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SYSTEMATIC REVIEW

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Berberine and health outcomes: an overview of systematic reviews

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Abstract

Background Berberine is an isoquinoline alkaloid isolated from Chinese herb coptis chinensis and other berberis plants which can be used to treat a wide range of chronic diseases. However, the current research evidence on the therapeutic effects of berberine has not been summarized. We aimed to synthesize the current evidence on the systematic review (SRs) of berberine for the treatment of diverse conditions.

Methods A comprehensive search of the Cochrane Library, PubMed, EMBASE, Web of Science, CNKI, Wanfang, VIP, and SinoMed was performed from the database inception to April 11, 2024. SRs on berberine were included and evaluated. The methodological quality and the reporting quality of each SR were assessed using the AMSTAR-2 tool and PRISMA checklist, respectively. The quality of evidence was appraised based on the GRADE.

Results Fifty-four SRs were included and analyzed. Overall, associations were found between berberine and 70 health outcomes concerned with 9 diseases. Berberine has improved most outcomes of these diseases: 78% (25/32) cardiovascular disease outcomes, 92.59% (25/27) type 2 diabetes mellitus outcomes, 94.74% (18/19) gastrointestinal disorders outcomes, 72.22% (13/18) polycystic ovary syndrome (PCOS) outcomes, 86.67% (13/15) non-alcoholic fatty liver disease (NAFLD) outcomes, 92.31% (12/13) schizophrenia outcomes, 90.91% (10/11) metabolic syndrome outcomes, 57.14% (4/7) obesity outcomes, and 100.00% (6/6) dyslipidemia outcomes. There was a high overlap of primary studies (CCA > 15%) in the SRs of PCOS, NAFLD, obesity, and schizophrenia. Only one SR was rated as high quality while eight SRs were rated as low quality and forty-five SRs as very low quality according to AMSTAR-2. Regarding the reporting quality, Item 14, 15, 21, and 22 were poorly reported for the included SRs in terms of PRSMA assessment. For GRADE, eight outcomes were rated as high quality evidence, twenty-two outcomes were rated as moderate quality, and 110 outcomes were rated as low quality.

Conclusion Current evidence suggests that berberine has beneficial effects on a range of health outcomes for people with chronic diseases. Specifically, berberine significantly improves type 2 diabetes, gastrointestinal disorders, schizophrenia, metabolic syndrome, and dyslipidemia outcomes. However, caution is needed considering the shortcomings in the quality of the relevant system reviews included.

Keywords Berberine, Systematic review, Overview

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Background

The Global Burden of Disease Survey shows that the prevalence of various chronic diseases has remained high for a long time with a trend to increase yearly [1]. Chronic diseases constitute the leading global mortality factor, imposing substantial public health burdens through their progressive, irreversible nature while consuming significant healthcare resources. First-line treatments for chronic diseases remain challenged by treatment resistance, adverse effects, and disease progression requiring prolonged pharmacotherapy, collectively impairing patient quality of life [2]. Herbal extracts have a high level of acceptance among patients, especially in developing countries, where about 80% of the population relies on traditional herbal medicines [3]. Herbal medicines are relatively inexpensive as they are of natural origin and easily accessible. Plants have long been recognized for their therapeutic properties throughout human history [4]. Medicinal plants serve as an important source for chemical entities supporting drug discovery and a safe source of many active compounds for pharmaceuticals [5] including cardiovascular diseases (e.g., statins [6]) and multiple sclerosis (e.g. fingolimod [7]). Many natural compounds, such as alkaloids, phenylpropanoids, polyketides, terpenoids, etc., have been proven to possess good clinical potential, viz., antitumor, antimicrobial, antioxidant, immunosuppressant, antiprotozoal, and other effects. Most parts of plants have been used as extracts and may possess anti-inflammatory and antioxidant properties related to diseases such as diabetes, atherosclerosis, neurodegenerative, or cancer [8] with different types of phytochemicals such as flavonoids, vitamins, resveratrol, anthocyanin, curcumin, and phenolic acid are often found in the plant-based medicines [9].

Traditional Chinese medicine (TCM) has made use of herbs and herbal extracts to treat a variety of diseases and disorders for over 2000 years and herbal medicines are regulated as drug products in China [10]. Chinese herbs particularly together with routine treatment strategy, which are proven beneficial in treating various kinds of diseases. Numerous studies in China showed that various herbs can treat chronic diseases comparable to or even better than conventional chemical drugs. For example, the symptoms of diabetic kidney disease by ophiocordyceps sinensis [11], disorders of carbohydrate and lipid metabolism can be restored by schisandra chinensis fruits [12], inhibiting the growth of breast cancer stem cells by scutellarin [13], suppressing preadipocyte adipogenic differentiation by epigallocatechin gallate [14], improving rheumatoid arthritis by tripterygium wilfordii Hook. f [15]., and reducing kidney damage in diabetic kidney disease by quercetin [16, 17]. Among these herbs that have significant therapeutic effects and are widely used, there is an herbal extract called berberine has been extensively studied.

Berberine (BBR), extracted from the coptidis rhizoma, is a quaternary ammonium isoquinoline alkaloid which belongs to monomer compounds [18, 19]. It has been investigated that BBR is widely utilized in diverse complementary alternative medicine such as TCM, Ayurvedic medicine, and Iranian medicine [20, 21]. Existing studies elucidate that BBR exhibits pleiotropic biological effects and can be extensively employed for the treatment of type 2 diabetes mellitus (T2DM) [22], dyslipidemia [23], metabolic syndrome [24], obesity [25], cardiovascular disease [26], non-alcoholic fatty liver disease (NAFLD) [27], gastrointestinal disease [28], polycystic ovary syndrome (PCOS) [29], schizophrenia [24], and other chronic diseases. Among these diseases, dyslipidemia, metabolic syndrome, cardiovascular disease, and NAFLD are all associated with glucolipid metabolism [30–33]. Whereas T2DM, obesity, and gastrointestinal diseases are not only associated with glycolipid metabolism, but also have an equally strong association with gut microbiota [34, 35]. BBR directly activates AMP-activated protein kinase (AMPK), which is a well-known anti-diabetic mechanism, while lipid metabolism is regulated by BBR via the gut microbiota [36]. Therefore, both of them are able to improve the health outcomes of the above mentioned diseases.

In recent years, high quality RCTs have been published in studies on BBR [27, 37, 38]. Given the widespread clinical use of BBR, many systematic reviews (SRs) have been published to evaluate its efficacy and safety in diverse conditions, including diabetes, cardiovascular disease, and NAFLD [26, 39, 40]. However, in the absence of a comprehensive synthesis of these reviews, the landscape of which health outcomes BBR improves and to what extent is currently unclear. To bridge this gap in evidence and contribute to the ongoing discussion on the mechanisms of role of BBR in chronic diseases, we did an overview to provide a comprehensive summary of SRs of BBR for the sake of exploring its efficacy in a range of conditions.

Methods

It is an overview of SRs of this study. This overview was reported according to the preferred reporting items for overviews of reviews (PRIOR) statement [41]. The protocol was prospectively registered on PROSPERO (CRD42023482895) before initiating the search process, ensuring transparency and consistency in the review process.

Search strategy

The databases of human SRs published in Chinese or English were searched; Chinese databases included

Chinese National Knowledge Infrastructure (CNKI), Wanfang Database, VIP Database, and SinoMed; English databases included Cochrane Library, PubMed, EMBASE, and Web of Science. The first search was performed on 13 October 2023, and the updated search was completed on 11 April 2024 to capture any additional reviews. Reference lists of eligible studies were also scrutinized. The full search strategy and search terms are provided in the Supplementary File 1.

Eligibility criteria

The eligibility criteria followed the PICOS (population, intervention, comparison/control, outcome, study design) framework. Inclusion encompassed SRs targeted the efficacy of BBR, regardless of the specific condition being addressed. The interventions of the included reviews were required to use BBR. No constraints were imposed on the comparison/control or outcomes. Regarding the types of studies included, only reviews with human subjects were included in this review.

Study screening and selection

All of the retrieved studies were imported into EndNote (Version X9; Clarivate Analytics). Following the removal of duplicates, the titles and abstracts of potentially relevant studies were screened against the predefined inclusion criteria. Initially, a dual extraction process was conducted by randomly selecting 15% of the studies earmarked for inclusion (W. Y. Wang and L.J. Shi). Upon attaining an 80% consensus rate for consistency, subsequent extractions were carried out by a single reviewer (L. J. Shi). Extracted data included general characteristics, meta-analysis results, and conclusions derived from all included SRs. The extracted data were subjected to discussion among the reviewing team to ensure consensus.

Assessment of reporting quality

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) [42] was applied to assess the reporting quality of all SRs based on 27 items. Each item could be assessed as "Yes" or "No" and its compliance could be calculated. For each item, 1 point is given for reporting "Yes" and 0 point for reporting "No". For each item, the number of SRs reporting "Yes" was divided by the percentage of 54 SRs as the compliance for each item. Item 10, 13, 16, 20, 23, and 24 of the PRISMA 2020 statement contained multiple sub-items. The average score of the sub-items of each item was used as the total score for that item. A total score of 21–27 indicated that the report was relatively complete; a score of 15–21 suggested that there were deficiencies in the report; and a total score of less than 15 indicated that there were serious deficiencies in the report [43].

Assessment of methodological quality

A MeaSurement Tool to Assess systematic Reviews (AMSTAR 2) was utilized for evaluating methodological quality, with assessment items categorized into critical and non-critical domains [44]. AMSTAR 2 was applied to assess the methodological quality based on 16 items. Each item could be assessed as "Yes", "Partial Yes", or "No" and 7 items were defined as critical items which could mainly influence the quality of SRs. Overall confidence rating of SR quality assessment results: "high" indicates no or only one non-critical weakness; "medium" indicates more than one non-critical weakness; "low" indicates one critical flaw with or without non-critical weakness; and "critically low" indicates more than one flaw with or without non-critical weaknesses.

Assessment of evidence quality

For this review, the evidence quality of the included SRs was assessed using Grading of Recommendations Assessment, Development, and Evaluation (GRADE). The GRADE facilitates the grading of evidence quality for the validity of each outcome of SRs. Reasons for lowering grades of evidence may result from factors including limitations, inconsistency, indirectness, imprecision, and publication bias [45]. Ultimately, each outcome was graded as high, moderate, low, or very low quality.

Data extraction

One author (W. Y. Wang) undertook the extraction of general characteristics and quality assessments of SRs, with a subsequent accuracy check conducted by a second author (C. Y. Jing). Any discrepancies were resolved through consensus with a third author (X. Liao). The extracted information included publication year, country, journal type, registration details, number of included RCTs, participants, disease type, intervention and control specifics, outcome measures, quality assessment, and results of meta analyses.

Data synthesis

Narrative analyses were used to summarize the general characteristics of included overviews. The GROOVE tool [46] was used to evaluate the degree of overlap in the primary studies between included SRs. Any primary study included in each SR was shown in the citation matrix to demonstrate the amount of study overlap. To mitigate potential bias resulting from multiple primary studies being included in more than one SR, a citation matrix was constructed, and the corrected coverage area (CCA) was calculated. The CCA serves to quantify the extent of overlap among primary studies within the included SRs. The calculation utilized the formula: $CCA = (N\text{-}r) / (rc\text{-}r)$, where N represents the total number of primary studies, including overlapping study recalculations, r denotes

the total number of primary studies excluding overlapping study recalculations, and *c* indicates the total number of SRs. The resulting overlap rate was presented as a percentage. Given the lack of restriction on disease types in this study, conditions were grouped before calculating the overlap rate. The overlap rate was assessed as 0% ~ 5% for slight overlap, 6% ~ 10% for moderate overlap, 11% ~ 15% for high overlap, and 15% or more for very high overlap [47].

Results

A total of 1676 records were initially identified through electronic search methods. Following the removal of 324 duplicates, the remaining titles and abstracts were screened. Subsequently, one hundred and forty SRs were identified for full-text review. The final 54 SRs were deemed suitable for inclusion in the analysis (Fig. 1).

Characteristics of included SRs

Among the 54 SRs, there is an increasing trend between 2012 and 2024, with the number of publications doubling in the last four years (15 SRs published between 2016 and 2019 vs. 29 SRs published between 2020 and 2024). Of these, twenty-three SRs were published in Chinese, whereas 31 were published in English. The primary affiliations of the first authors were predominantly from China (47, 87.04%), with additional contributions from Iran (5, 9.26%) and the United States (2, 3.70%). Regarding the quality of included primary studies in each SR, three common tools were used including the Cochrane risk of bias assessment tool (43, 79.62%), Jadad (12, 22.22%), and GRADE (9, 16.67%) as assessment tools. Funding details were disclosed in 27 SRs (52.94%), while others neither reported funding nor stated no financial support explicitly (Table 1).

The detailed characteristics of the included SRs are described in Supplementary File 2 Table S1. The number of participants included across the SRs was ranging from 197 to 4616. A small portion of included SRs (15, 27.78%) registered their protocol, while most of the SRs (39, 72.22%) neither registered nor disclosed their study protocols which may reduce adherence to the reported protocol. Interventions included in the SRs covered three types: BBR as monotherapy ($n = 14$), BBR in combination with conventional medicine ($n = 16$), and both included ($n = 24$). The control group consisted of conventional medicine ($n = 27$), placebo ($n = 6$), or both ($n = 15$); yet, three SRs [39, 48, 49] reported that the control group included conventional medicine, placebo, and no-treatment.

Related outcomes distributed in different conditions

The 54 SRs focused on nine conditions. The most common of these conditions was cardiovascular disease, involving 32 outcomes, among which BBR can improve 25 outcomes, while there was no statistical significance for TC, IL-6, HDL-C, ALT, DBP, complement C3, and complement C4 between BBR and the control group; followed by T2DM, involving 32 outcomes, among which BBR can improve 30 outcomes except for serum creatinine and blood urea nitrogen; and gastrointestinal disease, involving 19 outcomes, among which BBR could improve 17 outcomes except for incidence of Abdominal distention and incidence of vomiting; and PCOS, involving 18 outcomes, among which BBR could improve 13 outcomes except for HOMA-IR, follicle-stimulating hormone, AE, ER, and live birth. For NAFLD, 15 outcomes were involved, among which BBR could improve 15 outcomes except for FBG/FPG and AST. BBR for schizophrenia involved 13 outcomes, among which only one outcome (apolipoprotein A1) showed no statistical significance for BBR. In addition, 11 outcomes were measured in the metabolic syndrome and BBR showed statistical significance on interleukin-1β. BBR for the treatment of obesity involved 7 outcomes, with positive effects on BMI, WC, BW, and CRP. And then for dyslipidemia, involving 6 outcomes, all of which were improved by BBR. Detailed results are presented in Supplementary File 3 Table S2-10. Figure 2 illustrates the 10 most frequently reported effective outcomes for each condition.

Overlap of primary studies across the included SRs.

Considering the largest number of SRs on T2DM included, the overlap calculation of the primary studies across the included SR was demonstrated in Fig. 3. The overlap calculation for other conditions are presented in Supplementary File 4 Figure S1-10 and Table S11-20. Overlap percentages for various conditions ranged from slight (2.56% for cardiovascular disease) to high (40.00% for obesity).

Methodological quality of reviews

Figure 4 summarized the detailed results of the methodological quality assessment of 54 SRs, including the assessment of individual items and summary assessment. Of the 54 reviews, 45 (83.3%) were judged critically low, 8 low (14.81%), and one high (1.85%). The shortcomings identified mainly included: no information on the funding of the studies included in the review (98.15%), lacking a protocol (74.07%), and no reporting of the reasons for exclusion (70.37%). However, the review authors applied a formal tool to assess the risk of bias of primary studies (94.44%) and appropriate methods for statistical combination of results (100.00%).

Reporting quality of reviews

The reporting quality was shown in Supplementary File 5 Table S12 and Fig. 5. According to our predefined criteria, among the 54 included SRs, the quality of 11 SRs

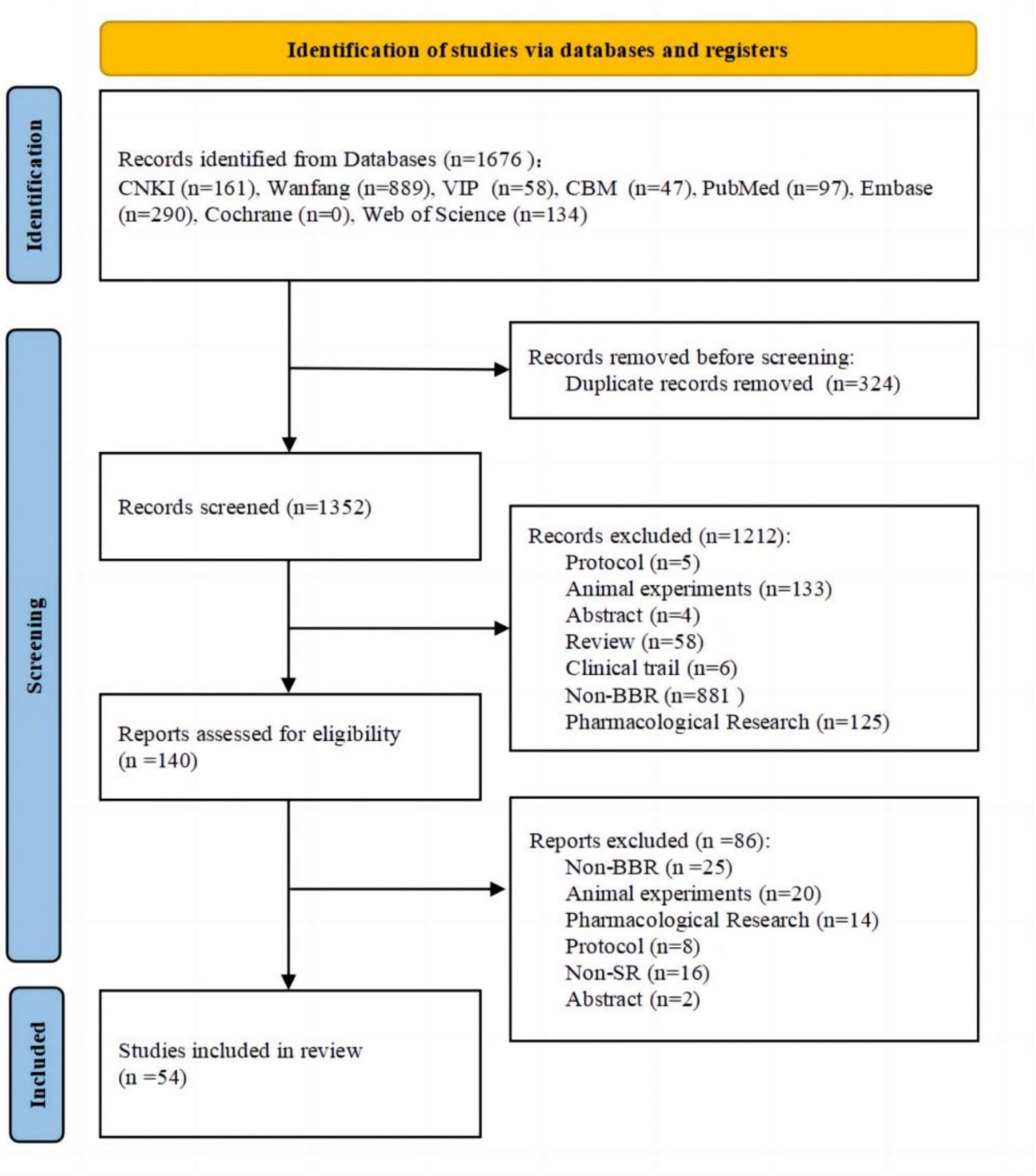

Fig. 1 Flow chart of literature search

was rated as relatively complete while the other 36 SRs and 7 SRs were rated as deficient and seriously deficient respectively. In the title, abstract, and introduction sections report compliance was above 50%. Some main deficiencies (compliance less than 50%) from method section were found as follows: 7.41% of SRs reported item 13b (describing any method required for presentation or synthesis), 7.41% of SRs reported item 14 (bias assessment of missing results), 12.96% of SRs reported item 15 (assessing the certainty of the evidence); and 42.59% of SRs reported item 13f (describing the methodology for the sensitivity analysis). Correspondingly, for the result section (compliance less than 50%), 3.70% of SRs reported item 16b (describing complete study selection),

Table 1 General characteristics of the included SRs. ($n = 54$)

Characteristics		Number	Percentage
Publication year			
	2012–2015	10	18.52
	2016–2019	15	27.78
	2020–2024	29	53.70
Language			
	Chinese	23	42.59
	English	31	57.41
Location of publication			
	China	47	87.04
	Iran	5	9.26
	USA	2	3.70
Rank for journal citation reports			
	Q1	13	24.07
	Q2	4	7.41
	Q3	0	0
	Q4	2	3.70
	No journal citation reports	35	64.81
Reporting guidelines mentioned			
	PRISMA	18	33.33
	No	36	66.67
Tools for quality assessment*			
	Cochrane risk of bias assessment tool	43	79.62
	Jadad	12	22.22
	GRADE	9	16.67
Funding support			
	Yes	29	53.70
	No/not reported	25	46.30

*Ten reviews used the Cochrane Risk of Bias Assessment Tool along with GRADE or Jadad

3.70% of SRs reported item 21 (giving risk of bias results for missing outcomes), and 12.96% of SRs reported item 22 (assessing certainty of evidence). In the section on other information (less than 50% adherence), only 27.78% of SRs reported items 24a and 24b (registered before implementation) and none of the SRs reported item 24c (amendment to registered program). Furthermore, only 22.22% of SRs reported Item 27 (providing access to publicly available data).

Certainty of evidence

The results of the GRADE assessment are presented in Supplementary File 6 Table S13. Among the 54 SRs, fifty SRs included 452 outcomes related to the effectiveness of BBR. Among these outcomes, the quality of evidence was rated as high in 8 (1.77%), moderate in 22 (4.86%), low in 110 (24.34%), and very low in 312 (69.03%) respectively. Publication bias ($n = 319$, 70.58%) was the most common downgrading factor, followed by imprecision ($n = 279$, 61.72%), risk of bias ($n = 274$, 60.62%), inconsistency ($n = 260$, 57.52%), and indirectness ($n = 0$, 0%). The GRADE confirmed high-quality evidence solely for four conditions: gastrointestinal disease (HpER, AE, peptic ulcer healing rate, relieving rate of clinical symptom), cardiovascular disease (BMI, BW), T2DM (AE), and obesity (BMI), with evidence certainty declining substantially across other assessed outcomes.

The efficacy and GRADE ratings of the primary outcomes for each condition are demonstrated in Table 2, and the complete results are shown in Table S23-31 in Supplementary File 7. For T2DM, the primary outcomes were 2hPBG/PPG, FBG/FPG, and HbAlc, with 80.00% (32/40) of the outcomes being positive ($p < 0.05$). Negative outcomes were 2hPBG/PPG and HbAlc when BBR was used as monotherapy. For dyslipidemia, the primary outcomes involved HDL-C, LDL-C, TC, and TG, with 82.76% (24/29) of the outcomes being positive. Negative outcomes were HDL-C and TC when BBR was used as monotherapy or in combination with conventional medicine. With PCOS, the primary outcomes were BMI, TC, TG, and TT, of which 35.29% (6/17) had positive outcomes, and TC was completely positive. In NAFLD, the primary outcomes were 2hPBG/PPG and TC, all of which were positive. In cardiovascular disease, the primary outcomes included ER, HDL-C, and LDL-C, with 66.66% (4/6) of the outcomes being positive, yet only HDL-C was negative. For metabolic syndrome, the primary outcomes covered IL-6 and TNF-α, both of which were positive. Regarding adverse effects, forty SRs were reported, specifically gastrointestinal reactions, rash, headache, elevated transaminases, liver enzyme abnormalities, and myalgia.

Discussion

We provided an evidence-based perspective on the effects of BBR on various health outcomes. The current review showed that BBR improved health outcomes in a range of chronic diseases, including T2DM (FBG/FPG, 2hPBG/PPG, HbAlc), dyslipidemia (TC, LDL-C, TC), PCOS (TC, LDL-C, TT), cardiovascular disease (ER, LDL-C, TG), metabolic syndrome (CRP, IL-6, TNF-α), NAFLD (2hPBG/PPG, TC, TG), obesity (BMI, WC, CRP), gastrointestinal disorders (HpER, AE, ER) and schizophrenia (LDL-C, HDL-C, TC).

The 54 SRs encompassed nine distinct clinical conditions, among which PCOS (CCA: 16.67%) and NAFLD (CCA: 39.29%) demonstrated particularly high overlap rates (Figures S4 and S8). This overlap has led to inadvertent overrepresentation of duplicate studies in SRs, stemming from their repeated inclusion across multiple reviews. Currently, a persistent lack of standardized protocols for managing duplication remains unaddressed. Few SRs have adopted proposed mitigation strategies, such as designating a primary reference SR, addressing overlap during data extraction/synthesis phases, or

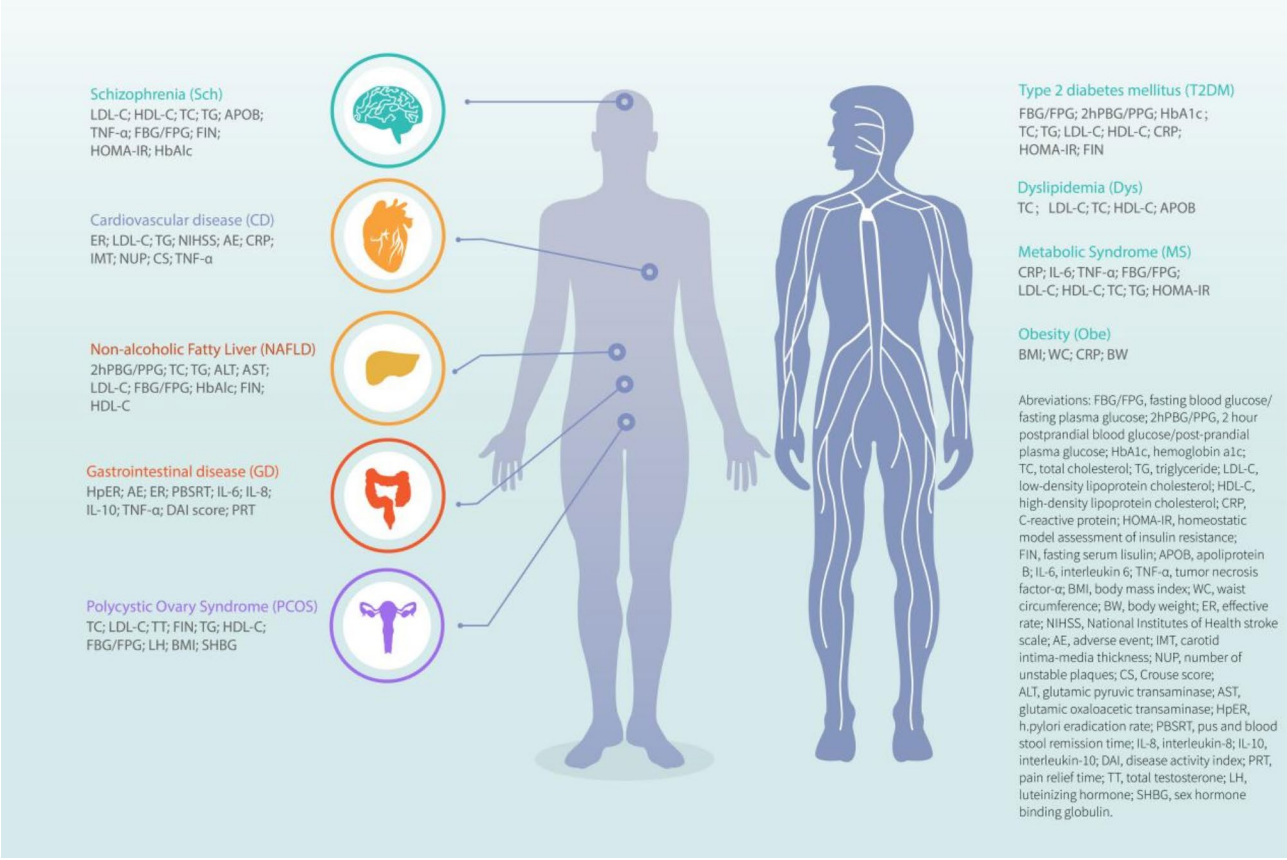

Fig. 2 The therapeutic scope and corresponding outcomes of berberine

transparently reporting overlap metrics [50]. The methodological quality of almost all of the 54 SRs assessed by AMSTAR 2 was rated as low quality (14.81%) or very low quality (83.3%%). Methodological quality limitations primarily stemmed from three deficiencies: no registered research protocol in advance, the lack of exclusion list, and no analyzed of funding. Future studies should prospectively register protocols, document exclusion list, and analyze funding sources to mitigate evaluation risk of bias. Regarding evidence quality assessed via the GRADE, our analysis revealed that risk of bias and imprecision in the primary RCTs constituted the contributors to evidence downgrades across the SRs. All evaluated outcomes exhibited deficiencies in ≥1 critical domains, including inadequate randomization, insufficient allocation concealment, absence of blinding implementation, or overly broad confidence intervals undermining reliability. These findings revealed systemic methodological vulnerabilities that should guide prioritization of critical enhancements in future clinical trial design—specifically emphasizing protocol standardization and statistical precision to mitigate identified limitations.

Clinical evidence demonstrates BBR's therapeutic efficacy across multiple chronic disease domains. Notably, BBR exerts hypoglycemic effects in T2DM through gut microbiota modulation—specifically by enhancing butyrate-producing bacterial taxa and improving intestinal barrier integrity [38]. Similarly, in PCOS, a condition intrinsically linked to insulin resistance and metabolic dysregulation, BBR ameliorates both hormonal imbalances and metabolic parameters [51]. These therapeutic outcomes are achieved through multi-target mechanisms involving AMPK activation, inflammatory pathway suppression, and sex hormone-binding globulin upregulation [52, 53]. BBR exhibits a favorable tolerability profile, with treatment-emergent adverse events predominantly limited to mild, self-limiting gastrointestinal disturbances (e.g. diarrhea, nausea, constipation) [27, 38]. The SRs included in this study revealed comparable or even lower adverse event rates due to adverse events compared to conventional therapies—specifically for metformin in T2DM, and for statins in dyslipidemia management [39]. This safety persists despite BBR's multi-pathway bioactivity, suggesting distinct pharmacokinetic properties that mitigate cumulative toxicity risks associated with prolonged use [54]. Despite its therapeutic potential, BBR remains conspicuously absent from clinical practice guidelines. This exclusion stems primarily from methodological limitations in existing evidence (e.g., inconsistent outcome reporting, small sample sizes) compounded

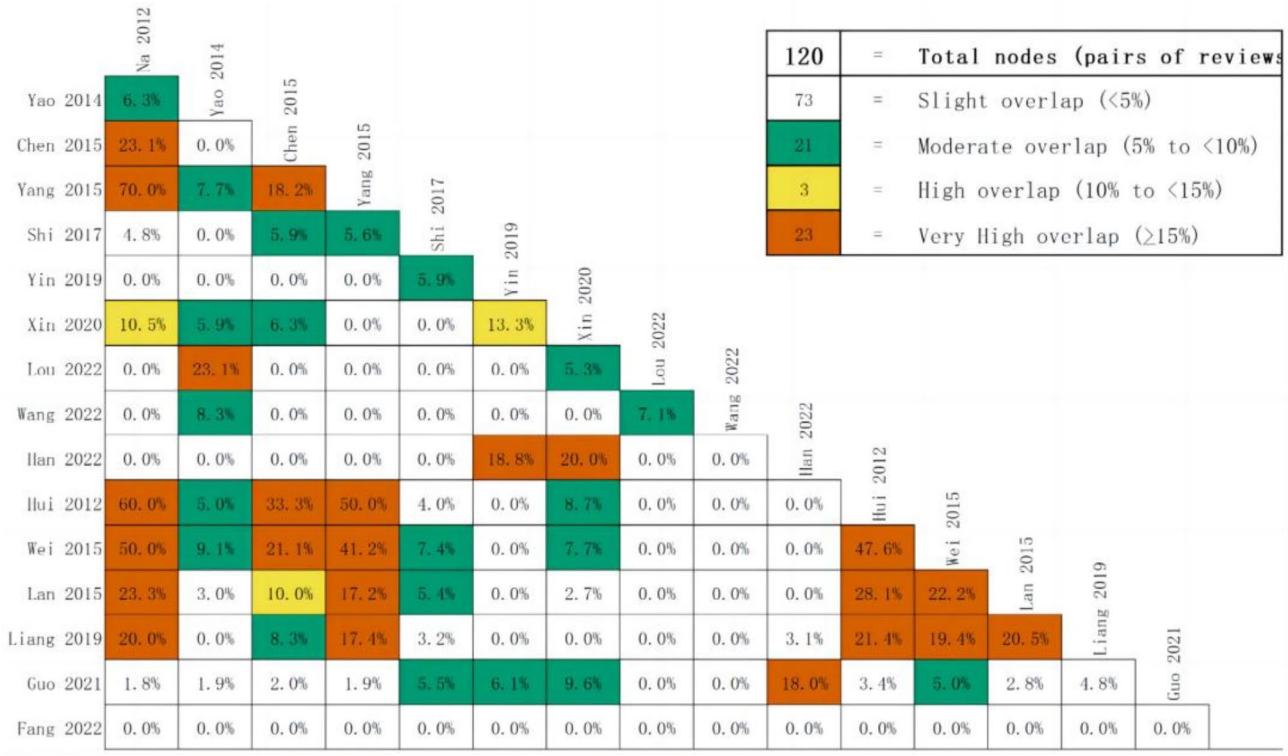

Fig. 3 Overlapping of primary studies included in SRs for type 2 diabetes mellitus

by critical demographic biases—notably the geographic homogeneity of trial populations. Current clinical trial originate overwhelmingly from Asia, especailly from with Chinese participants [55].

The glucose-lowering effect of BBR is mediated by suppression of the AMPK signaling pathway to suppress the expression of the key enzymes of hepatic gluconeogenesis, phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase) [56]. Abnormal increase in hepatic gluconeogenesis is an important cause of insulin resistance in patients with T2DM [57]. BBR has been shown to reduce insulin resistance by regulating glycolipid metabolism. and suppressing hepatic gluconeogenesis [58]. Compared with the commonly used clinical medications metformin and rosiglitazone, BBR has a similar effect in lowering FBG in patients with T2DM; however, BBR was also effective in lowering FBG in patients with comorbid chronic hepatitis B and C [22]. Meanwhile, the characteristics of dyslipidemia include high circulating TG and low HDL-C levels and are often accompanied by hepatic steatosis [59]. Metformin, widely used clinically, improves HDL-C and TC while inhibiting dyslipidemia, but induces gastrointestinal adverse effects potentially mediated through GLP-1-related intestinal hormone secretion [60]. BBR directly regulates the binding of key enzymes of the gluconeogenesis process by PEPCK and G6Pase to the hepatic HDL-C receptor to inhibit dyslipidemia in mice [61]. Additionally, the process of intestinal gluconeogenesis is found to be associated with weight gain and was able to prevent obesity-associated hepatic steatosis and conversion to NAFLD [62]. Among conventional medicines, semaglutide has been shown to provide the greatest weight loss of all obesity medications, but still carries the risk of accelerated heart rate [63]. However, BBR not only improves obesity symptoms by inhibiting hepatic gluconeogenesis via PEPCK and G6Pase; it also achieves the same effect by activating intestinal gluconeogenesis via short-chain fatty acids produced by gut microbiota [25, 64]. Further, patients with PCOS often have hyperandrogenemia, which inhibits the expression of PEPCK and G6Pase, key targets of gluconeogenesis, leading to elevated blood glucose concentrations [65]. Although metformin can be used to lower serum androgen levels through its modulatory effect on serum insulin and by increasing sensitivity to insulin, gastrointestinal side effects, and hypoglycemia can occur [66]. BBR regulates gluconeogenesis and modulates hormonal pathways through sex hormone-binding globulin elevation, androgen receptor signaling inhibition, and reduced androgen synthesis, thereby addressing hormone disorders [67]. Moreover, BBR is safer than metformin as a natural medicine with a lower rate of adverse effects, resulting in a very low risk of hypoglycemia [67].

The gut microbiota has always played an important role in the lipid metabolism, immunity, and inflammation

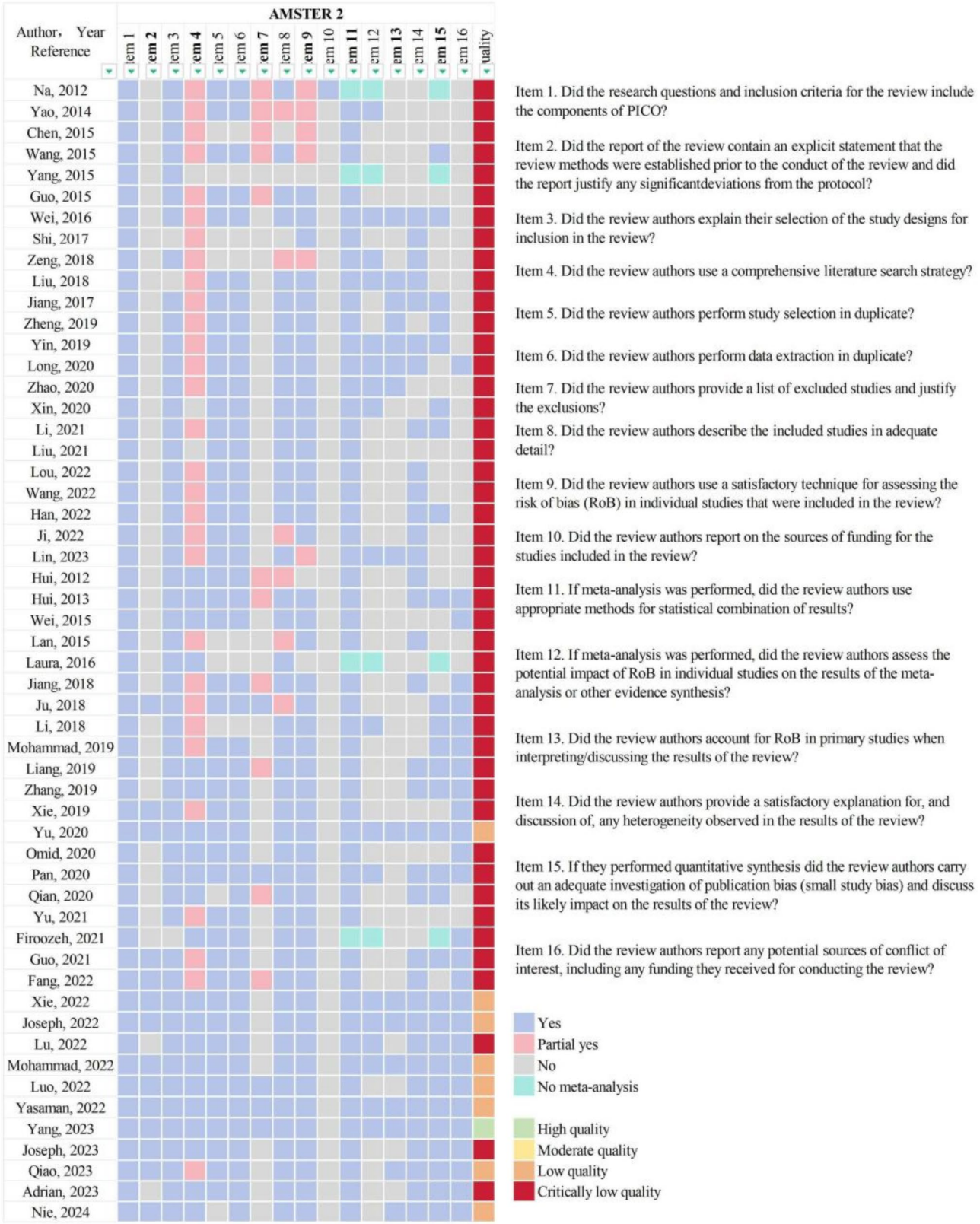

Fig. 4 Result of the AMSTAR 2 assessments for the included 54 SRs

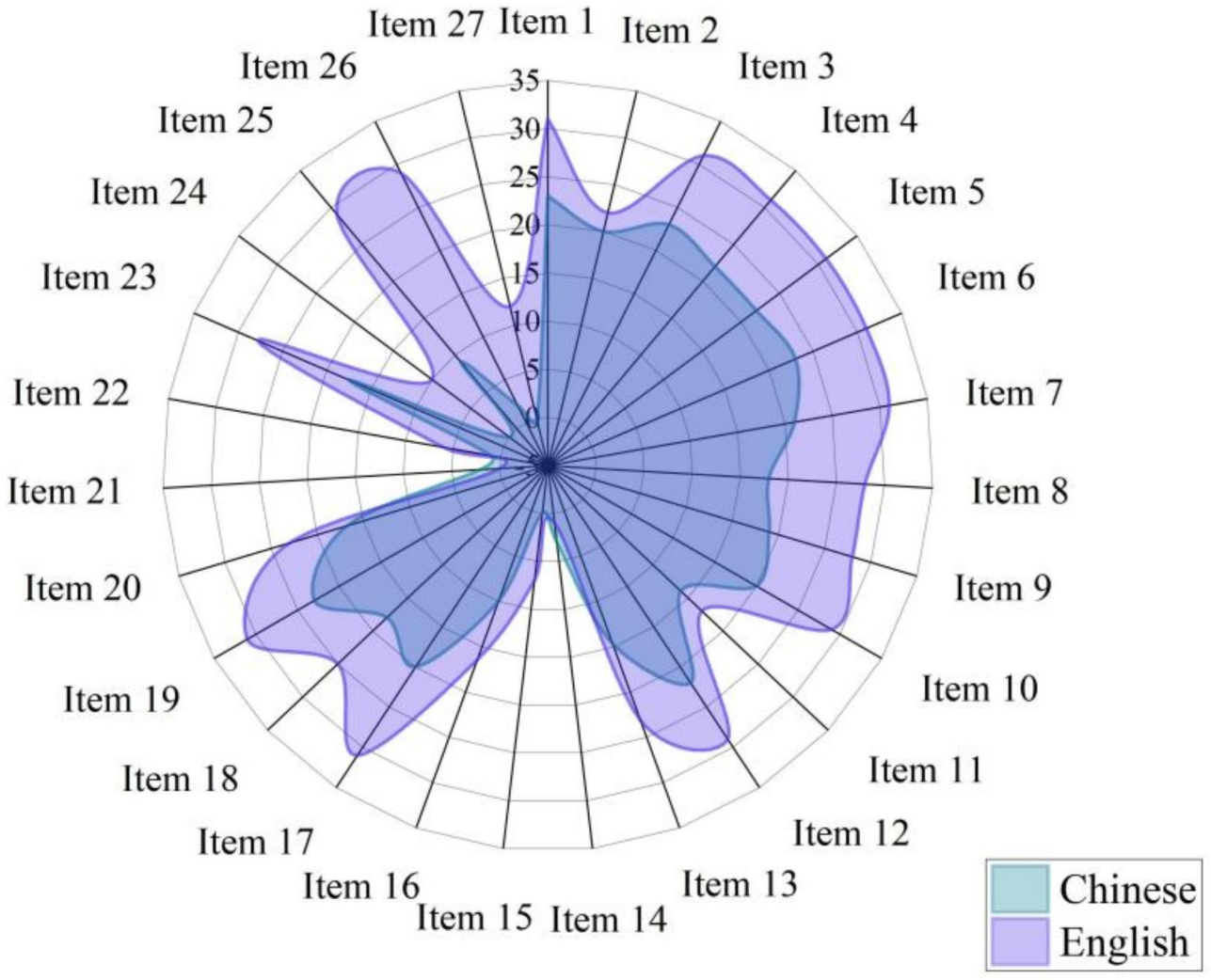

Fig. 5 Reporting quality of included SRs

of the host and is a target for the multifunctional action of BBR [68–70]. By analyzing the gut microbiome and metabolome in the Framingham Heart Study, gut microbiota can influence the development of cardiovascular disease through a variety of microbial pathways, such as human gut Oscillibacter [71]. Statins are commonly used clinically to improve blood lipids for cardiovascular disease, but a large HOPE-3 trial found that statins were associated with an increased risk of cataract surgery [72]. There is growing evidence that BBR improves cardiovascular disease outcomes by decreasing gut microflora diversity as well as fasting-induced adipose factor expression and energy metabolism in the AMPK and PGC1α pathways [73]. Also, the development of ulcerative colitis is associated with intestinal microbiologic factors [74]. Conventional medicines include antibiotics, corticosteroids, and immunomodulators, but are associated with gastrointestinal reactions, skin sensitization, and other adverse effects [75]. The same can be done by targeting the gut microbiota, combining BBR with dehydrocostus lactone to target the key beneficial bacterium, *Akkermansia*, to maintain a normal supply of intestinal proteins [76]. In addition, the metabolic syndrome is associated with alterations in the microbiota, including increases in the Firmicutes, Bacteroidetes, and Proteobacteria, as well as alterations in specific bacteria such as Lactobacillus and Clostridium [77]. Due to the low oral bioavailability of BBR, it directly interacts with gut microbiota and attenuates metabolic syndrome in mice compared to other drugs [78]. Furthermore, the development of NAFLD has been associated with dysbiosis of the gut microbiota involving *Faecalbacterium prausnitzii*, *Bilophila wadsworthia*, *Helicobacter pylori*, *Klebsiella pneumoniae*, and *Akkermansia muciniphila* [79]. Metformin treats NAFLD by AMPK-mediated inhibition of class II histone deacetylase and DNMT overexpression, while BBR activates SIRT-3 to regulate hepatic AMPK and reduce steatosis [80]. In cases where metformin is

Table 2 Efficacy and GRADE ratings of BBR for the primary outcome of different conditions.*

Condition	Outcomes	Comparison	Number of outcomes	*p* value	GRADE
T2DM	2hPBG/PPG	BBR vs. CM	3	▲	⊕⊖⊖⊖very low
		BBR + CM vs. CM	2	●	⊕⊕⊖⊖low
			9	●	⊕⊖⊖⊖very low
		BBR(+CM) vs. CM	2	●	⊕⊖⊖⊖very low
	FBG/FPG	BBR vs. CM	2	●	⊕⊖⊖⊖very low
		BBR + CM vs. CM	9	●	⊕⊖⊖⊖very low
	HbAlc	BBR vs. CM	5	●	⊕⊖⊖⊖very low
		BBR + CM vs. CM	3	●	⊕⊕⊖⊖low
			5	●	⊕⊖⊖⊖very low
Dyslipidemia	HDL-C	BBR vs. CM	2	●	⊕⊖⊖⊖very low
		BBR + CM vs. CM	3	▲	⊕⊖⊖⊖very low
	LDL-C	BBR vs. CM	2	●	⊕⊕⊖⊖low
		BBR + CM vs. CM	2	●	⊕⊖⊖⊖very low
		BBR(+CM) vs. CM	2	●	⊕⊖⊖⊖very low
	TC	BBR vs. CM	2	▲	⊕⊖⊖⊖very low
		BBR + CM vs. CM	4	●	⊕⊖⊖⊖very low
		BBR vs. PL/BK	2	●	⊕⊖⊖⊖very low
		BBR(+CM) vs. CM	2	●	⊕⊖⊖⊖very low
	TG	BBR vs. CM	3	●	⊕⊖⊖⊖very low
		BBR + CM vs. CM	3	●	⊕⊖⊖⊖very low
		BBR(+CM) vs. CM	2	●	⊕⊖⊖⊖very low
PCOS	BMI	BBR vs. CM	3	▲	⊕⊖⊖⊖very low
		BBR + CM vs. CM	3	▲	⊕⊖⊖⊖very low
	TC	BBR vs. CM	2	●	⊕⊖⊖⊖very low
			2	●	⊕⊕⊖⊖low
	TG	BBR vs. CM	2	▲	⊕⊖⊖⊖very low
	TT	BBR vs. CM	3	▲	⊕⊖⊖⊖very low
		BBR + CM vs. CM	2	●	⊕⊕⊖⊖low
NAFLD	2hPBG/PPG	BBR vs. CM	3	●	⊕⊖⊖⊖very low
	TC	BBR(+CM) vs. CM	2	●	⊕⊕⊖⊖low
Cardiovascular disease	ER	BBR + CM vs. CM	2	●	⊕⊖⊖⊖very low
	HDL-C	BBR + CM vs. CM	2	▲	⊕⊖⊖⊖very low
	LDL-C	BBR + CM vs. CM	2	●	⊕⊖⊖⊖very low
Metabolic syndrome	IL-6	BBR(+CM) vs. CM/PL	2	●	⊕⊕⊖⊖low
	TNF-α	BBR(+CM) vs. CM/PL	2	●	⊕⊕⊖⊖low

*Schizophrenia, gastrointestinal disorder, and obesity were not demonstrated because each of the outcomes occurred only once. ●: $p < 0.05$; ▲: $p > 0.05$

intolerant or refractory, BBR may be a suitable alternative to ensure tolerability and reduce the risk of adverse effects [81]. Moreover, the gut microbiota interacts with the central nervous system tract via the gut-brain axis and influences the pathological process of schizophrenia by modulating lipid and glucose related functions [82]. The dyslipidemia that can be induced by the currently clinically used schizophrenia medication olanzapine has only been validated in a female rat model, although it can be ameliorated to some extent by combining it with simvastatin [83]. While, the combination of BBR and metformin have a significant preventive effect on olanzapine-induced weight gain in rats, and it also suggests a potential mechanism of action to prevent olanzapine from reducing energy expenditure [84].

BBR, unlike chemical drugs with relatively single component, is an active ingredient isolated from herbs with multiple biological functions. Therefore, it can regulate the body through several pathways, such as improving insulin resistance, inducing cell cycle arrest, inhibiting the production of proinflammatory cytokines, and inhibiting the production of B-cell activating factors [85]. Gluconeogenesis and gut microbiota are also two regulatory pathways of BBR. BBR regulates gut microbiota metabolism through ATP/NADH reduction and butyrate synthesis to lower lipid/glucose levels, while inhibiting hepatic gluconeogenesis/fatty acid oxidation via mitochondrial pyruvate carrier 1 and enhancing peripheral glucose uptake [85]. In terms of lipid and energy metabolism, these two pathways can interact with each other, which in

one way explains the ability of BBR to treat a wide range of diseases. Population aging and socioeconomic development have driven increased life expectancy, establishing multimorbidity as an emerging population health paradigm. A global overview based on the UK biobank shows that there is already a trend toward comorbidities between complex conditions, with metabolic conditions having the highest rates of comorbidities across physiological systems [86]. In the future, the era of treating a single condition may not be in the mainstream, and how to develop multi-targeted interventions for comorbidities will become a new research direction.

To the best of our knowledge, the current overview is the first systematic investigation into SRs on BBR, providing a comprehensive summary of various health outcomes. Nonetheless, this study is not without limitations. Firstly, our inclusion criteria focused on SRs published in English and Chinese, thereby potentially overlooking studies published in other languages and their insights into the efficacy of BBR. Second, the quality assessment process may be subject to some degree of subjectivity. To mitigate this, we implemented a rigorous protocol whereby assessments by one researcher was verified by another, with any discrepancies resolved through consensus with a third party. Third, our research depends on the published SRs, and therefore, the inclusion of the original studies and the reliability of the implementation quality will affect our evaluation. The methodological and reporting deficiency highlighted in this overview suggested that studies of BBR with high quality should be conducted in the future to confirm its efficacy.

Conclusions

This overview analyzes health outcomes associated with BBR based on SRs. The available evidence suggests BBR could be beneficial for cardiovascular disease, T2DM, gastrointestinal disorders, PCOS, NAFLD, hyperlipidemia, metabolic syndrome, obesity, and schizophrenia. BBR is able to improve multiple outcomes, but the quality of evidence is still limited and further studies are needed. Considering the multifaceted effects of BBR, mechanistic studies should be conducted to comprehensively explore and sort out the pathogenic mechanisms by which BBR may ameliorate the disease. High-quality RCTs will also be conducted for related conditions, aiming to provide high-level evidence to support the clinical promotion of BBR to improve human health.

Abbreviations

TCM	Traditional Chinese medicine
FBG/FPG	Fasting blood glucose/fasting plasma glucose
2hPBG/PPG	2 h postprandial blood glucose/post-prandial plasma glucose
HbA1c	Hemoglobin a1c
TC	Total cholesterol
TG	Triglyceride
LDL-C	Low-density lipoprotein cholesterol
HDL-C	High-density lipoprotein cholesterol
CRP	C-reactive protein
HOMA-IR	Homeostatic model assessment of insulin resistance
FIN	Fasting serum lisulin
APOB	Apoliprotein B
IL-6	Interleukin 6
TNF-α	Tumor necrosis factor-α
BMI	Body mass index
WC	Waist circumference
BW	Body weight
ER	Effective rate
NIHSS	National Institutes of Health stroke scale
AE	Adverse event
IMT	Carotid intima-media thickness
NUP	Number of unstable plaques
CS	Crouse score
ALT	Glutamic pyruvic transaminase
AST	Glutamic oxaloacetic transaminase
HpER	h.pylori eradication rate
PBSRT	Pus and blood stool remission time
IL-8	Interleukin-8
IL-10	Interleukin 10
DAI	Disease activity index
PRT	Pain relief time
TT	Total testosterone
LH	Luteinizing hormone
SHBG	Sex hormone binding globulin
BBR	Berberine
NAFLD	Non-alcoholic fatty liver disease
PCOS	Polycystic ovary syndrome
T2DM	Type 2 diabetes mellitus
SR	Systematic reviews
AMPK	AMP-activated protein kinase
PEPCK	Phosphoenolpyruvate carboxykinase
G6Pase	Glucose-6-phosphatase

Supplementary Information

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Supplementary Material 1

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Not applicable.

Author contributions

SLJ and LX designed the study. SHL and WWY searched, selected, extracted and assessed the literature and performed the statistical analyses. LX supervised the study and arbitrated the disagreements. WWY and JCY contributed to study selection, data collection, and risk of bias assessment. SLJ drafted the manuscript, HJ and LX critically reviewed the manuscript. All authors revised the manuscript and approved the final version of the manuscript.

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Data availability

All data related to the research are included in the article and Supplementary Material. The included trials were published on open access websites and databases. If necessary, contact the first author for information. The review did not require prior ethical approval and consent from the participants because it only involved previously published systematic reviews.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

Competing interests
The authors declare no competing interests.

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References

1. Collaborators GCD. Global burden of 288 causes of death and life expectancy decomposition in 204 countries and territories and 811 subnational locations, 1990–2021: a systematic analysis for the global burden of disease study 2021. Lancet; 2024.
2. Fontana L. From chronic disease to chronic health: the evolving role of Doctors in the 21st century. Eur Heart J 2024.
3. Hamidah A, Rustam ZA, Tamil AM, Zarina LA, Zulkifli ZS, Jamal R. Prevalence and parental perceptions of complementary and alternative medicine use by children with cancer in a multi-ethnic Southeast Asian population. Pediatr Blood Cancer. 2009;52(1):70–4.
4. Wojcikowski K, Johnson DW, Gobe G. Herbs or natural substances as complementary therapies for chronic kidney disease: ideas for future studies. J Lab Clin Med. 2006;147(4):160–6.
5. Gobe GC, Wojcikowski K. Nontraditional (non-Western pharmaceutical) treatments for chronic kidney disease. Clin Nephrol. 2020;93(1):49–54.
6. Waltenberger B, Mocan A, Šmejkal K, Heiss EH, Atanasov AG. Natural products to counteract the epidemic of cardiovascular and metabolic disorders. Molecules 2016, 21(6).
7. Tintore M, Vidal-Jordana A, Sastre-Garriga J. Treatment of multiple sclerosis - success from bench to bedside. Nat Rev Neurol. 2019;15(1):53–8.
8. Rodríguez-Yoldi MJ. Anti-Inflammatory and antioxidant properties of plant extracts. Antioxid (Basel) 2021, 10(6).
9. Rapa SF, Di Iorio BR, Campiglia P, Heidland A, Marzocco S. Inflammation and oxidative stress in chronic kidney Disease-Potential therapeutic role of minerals, vitamins and Plant-Derived metabolites. Int J Mol Sci 2019, 21(1).
10. Li C, Jia WW, Yang JL, Cheng C, Olaleye OE. Multi-compound and drug-combination Pharmacokinetic research on Chinese herbal medicines. Acta Pharmacol Sin. 2022;43(12):3080–95.
11. Yan G, Chang T, Zhao Y, Yu M, Mi J, Wang G, Wang X, Liao X. The effects of ophiocordyceps sinensis combined with ACEI/ARB on diabetic kidney disease: A systematic review and meta-analysis. Phytomedicine. 2023;108:154531.
12. Gu M, Song H, Li Y, Jiang Y, Zhang Y, Tang Z, Ji G, Huang C. Extract of schisandra chinensis fruit protects against metabolic dysfunction in high-fat diet induced obese mice via FXR activation. Phytother Res. 2020;34(11):3063–77.
13. Ma H, Yue GG, Lee JK, Gao S, Yuen KK, Cheng W, Li X, Lau CB. Scutellarin, a flavonoid compound from scutellaria Barbata, suppresses growth of breast cancer stem cells in vitro and in tumor-bearing mice. Phytomedicine. 2024;128:155418.
14. Peng H, Lin X, Wang Y, Chen J, Zhao Q, Chen S, Cheng Q, Chen C, Sang T, Zhou H, et al. Epigallocatechin gallate suppresses mitotic clonal expansion and adipogenic differentiation of preadipocytes through impeding JAK2/STAT3-mediated transcriptional cascades. Phytomedicine. 2024;129:155563.
15. Li H, Hu R, Xu S, Dai Z, Wu X, Hu J, Liao X. Tripterygium wilfordii Hook. F. Preparations F.r rheumatoid arthritis: an overview of systematic reviews. Evid Based Complement Alternat Med. 2022;2022:3151936.
16. Guo X, Wen S, Wang J, Zeng X, Yu H, Chen Y, Zhu X, Xu L. Senolytic combination of dasatinib and Quercetin attenuates renal damage in diabetic kidney disease. Phytomedicine. 2024;130:155705.
17. Liu C, Huang J, Qiu J, Jiang H, Liang S, Su Y, Lin J, Zheng J. Quercitrin improves cardiac remodeling following myocardial infarction by regulating macrophage polarization and metabolic reprogramming. Phytomedicine. 2024;127:155467.
18. Meng FC, Wu ZF, Yin ZQ, Lin LG, Wang R, Zhang QW. Coptidis rhizoma and its main bioactive components: recent advances in chemical investigation, quality evaluation and Pharmacological activity. Chin Med. 2018;13:13.
19. Meng J, Qiu S, Zhang L, You M, Xing H, Zhu J. Berberine alleviate Cisplatin-Induced peripheral neuropathy by modulating inflammation signal via TRPV1. Front Pharmacol. 2021;12:774795.
20. Kunwar RM, Nepal BK, Kshhetri HB, Rai SK, Bussmann RW. Ethnomedicine in Himalaya: a case study from Dolpa, Humla, Jumla and Mustang districts of Nepal. J Ethnobiol Ethnomed. 2006;2:27.
21. Cicero AF, Baggioni A. Berberine and its role in chronic disease. Adv Exp Med Biol. 2016;928:27–45.
22. Zhang H, Wei J, Xue R, Wu JD, Zhao W, Wang ZZ, Wang SK, Zhou ZX, Song DQ, Wang YM, et al. Berberine lowers blood glucose in type 2 diabetes mellitus patients through increasing insulin receptor expression. Metabolism. 2010;59(2):285–92.
23. Blais JE, Huang X, Zhao JV. Overall and Sex-Specific effect of Berberine for the treatment of dyslipidemia in adults: A systematic review and Meta-Analysis of randomized Placebo-Controlled trials. Drugs. 2023;83(5):403–27.
24. Chan M, Qin Z, Man SC, Lam M, Lai WH, Ng RMK, Lee CK, Wong TL, Lee EHM, Wong HK, et al. Adjunctive Berberine reduces antipsychotic-associated weight gain and metabolic syndrome in patients with schizophrenia: a randomized controlled trial. Psychiatry Clin Neurosci. 2022;76(3):77–85.
25. Ilyas Z, Perna S, Al-Thawadi S, Alalwan TA, Riva A, Petrangolini G, Gasparri C, Infantino V, Peroni G, Rondanelli M. The effect of Berberine on weight loss in order to prevent obesity: A systematic review. Biomed Pharmacother. 2020;127:110137.
26. Yang L, Zhu W, Zhang X, Zhou X, Wu W, Shen T. Efficacy and safety of Berberine for several cardiovascular diseases: A systematic review and meta-analysis of randomized controlled trials. Phytomedicine. 2023;112:154716.
27. Harrison SA, Gunn N, Neff GW, Kohli A, Liu L, Flyer A, Goldkind L, Di Bisceglie AM. A phase 2, proof of concept, randomised controlled trial of Berberine ursodeoxycholate in patients with presumed non-alcoholic steatohepatitis and type 2 diabetes. Nat Commun. 2021;12(1):5503.
28. Chen S, Shen W, Liu Y, Dong Q, Shi Y. Efficacy and safety of triple therapy containing Berberine, amoxicillin, and Vonoprazan for Helicobacter pylori initial treatment: A randomized controlled trial. Chin Med J (Engl). 2023;136(14):1690–8.
29. He S, Li H, Zhang Q, Zhao W, Li W, Dai C, Li B, Cheng J, Wu S, Zhou Z, et al. Berberine alleviates inflammation in polycystic ovary syndrome by inhibiting hyaluronan synthase 2 expression. Phytomedicine. 2024;128:155456.
30. Nepomuceno R, Vallerini BF, da Silva RL, Corbi SCT, Bastos AS, Dos Santos RA, Takahashi CS, Orrico SRP, Scarel-Caminaga RM. Systemic expression of genes related to inflammation and lipid metabolism in patients with dyslipidemia, type 2 diabetes mellitus and chronic periodontitis. Diabetes Metab Syndr. 2019;13(4):2715–22.
31. McLaren JE, Michael DR, Ashlin TG, Ramji DP. Cytokines, macrophage lipid metabolism and foam cells: implications for cardiovascular disease therapy. Prog Lipid Res. 2011;50(4):331–47.
32. Segura J, Campo C, Roldán C, Christiansen H, Vigil L, García-Robles R, Rodicio JL, Ruilope LM. Hypertensive renal damage in metabolic syndrome is associated with glucose metabolism disturbances. J Am Soc Nephrol. 2004;15(Suppl 1):S37–42.
33. Pawlak M, Lefebvre P, Staels B. Molecular mechanism of PPARα action and its impact on lipid metabolism, inflammation and fibrosis in non-alcoholic fatty liver disease. J Hepatol. 2015;62(3):720–33.
34. Aron-Wisnewsky J, Warmbrunn MV, Nieuwdorp M, Clément K. Metabolism and metabolic disorders and the microbiome: the intestinal microbiota associated with obesity, lipid metabolism, and metabolic Health-Pathophysiology and therapeutic strategies. Gastroenterology. 2021;160(2):573–99.
35. Zhong Y, Xiao Q, Huang J, Yu S, Chen L, Wan Q, Zhang Z, Luo L, Song L, Zhao H, et al. Ginsenoside Rg1 alleviates ulcerative colitis in obese mice by regulating the gut Microbiota-Lipid Metabolism-Th1/Th2/Th17 cells axis. J Agric Food Chem. 2023;71(50):20073–91.
36. Fang X, Wu H, Wang X, Lian F, Li M, Miao R, Wei J, Tian J. Modulation of gut microbiota and metabolites by Berberine in treating mice with disturbances in glucose and lipid metabolism. Front Pharmacol. 2022;13:870407.
37. Chen YX, Gao QY, Zou TH, Wang BM, Liu SD, Sheng JQ, Ren JL, Zou XP, Liu ZJ, Song YY, et al. Berberine versus placebo for the prevention of recurrence of colorectal adenoma: a multicentre, double-blinded, randomised controlled study. Lancet Gastroenterol Hepatol. 2020;5(3):267–75.

38. Zhang Y, Gu Y, Ren H, Wang S, Zhong H, Zhao X, Ma J, Gu X, Xue Y, Huang S, et al. Gut microbiome-related effects of Berberine and probiotics on type 2 diabetes (the PREMOTE study). Nat Commun. 2020;11(1):5015.
39. Xie W, Su F, Wang G, Peng Z, Xu Y, Zhang Y, Xu N, Hou K, Hu Z, Chen Y, et al. Glucose-lowering effect of Berberine on type 2 diabetes: A systematic review and meta-analysis. Front Pharmacol. 2022;13:1015045.
40. Wei X, Wang C, Hao S, Song H, Yang L. The Therapeutic Effect of Berberine in the Treatment of Nonalcoholic Fatty Liver Disease: A Meta-Analysis. *Evid Based Complement Alternat Med* 2016, 2016:3593951.
41. Gates M, Gates A, Pieper D, Fernandes RM, Tricco AC, Moher D, Brennan SE, Li T, Pollock M, Lunny C, et al. Reporting guideline for overviews of reviews of healthcare interventions: development of the PRIOR statement. BMJ. 2022;378:e070849.
42. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
43. Chen G, Lu J, Li B, Zhao M, Liu D, Yang Z, Liu F. Efficacy and safety of Shenqi Fuzheng injection combined with chemotherapy for cancer: an overview of systematic reviews. Phytomedicine. 2024;125:155293.
44. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017;358:j4008.
45. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, Norris S, Falck-Ytter Y, Glasziou P, DeBeer H, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64(4):383–94.
46. Pérez-Bracchiglione J, Meza N, Bangdiwala SI, Niño de Guzmán E, Urrútia G, Bonfill X, Madrid E. Graphical representation of overlap for overviews: GROOVE tool. Res Synth Methods. 2022;13(3):381–8.
47. Pieper D, Antoine SL, Mathes T, Neugebauer EA, Eikermann M. Systematic review finds overlapping reviews were not mentioned in every other overview. J Clin Epidemiol. 2014;67(4):368–75.
48. Vahedi-Mazdabadi Y, Shahinfar H, Toushih M, Shidfar F. Effects of Berberine and barberry on selected inflammatory biomarkers in adults: A systematic review and dose-response meta-analysis of randomized clinical trials. Phytother Res. 2023;37(12):5541–57.
49. Lin Y, Xu X, Luo T, Zhou Y. Meta analysis of the effects of Berberine on glycolipid metabolism and Proinflammatory cytokines in schizophrenia. Med Health Vol. 2023;6:0055–61.
50. Lunny C, Brennan SE, Reid J, McDonald S, McKenzie JE. Overviews of reviews incompletely report methods for handling overlapping, discordant, and problematic data. J Clin Epidemiol. 2020;118:69–85.
51. Wei W, Zhao H, Wang A, Sui M, Liang K, Deng H, Ma Y, Zhang Y, Zhang H, Guan Y. A clinical study on the short-term effect of Berberine in comparison to Metformin on the metabolic characteristics of women with polycystic ovary syndrome. Eur J Endocrinol. 2012;166(1):99–105.
52. Hotamisligil GS. Inflammation and metabolic disorders. Nature. 2006;444(7121):860–7.
53. Grahame Hardie D. AMP-activated protein kinase: a key regulator of energy balance with many roles in human disease. J Intern Med. 2014;276(6):543–59.
54. Han Y, Xiang Y, Shi Y, Tang X, Pan L, Gao J, Bi R, Lai X. Pharmacokinetics and Pharmacological activities of Berberine in diabetes mellitus treatment. Evidence-based Complement Altern Med 2021.
55. Pirro M, Vetrani C, Bianchi C, Mannarino MR, Bernini F, Rivellese AA. Joint position statement on nutraceuticals for the treatment of hypercholesterolemia of the Italian society of diabetology (SID) and of the Italian society for the study of arteriosclerosis (SISA). Nutr Metab Cardiovasc Dis. 2017;27(1):2–17.
56. Zhang M, Lv X, Li J, Meng Z, Wang Q, Chang W, Li W, Chen L, Liu Y. Sodium Caprate augments the hypoglycemic effect of Berberine via AMPK in inhibiting hepatic gluconeogenesis. Mol Cell Endocrinol. 2012;363(1–2):122–30.
57. Barroso E, Jurado-Aguilar J, Wahli W, Palomer X, Vázquez-Carrera M. Increased hepatic gluconeogenesis and type 2 diabetes mellitus. Trends Endocrinol Metab 2024.
58. Xu Y, Yu T, Ma G, Zheng L, Jiang X, Yang F, Wang Z, Li N, He Z, Song X, et al. Berberine modulates deacetylation of PPARγ to promote adipose tissue remodeling and thermogenesis via AMPK/SIRT1 pathway. Int J Biol Sci. 2021;17(12):3173–87.
59. Semple RK, Sleigh A, Murgatroyd PR, Adams CA, Bluck L, Jackson S, Vottero A, Kanabar D, Charlton-Menys V, Durrington P, et al. Postreceptor insulin resistance contributes to human dyslipidemia and hepatic steatosis. J Clin Invest. 2009;119(2):315–22.
60. Al-Ani B, Alzamil NM, Hewett PW, Al-Hashem F, Bin-Jaliah I, Shatoor AS, Kamar SS, Latif NSA, Haidara MA, Dawood AF. Metformin ameliorates ROS-p53-collagen axis of fibrosis and dyslipidemia in type 2 diabetes mellitus-induced left ventricular injury. Arch Physiol Biochem. 2023;129(3):734–40.
61. Xiao HB, Sun ZL, Zhang HB, Zhang DS. Berberine inhibits dyslipidemia in C57BL/6 mice with lipopolysaccharide induced inflammation. Pharmacol Rep. 2012;64(4):889–95.
62. Vily-Petit J, Soty-Roca M, Silva M, Raffin M, Gautier-Stein A, Rajas F, Mithieux G. Intestinal gluconeogenesis prevents obesity-linked liver steatosis and non-alcoholic fatty liver disease. Gut. 2020;69(12):2193–202.
63. Chao AM, Tronieri JS, Amaro A, Wadden TA. Semaglutide for the treatment of obesity. Trends Cardiovasc Med. 2023;33(3):159–66.
64. De Vadder F, Kovatcheva-Datchary P, Goncalves D, Vinera J, Zitoun C, Duchampt A, Bäckhed F, Mithieux G. Microbiota-generated metabolites promote metabolic benefits via gut-brain neural circuits. Cell. 2014;156(1–2):84–96.
65. Teede HJ, Tay CT, Laven J, Dokras A, Moran LJ, Piltonen TT, Costello MF, Boivin J. Recommendations from the 2023 international Evidence-based guideline for the assessment and management of polycystic ovary syndrome. Fertil Steril. 2023;120(4):767–93.
66. Daneshjou D, Soleimani Mehranjani M, Zadeh Modarres S, Shariatzadeh MA. Sitagliptin/Metformin: A new medical treatment in polycystic ovary syndrome. Trends Endocrinol Metab. 2020;31(12):890–2.
67. Zhang SW, Zhou J, Gober HJ, Leung WT, Wang L. Effect and mechanism of Berberine against polycystic ovary syndrome. Biomed Pharmacother. 2021;138:111468.
68. Kamada N, Seo SU, Chen GY, Núñez G. Role of the gut microbiota in immunity and inflammatory disease. Nat Rev Immunol. 2013;13(5):321–35.
69. Greer RL, Morgun A, Shulzhenko N. Bridging immunity and lipid metabolism by gut microbiota. J Allergy Clin Immunol. 2013;132(2):253–62. quiz 263.
70. Habtemariam S. Berberine Pharmacology and the gut microbiota: A hidden therapeutic link. Pharmacol Res. 2020;155:104722.
71. Li C, Stražar M, Mohamed AMT, Pacheco JA, Walker RL, Lebar T, Zhao S, Lockart J, Dame A, Thurimella K, et al. Gut Microbiome and metabolome profiling in Framingham heart study reveals cholesterol-metabolizing bacteria. Cell. 2024;187(8):1834–e18521819.
72. Yusuf S, Bosch J, Dagenais G, Zhu J, Xavier D, Liu L, Pais P, López-Jaramillo P, Leiter LA, Dans A, et al. Cholesterol Lowering in Intermediate-Risk persons without cardiovascular disease. N Engl J Med. 2016;374(21):2021–31.
73. Anlu W, Dongcheng C, He Z, Qiuyi L, Yan Z, Yu Q, Hao X, Keji C. Using herbal medicine to target the microbiota-metabolism-immunity axis as possible therapy for cardiovascular disease. Pharmacol Res. 2019;142:205–22.
74. Abegunde AT, Muhammad BH, Bhatti O, Ali T. Environmental risk factors for inflammatory bowel diseases: evidence based literature review. World J Gastroenterol. 2016;22(27):6296–317.
75. Abraham BP, Ahmed T, Ali T. Inflammatory bowel disease: pathophysiology and current therapeutic approaches. Handb Exp Pharmacol. 2017;239:115–46.
76. Xu C, Zhao L, Zhou W, Li Y, Hu H, Wang Z. Synergistic effect of Berberine hydrochloride and dehydrocostus lactone in the treatment of ulcerative colitis: take gut microbiota as the target. Int Immunopharmacol. 2023;124(Pt B):111009.
77. Bishehsari F, Voigt RM, Keshavarzian A. Circadian rhythms and the gut microbiota: from the metabolic syndrome to cancer. Nat Rev Endocrinol. 2020;16(12):731–9.
78. Li J, Li J, Ni J, Zhang C, Jia J, Wu G, Sun H, Wang S. Berberine relieves metabolic syndrome in mice by inhibiting liver inflammation caused by a High-Fat diet and potential association with gut microbiota. Front Microbiol. 2021;12:752512.
79. Quesada-Vázquez S, Aragonès G, Del Bas JM, Escoté X. Diet, gut microbiota and Non-Alcoholic fatty liver disease: three parts of the same axis. Cells 2020, 9(1).
80. Sodum N, Kumar G, Bojja SL, Kumar N, Rao CM. Epigenetics in NAFLD/NASH: targets and therapy. Pharmacol Res. 2021;167:105484.
81. Imenshahidi M, Hosseinzadeh H. Berberine and barberry (Berberis vulgaris): A clinical review. Phytother Res. 2019;33(3):504–23.
82. Nguyen TT, Kosciolek T, Daly RE, Vázquez-Baeza Y, Swafford A, Knight R, Jeste DV. Gut Microbiome in schizophrenia: altered functional pathways related to immune modulation and atherosclerotic risk. Brain Behav Immun. 2021;91:245–56.
83. Liu XM, Zhao XM, Deng C, Zeng YP, Hu CH. Simvastatin improves olanzapine-induced dyslipidemia in rats through inhibiting hepatic mTOR signaling pathway. Acta Pharmacol Sin. 2019;40(8):1049–57.

84. Hu Y, Young AJ, Ehli EA, Nowotny D, Davies PS, Droke EA, Soundy TJ, Davies GE. Metformin and Berberine prevent olanzapine-induced weight gain in rats. PLoS ONE. 2014;9(3):e93310.
85. Song D, Hao J, Fan D. Biological properties and clinical applications of Berberine. Front Med. 2020;14(5):564–82.
86. Dong G, Feng J, Sun F, Chen J, Zhao XM. A global overview of genetically interpretable multimorbidities among common diseases in the UK biobank. Genome Med. 2021;13(1):110.

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