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REVIEW

Berberine in traditional Chinese medicine: Modulating gut microbiota for gout management - mechanisms and clinical perspectives

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Abstract: Gout, a metabolic inflammatory arthritis driven by hyperuricemia, has rising global prevalence linked to high-purine and high-fructose diets. Gut dysbiosis, characterized by depleted beneficial microbes and overgrown pathogenic strains, disrupts uric acid (UA) excretion and exacerbates systemic inflammation, serving as a core pathological driver of gout. Conventional Western anti-gout drugs only relieve transient symptoms and carry severe side effects, whereas berberine (BBR), a bioactive alkaloid from traditional Chinese medicine (TCM), exerts multi-target anti-gout activity via gut microbiota regulation; however, its integrated intestinal mechanisms remain unsystematically summarized. This review elucidates the multi-pathway mechanisms through which BBR ameliorates gout by remodeling gut microbiota homeostasis and discusses its clinical translational prospects for gout management. This review retrieved English (PubMed, Web of Science, Scopus, EMBASE) and Chinese (CNKI, Wanfang) databases for peer-reviewed *in vitro*, animal and clinical studies published up to December 2024, combining gut microbiota, UA metabolism and berberine-related keywords; case reports, abstracts and duplicate papers were excluded. BBR restores intestinal microecology by elevating beneficial bacteria (*Lactobacillus*, *Akkermansia*, *Bifidobacterium*) and suppressing pro-inflammatory pathogens. It boosts butyrate production, upregulates intestinal ABCG2 to accelerate UA fecal excretion, and directly inhibits xanthine oxidase to reduce UA synthesis. Gut microbiota biotransforms BBR into DHB, OBR and other derivatives with higher bioavailability; these metabolites further inhibit renal UA reabsorption and block NLRP3 inflammasome activation to lower IL-1β/IL-18. The bidirectional BBR-microbiota interaction creates a positive feedback loop that amplifies hypouricemic and anti-inflammatory effects. BBR achieves comprehensive gout intervention via gut microbiota-centered multi-target regulation, representing a promising TCM-derived therapeutic strategy. Restricted oral bioavailability and insufficient large-scale human clinical data currently limit its clinical application; novel delivery systems, probiotic combination therapy and long-term clinical trials are required to advance its translational use in gout treatment.

Keywords: Berberine; Gout; Gut microbiota; Traditional Chinese medicine; Uric acid metabolism

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INTRODUCTION

With continuous improvements in living standards, significant changes have occurred in lifestyle and dietary patterns. Globally, the consumption of high-protein, high-fructose and high-purine foods has steadily increased, directly contributing to the rising prevalence of gout. The underlying mechanism involves purines serving as precursors to uric acid (UA), with excessive intake of such foods promoting elevated UA levels. Furthermore, fructose not only enhances UA production but also impairs its renal excretion. This dual effect leads to sustained increases in serum UA concentrations, ultimately elevating the risk of developing gout. A 2024 systematic analysis of the global burden of gout across three to five countries revealed that the age-standardized prevalence rate of gout in 2020 was approximately 660 cases per 100,000 individuals, reflecting a 22.5% increase over the past three decades (Punjwani *et al.,* 2024). In China, the prevalence of gout has reached 1–3% (Keller and Mandell, 2021). A recent report projected that due to population growth and aging, the number of gout cases worldwide is expected to rise by over 70% by 2050, reaching a total of 95.8 million affected individuals. The prevalence of gout exhibits an age-dependent increase, with males being 3.26 times more likely to develop the condition than females (GBD 2021).

Gout is an inflammatory joint disease resulting from dysfunction in purine metabolism or reduced UA excretion. Its clinical presentation includes recurrent acute arthritis, chronic joint inflammation, tophi formation, kidney stones and urate-related kidney damage (Dalbeth *et al.,* 2021). The disease exhibits a predilection for the lower extremities, with affected joints and surrounding soft tissues frequently presenting with swelling, erythema, severe pain and localized warmth, leading to persistent impairment of patients' quality of life. Furthermore, gout is significantly associated with the development of various metabolic and cardiovascular disorders, such as obesity, hypertension, ischemic heart disease, hyperlipidemia,

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atherosclerotic disease, diabetes mellitus and impaired insulin sensitivity (Smith *et al.,* 2014; Wilson and Saseen, 2016; Ragab *et al.,* 2017).

The treatment of gout primarily involves medications aimed at alleviating acute symptoms and employing anti-inflammatory therapy. This is achieved through mechanisms that inhibit UA synthesis, enhance renal UA excretion, or reduce serum urate levels. Currently, conventional Western medicine serves as the cornerstone of therapeutic strategies for gout and hyperuricemia. For acute gout flares, first-line pharmacotherapy typically includes colchicine, corticosteroids, and nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin, ibuprofen, and naproxen to alleviate inflammatory symptoms. For long-term urate-lowering therapy, xanthine oxidoreductase inhibitors-including allopurinol, oxypurinol and febuxostat, are employed as first-line agents to effectively reduce serum UA levels (Guo *et al.,* 2025). However, these pharmacological interventions primarily provide short-term symptomatic relief rather than curative effects.

NSAIDs and colchicine are effective for acute-phase analgesia and anti-inflammation, yet they do not rectify the underlying metabolic dysregulation associated with UA nor prevent disease recurrence (Tang *et al.,* 2023; Chen *et al.,* 2024b). Furthermore, Western medications are often linked to significant adverse effects. Prolonged use of NSAIDs may lead to gastric ulcers, gastrointestinal bleeding and renal complications (Tang *et al.,* 2023). Urate-lowering agents such as allopurinol can induce hepatic dysfunction or severe hypersensitivity reactions, including Stevens-Johnson syndrome (Anna Koczwara *et al.,* 2024), while excessive administration of colchicine may result in myelosuppression or neuromuscular toxicity (Chen *et al.,* 2024b). Importantly, long-term dependence on these medications frequently leads to recurrent attacks, as they do not address the fundamental pathological mechanisms of gout. In contrast, Traditional Chinese Medicine (TCM) has demonstrated significant advantages in overall regulation, reducing side effects, and providing long-term efficacy.

In recent years, advances in understanding the pathogenesis of gout have increasingly elucidated the role of gut microbiota in purine metabolism and UA excretion has been increasingly elucidated, providing novel therapeutic insights. This discovery offers a scientific rationale for the application of TCM in gout management, particularly through bioactive components with gut microbiota-modulating properties, such as berberine (BBR). BBR, an isoquinoline alkaloid derived from medicinal herbs, exhibits a broad range of pharmacological activities. Emerging evidence suggests that BBR not only regulates urate metabolism through multi-target mechanisms but also restores gut microbial homeostasis, demonstrating significant potential in treating gout and related metabolic disorders. This review systematically summarizes recent research progress and explores the underlying mechanisms by which BBR ameliorates gout through gut microbiota modulation, along with its clinical therapeutic prospects.

Search strategy

Searches were performed in both English databases (PubMed, Web of Science, Scopus, EMBASE) and Chinese databases (CNKI, Wanfang Data) for publications up to December 2024. The keywords employed included combinations of related to gout (gout, hyperuricemia, urate metabolism), gut microbiota (gut microbiota, intestinal flora, butyrate) and BBR/TCM-related terms. The literature screening procedure is shown in figure1.

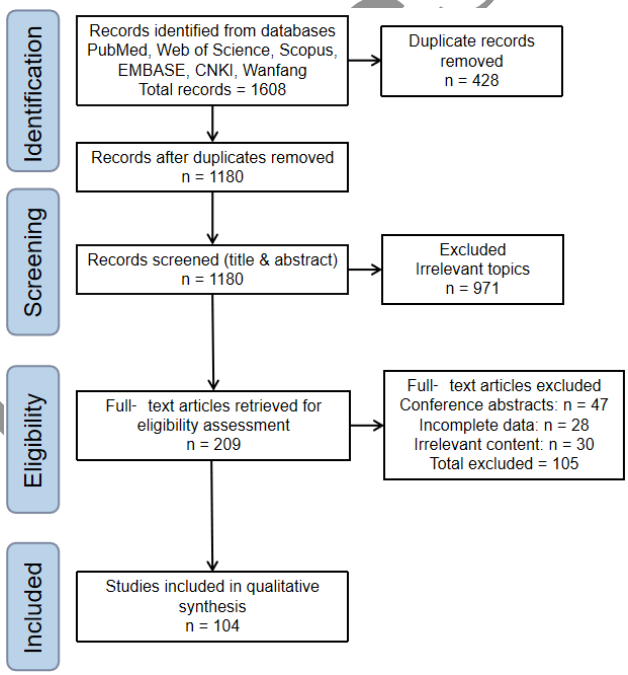

Fig. 1: Flow diagram

Inclusion and exclusion criteria

Criteria encompassed peer-reviewed full-text articles in both English and Chinese that focused on the role of gut microbiota in gout or the effects of BBR/TCM on gout through gut microbiota. These studies included *in-vitro*, animal and clinical research with complete reporting of study design and outcome data. Excluded studies were case reports, conference abstracts, duplicates and studies with off-topic research scope, and publications lacking essential methodological or result information.

TCM approaches to gout

TCM theory of gout

Although TCM lacks a precisely defined concept comparable to modern medicine, it has documented gout-like disorders for over two millennia.

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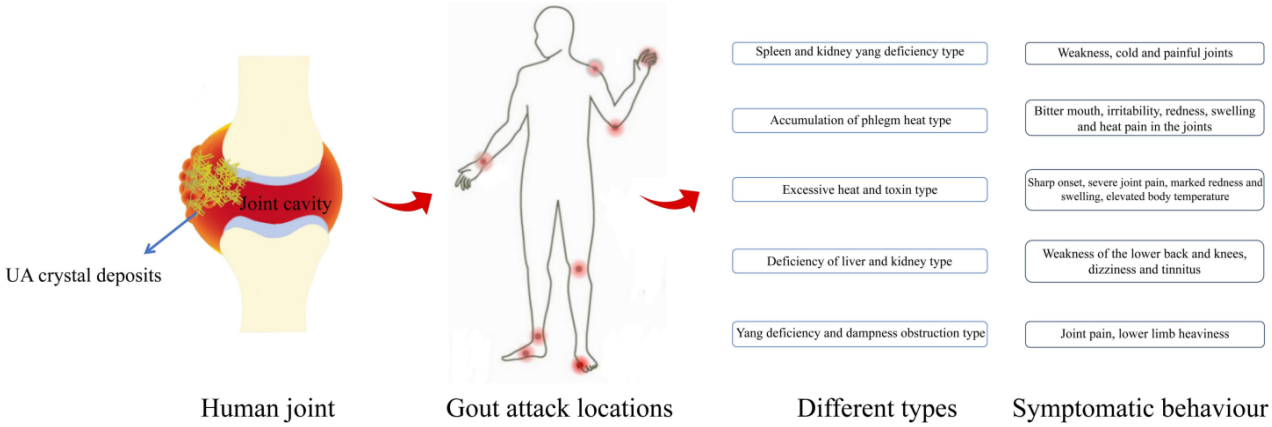

Fig. 2: TCM syndrome types and joint symptoms of gout. UA = Uric Acid.

During the Warring States period (475-221 BCE), the Huangdi Neijing classified these conditions under the category of 'Bi syndrome', attributing their etiology primarily to pathogenic wind, cold and dampness. This manifests as migratory arthralgia (Xing Bi), cold-dominant arthralgia (Han Bi) or dampness-predominant arthralgia (Shi Bi) (Chi *et al.,* 2020). Ancient TCM practitioners postulated that these disorders resulted from excessive blood heat encountering cold stimuli such as chilled water, damp environments or cold wind. This pathological state of internal heat interacting with external cold was believed to cause visceral distress and characteristic pain, particularly during nighttime when yin-phase circulation predominates (Mei Zhong, 2019). Building upon previous research, contemporary TCM has established a systematic theoretical framework for understanding gout, characterizing its etiology and pathogenesis as multifactorial and dynamically evolving (Du *et al.,* 2018; Wang *et al.,* 2018; Xu *et al.,* 2012; Zhang *et al.,* 2018; Zhu *et al.,* 2018). Studies identify 'phlegm-dampness and blood stasis obstruction' as the core pathogenesis, with its fundamental nature being 'liver-kidney dysfunction with exogenous pathogen invasion'. This condition presents as a complex interplay of 'spleen-kidney yang deficiency as the root, with dampness-heat and blood stasis as manifestations'. Pathogenetically, the initial impairment of spleen-stomach transportation leads to the accumulation of damp-turbidity, which subsequently transforms into heat, generating phlegm and accumulation that obstructs the meridians. This process ultimately evolves into a pathological condition where 'dampness serves as the initiating factor and collateral obstruction becomes the critical juncture'. These theories collectively construct a comprehensive conceptual framework of gout as 'root deficiency with surface excess, phlegm-stasis interaction and meridian-collateral obstruction.' Clinical observations of male patients with acute gouty arthritis (AGA) have allowed TCM practitioners to classify gout into distinct syndrome patterns, each defined by specific clinical manifestations (Fig. 2). This syndrome differentiation provides precise guidance for clinical treatment strategies.

Compound and single-herb TCM for gout treatment

In recent years, the application of compound TCM in the treatment of gout has garnered increased attention due to its multi-target and multi-pathway mechanisms, which demonstrate significant anti-inflammatory, urate-lowering and symptom-alleviating effects. Clinically, compound TCM has exhibited remarkable efficacy in treating AGA. For instance, a meta-analysis involving 2,100 participants revealed that compound TCM significantly improved the overall treatment response rate and reduced visual analog scale scores, serum UA levels, erythrocyte sedimentation rate, C-reactive protein levels and TCM syndrome scores. Furthermore, the incidence of adverse reactions was significantly lower than that associated with conventional Western medications, indicating superior safety (Zhao *et al.,* 2025).

Various TCM formulations exert anti-gout effects through distinct mechanisms. The Huangqin Qingre Chubi capsule modulates the lncRNA H19/APN pathway, ameliorating lipid metabolism disorders and inflammation while downregulating lncRNA H19 and IL-1β and upregulating adiponectin and IL-4 levels (Zhang *et al.,* 2023). The Huazhuo Tongbi Decoction regulates gut microbiota and suppresses the NLRP3 inflammasome, thereby reducing pro-inflammatory cytokines such as IL-1β and IL-6, which alleviates joint swelling and inflammation and improving hyperuricemia and gout symptoms (Song *et al.,* 2023). The Simiao Pill modulates triglyceride, amino acid and purine metabolism, restoring UA homeostasis and mitigating inflammation (Huang *et al.,* 2019). The combination of Ermiao Powder and Siwu Decoction enhances UA excretion, thereby reducing serum urate levels and improving renal function markers (Guo *et al.,* 2015).

Single-herb TCMs demonstrate distinct therapeutic advantages. *Salvia miltiorrhiza* (Danshen) inhibits NLRP3 inflammasome activation, IL-1β, TNF-α and IL-6 levels (Wang *et al.,* 2025). BBR, the active component of *Coptis chinensis* (Huanglian), suppresses inflammatory mediators such as IL-1β, TNF-α and PGE2 through the TLR4/NF-κB signaling pathway (He *et al.,* 2022).

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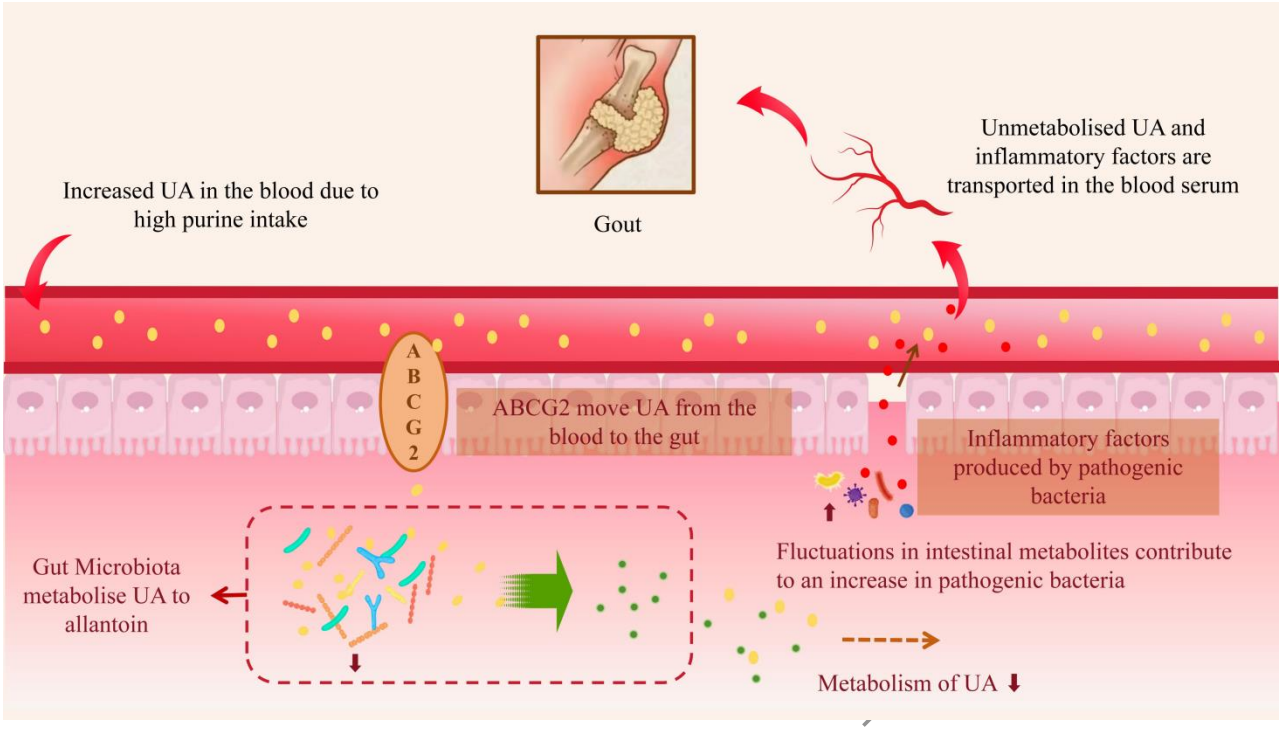

Fig. 3: Mechanism of gout onset: associations among gut microbiota, UA transporters, and purine metabolism
The UA transporter ABCG2 transports UA from the blood to the gut, where gut microbiota can metabolize UA into allantoin. On the other hand, fluctuations in intestinal metabolites lead to an increase in pathogenic bacteria. Inflammatory factors produced by pathogenic bacteria and unmetabolized UA are transported in the bloodstream and contribute to the onset of gout. Meanwhile, UA metabolism is also affected (metabolism is inhibited). UA = Uric Acid.

Paeonia lactiflora (Chishao) downregulates the NLRP3/ASC/Caspase-1 axis and modulates TLRs/JNK signaling to exert its anti-inflammatory effects (He *et al.,* 2022). *Smilax riparia* (Tufuling) exhibits dual regulation of urate metabolism by inhibiting production and promoting excretion (Mahomoodally *et al.,* 2024), whereas *Gentiana macrophylla* (Qinjiao) integrates uricosuric, anti-hyperuricemic and anti-inflammatory actions through multi-target mechanisms (Xu *et al.,* 2021). Collectively, these agents underscore the unique advantages of TCM in the treatment of gout, leveraging multi-component and multi-target approaches.

Gut microbiota and its role in gout pathogenesis

The gut microbiota serves as a critical modulator of human physiology, with increasing evidence implicating its dysregulation in the pathogenesis of gout. This inflammatory arthropathy, characterized by monosodium urate (MSU) crystal-induced synovitis, primarily arises from chronic hyperuricemia. As research into the regulatory effects of gut microbiota on human health progresses, the relationship between gut microbiota and hyperuricemia has become increasingly apparent. Recent studies have indicated potential associations between gut flora composition and gouty arthritis (Chu *et al.,* 2021). The gut microbial ecosystem influences UA metabolism, inflammatory responses and disease development through multiple pathways, establishing it as a novel therapeutic target for gout management. Figure 3 illustrates the relationship between gut microbiota, UA transport and hyperpurine metabolism during gout development.

Gut microbiota-mediated modulation of UA metabolism

The gastrointestinal tract harbors a highly diverse microbiota that synergistically interacts with the intestinal epithelial barrier, microbial-derived metabolites and gut-associated lymphoid tissue, forming an integrated ecosystem that is critically involved in metabolic regulation. Approximately two-thirds of UA is excreted through renal elimination, while the remainder is primarily eliminated via feces or further catabolized by gut microbiota (Hosomi *et al.,* 2012). In patients with gout and impaired renal excretion pathways, the intestinal elimination route becomes the predominant means of UA clearance (Pan *et al.,* 2020). Humans lack functional urate oxidase due to a nonsense mutation in exon 2, which normally converts UA to the more soluble allantoin. Current research suggests that the human gut microbiota may have evolved a compensatory purine degradation pathway as an adaptive mechanism, capable of converting UA into allantoin to maintain UA homeostasis (Vieira *et al.,* 2015).

ABCG2, also known as breast cancer resistance protein, is a high-capacity urate transporter that facilitates the efflux of UA from the bloodstream into the intestinal lumen. In

established murine hyperuricemia models, ABCG2 knockout mice exhibited persistently elevated serum UA levels and significantly reduced intestinal UA clearance(Ichida *et al.,* 2012). Following its secretion into the gut, UA undergoes rapid microbial metabolism by gut microbiota, including species such as *Escherichia coli* and *Lactobacillus* (Crane, 2013). Current research has elucidated the crucial role of gut microbiota in modulating UA metabolism through two primary mechanisms: First, specific bacterial species directly participate in purine metabolism - for instance, E. coli secretes xanthine dehydrogenase (a key enzyme in purine oxidative metabolism) (Palfey *et al.,* 2001). Additionally, gut bacteria belonging to the phyla *Bacillota*, *Fusobacteriota* and *Pseudomonadota*, among others, can utilize various purines, including UA, as carbon and energy sources for anaerobic metabolism (Kasahara *et al.,* 2023). Evidence suggests that certain strains of *Lactobacillus* may participate in UA metabolism by degrading purine nucleosides or UA, potentially converting it into allantoin. For instance, *Limosilactobacillus reuteri HCS02-001* and *Lacticaseibacillus paracasei HCS17-040* exhibit robust purine nucleoside degradation activity *in vitro*, as demonstrated in cell-based assays using cultured bacterial strains incubated with purine substrates (Hussain *et al.,* 2024). *Lactobacillus casei ZM15* demonstrated a significant reduction in serum UA levels in a potassium oxonate (PO)- and high-purine diet-induced hyperuricemic rat model following 14 days of oral administration (Punjwani *et al.,* 2024). Specifically, after 7 days of treatment, serum UA levels in the ZM15 group decreased significantly compared to the hyperuricemic model group ($P < 0.01$) and a further significant reduction was observed after 14 days ($P < 0.05$). The strain's UA-lowering effect appears mechanistically linked to the intracellular catabolism of purine precursors. Mass spectrometry analysis detected elevated intracellular levels of purine intermediates - xanthine (0.040-0.063 μmol/L), hypoxanthine (0.033-0.058 μmol/L) and guanine (0.439-0.858 μmol/L) - at 2 to 24 hours post-incubation, all significantly higher than in control cells ($P < 0.01$), while UA and allantoin remained undetectable intracellularly or extracellularly. Additionally, degradation assays confirmed that nucleotide and nucleoside breakdown occurred intracellularly, as cell lysates - but not cell-free supernatants - exhibited enzymatic activity (Punjwani *et al.,* 2024). These findings indicate that such strains may regulate UA homeostasis by catabolizing UA precursors intracellularly - as evidenced by mass spectrometry detection of elevated intracellular purine intermediates (xanthine, hypoxanthine, guanine) without detectable UA or allantoin - or by competing with intestinal epithelial cells for purine absorption, thereby reducing systemic UA production.

In addition, *Lactobacillus spp.* have been shown to suppress xanthine oxidase (XO) activity via an SCFA dependent mechanism, rather than a β-lactam-dependent one, as demonstrated *in vitro* using bacterial culture supernatants and enzyme activity assays, with subsequent validation in hyperuricemic mouse models(Ni *et al.,* 2021). A recent study revealed that the anaerobic 2,8-dioxopurine pathway is involved in purine degradation by gut bacteria. This pathway uses a novel selenium-dependent enzyme, 2,8-dioxopurine dehydrogenase (DOPDH), along with seven other enzymes, to link purine metabolism with ATP production and SCFA generation. These findings were derived from *in-vitro* biochemical assays using isolated bacterial strains and recombinant enzymes, complemented by metabolomic and genomic analyses(Liu *et al.,* 2025).

Second, certain gut microbes (e.g., *Akkermansia muciniphila*) can modulate the expression ($p < 0.001$ vs. Model) of renal urate transporters (ABCG2, URAT1, GLUT9) to influence UA excretion. This mechanism has primarily been demonstrated in mouse models, where colonization or supplementation with A. muciniphila altered the mRNA and protein levels of transporters in renal tissues, subsequently affecting serum and urinary UA concentrations (Zhang *et al.,* 2022). However, human clinical data supporting this specific mechanism remain limited. Experimental evidence from a rodent study indicates that fecal microbiota transplantation (FMT) from hyperuricemic donors to normouricemic recipients significantly elevates serum UA levels in recipient rats within three weeks post-transplantation, thereby supporting a causal role of gut microbiota in hyperuricemia (Liu *et al.,* 2020). In a human pilot study involving 11 patients with acute or recurrent gout, washed microbiota transplantation (WMT)-a refined form of FMT resulted in a statistically significant reduction in serum UA levels ($p = 0.031$) and marked improvements in clinical symptoms, including decreased frequency and duration of gout flares ($p < 0.01$) (Xie *et al.,* 2022). The rodent study employed a controlled design, wherein recipient rats received microbiota from either hyperuricemic or normal donors, with UA levels measured after three weeks; no adverse events were reported (Liu *et al.,* 2020). The human pilot study was an open-label, single-arm trial with a median follow-up of 12 weeks. Donors were rigorously screened healthy adults. Following WMT, biomarkers of intestinal barrier integrity (DAO, endotoxin) also improved significantly ($p < 0.05$), suggesting restoration of gut barrier function. No serious adverse events were reported, consistent with WMT's favorable safety profile (Xie *et al.,* 2022). These findings indicate that gut microbiota play a pivotal role in UA homeostasis and gout pathogenesis through enzymatic regulation and transporter intervention mechanisms.

Effects of the gut microbiota metabolite butyrate on gout

In addition to its direct effects on urate excretion via XO activity and tubular transport systems, the gut microbiota exhibits indirect urate-modulating properties through its

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metabolic output. Chief among these are SCFAs such as butyrate and propionate, which are principal end-products of microbial fiber catabolism and significantly influence UA metabolic pathways. The regulatory effect of butyrate on UA has been widely studied. Numerous gut microorganisms are capable of producing butyrate, with key producers primarily belonging to the phylum Firmicutes. Notable producers include *Faecalibacterium prausnitzii*, *Eubacterium rectale*, various species of the genus *Roseburia*, *Ruminococcus bromii* and *Clostridium chartatabidum* (Baxter *et al.,* 2019; Hays *et al.,* 2024).

Recent studies suggest that butyrate regulates UA levels through multiple mechanisms, including the enhancement of intestinal barrier function, modulation of UA transporter expression and suppression of inflammatory responses. The integrity of the intestinal barrier is critical for UA excretion; patients with hyperuricemia often exhibit intestinal barrier dysfunction, which leads to reduced UA excretion (Yang *et al.,* 2025). Emerging evidence indicates that butyrate modulates serum UA levels through multifaceted mechanisms: reinforcing intestinal barrier integrity, upregulating urate transporters and dampening gut inflammation. Intestinal barrier dysfunction in HUA is associated with diminished fecal SCFAs and impaired UA excretion. Butyrate counteracts this dysfunction by restoring expression of ZO-1, occludin and MUC2. In murine HUA models, oral sodium butyrate (200 mg·kg^{-1}·d^{-1}) reduced serum UA levels by approximately 30% while normalizing barrier protein levels (Li *et al.,* 2023). Butyrate enhances UA efflux through the PPARγ-ABCG2 and Wnt5a/β-catenin pathways. For instance, butyrate derived from *Lactobacillus johnsonii* activates Wnt5a/β-catenin signaling, which upregulates intestinal ABCG2, thereby promoting UA excretion and reducing systemic UA levels (Han *et al.,* 2025). Concurrently, butyrate mitigates intestinal inflammation by suppressing TNF-α and IL-1β, thereby preserving mucosal architecture and metabolic homeostasis in HUA mice (Bian *et al.,* 2024). A recent murine study further corroborates the anti-inflammatory and urate-lowering effects of butyrate in the context of age-related gout (Song *et al.,* 2025a). In this controlled experimental design, FMT from young donor mice (n = 8-10 per group) to aged recipient mice (20–24 months old) significantly suppressed activation of the NLRP3 inflammasome pathway and modulated UA metabolism. Donor criteria were based on age (young, 8-12 weeks) and the absence of metabolic or inflammatory disorders; no adverse events were reported. The intervention lasted for four weeks post-transplantation, during which serum UA levels in aged recipients decreased by approximately 35% compared to non-transplanted aged controls. Post-FMT, 16S rRNA sequencing revealed a significant increase in beneficial genera, particularly *Bifidobacterium* and *Akkermansia*, alongside enhanced expression of genes involved in butanoate metabolism. Exogenous oral butyrate supplementation (150 mg/kg/day) in aged mice replicated these effects. It significantly attenuated MSU-induced joint inflammation and further reduced serum UA by an additional 22% compared to FMT alone (Song *et al.,* 2025a). Histological and cytokine analyses confirmed reduced synovial infiltration and lower levels of IL-1β and TNF-α, supporting butyrate's dual role in suppressing inflammation and promoting UA excretion. These findings underscore the significance of gut microbiota-derived metabolites, particularly butyrate, in modulating UA levels and potentially ameliorating the pathogenesis of gout.

Impact of gut dysbiosis on gout pathogenesis

The homeostasis and disruption of gut microbiota play a critical role in the initiation and progression of gout. In healthy individuals, the gut microbiota maintains stable diversity and establishes complex ecological networks. Conversely, microbial dysbiosis has been shown to significantly contribute to the pathogenesis of gout. Comparative studies have identified substantial alterations in both the diversity and composition of gut microbiota in gout patients compared to healthy controls, characterized by notable reductions in beneficial bacterial species. Particularly noteworthy is the decreased abundance of *Lactobacillus* species, which typically maintain intestinal barrier function and modulate immune responses. This reduction may be linked to impaired gut barrier integrity and an increased release of inflammatory mediators (Ul-Haq *et al.,* 2022). Other diminished protective bacteria include *Bifidobacterium*, which regulates microbial equilibrium and inhibits pathogenic overgrowth (Chen *et al.,* 2023a) as well as butyrate-producing *Faecalibacterium prausnitzii*, known for its anti-inflammatory and immunomodulatory effects (Renton *et al.,* 2025). Furthermore, gout patients exhibit significant enrichment of various pathogenic bacteria in their gut microbiota, exacerbating UA metabolism dysregulation and inflammatory responses. Table 1 summarizes the characteristic changes in both beneficial and pathogenic bacterial populations observed in the gut microbiome of gout patients. These findings collectively highlight the crucial role of gut microbial imbalance in the development of gout through multiple interconnected mechanisms involving both the depletion of protective microbiota and the overgrowth of pathogenic bacterial.

The herbal compound BBR may ameliorate gout through modulation of gut microbiota

BBR exhibits anti-gout effects

BBR, a quaternary ammonium salt isoquinoline alkaloid, possesses a complex polycyclic structure characterized by the molecular formula $C_{20}H_{18}NO_4^+$3. The presence of multiple functional groups, including methyl, hydroxyl and methoxy groups in its structure, endows BBR with unique physical and chemical properties. BBR is extracted from medicinal plants such as Coptis chinensis (huanglian) and *Phellodendron amurense* (huangbai).

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Table 1: Gout influences alterations in gut microbiota.

Type	Name	Abundance	Function	Reference
Beneficial	*Lactobacillus*	↓	Participates in xanthine oxidase generation, which enzymatically mediates the oxidative degradation of UA to urea.	(Ul-Haq *et al.*, 2022)
	Bifidobacterium	↓	It produces organic acids, lowers the intestinal pH, inhibits the growth of harmful bacteria, and secretes antibacterial substances that directly combat pathogenic bacteria, promote anti-inflammatory response, and maintain immune balance.	(Chen *et al.*, 2023a)
	Faecalibacterium prausnitzii	↓	The bacteria that produce the typical short chain fatty acids (SCFA) in the human gut have anti-inflammatory properties and promote gut health by producing butyrate.	(Renton *et al.*, 2025)
	Akkermansia muciniphila	↓	It feeds on mucin in the intestinal mucus layer, promotes regeneration and repair of the mucus layer, maintains a healthy mucus layer, and produces beneficial metabolites.	(Shirvani-Rad *et al.*, 2023)
	Oscillibacter	↓	Produces butyrate, which helps reduce inflammation and strengthen the intestinal barrier.	(Song *et al.*, 2025b)
	Butyricicoccus	↓	It produces butyrate, maintains intestinal mucosal barrier function, promotes the expression of tight junction protein, strengthens intestinal physical barrier, and has anti-inflammatory characteristics.	(Chu *et al.*, 2021)
	Clostridium butyricum	↓	By regulating miR-146a expression and macrophage polarization, it has the potential to combat gouty arthritis.	(Chen *et al.*, 2024a)
Pathogenic	*Alistipes*	↑	Promotes inflammatory response by producing lipopolysaccharide (LPS), which aggravates kidney damage.	(Feng *et al.*, 2023)
	Prevotella	↑	May be involved in the regulation of UA metabolism enzymes, and then affect the level of UA.	(Lee and Park, 2022)
	Klebsiella pneumoniae	↑	May increase the host's sensitivity to inflammation caused by urate crystal deposition.	(Chen *et al.*, 2023a)
	Bacteroides	↑	By affecting UA metabolism and inflammatory response, gout symptoms are aggravated.	(Chu *et al.*, 2021)
	Fusobacterium	↑	By affecting uric metabolism and leads to elevated serum UA levels, which may trigger inflammatory responses and promote the pathological process of gout.	(Shirvani-Rad *et al.*, 2023)
	Helicobacter	↑	Destroys the balance of intestinal flora, activates the NLRP3 inflammasome pathway, increases the level of pro-inflammatory factors, and induces acute attacks.	(Lin *et al.*, 2023)

Figure 4 illustrates several Chinese herbal plants containing BBR. As a phytochemical with broad pharmacological activities, BBR has demonstrated therapeutic potential across various diseases. Emerging evidence supports its applications in Alzheimer's disease, infectious diseases, metabolic disorders, and inflammatory conditions (Yang *et al.,* 2024; Xiao *et al.,* 2025; Baska *et al.,* 2021; Wei *et al.,* 2023). In recent years, BBR has demonstrated significant therapeutic potential in managing gout and related disorders. Within TCM, several BBR-containing compound decoctions, such as Simiao Pill, Jinhuang ointment and Gout decoction, have exhibited notable anti-gout effects (Wang *et al.,* 2010; Wang and Wang, 2020).

The mechanisms underlying BBR's therapeutic effects in gout are multifaceted. Central to its anti-gout efficacy is the dual modulation of UA homeostasis, which involves the inhibition of hepatic UA biosynthesis and the promotion of renal UA excretion.

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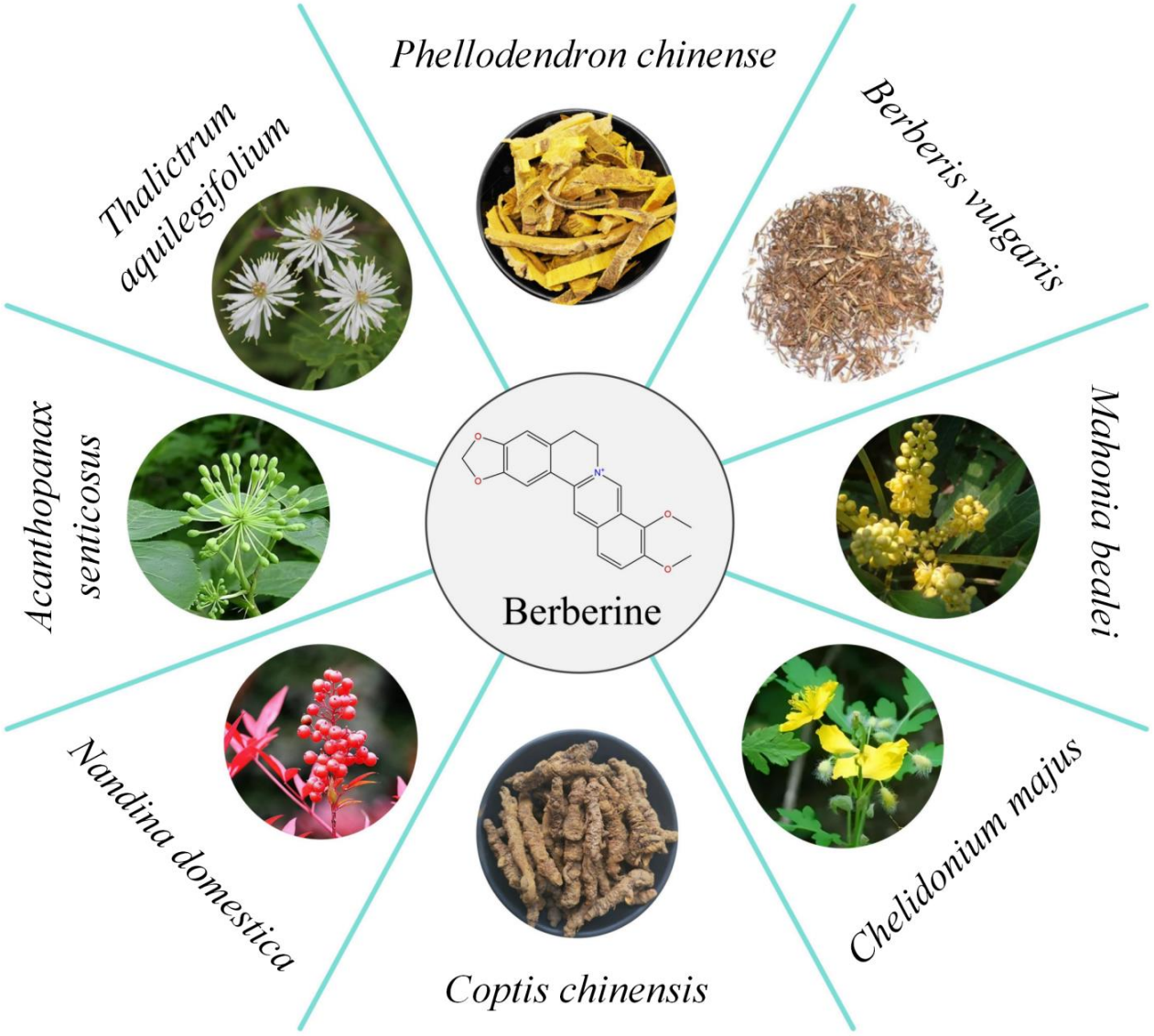

Fig. 4: The herbal source of berberine

As a critical regulator of purine metabolism, XO catalyzes the terminal steps of UA generation. BBR potently suppresses XO activity, thereby attenuating systemic UA production. Notably, BBR is the most abundant and bioactive constituent in Phellodendron amurense. In a murine model of hyperuricemia induced by intraperitoneal injection of PO at a dose of 300 mg/kg combined with intragastric administration of hypoxanthine (HX, 300 mg/kg), oral treatment with ethanol extracts of P. amurense at doses ranging from 200 to 800 mg/kg significantly reduced serum UA, serum creatinine (Cre) and blood urea nitrogen (BUN) levels ($p < 0.01$). Concomitantly, liver UA levels and XOD activity were significantly decreased ($p < 0.01$). These findings demonstrate that the extract of *P. amurense* predominantly containing BBR-exerts significant urate-lowering and nephroprotective effects in hyperuricemic mice, likely through the inhibition of XOD activity (Xu *et al.*, 2022). Furthermore, metabolites of BBR, such as oxyberberrubine (OBR), exhibit similar inhibitory effects. In a relevant study, a hyperuricemic mouse model was established via induction with PO and hypoxanthine (HX). Subsequently, the mice were administered OBR by gavage at doses of 5 mg/kg, 10 mg/kg and 20 mg/kg daily for one consecutive week. The results demonstrated that OBR significantly reduced levels of serum UA, Cr and BUN in the mice (all $p < 0.01$) (Zhong *et al.*, 2023). Additionally, in a murine model of hyperuricemia induced by intraperitoneal injection of PO (250 mg/kg) combined with intragastric administration of hypoxanthine (500 mg/kg), treatment with BBR at doses of 50 and 100 mg/kg/day significantly reduced serum levels of UA, Cr and BUN ($p < 0.01$). Moreover, the administration of BBR significantly downregulated the expression of the urate reabsorption protein URAT1 ($p < 0.01$). Molecular docking analyses further revealed a strong binding affinity between BBR and URAT1, indicating that BBR can promote UA

elimination through this regulatory mechanism (Li *et al.,* 2021). Accumulating evidence demonstrates the anti-inflammatory potential of BBR in gouty arthritis, with both clinical and experimental studies providing mechanistic insights. In one such study, peripheral blood mononuclear cells (PBMCs) were isolated from 24 patients with acute-phase (AP) gout, 41 patients with non-acute-phase (NAP) gout and 30 healthy controls (HCs). Additionally, macrophages derived from the spontaneously immortalized monocytic cell line (THP-1) were utilized to complement the in vitro analysis. These cellular models were treated with varying concentrations of BBR under stimulation with MSU at 100 μg/mL. Specifically, PBMCs and THP-1-derived macrophages were administered either 25 μmol/L BBR alone or a combination of MSU plus BBR at concentrations of 10, 25, or 50 μmol/L. The results indicated that BBR mediates significant anti-inflammatory effects in gouty arthritis through selective modulation of critical signaling pathways, notably the TLR4/NF-κB axis and NLRP3 inflammasome activation. This targeted intervention effectively reduces the secretion of pro-inflammatory mediators, particularly IL-1β and IL-18, leading to a substantial suppression of the inflammatory cascade(Dang *et al.,* 2023). In exploring the renoprotective mechanisms of BBR under hyperuricemic conditions, a study utilized Uox gene-knockout (Uox-KO) mice on a C57BL/6J background as a model for hyperuricemia and UA nephropathy. These mice were administered BBR via gavage at a dose of 100 mg/kg per day over a continuous four-week treatment period. The results indicated that BBR modulates macrophage polarization through the AMPK signaling pathway, effectively reducing M1 macrophage infiltration and the resultant renal damage (Gong *et al.,* 2024).

Effects of BBR on gut microbiota

BBR has demonstrated significant therapeutic efficacy in various intestinal disorders, primarily due to its regulatory effects on gut microbiota. In cases of ulcerative colitis (UC) and inflammatory bowel disease (IBD), BBR alleviates intestinal inflammation by inhibiting the PI3K/AKT/mTOR signaling pathway and modulating the composition of gut microbiota (Meng *et al.,* 2024; Kim *et al.,* 2024).

The primary impact of BBR on gut microbiota is its capability to restructure microbial communities. Numerous studies indicate that BBR restores the gut microecological balance by enhancing the population of beneficial bacteria while diminishing harmful species, thereby improving intestinal barrier function and alleviating inflammatory responses. In a murine model of colitis, BBR reinstated gut microbial homeostasis by increasing the abundance of *Lactobacillus*, *Verrucomicrobia*, *Bacteroides* and *Akkermansia muciniphila* (Li *et al.,* 2024). Clinical studies involving type 2 diabetes (T2D) have shown that BBR fosters the growth of beneficial bacteria (e.g., *Bacteroides*, *Bifidobacterium* and *Lactobacillus*) while reducing pathogenic bacteria (e.g., *Escherichia coli*), thus enhancing glycemic control, lowering serum lipids and mitigating chronic inflammation. Notably, BBR exhibits enhanced therapeutic efficacy when combined with probiotics (Chen *et al.,* 2023c). Inflammatory bowel disease (IBD) disrupts the balance of gut microbiota, exacerbating intestinal inflammation. A composite of fructan nanoparticles and BBR (BBRNPs) effectively modulated microbial dysbiosis in colitis, restoring the relative equilibrium between the detrimental Enterobacteriaceae and Shigella and the beneficial *Ruminococcaceae* and *Akkermansiaceae* (Pan *et al.,* 2023). This regulatory mechanism also operates in the context of gout. In a study investigating BBR's effects on PO-induced hyperuricemia in mice, BBR (100 mg/kg/day) ameliorated hyperuricemia by modulating gut microbiota, notably increasing the abundance of beneficial bacteria such as *Lactobacillus* and *Akkermansia* (Shan *et al.,* 2022). Similarly, another study examining BBR's influence on UA metabolism and gut microbiota in rats found that BBR (200 mg/kg/day) elevated Bifidobacterium levels while reducing the abundance of Prevotella and Bacteroides (Chen *et al.,* 2023b).

The alterations in microbial composition induced by BBR subsequently affect the levels of microbial metabolites, such as butyrate. In one study, BBR activated PPARδ and promoted gut microbiota-derived butyrate to suppress hepatocellular carcinoma proliferation (Shou and Shaw, 2023). Notably, butyrate plays a crucial role in UA metabolism. These findings suggest that BBR can partially restore gut dysbiosis in gout patients, enhancing intestinal UA metabolism and further reducing serum urate levels to alleviate gout symptoms.

Additionally, fig. 5 illustrates the chemical structures of several secondary metabolites of BBR. The metabolic products of BBR by gut microbiota may further regulate UA levels, reflecting that BBR interacts bidirectionally with the gut microbiota: while BBR modulates microbial composition and metabolism, the gut microbiota metabolizes BBR into more bioavailable forms, such as dihydroberberine (DHB). Specifically, microbial nitroreductases catalyze the reduction of BBR to DHB, which exhibits approximately five-fold higher intestinal absorption compared to its parent compound. After absorption, DHB is re-oxidized back to BBR in intestinal tissues before entering systemic circulation (Feng *et al.,* 2015). In hyperuricemic mice, DHB effectively binds to the active site of XOD, significantly inhibiting its enzymatic activity. DHB (25 mg/kg, 50 mg/kg) demonstrates dose-dependent nephroprotective effects, manifested by reduced serum Cre and BUN levels (P<0.01), decreased release of proinflammatory cytokines (TNF-α, IL-1β, IL-6 and IL-18) and amelioration of renal histopathological damage. The therapeutic mechanisms involve downregulation of renal URAT1, GLUT9 and NOD-related gene expressions (Xu *et al.,* 2021).

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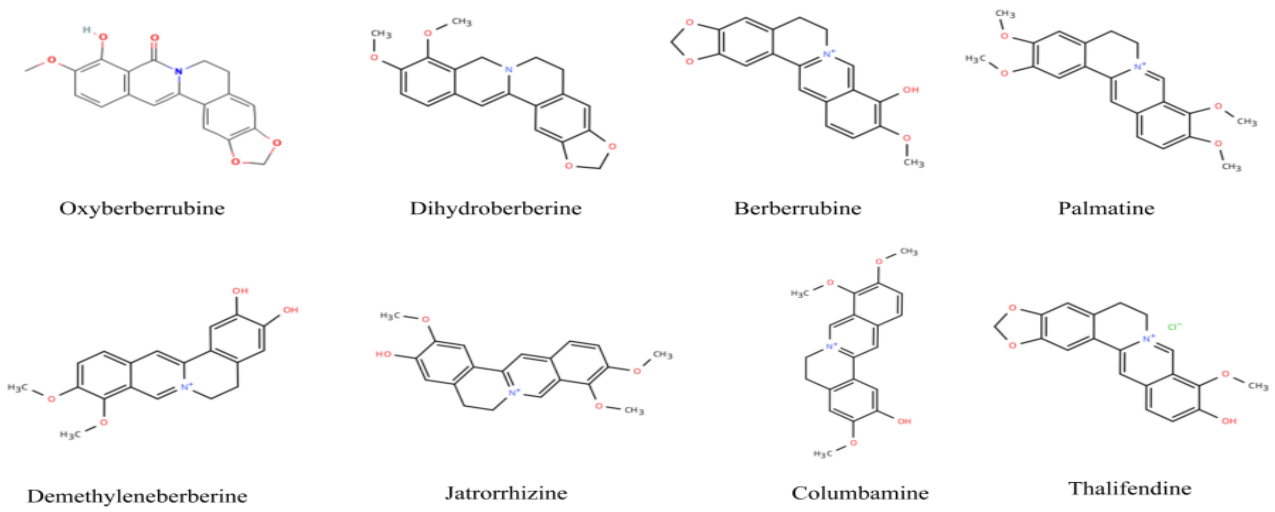

Fig. 5: Chemical structure of eight secondary metabolites of BBR.

Berberrubine (BBB), an active metabolite of BBR, exhibits significant antihyperuricemic and nephroprotective effects in a hyperuricemic mouse model induced by PO and HX. Treatment with BBB at doses of 6.25, 12.5 and 25.0 mg/kg/day results in a dose-dependent reduction in serum UA levels (P<0.01) accompanied by notable improvements in renal function parameters, including UA, BUN and CRE (all P<0.01), alongwith attenuation of renal pathological damage. The therapeutic effects are mediated through multiple mechanisms involving inhibition of hepatic XOD activity, modulation of urate transporters (downregulation of GLUT9 and URAT1 versus upregulation of OAT1/3 and ABCG2) and suppression of the activation of the JAK2/STAT3 signaling pathway. BBB treatment significantly reduces circulating levels of proinflammatory cytokines, including IL-1β, IL-6 and TNF-α (Lin *et al.*, 2021). Similarly, OBR demonstrates significant urate-lowering and renoprotective effects in hyperuricemic mice. OBR effectively reduces serum UA levels and inhibits hepatic XOD and ADA activities, with marked downregulation of XOD expression at both mRNA and protein levels. Concurrently, OBR improves renal function parameters, as evidenced by reduced Cre and BUN levels, decreased inflammatory cytokines (TNF-α, IL-1β, IL-6, and IL-18) and repaired renal tissue damage. The therapeutic mechanisms involve the downregulation of renal URAT1, GLUT9, NLRP3, ASC and caspase-1 expressions (all P<0.01) (Zhong *et al.*, 2023). This biotransformation not only significantly enhances BBR's bioavailability but also provides novel insights into its broad pharmacological mechanisms (Feng *et al.*, 2015). This mutual interaction enhances BBR's therapeutic potential in metabolic disorders, inflammatory diseases and cancer (Cheng *et al.*, 2022; Wang *et al.*, 2022). Fig. 6 illustrates how BBR in the gut improves gout by regulating gut microbiota and other mechanisms.

Future research direction

The gut microbiota serves as a crucial ecosystem within the human body and has been shown to play a pivotal role in UA metabolism and the pathogenesis of gout. Modulating the gut microbiota not only enhances UA metabolism but may also provide novel strategies for the prevention and treatment of gout. Significant differences exist between the gut microbiota of gout patients and healthy individuals, with gout patients displaying reduced microbial diversity and a decreased abundance of anti-inflammatory bacteria such as *Lactobacillus*.

FMT, a therapeutic approach that involves transferring gut microbiota from healthy donors to patients, has demonstrated promise in restoring microbial balance. Research indicates that FMT can significantly improve UA metabolism and improve inflammatory status in patients with gout, including reductions in serum urate levels and mitigation of acute gout flare frequency and duration. Additionally, FMT has been shown to repair impaired intestinal barrier function (Xie *et al.*, 2022). However, the long-term safety and efficacy of FMT require further validation (Dawwas *et al.*, 2022) and patient acceptance remains low due to limited understanding of gut microbiota dynamics (Benech *et al.*, 2022). Emerging evidence suggests that analyzing gut microbiota profiles, rather than relying solely on serum urate measurements, may enable earlier and more precise gout prediction (Guo *et al.*, 2016).

Probiotics have emerged as a natural and safe therapeutic option with considerable potential in gout and hyperuricemia management. Strains such as *Lacticaseibacillus casei JS-2*, *Limosilactobacillus reuteri HCS02-001* and *Lactobacillus paracasei 259* have demonstrated notable efficacy in regulating urate metabolism, reshaping gut microbiota and exerting anti-inflammatory and immunomodulatory effects (Hussain *et al.*, 2024; Wu *et al.*, 2025; Bi *et al.*, 2024). BBR, a natural alkaloid, has shown significant benefits in modulating urate metabolism and gut microbiota.

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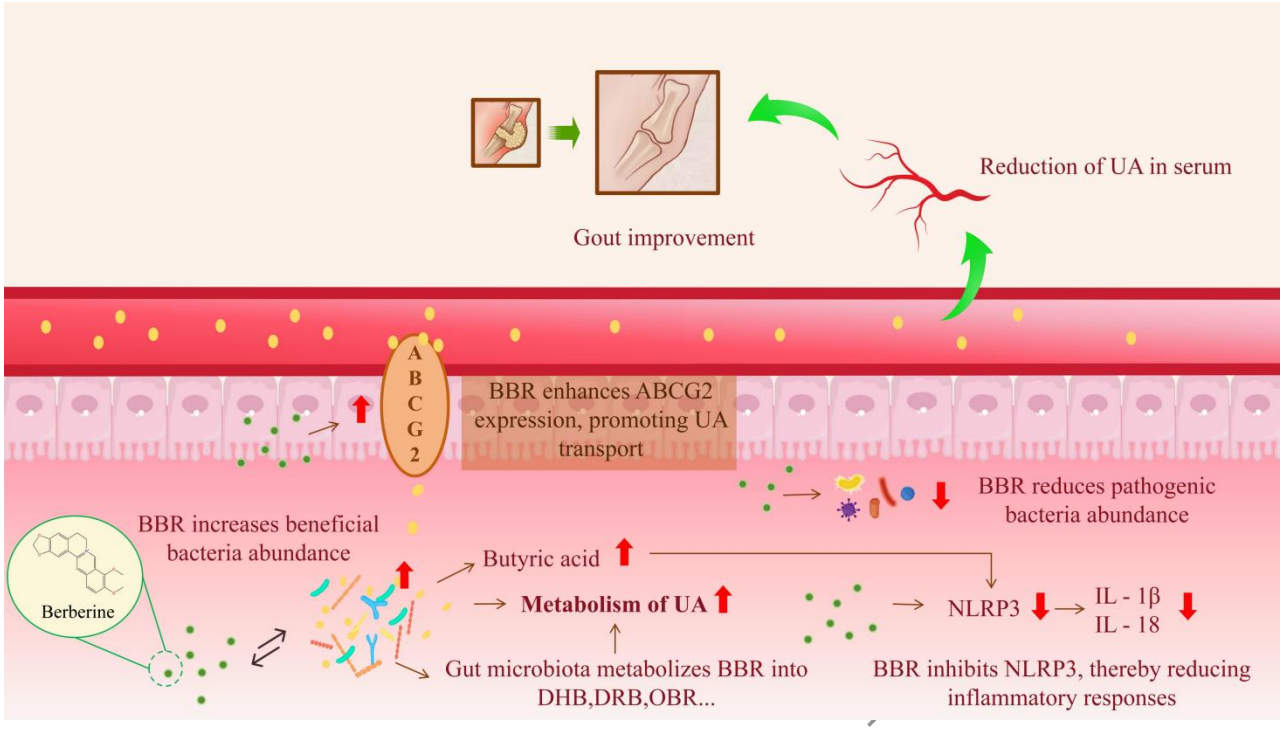

Fig. 6: BBR alleviates gout through multiple intestinal mechanisms.
BBR increases the abundance of beneficial intestinal bacteria while reducing the abundance of pathogenic bacteria; Gut microbiota metabolizes BBR into products such as DHB, DRB, and OBR. On one hand, this promotes the production of butyric acid to enhance uric acid (UA) metabolism. On the other hand, BBR can up - regulate the expression of ABCG2 protein, promoting the transport and excretion of UA; BBR can inhibit the activation of the NLRP3 inflammasome, thereby reducing the levels of pro - inflammatory factors IL - 1β and IL - 18 to alleviate the inflammatory response; The enhanced metabolism and transport of UA, along with the alleviated inflammation, collectively reduce the UA level in serum, ultimately improving gout symptoms. BBR, Berberine; DHB, Dihydroberberine; DRB, Dihydro-berberrubine; OBR, Oxyberberrubine; UA, Uric Acid.

Synergistic effects have been observed when BBR is combined with probiotics in treating various conditions, including diarrhea, type 2 diabetes, obesity, metabolic syndrome and colon cancer (He *et al.*, 2024; Kasahara *et al.*, 2023; Shehata *et al.*, 2022; Huang *et al.*, 2022). This suggests that BBR-probiotic co-therapy may hold substantial promise for gout treatment. BBR creates a favorable gut microenvironment for probiotic colonization and activity, while probiotics may amplify BBR's urate-lowering effects by enhancing intestinal barrier integrity and reducing inflammation. Nevertheless, current evidence is primarily derived from animal studies, necessitating clinical trials to validate efficacy and safety in humans.

Despite its therapeutic potential, BBR's clinical application is hindered by its low oral bioavailability (<1%), which is attributable to factors such as poor solubility, low permeability, P-glycoprotein (P-gp) efflux and extensive hepatic/intestinal metabolism. To address these challenges, advanced strategies such as novel drug delivery systems, structural modifications and absorption enhancers have been explored (Cui *et al.*, 2024). In animal models (rats and mice), gout and hyperuricemia research has yielded promising results with novel BBR-loaded delivery systems. Specifically, manganese-doped albumin-gelatin nanocomposite hydrogels (MAGN) loaded with BBR (Ber-MAGN) exhibit a sustained release effect that significantly improves the bioavailability of BBR and this formulation has been shown to significantly alleviate gouty arthritis in rats (Sun *et al.*, 2023). Similarly, sodium taurocholate (STC)-based self-assembled BBR nanoparticles (STC@BBR-SANPs) offer advantages in drug distribution: compared with free BBR, STC@BBR-SANPs significantly increase the distribution concentration of BBR in multiple organs, with higher BBR levels detectable especially in the liver, heart, lungs, kidneys and intestines. This nanoparticle system also improved urate levels and reduced renal injury in hyperuricemic mice (Qin *et al.*, 2023). Collectively, these findings provide optimized delivery approaches for clinical translation.

Finally, BBR, as a component derived from TCM, has shown promise in combination therapies with conventional drugs. Preliminary evidence from clinical studies indicates that BBR combined with other agents exhibits synergistic efficacy in treating conditions such as hyperuricemia, gout, diabetes mellitus and metabolic syndrome, with favorable

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safety profiles. The drug-drug interactions primarily manifest as enhanced metabolic regulation and improved bioavailability, with no significant toxic reactions reported. Its multi-target pharmacological effects and low toxicity complement agents like benzbromarone, amlodipine, and silymarin (Cai, 2017; Huang, 2013; Wang *et al.*, 2018; Guarino *et al.*, 2017).

CONCLUSION

In summary, BBR demonstrates therapeutic potential for hyperuricemia and gout by regulating UA metabolism, improving gut microbiota structure and suppressing inflammatory responses. However, current studies are primarily based on animal models, and there is a lack of large-scale, long-term and multicenter clinical trial data in humans. This gap makes it difficult to fully validate the clinical efficacy and safety of BBR in the treatment of gout. Regarding BBR's safety, although its toxicity is low, potential issues remain. Long-term high-dose use may cause adverse reactions such as gastrointestinal discomfort and abnormal liver and kidney function, and its interactions with other drugs remain unclear. As a natural compound, BBR's multifaceted mechanisms offer new possibilities for gout treatment, warranting further exploration and application. Looking ahead to future clinical applications, as a component derived from TCM, BBR possesses multi-target pharmacological effects and low toxicity, holding promise for combination use with conventional drugs to enhance urate-lowering efficacy and improve comorbidities such as metabolic disorders and hypertension. Meanwhile, to address the issue of BBR's low oral bioavailability, advanced strategies such as developing novel drug delivery systems, conducting structural modifications and using absorption enhancers can be adopted to improve its bioavailability, providing new approaches for gout treatment. Additionally, combined therapy with BBR and probiotics also shows great potential. Future clinical studies are needed to further verify its efficacy and safety and promote the widespread application of BBR in gout treatment.

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None.

Authors' contributions
Guoming Wang: Conceptualization, writing – review and editing, writing–original draft, validation, project administration and investigation; Yanmei Wu: Project administration and investigation; Qing Qi and Jing Yu: Investigation; Mingli Gao and Tianye Deng: Visualization. Pengyuan Sun: Conceptualization, writing–review and editing.

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Data availability statement
The datasets generated during the current study are available from the corresponding author on reasonable request.

Ethical approval
Not applicable.

Conflict of interest
The authors declare no conflict of interest.

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