(28)
Wistar rats	150 mg/kg via intragastric for 1 month	Species diversity↓ The amount of intestinal microbiota↓ It did not show any improvement in PCOS.	(29)
C57BL/6J mice	200 mg/kg for 14 weeks	Akkermansia↑ Eubacterium↑ Ruminococcus↑ Microbial richness and diversity↓ BBR may improve glucose and lipid metabolism disorders.	(30)
C57BL/6 mice	0, 3, 10, 30, 100, 300 mg/kg of BBR via gavage for 2 weeks	BBR is a broad spectrum antibiotic. *Bacteroide*↑ *Ruminococcus*↓	(57)
ApoE−/− mice and C57BL/6J mice	100 mg/kg BBR hydrochloride 50 mg/kg BBR by gavage once a day for 13 weeks	Both high and low doses *Turicibacter*↑ High dose BBR; Alistipes↑ Roseburia↑ Bacteroidetes↓ Low dose BBR; Allobaculum↑ Blautia↑ Both high and low doses of BBR can alleviate HFD-induced atherosclerosis.	(74)

* PCOS: Polycystic ovary syndrome

association with the intestinal microbiota, as the effect of berberine is significantly reduced in the absence of *Blautia* and in metagenomic analysis, the key species most enriched by berberine was found to be the *Blautia* genus of *B. producta* (35, 36).

In a study, 83 hyperlipidemic patients were administered 1 g of oral berberine or a placebo daily for three months, and it was found that berberine significantly reduced serum levels of triglycerides (TG), total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-c) compared to the placebo group (35). Another study demonstrated that oral administration of berberine (BBR) promotes butyrate production in the gut microbiota, which subsequently leads to berberine entering the bloodstream and reducing blood lipid and glucose levels (37).

Modern pharmacological studies emphasize the importance of gut microbiota in the development stages of type 2 diabetes mellitus (T2DM), akin to genetic, environmental, and dietary factors. Berberine, when administered intragastrically at a dose of 136.5 mg/kg in db/db mice, increases the ratio of *Butyricimonas*, *Coprococcus*, and *Ruminococcus* bacteria, which produce short-chain fatty acids. These short-chain fatty acids lead to increased secretion of glucagon-like peptide-1 (GLP-1), improve insulin secretion, and suppress glucagon secretion to improve blood sugar levels. Gegen Qinlian decoction (containing BBR as the main component) and BBR alone enrich bacteria producing butyrate, such as *Faecalibacterium* and *Roseburia*, and increase SCFA levels in feces (2).

Exploring berberine's impact on restoring gut diversity and bacterial abundance

Berberine's effect on intestinal microbiota composition is known not only by increasing SCFA-producing bacteria but also by selectively inhibiting harmful bacteria (39). In a corroborative study, it is highlighted that berberine facilitates the growth of *Akkermansia* by triggering increased mucin secretion in the colon (25). As shown in Table 1, some human and animal studies have revealed that BBR can regulate gut microbiota composition, promote the increase of beneficial bacteria such as SCFA, reduce disease symptoms, and provide microbial restoration(20, 24, 31, 32, 35, 36, 38-55). Furthermore, BBR can regulate intestinal microbiota-associated metabolites (such as LPS, SCFAs, BAs) and reverse metabolic disorders by reversing the changes in the amount, structure, and composition of the intestinal microbiota (17). Among these studies, the three most commonly used models are the high-fat diet (HFD) induced disease model, the type 2 diabetes model, and the models compared to metformin or probiotics. Dietary berberine was observed in this study to increase the abundance of beneficial bacteria such as *S. variabile*, which inhibits food allergy in mice, and *L. johnsonii*, which can be considered as probiotics, by improving the intestinal mucosal immune response. In contrast, it has also been noted that dietary berberine may cause systemic autoimmunity because it promotes decreased interleukin-18 production by reducing the abundance of *P. Copri* (22).

In examining some animal studies, it was seen that berberine could improve intestinal microbiota dysbiosis and restore the intestinal barrier by enriching SCFA-producing bacteria such as *Bacteroides* and *Blautia* in rats with obesity induced by a high-fat diet (11). Berberine intervention in rats with HFD-induced metabolic syndrome (MS) has been shown to cause positive microbial changes by increasing the abundance of beneficial microflora such as *Akkermansia muciniphila* (*A. muciniphila*), *Bacteroides*, and selectively reducing the abundance of harmful microflora, and it has been suggested that it may have benefits in the treatments of obesity and insulin resistance (46). Despite this, some studies observed that berberine did not have any impact on the prevalence of the *Bacteroidetes phylum*, which is known for its beneficial effects (27) while other studies reported a significant increase in the number of *Bacteroides* after berberine treatment (54).

Looking at the changes observed in another High-fat diet (HFD) + BBR (150 mg/kg/day, 4 months) group, the enriching effect of berberine intervention on the *Bacteroides phylum* confirmed to produce SCFA was clearly seen ($p < 0.05$). Moreover, the abundance of several genera within the *Firmicutes phylum,* including *Roseburia, Dorea*, and *Blautia*, which experienced an increase due to the high-fat diet, was reversed with the administration of berberine (42). Intragastric administration of 200 mg/kg berberine for 6 weeks on diabetic rats was found to reduce the rela-

tive abundance of the *phylum Proteobacteria* and *Verrucomicrobia* while increasing the relative abundance of *Bacteroides* and probiotic *Lactobacillaceae*, which is negatively correlated with the risk of T2DM(10). Moreover, upon comparing the impact of BBR and metformin (MTF) in ApoE (-/-) mice subjected to a high-fat diet, similar alterations in intestinal microbial composition were noted. This included a notable reversal of reduced gut microbiota α-diversity, mitigating the dysbiosis induced by the high-fat diet (55). In a study on db/db mice comparing metformin and berberine, it was observed that both the diversity and richness of the gut microbiome were reduced by berberine intervention, unlike metformin. Intervention with metformin or berberine has been shown to positively affect the gut microbiota by increasing the abundance of probiotic bacteria, including *Lactobacillus* and *Akkermansia*, in db/db mice (41). Additionally, in a study investigating the combination of metformin at a dosage of 250 mg/kg and berberine at 125 mg/kg in db/db mice, it was observed that significant changes occurred in the intestinal microbial communities, especially *Verrucomicrobia*, and insulin sensitivity increased in these mice compared to individual mice (44).

Berberine intervention at 150 mg/kg/day for a month in NASH mice alleviated HDF-induced intestinal dysbiosis by increasing *Bacteroidetes* and *Lactobacillaceae,* and modulated gut microbiota associated with bile acid de-conjugation and transformation. This modulation was evidenced by changes in bile acid species, such as deoxycholic acid and ursodeoxycholic acid (48). Moreover, in a study investigating its relationship with NAFLD, berberine was shown to significantly reduce bacterial diversity in the intestinal flora (OTUs) and promote the increase of SCFAs by increasing *Bacteroidetes* which may have protective effects on NAFLD. Notably, berberine increased *Bacteroidetes* and decreased *Firmicutes* compared to previous results (20). In addition, the *Firmicutes/Bacteroidetes* ratio has a higher *Firmicutes* content. At a dose of 150 mg/kg, berberine intervention appeared to reduce the abundance of *Firmicutes* and restore balance with a slight increase in *Bacteroidetes* (56). In summary, BBR can increase microbial diversity by regulating the composition of both animal and human gut microbiota, have probiotic-like effects by supporting the growth of beneficial bacteria, and alleviate T2D and other diseases by reshaping the disrupted microbiota caused by HFD.

Berberine may positively influence gut microbiota by regulating bacterial abundance and diversity. In this context, it is suggested that berberine could contribute to maintaining a healthy intestinal environment, potentially offering health benefits. Therefore, the interactions between berberine and gut microbiota play a significant role in understanding crucial biological effects on health. In a group of HFD-fed Apoe-/- mice, berberine intervention has been reported to contribute to a healthy intestinal environment by increasing the relative abundance of *Bacteroides* and *Akkermansia* (40, 46). A study observed correlations between berberine concentrations and the composition of gut flora, highlighting negative correlations with bacteria such as *Ruminococcus gnavus, Ruminococcus schinkii, Lactobacillus acidophilus, Lactobacillus murinus,* and *Lactococcus lactis* (57). As shown in Table 2, some studies on animal models have found data that berberine reduces overall microbial diversity and causes dysbiotic microbiota formation. When alpha diversity analysis was examined in this study, it was seen that berberine; consistent with previous reports, it was observed that it significantly reduced the variety and diversity of the intestinal microbiota. The emphasized feature of berberine at this stage is that it acts as a broad-spectrum antimicrobial agent against pathogens in the microbiota (40).

In another research examining the effect of berberine alone in combination with antibiotics on microbial diversity, ob/ob mice receiving oral antibiotics for 3 days were simultaneously treated with berberine or antibiotics for 10 days. The study revealed that treatment with both berberine and antibiotics reduced the bacterial colony by 57% compared to berberine alone (37). Subsequent to the intervention of berberine hydrochloride, suggested to regulate intestinal microbial functions in Parkinson's patients, microbial diversity decreased in the berberine group compared to the control group (58). Similarly, intervention of berberine (200 mg/kg, e.g.) in normal rats showed that the number of species decreased and imbalance in the gut microbiota developed with the concentration of

SCFAs (short-chain fatty acids) in berberine-induced rats (59).

In a different study on rats, it was reported that berberine and metformin showed high similarity in enriching short-chain fatty acid-producing bacteria and inhibiting various intestinal microbes. The study also highlighted that high doses of berberine reduced the abundance of *Bacteroidetes*, whereas low doses of berberine and metformin did not have such an effect (45). Echoing these findings, in vivo results of another study on chickens also showed that increasing berberine dosage inhibited the growth of butyrate-producing bacterial strains (15).

Microbial diversity as an indicator of health

The microbial profiling approach, based on the 16S rRNA gene, has played a crucial role in systematically characterizing microbial communities. This method has provided valuable insights into the microbiome of healthy individuals, establishing connections between microbial changes and various diseases and health conditions. Our understanding in this field has expanded significantly, thanks to research on the human gut microbiota, which houses several hundred different bacterial species. Conducted across continents, extensive population-based studies have contributed valuable information. Sequencing techniques can currently identify between 100 and 200 different species of bacteria in a single sample, and phylogenetic classification is still unable to account for the physiological variations that species-level diversity causes among individuals (60). The gut microbiota is highly diverse, with each healthy adult human typically harboring more than 1,000 species of bacteria belonging to the dominant phyla *Bacteroidetes* and *Firmicutes* and relatively few other known bacterial phyla (61). Infections and inflammatory illnesses are caused by dysbiosis, a shift in the composition of gut microbes. Immune, metabolic, and neurobehavioral aspects of human health are all significantly influenced by gut microbes (62). Researchers discovered in a study that T2DM patients had a GM imbalance and had fewer *Lactobacillus* and *Bifidobacterium* than controls. The study also found a possible link between decreased microbial diversity and an increased risk of developing diabetes mellitus and developing insulin resistance (56). Dysbiosis in the gut microbiota has been associated with a range of human diseases, including diabetes, inflammatory bowel disease, anxiety, hypertension, cardiovascular diseases, liver disease, heart disease, obesity, and depression (63, 64). It has been reported that the alpha diversity of the gut microbiome is associated with human health, and lower diversity levels have been found to be linked to various acute and chronic diseases. When previous analyses of gut community composition and alpha diversity are examined, a negative relationship is often observed with the *Bacteroidetes phylum*. However, comparisons of gut microbiomes between rural Africans and urban Europeans have revealed the opposite, showing higher diversity and corresponding *Bacteroidetes* richness in rural Africans. Therefore, a single measurement such as the *Firmicutes/Bacteroidetes* (F/B) ratio, *Bacteroidetes* ratio, or microbial diversity may not allow us to reach a comprehensive and accurate conclusion for overall health (65). While a decrease in metagenomic richness is identified as an indicator of metabolic syndrome, the concept of dysbiosis lacks a precise definition due to the absence of a universally accepted norm for healthy microbiota. In adults, the diversity of the microbiota is considered a potential indicator linked to states of health or disease. Diminished microbial diversity, quantified through measures like Simpson, Shannon, Chao1, or phylogenetic diversity, has been documented in various disease states. Due to the absence of a precise definition of a healthy or normal microbiota, the concept of dysbiosis remains controversial. However, analyses in infants have reported that certain factors, like diminished microbial diversity or abnormal microbial composition, are associated with diseases such as asthma, intestinal diseases, inflammatory bowel disease, and metabolic disorders that occur in later stages of life, including in the infant. It has also been reported that the gut microbiota in breastfed infants exhibits lower diversity than in bottle-fed babies (19). Diversity analyses of the gut microbiome have associated the gut microbiome of people with large social networks with higher diversity, while the gut microbial diversity of people experiencing, stress, and anxiety is associated with a lower diversity and an altered microbiome (66). Recent research has implicated gut microorganisms in various human diseases such

as psoriasis, obesity, autism, and mood disorders (67). Unlikely, obesity, type 2 diabetes, and inflammatory bowel diseases, whose prevalence has increased sharply in recent years, have been associated with a reduction in gastrointestinal microbiome biodiversity. Loss of dietary biodiversity, one of the most important factors affecting microbial diversity, has been implicated as a critical factor in the development of obesity linked to reduced gastrointestinal microbiome diversity (68). Although there is ongoing disagreement regarding the relative importance of different intestinal taxa, it is generally agreed that having a diverse gut microbiome is beneficial. Studies that assess the functions that bacteria contribute, as opposed to variety, are also available. According to the study, this is because a diverse community appears to have a stronger correlation with health as it encompasses a wider range of functional domains. The investigation also noted that complex connections between shared species offer advantages that no single species can provide (60).

The therapeutic role of berberine in clinical diseases in the future

Since the introduction of the microbiome concept to the scientific community, we have been navigating a process that not only uncovers more profound insights into health and disease but also allows us to gain deeper knowledge through analyses, thanks to technological advancements. Although we know a lot about the microbiome thanks to valuable studies, the microbiome is an area that has not yet been fully elucidated and needs deeper and long-term observations. Healthy microbiota and dysbiosis do not yet have a precise profile definition. In addition to the many benefits of berberine, the fact that it reduces intestinal microbial diversity and causes the formation of a dysbiotic environment with its broad-spectrum antibiotic effect is an issue that needs to be further researched and clarified. Berberine is considered a promising compound in the treatment of diseases, as it enhances the growth of beneficial bacteria that produce health-related metabolites, especially SCFA and butyrate. It also modulates the disrupted microbial composition in metabolic diseases, promoting beneficial bacteria while reducing harmful ones, effectively acting as a probiotic. A meta-analysis of 21 clinical studies found that berberine had therapeutic effects comparable to other therapeutic regimens on T2DM, hyperlipidemia, and hypertension (69). The pro-inflammatory condition that dysbiosis induces in the gut damages the intestinal barrier's ability to function, which allows bacterial endotoxins to translocate and triggers a systemic immune response, which could be one reason why NAFLD occurs. Studies on humans and animals that connect microbial dysbiosis with gut inflammation provide credence to this theory (56). As a result of a study investigating the intestinal barrier protective effect of berberine against NAFLD in rats, it was observed that berberine reduced serum lipids and improved intestinal mucosal barrier dysfunction (70). In addition to these data, the examination of whether microbial diversity was restored in the long term as a result of the berberine intervention, optimal dose rates, and dose-dependent personalized microbial responses was not undertaken. To the best of our knowledge, one of the first analyses of the microbiome profiles of functional constipation patients individually and a study using a personalized diet modulation intervention based on the literature was conducted by us. In our study, it was determined that symptoms and quality of life of functional constipation patients were improved through personalized microbiome modulation with dietary intervention based on artificial intelligence-supported fecal microbiome profiling (71). The importance of personalized microbial responses is emphasized by our study, which is the first in the literature to compare the therapeutic effect of an AI-based personalized diet for irritable bowel patients. In our study, machine learning was utilized to identify a personalized diet to modulate the microbiota of an irritable bowel syndrome patient population to a similar "healthy" state. Consequently, it was demonstrated in our study that the score improvement for the personalized diet group was significantly higher than the standard irritable bowel syndrome diet group, highlighting the importance of personalized microbial responses (72). Both high (100 mg/kg) and low (50 mg/kg) doses of Berberine (BBR) administered alleviate atherosclerosis induced by a high-fat diet (HFD) in ApoE-/- and C57BL/6J mouse models, and may impact different components of gut microbiota (73). Therefore, the proposed berberine intervention for the treatment

of complex and multifactorial metabolic and chronic diseases necessitates more detailed studies, the assessment of individual microbial responses, and long-term follow-up studies of microbiome effects.

CONCLUSIONS

The interaction between berberine and the gut microbiota has significant health implications. Our literature review elucidates the multifaceted effects of berberine on the composition and diversity of the gut microbiota, shedding light on its therapeutic potential. Berberine promotes the growth of beneficial bacteria while targeting specific pathogens and exhibiting antimicrobial properties. Studies, particularly in obese or Type 2 Diabetic models, suggest potential benefits in improving gut microbiota and diversity (20, 24, 31, 32, 35, 36). However, the lack of a defined optimal dosage and unassessed individual microbial responses have been linked to the formation of dysbiotic microbiota profiles (15, 38, 57).

It is apparent that berberine may have benefits arising from its interaction with the gut microbiota. Throughout various studies, the variety of the gut microbiota was significantly enhanced by berberine intervention, although some studies observed the opposite. Understanding the impact of berberine on the composition of the gut microbiota will improve the efficacy of this compound in the treatment of metabolic and chronic diseases by elucidating its long-term efficacy, elucidating individual microbiota-dependent responses, and determining optimal dosage.

Further research into the long-term effects, individual microbial responses, optimal dosage rates, and personalized interventions based on microbial profiles will enhance our understanding of berberine's therapeutic role in complex metabolic and chronic diseases. Such research will pave the way for more tailored and effective treatments.

Conflict-of-interest and financial disclosure

The authors declare that they have no conflict of interest to disclose. The authors also declare that they did not receive any financial support for the study.

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