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Review

Berberine as a Natural Modifier of Gut Microbiota to Promote Metabolic Status in Animal Studies and Clinical Trials: A Systematic Review

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Abstract

As a phytochemical, berberine can modulate metabolic parameters via altering gut flora. However, findings are conflicting. In the present systematic review, we aimed to summarize the effects of berberine on gut microbiota in the models of metabolic disorders in both animal studies and clinical trials. Publications in five electronic databases including PubMed, Scopus, Embase, Web of Science, and Cochrane Library were searched systematically up to 31 May 2021 to find relevant articles with English language. Out of 4102 studies (including 2125 duplicates), 35 studies were included. In animal studies, various effects of berberine on beneficial and harmful microbiota were reported. However, findings also indicated that berberine can decrease the Firmicutes to Bacteroidetes (F/B) ratio. Three out of five studies showed positive effects of berberine on the production of short-chain fatty acids (SCFA), particularly butyrate. In three animal studies, lipopolysacaride (LPS) concentrations decreased with berberine administration. In clinical trials (n=3) positive effects on microbiota and metabolic status were also reported. However, the quality of clinical trials was mainly low. The present systematic review showed that berberine can modulate key metabolic parameters through improving the balance of intestinal microbiome, decreasing the abundance of harmful microbiota and LPS concentrations, and increasing the production of SCFAs, particularly butyrate in animal models. However, there are limited high-quality evidence regarding the effects of berberine on gut flora in clinical trials. Although berberine can be an effective prebiotic supplement to modulate metabolic parameters, further high-quality clinical trials are needed to confirm this potential.

Keywords: Berberine; Gut flora; Metabolic status; Systematic review

Introduction

Cardiometabolic diseases are main public concerns that their prevalence is growing in the considerable parts of the world. Obesity, type 2 diabetes mellitus (T2DM), dyslipidemia, atherosclerosis, and hypertension are examples of such metabolic disorders [1].

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Apart from the increasing rate of mortality following this health problem, psychological and economic dimensions of life are remarkably affected by such problems in the society [2,3]. Thus, identification of effective strategies can be helpful to control the consequences of the diseases and their related complications.

Various factors including genetic, environment, and personal behaviors such as unhealthy diet, low physical activity, smoking, and sleep problems take part in the development and the progression of such health problems through various metabolic pathways [4].

Despite some natural components showed a positive effect on the modulation of metabolic parameters, in most cases making a certain decision on their effectiveness have remained impossible due to limited studies [5,6]. One of the possible mechanisms for medicinal herbs and their components which attracted the attention of both researchers and clinicians is the modulation of gut flora [7]. Recent animal and human studies reported prebiotic effects of various herbs and natural components such as berberine on the modulation of the intestinal microbiota composition, and through this positive effects on key metabolic parameters are emerged [8-10].

Berberine is a pentacyclic isoquinoline alkaloid with distinctive yellowish color found in a wide range of medicinal herbs such as the genus Berberis, the rhizomes of *Argemone mexicana* L., *Coptis chinensis* Franch. (Chinese goldthread), *C. teeta* Wall., C. *japonica* (Thunb.) Makino, and *Eschscholzia californica* Cham. *In vitro* animal, and human studies noted the pharmacological effects of berberine on metabolic status [11]. Antihyperlipidemic, antidiabetic, anti-obesity, anticancer, and cardioprotective properties for this phytochemical have been shown. Its positive impacts on key metabolic parameters are mostly attributed to its antioxidant and anti-inflammatory characteristics [12,13].

In addition, a number of animal and human studies revealed its positive effects on the modulation of gut flora [14-20]. Zhang et al., reported that the effects of berberine on glycemic status, intestinal microbiota, and inflammation were similar to metformin in diabetic mice [21]. The production of short chain fatty acids (SCFAs), affecting the ratio of Firmicutes to Bacteroidetes (F/B), decreasing the level of serum endotoxin (LPS) via reducing intestinal permeability are reported in the models of metabolic disorders following berberine administration [22].

To the best of our knowledge, no systematic reviews have covered the effects of berberine on main metabolic parameters through the modulation of gut flora. Only two recent narrative reviews have introduced berberine as a possible therapeutic natural component for promoting health through changing the gut microbiota [11,13]. Accordingly, in the present systematic review we aimed to shed light on the effects of berberine on gut microbiota in the models of metabolic disorders in both animal studies and clinical trials.

Methods

For the present systematic review, publications in five electronic databases including PubMed, SCOPUS, EMBASE, Web of science, and Cochrane Library were searched up to 31 May 2021 to find papers with English language in which the effects of berberine on gut microbiota were examined. Both relevant MESH and non-MESH keywords were extracted and considered in the search strategy adopted to each database by a librarian (R.A). For instance, search strategy for PubMed was as follows: (Berberine [TIAB] OR berberin [TIAB] OR Umbellatine [TIAB] OR "Berberine Alkaloids"[Mesh] OR "Dioxolanes"[Mesh] OR Berbines [TIAB] OR berberis [TIAB] OR berberina [TIAB] OR berberol [TIAB] OR barberry [TIAB] OR barberries [TIAB] OR berberol [TIAB] OR "Hydrastis" [Mesh] OR Hydrasti*[TIAB] OR “Golden Seal” [TIAB] OR “Golden Seals” [TIAB] OR Goldenseal [TIAB] OR Goldenseals [TIAB] OR BBR [TIAB] OR Huangliansu [TIAB] OR “Xiao bo jian” [TIAB] OR berberinum [TIAB] OR Mahonia [TIAB] OR Mahonias [TIAB] OR "Mahonia"[Mesh] OR berbines [TIAB] OR “tetrahydroprotoberberine derivative” [TIAB] OR “Hydrastis Canadensis” [TIAB] OR “yellow root” [TIAB] OR Berberi[TIAB]) AND ("Microbiota"[Mesh] OR Microbiota*[TIAB] OR Microbial[TIAB] OR Microbiome*[TIAB] OR Microflora [TIAB] OR Flora[TIAB] OR bacteria[-TIAB] OR bacterium[TIAB] OR microbe*[TIAB] OR Lactobacillus[TIAB] OR "Mycobiome"[Mesh] OR Mycobiomes[TIAB] OR "Virome"[Mesh] OR Virome*[TIAB] OR Phageome*[TIAB] OR "Periphyton"[Mesh] OR Periphyton*[TIAB] OR "Lactobacillus"[Mesh] OR microorganism*[TIAB] OR bacterial [TIAB] OR micro-biome [TIAB] OR Enterobacteriaceae [TIAB] OR enterobacteria [TIAB] OR enterobacteriacea [TIAB] OR enterobacterium [TIAB] OR Betabacterium [TIAB] OR Lactobacileae [TIAB] OR Lactobacilleae [TIAB] OR lactobacilli[TIAB] OR Lactobacteria [TIAB] OR myco-biome [TIAB] OR Betabacterium [TIAB] OR “periphytic organism” [TIAB] OR “periphytic organisms” [TIAB] OR “periphytic species” [TIAB] OR “viral biome” [TIAB] OR “viral microbiome” [TIAB] OR “virus microbiome” [TIAB]).

Apart from the aforementioned electronic databases, bibliographies of the relevant papers were also checked to avoid missing any eligible publications. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline (PRISMA) version 2020 were used in the present systematic review [23].

Inclusion criteria

Publications were considered in the current systematic review if they met the following criteria: (i) animal study; (ii) clinical trial (either with parallel or cross-over design), (ii) study considered berberine (oral, intravenous, intraperitoneal, etc.) intake as an intervention and reported gut microbiota changes as an outcome, and (iii) reported at least one of metabolic syndrome components. In this systematic review, gut flora was our primary outcome and the effects of berberine on metabolic parameters (glycemic status, lipid profile, weight, other anthropometric indices, etc) were considered as secondary outcomes.

Exclusion criteria

Studies were excluded if they (i) were *in vitro* model, (ii) studied berberine in combination with other herbal or biochemical components; (iii) review study; (iv) grey literatures (conference abstract, thesis, interview, etc); and (v) were not written in English. Full texts of unavailable eligible papers were provided through requesting the authors via emails. When they could not be obtained even after the request, they were not included.

After exporting all retrieved publications into Endnote library by a librarian (R.A), titles and abstracts were independently screened by two reviewers (A.M and N.N) in the first step of screening and in case of confliction, third reviewer (M.H.A) made the final decision; then, they assessed the full text of possible eligible articles in the second round of screening to reach relevant publications. All stages were supervised by the principal investigator (M.H.A).

Data extraction

Two separate extraction tables were provided for animal studies (Table 1) and clinical trials (Table 2). For animal studies, the extracted parameters were as follows: first authors' last name, publication year, name of study animal, sample size, types of model, dosage of berberine, duration of the intervention, comparison group, methods of microbiota analysis, results of microbiome changes, and findings of metabolic parameters. The following data were extracted from eligible clinical trials: first authors' last name, publication year, health status, study design, sample size, age, sex, berberine dosage, duration of the intervention, control group, methods of microbiota analysis, results of microbiome changes, and findings of metabolic parameters. Notably, comparison meant the comparison of berberine with a control group on metabolic models. Wherever, the comparison of irrelevant groups was reported, their findings were not extracted. Data extraction was conducted by two researchers (A.M and Z.A) and the principal researcher (M.H.A) supervised this step as well.

Table 1. The effects of berberine on gut flora in the metabolic models of animal studies

	Study (year)	Animal/sample size	Model	Intervention / dosage / duration	Comparison	Results of microbiome change	Other outcomes
1	Xie et al., 2011	C57BL/6J mice / 12	HFD 4 w old male	Berberine 200 mg/kg oral gavage for 8 w	HFD	↓ *Firmicutes* ↓ *Bacteroidetes* ↓ fecal bacteria ↓ *Lactobacillus* sp. No sig. change in F/B ratio	↓ BG, ↓ TC, ↓ FC, ↓ FPS, ↓ BW No sig. change in TG, FTG
2	Zhang et al., 2012	Wistar rats / 40	HFD 8 w old, male	Berberine 100 mg/kg orally for 12 w	HFD	Sig. change in total GM structure, ↓ total bacteria, ↓ *Actinobacteria,* ↓ *Verrucomicrobia,* ↑ *Allobaculum,* ↑ *Blautia,* ↑ *Bacteroides,* ↑ *Butyricimonas,* ↑ *Phascolarctobacterium,* ↑ *Prevotella* , ↑ unclassified *Porphyromonadaceae*, ↑ unclassified *Ruminococcaceae* No sig. change in *Firmicutes, Bacteroidetes, Proteobacteria*, F/B ratio	↓ BW, ↓ adiposity index, ↓ FBG, ↓ FINS, ↓ HOMA-IR, ↓ MGP-1, ↓ leptin, ↑ adiponectin, ↓ appetite
3	Gu et al., 2015	LVG Syrian hamsters/ NR	HFD Male 8 w old	Berberine 100 mg/kg oral gavage for 2 w	HFD	↓ *Firmicutes,* ↓ *Bacteroidetes*, ↑ F/B ratio	↓ BW, ↓ TC, ↓ TG, ↓ LDL-C, ↓ HDL-C, preventing ↑ FFA, amino acids. ↑ cholic acid level
4	Zhang et al., 2015	Wistar rats/50	HFD 8–10 w old male	Berberine 100 or 200 mg/ kg oral gavage for 10 w	HFD, metformin	↓ GM (Dose dependent), ↓ richness, ↓ diversity, ↑ *Blautia*, ↑ *Bacteriodes*, ↑ *Butyricoccus*, *Phascolarctobacterium*, ↑ *Parasutterella,* ↑*Allobaculum,* ↓ Bacteroidetes, ↑ Proteobacteria No sig. change in F/B ratio	↓BW (Dose dependent)

5	Cao et at., 2016	C57BL/6J Mice/30	HFD 18 – 22 g male	Berberine 200 mg/kg oral gavage for 13 w	HFD	↑ *Bacteroidete,* ↑ *Lactobacillus,* ↑ *Bifidobacterium*, ↑ F/B ratio	↓ BW, ↓ epididymal fat index, ↓ TG, ↓ TC, ↓ FBG, ↓ plasma insulin, ↓ HOMA-IR, ↓ AST, ↓ ALT, ↓ NASH, ↓ IL-1, ↓ IL-6, ↓ TNF-a
6	Sun et al., 2016	Sprague Dawley rats/18	HFD 12 w old male	Berberine 150 mg/kg orally for 16 w	HFD	↓ species diversity, ↓ *Coriobacteriia (Actinobacteria phylum),* ↓ *Erysipelotrichi (Firmicutes phylum),* ↓ *Gammaproteobacteria (Proteobacteria),* ↑ *Bacteroidaceae,* ↑ *Rikenellaceae,* ↓ *Christensenellaceae,* ↓ *Dehalobacteriaceae,* ↓ *Erysipelotrichaceae,* ↓ *Peptococcaceae,* ↑ *Alcaligenaceae (Proteobacteria Phylum),* ↑ *Bacteriodes,* ↑ *Firmicutes,* ↑ *Anaerofilum*, ↑ F/B ratio	↓ BW, ↓ LDL-C, ↓ TC, ↓ FINS, ↓ HOMA-IR, ↓ rate of glycerol appearance, ↑ GLP-1, ↓ NPY No sig. change in FBG,
7	Cao et al., 2017	Kunming mice/40	T2DM Male weighing 20-22 g	Berberine 100 mg/kg oral gavage or 10 mg/kg intraperitoneal injection for 6 w	Healthy HFD, T2DM with StD	↓ *Enterobacter,* ↓ *Enterococcus,* ↓ *Lactobacillus,* ↓ *Bifidobacterium,* ↓ *Bacteroidetes* (dose dependent)	↓ *TLR4,* ↓ T*NF-α,* ↓ *IL-1β,* ↓ *IL-6,* ↑ pancreatic islet cells *(dose dependent)*
8	Huang et al., 2017	Spraguee Dawley rats/60	HFD male, 6 w old	Berberine 150 mg/kg oral gavage for 4 w	HFD	↑ *Bacteroides,* ↑ *Lachnospiraceae,* ↑ *Coprococcus,* ↑ *Ruminococcus gnavus (R. gnavus),* ↑ *Butyricicoccus,* ↑ *pulliceacorum,* ↑ *Clostridiales,* ↑ *Enterobacteriaceae,* ↑ *Ruminococcaceae,* ↑ *Ruminococcus torques (R. torques),* ↑ *Bacteroides eggerthii (B. eggerthii),* ↑ *Pseudoramibater enbacterium,* ↑ *Ruminococcus,* ↑ *Enbacterium dolichum,* ↑ *Akkermansia muciniphila,* ↑ *Oscillospira,* ↑ *Anearofustis,* ↑ *Blautia producta,* ↑ *Verrucomicrobia,* ↓ *Cyanobacteria/YS2,* ↑ *Lachnospiraceae,* ↑ *A. muciniphila,* ↑ *Bacteroides,* ↑ *Ruminococcus,* ↑ *Blautia,* ↑ *Bilophila,* ↓ *C. Arthromitus,* ↓ *Prevotella,* ↓ *Phascolarctobacterium*	No sig. change in epididymal fat weight, LDL-C, HDL-C
9	Li et al., 2017	Sprague-Dawley rat/	HFD 6 w old male weighing 180–200 g	Berberine 150 mg/kg oral gavage for 4 w	HFD	↓ *F. prausnitzii,* ↑ bacteroides	↓ BW, ↓ liver index, ↓ TC, ↓ TG, ↓ LDL-C, ↓ AST, ↓ ALT, ↓ plasma endotoxin, ↓ I-FABP, ↓ intestinal mucosal changes, ↑ occludin
10	Wang et al., 2017	Sprague–Dawley rats/ 18	HFD 180–200 g male	Berberine 10 microg/ml for culture of 2g of the colon contents	Not using berberine for the culture	↑ *E. faecium,* ↑ *B. longum,* ↑ *B. breve,* ↑ *L. acidophilus,* ↑ *L. casei,* ↑ *C. butyricum*	↑ butyrate production
		Sprague–Dawley hamsters/ 42	HFD 140–160 g, male	Berberine 100 mg/kg orally for 10 d1.4 w	HFD		↑ butyrate production, ↓ TC, ↓ TG, ↓ LDL-C
		Ob/ob mice/ 18	StD 40-50 g	Berberine 100 mg/kg orally or 20 mg/kg intraperitoneal injection for 1.4 w	Butyrate 200 or 400 mg/kg orally	↓ total GM	↓ TC, ↓ TG, ↓ FBG, ↓ BW No sig. change in butyrate

11	Wang et al., 2017	Syrian golden hamsters/ 52	HFD 8 w old, 110–140 g male	berberine 100 mg/kg orally for 1.4 w	StD hamsters using berberine 100 mg/kg for 10 d	↑ *Bacteroides*, ↑ *Escherichia−Shigella*, ↑ *Bifidobacterium*	↓ TC, ↓ TG, ↓ LDL-C, ↑ NR activity, ↑ berberine intestine, liver, lung, heart tissue and blood concentration,
12	Cui et al., 2018	Sprague-Dawley rats/ 32	HFD diabetic 180–200 g, male	Berberine fumarate 500 mg/kg oral gavage for 4 w	HFD T2DM	↑ Normalization and richness of GM, ↓ *Firmicutes*, ↓ *Bacteroidetes*,	↑ FINS, ↑ T-SOD, ↑ GSH-PX, ↑ GLP-1, ↓ FBG, ↓ HOMA-IR, ↓ TG, ↓ TC, ↓ GSP
13	Liu et al., 2018	Wistar rats/ 40	HFD male aged 6 w, weight 210 ± 10 g	Berberine 200 mg/kg oral gavage for 8 w	HFD	↑ *Lactobacillus*, ↑ *Bifidobacterium*, ↓ *Escherichia coli*, ↓ *Enterococcus spp.*	↓ Liver weight, ↓ FBG, ↓ FINS, ↓ HOMA-IR, ↓ TG, ↓ LDL-C, ↓ plasma endotoxin, ↓ lobular inflammation No sig, change in BW, fat mass, TC, HDL-C
14	Shi et al., 2018	C57BL/6J Mice/ 32	HFD 7 w old male apoE-/-	Berberine 50 mg/kg oral gavage for 12 w	HFD	↑ *Firmicutes*, ↓ *Bacteriodetes*, ↓ *Proteobacteria*, ↑ *verrucomicrobia*	↓ MMP-2, ↓ IL-6, ↓ ICAM-1, ↓ TNF-a, ↓ MCP-1, ↓ IL-1b, ↓ VCAM-1, ↓ TC, No sig. change in BW, TG, HDL-C, LDL-C
15	Sun et al., 2018	C57BL/6J mice/20	HFD 8 w aged male	Berberine 100 mg/kg orally for 8 w	HFD	↓ ACE index, ↓ *Firmicutes*, ↑ *Bacteriodetes*, ↓ *clostridiales.g*, ↓ *oscillospira*, ↑ *parabacterioides*, ↑ *mogibacteriaceae.g*, ↓ F/B ratio	↓ BW, ↓ tissue weight, ↓ LDL-C, ↓ TC, ↓ TG, ↑ HDL-C, ↓ FBG, ↓ FINS, ↓ HOMA-IR, ↓ GTT, ↓ G6Pase, ↓ PEPCK, ↑ GLP-1, ↑ GCG, ↑ GPR43, ↓ tissue ATP, ↑ butyric acid, ↑ acetic acid, ↑ propionic acid, ↑ isobutyric acid, ↑ isovaleric acid, ↑ valeric acid
16	Wang et al., 2018	C57BL/6J-Apc min/+ mice/ 10	HFD male	Berberine 0.5 mg for 12 w (rout of administration not mentioned)	HFD	↓ alpha-deversity of GM, ↑ normalization of GM, ↓ GM variation, ↓ *Verrucomicrobia* No sig. change in *Firmicutes*, *Bacteroides*	↓ BW, ↓ adenoma tumor formation,
17	Zhu et al., 2018	C57BL Apoe_/_ mice/NR	HFD 5 w old female	Berberine 0.5 g/L of water orally in drinking water for 14 w	HFD	↓ GM diversity, ↓ *Desulfovibrio* spp., ↑ *Verrucomicrobia*, ↑ *Akkermansia*, ↑ *Bacteroides*	↓ BW, ↓ atherosclerotic lesions, ↓ TC, ↓ TNF-a, ↓ IL-1b, ↓ LPS, ↓ VCAM-1, ↓ MMP-2, ↑ occludin No sig. change in appetite, TG, HDL-C
			StD 5 w old female		StD	↓ GM diversity, ↑ *Verrucomicrobia*	↓ BW No sig. change in appetite, atherosclerotic lesions, HDL-C, TC, TG, IL-1b, TNF-a, LPS, occluding, MMP-2, VCAM-1

18	Guo et al., 2019	Syrian golden hamsters/35	HFD 6 w old, male, 110–140 g	Berberine 50 mg/kg oral gavage for 5 w	HFD	↓ GM richness, ↑ *Bacteroidetes,* ↓*Firmicutes*, ↑ *Bacteroides,* ↑ *Phascolarctobacterium,* ↑ *Akkermansia muciniphila,* ↓ *Allobaculum*, ↓ *Desulfovibrio,* ↑ F/B ratio No sig. change in GM diversity, total bacterial population	↑ acetate, ↑ propionate, ↓ TG, ↓ FBG, ↓ BW No sig. change in butyrate, LPS, TC, LDL-C, AST, ALT
		Syrian golden hamsters/35		Berberine-CS/PT-NP 50 mg/kg oral gavage for 5 w			↑ butyrate, ↑ propionate, ↑ acetate, ↑ GLP-1, ↑ pancreatic b-cells, ↓ LPS, ↓ BW, ↓ TG, ↓ TC, ↓ LDL-C, ↓ FBG, ↓ TNF-a, ↓ IL-1b, ↓ IL-6, ↓ AST, ↓ ALT
19	Li et la., 2019	db/db mice/11	T2DM	Berberine 100 mg/kg oral gavage for 7.8 w	T2DM db/db	↓ total GM, ↓ diversity, ↓ richness, ↓ *Saccharibacteria,* ↓ *Deferribacteres,* ↓ *Actinobacteria,* ↓ *Firmicutes,* ↑ *Verrucomicrobia*	↓ FBG, ↓ BG, ↓ glucagon, No sig. change in HbA1C
20	Pan et al., 2019	Juvenile grass carp/NR	mean BW 34.0±0.73 g and mean total length 14.8±0.26 cm	Berberine 30 mg/Kg orally for 1 w	StD	Sig. change in composition of GM, ↓ GM diversity, ↓ *Bacteroides,* ↑ *Firmicutes,* ↑ *acintobacteria,* ↑ *Bacteroidetes,* ↑ *Proteobacteria,* ↓ *Fusobacteria,* ↓ F/B ratio	↓ BG, ↓ TC, ↓ TG, ↑ liver TC, ↑ liver TG No sig. change in BW
21	Yue et al., 2019	C57BL/6J mice/16	Std 5 w old male	Berberine 200 mg/kg oral gavage for 10 w	StD	↑ *Firmicutes,* ↓*Bacteroidetes,* ↑ *Akkermansia,* ↓ *Clostridiales*, ↓ *Streptococcaceae*, ↓ *Clostridiaceae*, ↓ *Prevotellaceae*, ↓ *Streptococcus*, ↓ *Prevotella,* ↓ F/B ratio	↓ LDL-C No sig. change in BW, appetite, AST, ALT, TC, TG, HDL-C, FFA, fat mass, FBG, FINS, HOMA-IR
			HFD 5 w old male		HFD		↓ BW, ↓ fat mass, ↓ ALT, ↓ AST, ↓ TC, ↓ TG, ↓ HDL-C, ↓ LDL-C, ↓ FFA, ↓ FBG, ↓ HOMA-IR No sig. change in appetite
22	Zhang et al., 2019	C57BLKS/JNju db/db T2DM mice/ 10	T2DM	Berberine 113.75 mg/kg oral gavage for 11 w	Db/db T2DM	↑ *Butyricimonas,* ↑ *Lactobacillus,* ↑ *Coprococcus,* ↑ *Ruminococcus,* ↑ *Akkermansia,* ↓ *Prevotella,* ↓ *Proteus,* ↑ *adlercreutzia,* ↑ *AF12,* ↑ *Rikenella,* ↑ *odoribacter,* ↑ *turicibacter,* ↑ *anaerotruncus,* ↑ *holdemania,* ↑ *eubacterium,* ↑ *sutterella,* ↑ *trabulsiella* ↓ *bilophila,* ↓ *allobaculum,* ↓ *ruminococcus,* ↓ *dorea,* ↓ F/B ratio No sig. change in richness	↓ appetite, ↓ BW, ↓ BG, ↓ HbA1C, ↓ TNF-a, ↓ LPS, ↑ acetate No sig. change in propionate, butyrate
23	Cao et a., 2020	KKAy mice/6	HFD 8 w old female	Berberine 100 mg/kg oral gavage for 8 w	HFD	↓ total GM, ↑ *Verrucomicrobia,* ↓ *Deferribacteres,* ↓ *Proteobacteria,* ↑ *Bacteroidaceae,* ↑ *Akkermansiaceae,* ↓ *Lachnospiraceae,* ↓ *Desulfovibrionaceae,* ↓ *Lactobacillaceae* No sig. change in F/B ratio	↓ BG, ↓ HbA1C, ↓ HOMA-IR, ↓ BW, ↓ appetite, ↓ FINS, ↓ IL-1β, ↓ TNF-a, ↓ IL-6, ↓ CRP, ↓ total SCFAs, ↓ butyric, ↓ pentanoic, ↓ isopentanoic, ↓ hexanoic, ↓ isohexanoic acids No sig. change in glucagon, MCP-1, IL-10,

24	Li et al., 2020	C57BL/6J mice/ 13	Ethanol fed 6-8 w old	Berberine 10 or 50 or 100 mg/kg oral gavage for 4.7 w	Ethanol fed	Dose-independent: ↓ *Verrucomicrobia,* ↑ *Proteobacteria,* ↓ diversity, ↓ total GM, ↑ Terrisporobacter, ↑ Helicobacter, ↓ Pseudoflavonifractor, ↓ Mucisirillum, ↓ Alistipes, ↓ Ruminiclostridium, ↓ Lachnoclostridium,	Dose-independent: ↓ AST, ↓ ALT, ↓ IFN-γ, ↓ TNF-α, ↓ IL-1β *No sig. change in* IFN-β, MCP-1, IL-17A, IL-27, IL-10, GM-CSF
25	Wang et la., 2020	Sprague-Dawley rats / 33	HFD Male weighted 200 ± 10 g	Berberine 150 mg/kg oral gavage for 4 w	HFD, StD	↓ diversity, ↑ Bacteroidetes, ↑ Proteobacteria, ↓ Firmicutes, ↓ Cyanobacteria	↓ BW, ↓ AST, ↓ ALT, ↓ TC, ↓ TG, ↓ endotoxin, ↓ I-FABP, ↓ D-lactate, ↓ swelling of hepatocytes, ↑ hepatocyte arrangement
26	Wu et al., 2020	ApoE-/- mice/24	HFD 6 w old male	Berberine 50 mg/kg oral gavage for 13 w	HFD	↑ richness, ↓ *Proteobacteria,* ↑ *Actinobacteria,* ↑ *Turicibacter,* ↑ *Allobaculum,* ↑*Blautia,* ↑ *Bilophila,* ↓ *Alistipes* No sig. change in *Firmicutes, Bacteroidetes*	↓ atherosclerotic lesion size, ↓ plaque area, ↓ TC, ↓ APOB100, ↓ VLDL-C, ↓ TNF-a, ↓ IL-1b, ↓ IL-6, ↑ IL-10, ↑ adiponectin No sig. change in TG, LDL-C, HDL-C, LP
				Berberine 100 mg/kg oral gavage for 13 w			↓ atherosclerotic lesion size, ↓ plaque area, ↓ TC, ↓ APOB100, ↓ VLDL-C, ↓ TG, ↓ HDL-C, ↓ LDL-C, ↓ LP, ↓ TNF-a, ↓ IL-1b, ↓ IL-6, ↑ IL-10, ↑ adiponectin
27	Yao et al., 2020	Sprague-Dawley rats/ 50	T2DM Male weighing 220 ± 20 g	Berberine 200 mg/kg oral gavage for 6 w	T2DM	↑ *Lactobacillaceae,* ↑ *Peptostreptococcaceae,* ↑ *spirochaetaceae,* ↓ *enterobacteriaceae,* ↓ *verrucomicrobiaceae,* ↓ *proteobacteria,* ↓ *verrucomicrobia* No sig. change in *firmicutes, bacteriodetes*	↓ FBG, ↓ HOMA-IR, ↓ BG, ↓ TG, ↓ TC, ↓ LDL-C, ↑ HDL-C
28	Yu et al., 2020	Blunt snout bream/ 360	HFD, HCD or StD Mean BW: 44.83±0.06g	Berberine 50 mg/kg orally for 8 w	StD, HFD, HCD	↓ *Planctomycetes,* ↓ *Verrucomicrobia,* ↓ *Chloroflexi*, ↓ *Dependentiae* No sig. change in richness,	↓ TNF-, ↓ IL-6 No sig. change in plasma IgM, plasma IgG
29	Li et al., 2021	C57BL/6J mice/ 20	HFD 8 w old female	Berberine 100 or 200 mg/kg oral gavage for 6 w	HFD	↑ richness, ↓ non-TMA-producing strains (more in *Clostridium perfringens*, *Escherichia coli, Bacteroides fragilis*, and *Bacteroides thetaiotaomicron*), ↓ TMA producing Bacteria (more in *A. hydrogenalis* and *C. sporogenes*)	↓ TMAO, ↓ TMA, ↓ choline metabolism, ↓ atherosclerotic lesion, ↓ lipid accumulation in aorta No sig. change in TC, LDL-C, HDL-C, BW, AST, ALT
30	Neyrinck et al., 2021	B6.V-Lep ob/ob JRj mice/ 36	StD 6 w old male	Berberine 0.1% of diet orally for 4 w	StD	↓ total GM, ↓ *Lactobacilli,* ↑ *Bifidobacterium* spp., ↑ *Akkermansia spp.* ↑ No sig. change in bacteroides spp.	↓ appetite, ↓ BW, ↓ TG, ↓ ALT No sig. change in FBG, FINS, TC, TNF-a, IL-6
31	Wang et a., 2021	Zucker (ZDF; fa/fa) rats/20	diabetic fatty aged 6 w, 190–210 g	Berberine 100 mg/kg oral gavage for 3 w	T2DM	↑ richness, ↑ diversity, ↑ *Firmicutes,* ↓ *Bacteroidetes,* ↑ *Bacteroides,* ↑ *Oscillospira,* ↑ *Akkermansia,* ↑ *Aggregatibacter,* ↑ *Clostridium,* ↑ *Roseburia,* ↑ *Eubacterium,* ↓ *Prevotella*	↓ FBG, ↓ glucagon, ↓ HOMA-IR, ↓ appetite, ↓ BG, ↓ ALT, ↓ AST, ↓ uric acid, ↓ TC, ↓ TC, ↓ HDL-C, ↓ LPS, ↓ TNF-a, ↑ GLP-2 No sig. change in FINS, BUN, Cr

32	Yu et al., 2021	C57BL/6J mice/ 40	HFD 5 w of age male	Berberine 1400 mg/kg orally for 20 w	HFD	↓ richness, ↓ diversity, ↑ *Akkermansia,* ↑ *Bacteroides,* ↑ *Enterococcus*, ↑ *Ruminococcus,* ↓ *Allobaculum,* ↓ *Anaerotruncus,* ↓ *Bifidobacterium,* ↓ *Christensenellaceae,* ↓ *Coprococcus*, ↓ *Sutterella*	↓ TC, ↓ TG, ↓ FBG, ↓ BG, ↓ ALT, ↓ BW, ↓ liver lipid deposition, ↓ fat mass, No sig. change in appetite,
33	Zhao et al., 2021	GK rats/ 30	T2DM 6 w old male	Berberine 200 mg/kg oral gavage for 8 w	T2DM	↑ *Firmicutes,* ↓ *Bacteroidetes,* ↓ *Desulfobacterota,* ↑ *Verrucomicrobiota,* ↑ *Allobaculum,* ↓ *Muribaculaceae*, ↓ *Lachnospiraceae*, ↓ *Desulfovibrionaceae*, ↓ *Clostridia_UCG-014*, ↑ *Akkermansia,* ↓ F/B ratio	↓ BW, ↓ FBG, ↓ HOMA-IR, ↑ GLP-1, ↓ TC, ↑ pancreatic β cells No sig. change in FINS, TG

Legend: W: week, HFD: high-fat diet-fed, BG: blood glucose, TC: serum total cholesterol, FC: fecal cholesterol, FPS: fecal polysaccharides, TG: serum triglyceride, FTG: fecal triglyceride, BW: body weight, FINS: fasting insulin, HOMA-IR: homeostasis assessment of insulin resistance, MGP-1: monocyte chemoattractant protein-1 (an indicator of inflammation), GM: gut microbiota, LDL-C: low density level cholesterol, HDL-C: high density cholesterol, NR: not reported, NPY: neuropeptide Y, NR: Nitroreductases, GLP: glucagon-like peptide, StD: Standard diet, MMP-2: Matrix metalloproteinase-2, VCAM: vascular cell adhesion molecule, LPS: lipopolysaccharide, FFA: free fatty acids, HbA1C: hemoglobin A1c, CRP: C-reactive protein, SCFA: short chain fatty acid, IFN: interferon, I-FABP: intestinal fatty acid binding proteins, VLDL-C: vero low density cholesterol, APOB100: Apolipoprotein B100, LP: lipoprotein, Ig: immunoglobulin,, HCD: high carbohydrate diet, TMAO: Trimethylamine-N-oxide, TMA: Trimethylamine, BUN: blood urea nitrogen, Cr: creatinine, PCR: polymerase chain reaction, GSP: glycosylated serum protein: ISI: insulin sensitivity index, T2DM: type 2 diabetes mellitus, TNF-a: tumor necrosis factor-a, IL: interleukin, F/B ratio: firmicutes to Bacteroidetes ratio

Table 2. Main characteristics of the included clinical trials

Number	Study (year)	Design of study / sample size	Population	Age / sex	Intervention group	Control group	Results of microbiome change	Other outcomes	Quality score (Jaded)
1	Chen et al., 2016	Before after clinical trial/ 30	T2DM	Mean:37.14/ both	Berberine 300 mg 3 times 30 minutes after major meals orally / 8 w	No control group	↑ total, *Bifidobacterium,* ↑ *B. longum,* ↑ *B. breve,* ↑ *B. adolescentis,* ↓ *B. infantis*	↓ BMI, ↓ FBG, ↓ FINS, ↓ HbA1C, ↓ HDL, ↓ LDL, ↓ TG, ↓ TC, ↓ CRP, ↓ TNF-a, ↓ LPS	1
2	Wang et al., 2017	randomized, controlled clinical trial/ 40	HFD	Mean:52.75/ both	Berberine 500 mg once orally	Berberine 500 mg once in normal diet population	↑ *Fusicatenibacter,* ↑ *Subdoligranulum*, ↑ *Enterobacter*, ↑ *Blautia,* ↑ *Lachnoclostridium*	↑ blood berberine level, ↑ NR activity	2
3	Zhang et al., 2020	randomized, double-blind, -placebo controlled clinical trial/ 409	T2DM	Range:42-61 / both	Berberine 600 mg BD orally before meal + placebo / 12w	1: placebo+ placebo 2: berberine + probiotic 3: probiotic+ placebo	↓ *Roseburia spp.,* ↓ *Ruminococcus bromii,* ↓ *Faecalibacterium* ↓ *prausnitzii,* ↓*Bifidobacterium* spp., ↑ *Bacteroides* spp., ↑ multiple taxa of γ-Proteobacteria, ↓ *R. bromii*	↓ HbA1C No sig. change in FBG, PPG, TGs, TC, LDL, HOMA-IR	5

Legend: PCR: polymerase chain reaction, T2DM: type 2 diabetes mellitus, BMI: body mass index, FBG: fasting blood glucose, FINS: fasting insulin, HbA1C: hemoglobin A1c, TC: serum total cholesterol, TG: serum triglyceride, LDL-C: low density level cholesterol, HDL-C: high density cholesterol, CRP: C-reactive protein, TNF-a: tumor necrosis factor-a, IL: interleukin, LPS: lipopolysaccharide, HOMA-IR: homeostasis assessment of insulin resistance, HFD: high fat diet, PPG: post-load plasma glucose, NR: Nitroreductases

Quality assessments

To clarify the quality of the included studies, standard quality checklists were used. The Jadad scale [24] was selected for the assessment of clinical trials. Accordingly, each clinical trial can reach the maximum of 5 scores. When a clinical trial obtained the score of 3 or higher it was categorized as high quality study, otherwise it was classified as a low quality one (Table 2). For animal studies, the 10-item SYRCLE checklist [25] was used. It is a qualitative checklist and for each item yes, no, or unclear statements were reported (Table 3).

Table 3. The SYRCLE scale for quality assessment of the included animal studies.

	Study (year)	1 Selection bias	2 Selection bias	3 Selection bias	4 Performance bias	5 Performance bias	6 Detection bias	7 Detection bias	8 Attrition bias	9 Reporting bias	10 Other
1	Xie et al., 2011										
2	Zhang et al., 2012										
3	Gu et al., 2015										
4	Zhang et al., 2015										
5	Cao et at., 2016 [										
6	Cao et al., 2017										
7	Huang et al., 2017										
8	Li et al., 2017										
9	Sun et al., 2016										
10	Wang et al., 2017										
11	Cui et al., 2018										
12	Liu et al., 2018										
13	Shi et al., 2018										
14	Sun et al., 2018										
15	Wang et al., 2018										
16	Zhu et al., 2018										
17	Guo et al., 2019										
18	Pan et al., 2019										
19	Yue et al., 2019										
20	Zhang et al., 2019										
21	Cao et a., 2020										
22	Li et la., 2019										
23	Li et al., 2020										
24	Wang et la., 2020										
25	Wu et al., 2020										
26	Yao et al., 2020										
27	Yu et al., 2020										
28	Li et al., 2021										
29	Neyrinck et al., 2021										
30	Wang et a., 2021										
31	Yu et al., 2021										
32	Zhao et al., 2021										
33	Xu et al., 2021 [34]										

Key
Yes
No
unclear

Statistical Analysis

Due to high heterogeneity in findings, doing a meta-analysis was impossible and results were only provided qualitative.

Results

Study selection

A total of 4102 studies (including 2125 duplicates) were identified through searching five electronic databases. In the first step of screening, 1896 publications were excluded because of irrelevant titles and abstracts. In the next step, 81 possible eligible full-texts were carefully assessed to clarify whether they were relevant or not. In addition, no studies were added after checking the bibliographies of the included studies. Forty-six papers were excluded in this process from the study due to the following reasons: Combination with other components (n=12), Conference abstract (n=6), Study correction (n=1), Protocol (n=2), Non-English paper (n=1), and Review article or irrelevant outcomes (n=24). Finally, 35 studies [14-20,26-53] met the eligible criteria and were considered in the present systematic review (Figure 1). Notably, in one study, both animal and clinical trial phases were provided.

Animal studies

Thirty-three animal studies [14-19,26-51,54] were included. They were published between 2011 and 2021. They examined the effects of berberine on gut flora in the models of metabolic disorders studying rats [14,16,29,32,34,35,42,45,48-50], mice [15,17,18,26-28,33,35,36,38,40,41,46,47,51], hamsters [16,30,31,54], grass carp [39], and blunt snout bream [46] fed with high-fat diet (HFD) (n=24), standard diet (StD) (n=7), high-carbohydrate diet (HCD) (n=1), or ethanol (n=1). In three studies, two types of diet were compared. Diabetic models were also observed in 8 studies [19,27,29,33,42,45,47,50].

Different units for the dosage of berberine were reported-mostly mg/kg. The dosages of berberine based on milligram per kilogram ranged from 10 [26] to 500 [29]. In addition, 0.1% of diet [38] and 0.5 g/L [51] were also observed for this phytochemical among studies. The duration of the study ranged from 1 week [39] to 20 weeks [18].

In all studies the method for microbiota analysis was

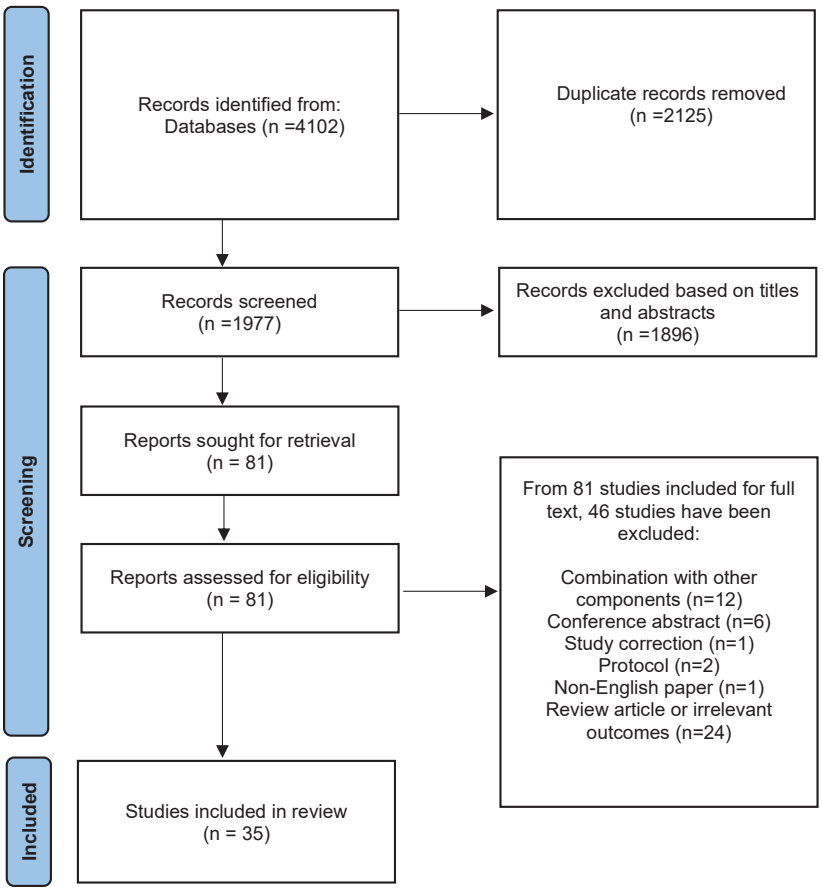

Figure 1. The flowchart of screening publications

16S rRNA gene polymerase chain reaction (PCR). As presented in table 1, the effects of berberine on gut microbiota were examined. Out of 35 included animal studies, changes in Firmicutes was reported in 13 studies [19,29-31,33,39,40, 42-45,49,50]. Findings also showed that berberine can either increase [19,39,40,42,50] or decrease [29-31,33,43,44] Firmicutes. However, some studies reported no significant effects on this type of bacteria following the intervention [17,45,49]. In 20 studies [16,17,19,26-32,39-45,49-51], changes in Bacteroidetes following the berberine were reported. Of which, 9 papers showed that this natural component can increase [16,26,28,31,32,41,43,49,51] or decrease (n=9) [19,27,29,30, 39,40,42,44,50] the levels of this microbiome. But in three studies no significant changes in Bacteroidetes were found [17,39,45]. The effects of berberine on the production of any SCFAs such as butyrate [16,26,31,41,47], acetic acid [31,41], and propionic acid [31,41,47] were examined in several studies (n=5) [16,26,31,41,47]. In two studies, no changes in the levels of SCFA were found [31,47]. All four studies [31,34,47,51,55] on the changes of lipopolysaccharide (LPS), except one study [51], showed that berberine can reduce this endotoxin parameter. The study by Zhu et al. showed significant reduction of LPS concentrations in HFD group using berberine, while consumption of berberine in StD group had no considerable effect [51]. Totally, in all included animal studies, changes in intestinal microbiota following different dosages and durations of berberine intervention were observed. Due to the wide differences between the examined types of microbiota, their species, study designs, and study models, comparing studies in all aspects was not applicable.

Apart from changes in microbiota following the intervention, the effects on metabolic parameters including glycemic status, anthropometric induces, lipid profiles, obesity-related hormones, liver enzymes, and inflammatory parameters were reported for the studies. Positive effects of berberine in most examined metabolic parameters were found among the included studies that mainly were related to the changes in gut flora following the intervention with berberine. However, in 19 studies [14,17-19,26,31,32,35-40,42,44,46,50,51], no significant effects on at least one metabolic parameters were obtained. Based on the quality assessment, most items (at least 5) of the SYRCLE checklist were considered in the 33 animal studies [14-19,26-32,34-46,48-50].

Clinical trials

Only three clinical trials [20,52,53] investigated the effects of berberine on gut microbiota in metabolic syndrome cases. According to Zhang et al. (2020), 1200 mg/day berberine for 12 weeks in patients with T2DM can reduce HbA1C compared to placebo or probiotic. However, reduction in other biochemical parameters were not significant [20]. The study by Chen et al. (2016) demonstrated that 300 mg berberine supplementation three time daily increased total Bifidobacterium and modulated its species along with reduction in LPS concentration in patients with T2DM after 8 weeks. Following this changes, improvement in body mass index (BMI), glycemic status, lipid profile, and inflammatory parameters have been observed. They concluded that berberine can improve T2DM through the modulation of Bifidobacterium species [52]. In the clinical phase of the study by Wang et al. (2017) indicated that the consumption of 500 mg of berberine once can increase the populations of Fusicatenibacter, Subdoligranulum, Enterobacter, Blautia, and Lachnoclostridium in healthy subjects [53]. However, the quality of the last two clinical trials were low based on the Jadad scale [52].

Discussion

The present study revealed that berberine can modulate key metabolic parameters through improving the balance of intestinal microbiome, decreasing the abundance of harmful microbiota and LPS concentrations as well as increasing the production of SCFAs in animal models. However, there are limited evidence on the effects of berberine on gut flora in human models.

Positive effects of berberine on various metabolic disorders such as diabetes [56,57], obesity [58,59], and other metabolic risk factors [60] have been revealed earlier. However, exploring underlying mechanisms instead of examining the impacts of this natural component alone can be more practical to reach novel and effective therapeutic approaches. Recently, the prebiotic effects of berberine have attracted the attention of researchers.

Approaching to gut microbiota is an innovative perspective to the effects of medicinal herbs and natural components on the modulation of metabolic status [61]. To the best of our knowledge, the present study is the first systematic review on the effects of berberine on gut flora. Only two recent narrative reviews discussed about this phytochemical effects on the modulation of microbiota [11,13]. Yang et al., concluded that berberine play a multifunctional role on atherosclerosis and metabolic diseases targeting gut microbiota. In another narrative review by Habtemariam and his colleagues showed that berberine can be an appropriate choice to alter the abundance of microbiota in order to improve metabolic status. Hence, both the aforementioned studies were narrative reviews, covering all relevant evidence were uncertain [11].

According to the evidence on microbiome, development and progression of a disease can be related

to changes in the fecal microbiome. In addition, one reason to obtain different responses to a certain therapeutic method may be contributed to the basic compositions of gut flora and its alterations following the treatment [62]. In healthy populations, main intestinal bacteria can be classified into five groups including phyla, Proteobacteria, Verrucomicrobia, Firmicutes, Actinobacteria, and Bacteroidetes. All these microorganisms play role in expressing genes of the production of some metabolites such as SCFAs, neurotransmitters, and ligands for G-protein-coupled receptors (GPCRs) that effects the host responses [62]. In any metabolic disorders, some changes can occur in the abundance of one or more mentioned gut bacteria categories.

Main metabolic disorders such as T2DM, obesity, and cardiovascular diseases can be classified as inflammatory diseases. Based on in vivo and *in vitro* studies, microbiota can affect the expression of peroxisome proliferator-activated receptors (PPARs) in both intestinal epithelial and immune modulatory cells and change the hosts responses to the inflammation. Meanwhile, rebalancing beneficial and harmful microbiota can indirectly modulate metabolic status. [63]. LPS is a well-known endotoxin composes the Gram-negative bacterial outer membrane like Escherichia coli. High level of LPS enhances permeability of the gastrointestinal wall and increases systemic and intestinal inflammation. Therefore, reducing circulating LPS concentrations is an approach to prevent some chronic diseases and their related complications.

Among the included animal papers, limited studies explored the effects of berberine on LPS concentrations [31,34,37,47,51]. However, all of them showed that berberine decreases the level of this endotoxin and exert positive effects on various metabolic parameters. Based on findings, berberine decreased decreases the levels of inflammatory parameters compared to control groups in all studies examined such factors (e.g. IL-1, IL-6, TNF-a) [17,26,28,31,35,38,40,42,46, 47,51].

In patients with T2DM, for instance, the abundance of phylum Proteobacteria increases, which is associated with enhancing systemic inflammation of the intestine. However, the frequency of Faecali bacterium prausnitzii and Akkermansia muciniphila decreases. These changes can increase inflammation and exert negative effects on some metabolic pathways. Consequently, T2DM may be developed or deteriorated. In the included animal studies, some showed the effects of berberine on decreasing Proteobacteria [17,26,40] and increasing Akkermansia muciniphila [18,19,26,42,47,50,51] abundance. Following such alterations, improvement in inflammatory parameters, glycemic status, and lipid profiles were observed. However, increasing effects of berberine on Proteobacteria following berberine supplementation were reported in several studies [14,35,39]. Nevertheless, due to increasing other beneficial bacteria and decreasing harmful bacteria, positive effects on metabolic status were also obtained in most cases.

Bacteroidetes and Firmicutes are the two main gut bacterial phyla in diabetic models. Evidences showed that the ratio of Firmicutes to Bacteroidetes (F/B ratio) adversely correlated with plasma glucose levels [64]. Our findings showed that in most studies examined the abundance of Firmicutes and Bacteroidetes, beneficial alterations were exerted. In the present systematic review, a number of studies reported that berberine attenuated the F/B ratio. Reduction in glucose levels and insulin resistance exert positive effects on reducing inflammation which involve in the progression of health problems such as dyslipidemia, cardiovascular diseases, obesity, and atherosclerosis. However, in some studies no effects on the components of this ratio was observed. Different results can be partly explained by differences in study models, dosage of berberine, and the duration of the intervention.

One metabolites of probiotics associated with reduction in obesity, T2DM, and related complications are SCFAs, including butyrate, acetate, and propionate. The SCFA particularly butyrate can improve hemostasis, insulin sensitivity, and mitochondrial function, particularly butyrate, in obese and T2DM patients. Thus, one target to promote health is by providing probiotics to increase SCFA producing bacteria.

We can summarize the main mechanisms of berberine as a prebiotic on metabolic parameters as follows: (i) altering gut microbiota, (ii) increasing the production of SCFAs particularly butyrate, (iii) reducing LPS concentrations, (iv) decreasing intestinal dysbiosis, (v) improving intestinal barrier functions, and (vi) modulation of the F/B ratio.

Although considerable numbers of animal studies assessed the effects of berberine on gut flora which can be a hidden therapeutic approach to control metabolic status, limited clinical trials have been conducted, so far. Due to high risk of bias, we cannot rely on their findings. As one of the challenging topics for berberine as a dietary supplement is its bioavailability, paying more attention on this can be helpful to provide an effective prebiotic supplement for both prevention and management of metabolic disorders. Several strategies are suggested to overcome this weakness: adjuvants, structural analogous, and new drug delivery systems like nanosized dosage forms, liposomes, microemulsions, phospholipid complexes, and muco-adhesive microparticles [65].

The present systematic review has three main limitations that should be addressed: (i) studies on other disease models were not included, (ii) *In vitro* studies have not been included, and (iii) due to diversity in

reporting parameters doing a meta-analysis was impossible. However, this is the first systematic review on the effects of berberine on gut flora and quality assessments were conducted using standard checklists. In additions, our findings clarified the functions of berberine as a perebiotic component and its pathways to modulate metabolic status.

Conclusion

Berberine can modulate key metabolic parameters through improving the balance of intestinal microbiome, decreasing the abundance of harmful microbiota and LPS concentrations, and increasing the production of SCFA, particularly butyrate, in animal metabolic models. However, there are limited high quality evidence regarding the effects of berberine on gut flora in human models. Further clinical trials with a low risk of bias are needed to clarify the effective dosage of berberine to affect the abundant of various gut microbiota. In other words, developing a berberine supplement with high bioavailability has a great potential to be a great prebiotic supplement for the prevention and management of some metabolic disorders through affecting intestinal flora.

Conflict of Interests

All authors declare no conflict of interest.

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