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Review

Concurrent management of gout and type 2 diabetes mellitus: combined therapy insights

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ABSTRACT

Gout and type 2 diabetes mellitus (T2DM) are prevalent metabolic disorders with a significant bidirectional association. The review article focuses on the interplay between serum uric acid and glucose/lipid metabolism, innate immunity, inflammation, and gut microbiota, proposing simultaneous treatment strategies. Gout, caused by monosodium urate crystal deposition due to hyperuricaemia, and T2DM, induced by high-fat, high-sugar diets disrupting metabolic balance, share common pathological mechanisms. Elevated uric acid levels contribute to lipid and glucose metabolic disorders, activate inflammatory pathways like the nucleotide-binding oligomerization domain-like receptor 3 inflammasome, and trigger innate immune responses. The gut microbiota also plays a significant role in both metabolic diseases, with dysbiosis affecting uric acid excretion and insulin resistance. This review article highlights promising therapeutic approaches, including the use of sodium-glucose cotransporter-2 inhibitors which reduce serum uric acid and lowers gout risk alongside glycaemic control. Additionally, targeting inflammatory pathways such as interleukin-1β offers potential benefits for both conditions. Combined pharmacological therapies, dietary adjustments, and gut microbiota interventions present new directions for simultaneous management. This review article provides a comprehensive analysis of the links between gout and T2DM, offering novel insights for clinical practice and future research.

1. Introduction

Gout is an acute or chronic inflammatory arthritis caused by monosodium urate (MSU) crystals from supersaturated hyperuricemic body fluids depositing in and about peripheral joints and surrounding tissues such as cartilage, tendons, and ligaments [1]. It recurs and, if untreated, can damage joints and impair quality of life [2]. Hyperuricaemia (i.e. high level of uric acid or urate in the blood), a gout precursor, is common

Abbreviations: ACC1, acetyl-CoA carboxylase 1; AKT, serine/threonine kinase 1; AMPK, AMP-activated protein kinase; AP-1, activated protein-1; FAS, fatty acid synthase; FMT, faecal microbiota transplantation; GP130, glycoprotein 130; GSDMD, gasdermin D; IL-1α, interleukin-1α; IL-1β, interleukin-1β; IL-6, interleukin-6; IRS-1, insulin receptor substrate-1; JAK2, Janus kinase 2; JNK, c-Junn-terminal kinase; LPCAT3, lysophosphatidylcholine acyltransferase 3; MSU, monosodium urate; NFκB, nuclear factor kappa-light-chain-enhancer of activated B; NLRP3, nucleotide-binding oligomerization domain-like receptor 3; NSAIDs, non-steroidal anti-inflammatory drugs; ROS, reactive oxygen species; SGLT2, sodium-glucose cotransporter-2; SREBP-1c, sterol regulatory element binding transcription factor 1c; STAT3, signal transducer and activator of transcription 3; T2DM, type 2 diabetes mellitus; TCM, traditional Chinese medicine; TLR, Toll-like receptors; TNF, tumor necrosis factor; TORC2, transducer of regulated cAMP response element-binding protein activity 2; XOD, xanthine oxidase.

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in developing countries with high obesity and alcohol consumption rates [3]. Globally, gout and hyperuricaemia prevalence is rising, posing a significant public health issue [4]. In mainland China, the prevalence of gout (with hyperuricaemia) is 13.3% [4]. Though gout is non-fatal, it's linked to hypertension, insulin resistance, diabetes, kidney disease, cardiovascular disease, and ischaemic stroke [5]. In the United States, 74% of gout patients have hypertension, 71% chronic kidney disease, 53% obesity, 26% diabetes, 11% heart failure, 14% myocardial infarction and 10% stroke [5]. Thus, controlling high levels of uric acid or urate in the blood is crucial for treating gout and related conditions.

Diabetes, a non-communicable disease, poses a significant global health challenge, with projections indicating a prevalence exceeding 642 million by 2040 [6,7]. Over the past three decades, the number of people with diabetes worldwide has quadrupled, ranking it as the ninth leading cause of death globally [8]. Type 2 diabetes mellitus (T2DM) constitutes over 90% of diabetes cases, imposing substantial psychological and physical burdens on patients due to its necessity for long-term management without a cure [9,10]. In recent years, the co-occurrence of T2DM and gout has gained significant attention due to their shared risk factors and potential interplay. A recent *meta*-analysis of 38 studies indicated that the prevalence of type 2 diabetes among patients with gout is as high as 16.7% [11], underscoring a significant clinical overlap and supporting the bidirectional association. However, a comprehensive understanding of the intricate interplay between these prevalent metabolic disorders remains elusive, hindered by insufficient conclusive evidence, thus presenting a significant challenge for clinical treatment.

Though the bidirectional association between gout and T2DM has been widely acknowledged, the understanding of their shared pathogenesis remains incomplete. Recent research studies have unveiled the complex interplay between uric acid metabolism and glucose/lipid metabolism, inflammatory responses, and the gut microbiota, offering new insights for simultaneous treatment. For instance, emerging evidence indicates that sodium-glucose cotransporter-2 (SGLT2) inhibitors not only effectively control blood glucose levels but also significantly reduce serum uric acid or urate levels and the risk of gout flares, providing robust clinical evidence for the simultaneous management of gout and T2DM [12]. Additionally, drugs targeting inflammatory pathways, such as interleukin-1β (IL-1β), have demonstrated potential therapeutic effects on both gout and T2DM [13]. However, a systematic and comprehensive treatment framework based on their shared pathophysiological mechanisms is still lacking.

This review article aims to provide a scientific basis for the management and treatment of these two modern epidemic metabolic diseases by summarising and analysing their potential interdependence. The article will detail the pathogenesis of gout (with hyperuricaemia) and T2DM, as well as the latest research advances, and propose combined treatment strategies based on their shared pathophysiological mechanisms, offering new ideas and methods for clinical treatment. By thoroughly analysing the potential links between gout and T2DM, this study not only fills the gap in current research but also provides new directions for future research studies and clinical practice.

2. Pathogenesis of gout and type 2 diabetes mellitus (T2DM)

2.1. Gout caused by hyperuricemia

Hyperuricaemia is the principal aetiology of gout, with its pathogenesis involving excessive production or decreased renal clearance of urate [14]. Uric acid, the end product of purine metabolism, is primarily synthesised in the liver and excreted *via* the kidneys and intestines [15]. At the acid pH of urine, uric acid itself is precipitated readily as small platelike crystals that may aggregate to form gravel or stones which may cause obstructive uropathy. Lifestyle factors such as a high-purine diet, alcohol consumption, and obesity can increase serum uric acid levels, thereby leading to hyperuricaemia (Fig. 1) [3]. Additionally, genetic factors and renal dysfunction can affect the excretion of uric acid [16]. When serum uric acid levels persistently rise, urate crystals deposit in joints and surrounding soft tissues, triggering local inflammatory responses and causing gout flares [17]. These crystals activate the immune system, releasing inflammatory mediators such as IL-1β, which induce severe pain, swelling, warmth, redness, and fever [17]. The metatarsophalangeal joint of the great toe is most often involved (podagra), but the instep, ankle, knee, wrist, and elbow are also common sites.

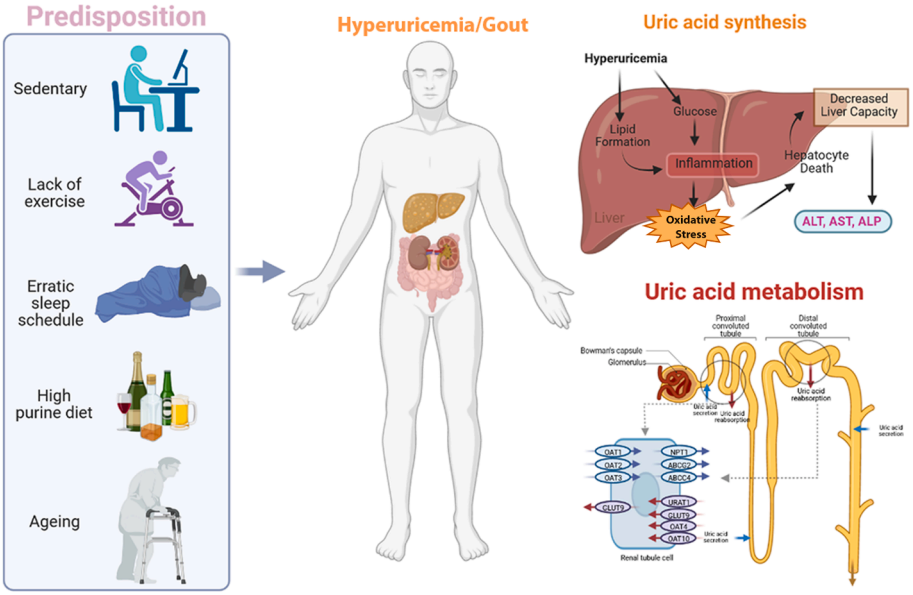


Fig. 1. Gout caused by high uric acid or urate levels in the blood. A sedentary lifestyle, lack of exercise and a high purine diet lead to elevated serum uric acid or urate levels in the body. Elevated serum uric acid interferes with glycolipid metabolism in the liver, which causes inflammation and oxidative stress in the liver and impairs liver function. In the kidney the GLUT9, URAT1 and OAT1 are responsible for the transport of uric acid. ABCC4, ATP-binding cassette transporter C4; ABCG2, ATP-binding cassette subfamily G member 2; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GLUT9, glucose transporter 9; NPT1, type 1 sodium-dependent phosphate transporter; OAT1, organic anion transporter 1; OAT2, organic anion transporter 2; OAT3, organic anion transporter 3; OAT4, organic anion transporter 4; OAT10, organic anion transporter 10; URAT1, urate transporter 1.

Research studies have shown that the interaction between serum urate crystals and cell membranes can activate the NOD-like receptor protein 3 (NLRP3) inflammasome, thereby further exacerbating the inflammatory response [18]. Therefore, controlling serum uric acid levels is crucial for the prevention and treatment of gout.

Through lifestyle interventions and pharmacological treatments, uric acid levels can be effectively reduced, thereby lowering the risk of gout flares [19]. For instance, medicines such as allopurinol and febuxostat, which inhibit uric acid synthesis, blockings an enzyme called xanthine oxidase (XOD), which is needed to make uric acid in the body controlling serum urate concentration. Both medicines offer effective treatment options for patients who have clinical signs of a build-up of crystals, including gouty arthritis (pain and inflammation in the joints) or tophi ('stones', larger deposits of urate crystals that can cause joint and bone damage) [20]. Moreover, medicines targeting inflammatory pathways are under investigation and hold promise for providing new therapeutic strategies for gout [21]. In summary, hyperuricaemia induces gout flares by triggering inflammatory responses *via* the deposition of urate crystals. Understanding this pathophysiology is vital for the development of more effective treatment regimens.

2.2. High-fat, high-sugar diet-fed induced T2DM

T2DM is a complex carbohydrate metabolic disorder with a multifactorial aetiology, encompassing lifestyle and genetic predisposition characterized clinically by hyperglycemia and insulin resistance [22]. A diet high in fat and sugar is one of the key precipitating factors for T2DM. This dietary pattern leads to an excess of energy intake, causing fat accumulation in the liver and muscles, which in turn induces IR and precipitates the onset of T2DM (Fig. 2) [23]. Research findings indicates that such a diet not only increases body weight but also directly interferes with glucose metabolism, rendering the body less responsive to insulin and thereby causing blood glucose levels to rise [24]. Under normal circumstances, the body stores glucose as glycogen for future use [25]. However, a high-fat, high-sugar diet disrupts this process. Firstly, it reduces the efficiency with which muscle tissue takes up and utilizes glucose, preventing it from entering cells for metabolism and secondly it stimulates the liver to overproduce glucose, further exacerbating hyperglycaemia [26]. Moreover, this dietary pattern leads to dyslipidaemia, with elevated levels of free fatty acids in the blood. These free fatty acids directly inhibit key molecules in the insulin signaling pathway, such as glucose transporter 4, thereby reducing glucose transport and utilization [27]. This dyslipidaemia not only affects insulin sensitivity in muscle cells but also triggers a series of inflammatory responses in the liver, further worsening insulin resistance [28].

In summary, a high-fat, high-sugar diet disrupts the body's glucose and lipid metabolic balance through multiple mechanisms, ultimately leading to the development of T2DM. This finding underscores the importance of a healthy diet in the prevention of T2DM and provides a theoretical basis for developing dietary intervention strategies for T2DM.

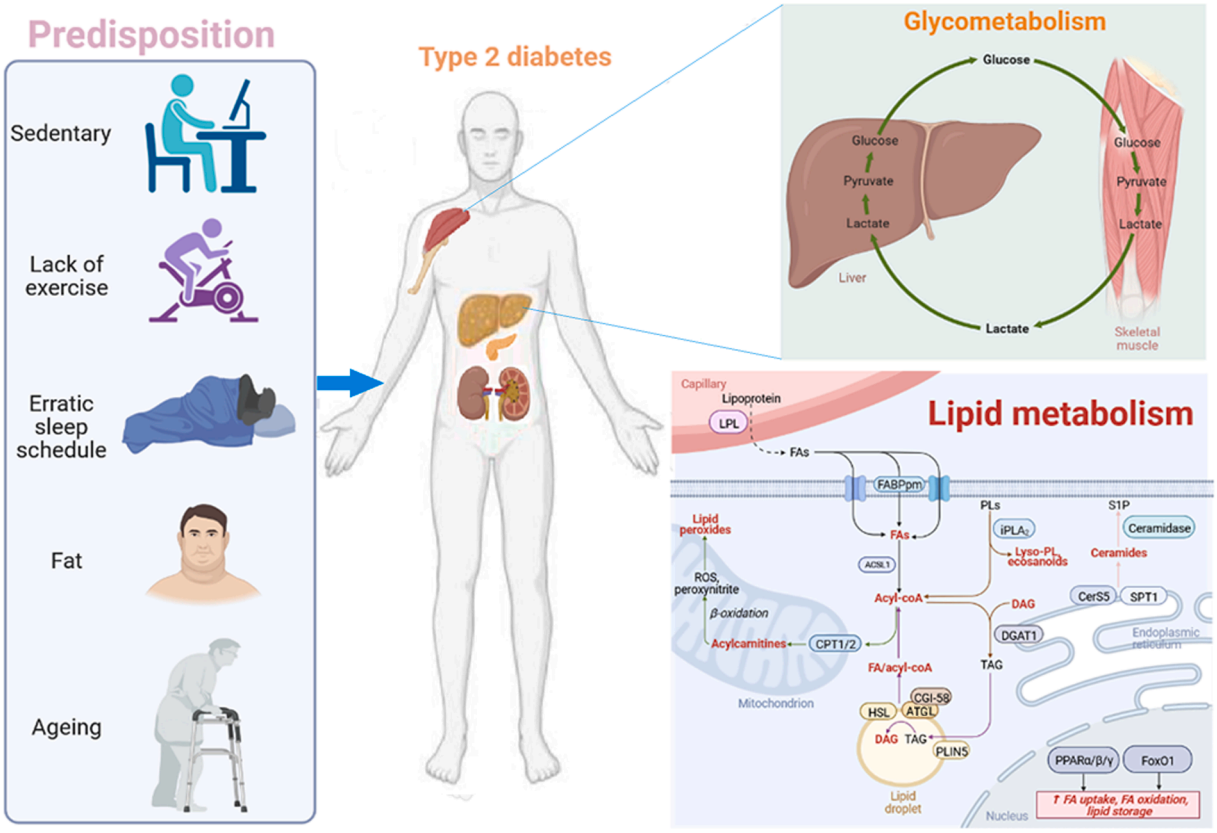


Fig. 2. Type 2 diabetes mellitus is caused by disturbances in glucolipid metabolism. Factors such as a sedentary lifestyle, lack of exercise and obesity lead to disturbances in glucolipid metabolism in the liver and skeletal muscle. The accumulation of lipids in the β cells of the pancreas and in the kidneys can further exacerbate the development of type 2 diabetes mellitus. ACSL1, acyl-CoA synthetase-1; ATGL, adipose triglyceride lipase; CerS5, ceramide synthase 5; CGI-58, comparative gene identification-58; CPT1/2, carnitine palmitoyltransferase 1 and 2; DAG, diacylglycerol; DGAT1, diacylglycerol acyltransferase 1; FABPpm, plasma membrane fatty acid-binding protein; FA, fatty acid; FAs, fatty acid synthase; FoXO1, forkhead box protein O1; HSL, hormone-sensitive lipase; $iPLA_2$, calcium-independent phospholipases; LPL, lipoprotein lipase; PLIN5, perilipin 5; PLs, phospholipids; PPARα/β/γ, peroxisome proliferator-activated receptor α/β/γ; ROS, reactive oxygen species; SPT1, serine palmitoyltransferase 1; S1P, sphingosine 1-phosphate; TAG, triacylglycerols.

3. Epidemiological rationale

In recent years, the comorbidity of gout and T2DM has garnered widespread attention in the medical community. This comorbidity pattern not only exacerbates the disease burden on patients but also poses greater demands on treatment.

Research indicates that age, gout 'tophi', obesity, hypertension, dyslipidemia, and renal insufficiency are significant risk factors for the comorbidity of gout and T2DM [29]. This suggests that a single-disease treatment model is insufficient to effectively address this comorbid state, and a simultaneous treatment strategy is of vital importance. In terms of therapeutic outcomes, SGLT2 inhibitors, a class of medications primarily used to manage T2DM that include canagliflozin, dapagliflozin, and empagliflozin, have demonstrated remarkable efficacy in reducing serum uric acid or urate levels and the risk of gout, particularly in patients already diagnosed with both gout and T2DM, outperforming traditional dipeptidyl peptidase-4 (DPP-4) inhibitors [11,30]. Moreover, SGLT2 inhibitors can also lower the risk of myocardial infarction and stroke, which is of great significance for gout patients [31]. Therefore, simultaneous treatment not only helps control blood glucose and uric acid levels but also reduces the risk of cardiovascular diseases and improves overall patient prognosis.

Hyperuricaemia is considered a potential cause of T2DM. A cross-sectional study in 2018 found that hyperuricaemia and increased uric acid excretion are independent risk factors for renal cysts in male and postmenopausal female T2DM patients [32]. Long-term clinical observations have shown that elevated uric acid or urate levels can predict the occurrence of diabetes and insulin resistance. This causal link is directly demonstrated in fructose-fed rat models, a well-established experimental system that concurrently induces hyperuricemia and insulin resistance. In this model, treatment with uric acid-lowering agents (such as allopurinol, febuxostat, and benzbromarone) not only normalizes serum uric acid and insulin levels but also improves associated metabolic parameters, including reductions in triglycerides and blood pressure [33]. However, antidiabetic drugs such as insulin, metformin, and sulfonylureas have no effect on gout treatment [33]. These findings suggest that hyperuricaemia may play a causal role in the development of diabetes, rather than diabetes causing gout.

In summary, given the high comorbidity rate and mutual influence of gout and T2DM, a simultaneous treatment strategy is a necessary choice for addressing this complex disease pattern. Future research should further explore the optimal simultaneous treatment protocols to enhance therapeutic outcomes and improve patient quality of life. This will not only help to improve the clinical prognosis of patients but also provide new directions for clinical practice.

4. Pathway for simultaneous treatment of gout and type 2 diabetes mellitus (T2DM)

4.1. Uric acid and glucose/lipid metabolism

Elevated serum uric acid levels disrupt lipid metabolism and glucose metabolism, thereby providing a theoretical basis for the simultaneous treatment of gout and T2DM (Fig. 3) [34]. Research studies have revealed that uric acid activates lysophosphatidylcholine acyltransferase 3 in the liver, inhibits the Janus kinase 2 / signal transducer and activator of transcription 3 (STAT3) signaling pathway, and promotes the transcription of lipogenic genes *via* sterol regulatory element binding transcription factor 1c, leading to increased intracellular accumulation of cholesterol and triglycerides [35]. Moreover, uric acid also triggers the development of fatty liver by activating the N-terminal kinase (JNK)/ activated protein-1 signaling pathway through reactive oxygen species mediation. These findings indicate that uric acid plays a significant role in lipid metabolic disorders, although the precise mechanisms require further investigation.

In terms of glucose metabolism, uric acid exerts a substantial influence. Inhibiting uricase activity leads to elevated blood glucose levels, hypertension, and renal damage, suggesting that uric acid may have a causal role in the development of hyperglycaemia [36]. *In vitro* studies have further confirmed that uric acid induces oxidative stress in HepG2 cell line, impairs insulin signaling, and reduces the phosphorylation levels of serine/threonine kinase 1 and insulin receptor substrate-1, effects that can be alleviated by antioxidants. Additionally, uric acid inhibits hepatic gluconeogenesis by suppressing AMP-activated protein kinase (AMPK) activation and phosphorylating transducer of regulated cAMP response element-binding protein activity 2, thereby affecting glucose regulation [37].

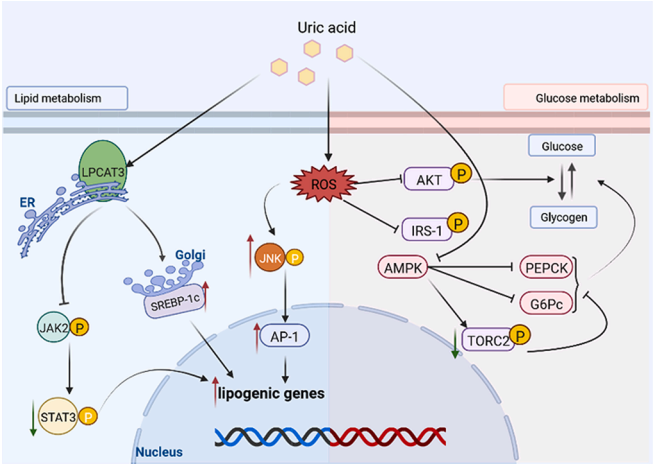


Fig. 3. Effects of uric acid on glycolipid metabolism. Uric acid inhibits the JAK2/STAT3 signaling pathway or activates SREBP-1c through LPCAT3, leading to upregulation of the lipid synthesis-related genes ACC1, FAS and SCD1 in the nucleus. In addition, uric acid promotes the upregulation of lipid synthesis-related genes through ROS-mediated activation of the JNK/AP-1 signaling pathway, disrupting lipid metabolism. Uric acid also promotes gluconeogenesis through direct inhibition of AMPK, leading to disruption of glucose metabolism. ACC1, acetyl-CoA carboxylase 1; AKT, protein kinase B; AMPK, AMP-activated protein kinase; AP-1, activated protein-1; FAS, fatty acid synthase; G6Pc, glucose-6-phosphatase; IRS-1, insulin receptor substrate-1; JAK2, janus kinase 2; JNK, c-Junn-terminal kinase; LPCAT3, lysophosphatidylcholine acyltransferase 3; PEPCK, phosphoenolpyruvate carboxykinase; ROS, reactive oxygen species; SCD1, stearoyl CoA desaturase 1; SREBP-1c, sterol regulatory element binding transcription factor 1c; STAT3, signal transducer and activator of transcription 3; TORC2, transducer of regulated cAMP response element-binding protein activity 2.

These research findings suggest that reducing serum uric acid levels may improve both lipid and glucose metabolism, offering a new approach for the simultaneous treatment of gout and T2DM. For instance, medicines such as allopurinol (a class of XOD inhibitors) and ferulic acid (a hydroxycinnamic acid derivative and a phenolic compound; naturally occurring antioxidant) not only lower uric acid levels but also enhance lipid and glucose metabolism, demonstrating promising therapeutic potential [33]. Therefore, developing combined therapeutic strategies targeting uric acid and glucose metabolism from a metabolic regulation perspective holds promise for providing more effective solutions for the treatment of these two metabolic diseases.

In summary, the close connection between uric acid and glucose metabolisms provides a scientific rationale for the simultaneous treatment of gout and T2DM. Future research should further explore the underlying mechanisms and therapeutic targets in this field to develop more effective combined treatment protocols and improve patients' quality of life.

4.2. Innate immunity and inflammation

Innate immunity and inflammation play a pivotal role in human

metabolism, with T2DM manifesting as systemic low-grade inflammation and gout characterised by localised inflammatory outbreaks in joints or tissues as well as low-grade inflammation in organs such as the liver and kidneys [38,39]. This suggests that inflammation may be the key to treating both diseases simultaneously.

In innate immunity, interleukin 1 (IL-1, including IL-1α and IL-1β) stimulates insulin secretion and β-cell proliferation by activating the IL-1 receptor 1 (IL-1R1), but chronic low-grade inflammation reduces cellular sensitivity to insulin and leads to β-cell apoptosis (Fig. 4) [40]. In gout, IL-1β released from MSU crystals triggers pro-inflammatory pathways involving nuclear factor kappa-light-chain-enhancer of activated B and JNK by acting through IL-1R1, resulting in an inflammatory response [41]. Dysregulation of the NLRP3 inflammasome further exacerbates IL-1β activation, presenting a new therapeutic target for the treatment of gout and T2DM.

Tumour necrosis factor (TNF), similar to IL-1, has a pro-apoptotic effect on pancreatic β-cells, worsening insulin resistance [42]. Although anti-TNF therapy has some effect on lowering blood glucose levels, its direct impact on glucose metabolism is limited and it is associated with more adverse events [43]. In contrast, IL-1 antagonists such as anakinra have shown better results in reducing blood glucose and inflammation [43].

Interleukin 6 (IL-6), abundant in inflammation, regulates muscle growth, glucose homeostasis and inflammatory responses [44]. It exacerbates insulin resistance and β-cell apoptosis synergistically with innate cytokines [42]. The effects of IL-6 on glucose metabolism vary with context and tissue, but it mainly promotes insulin resistance and β-cell dysfunction in states of obesity and inflammation [45]. Table 1 describes anti-inflammatory medicines that can treat gout and T2DM.

In summary, innate immunity and inflammation are significant in both gout and T2DM, and modulating inflammation and innate immunity holds promise for the simultaneous treatment of these two diseases. Future research should further explore the underlying mechanisms and therapeutic targets in this area to develop more effective combined treatment protocols and enhance patients' quality of life.

4.3. Gut microbiota

The gut microbiota, a complex ecosystem harboring a gene pool approximately 500 times larger than the human genome, has emerged as a critical regulator of host metabolism and immunity [51,52]. Its profound influence extends to the pathogenesis of gout and T2DM, positioning it as a fundamental link and a promising therapeutic target for these comorbid conditions [53].

A pivotal function of the gut microbiota is its role in systemic uric acid homeostasis. It is responsible for the excretion and metabolism of about one-third of bodily uric acid [53]. In hyperuricemia and gout, this microbial community becomes dysbiotic. Characteristic shifts include an increase in genera such as *Coccidioides* and a decrease in others like *Pseudotrophomonas* [54]. Animal models corroborate this, showing that hyperuricemic mice exhibit a reduced *Firmicutes/Bacteroidetes* ratio and increased *Proteobacteria* [55]. Crucially, this dysbiosis is not a passive

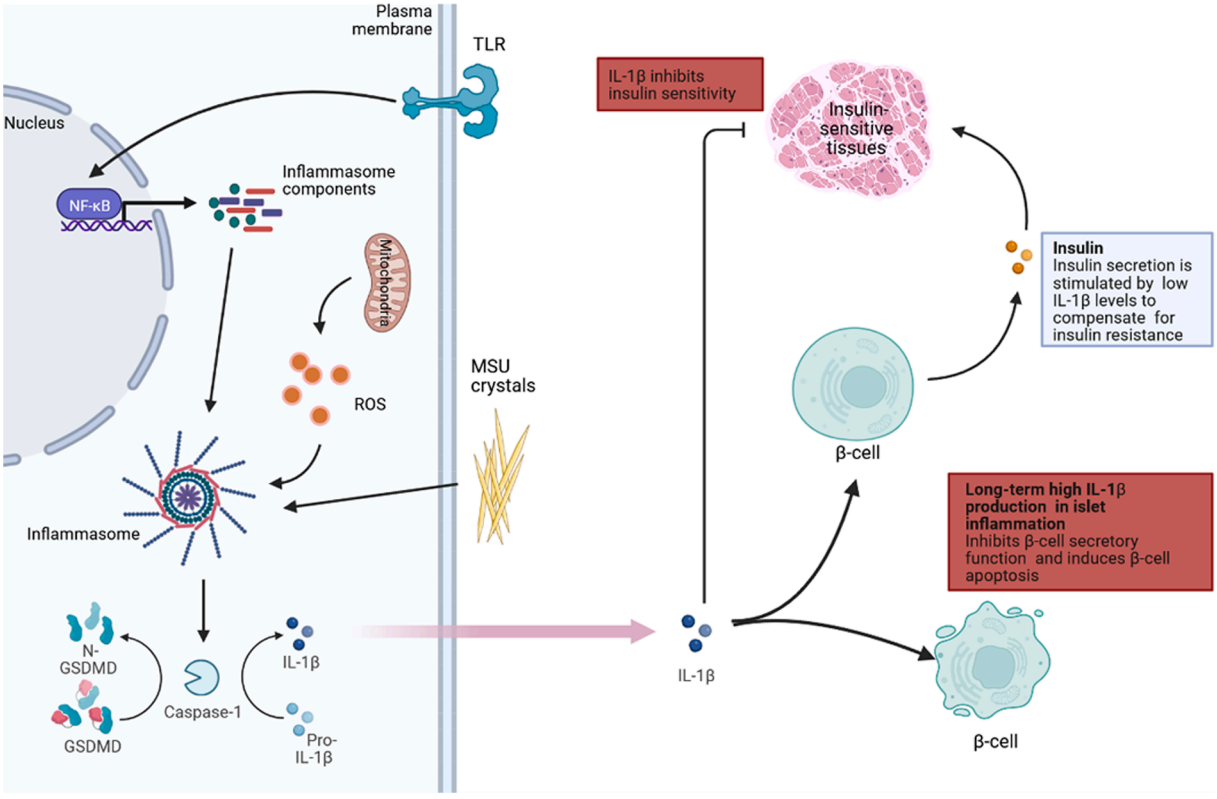


Fig. 4. IL-1β-mediated inflammatory responses in gout and type 2 diabetes mellitus. Activation of the NFκB signaling pathway by members of TLR family induces the expression of functional inflammasome components such as NLRP3. MSU crystals trigger the assembly of inflammasomes. Interaction of MSU crystals with the plasma membrane facilitates a cellular response that is currently unknown but includes features of NLRP3 activation, such as mitochondrial perturbation, leading to production and release of mitochondrial ROS into the cytoplasm. Caspase-1 is recruited then activated by autoprotein hydrolysis. Active Caspase-1 promotes proteolytic cleavage and maturation of pro-IL-1β into biologically active IL-1β. Caspase-1 also promotes GSDMD cleavage, producing N-terminal cleavage products that flocculate at the plasma membrane, leading to formation of pyrolytic pores. These pores disrupt cytoplasmic membrane integrity and may contribute to release of inflammatory mediators, including IL-1β. In a state of low-grade systemic inflammation, low levels of IL-1β lead to insulin resistance, but IL-1β also helps to stimulate compensatory insulin hypersecretion by beta cells to compensate for reduced insulin sensitivity. In the context of localised intra-islet inflammation, high intercellular IL-1β concentrations trigger β-cell dysfunction and apoptosis. GSDMD, gasdermin D; IL-1β, interleukin 1 beta; MSU, monosodium urate; NFκB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, nucleotide-binding oligomerization domain-like receptor 3; ROS, reactive oxygen species; TLR, Toll-like receptors.

Table 1
Anti-inflammatory medicines that can treat gout and type 2 diabetes mellitus.

Name	Mechanism of action	Clinical Trials	Therapeutic indications	References
Canakinumab (Ilaris)	Blocking IL-1β binding to type IL-1R1 and IL-1RAcP on the cell membrane surface, blocking inflammatory response pathway	Phase III	Canakinumab has been found to be superior to triamcinolone acetonide in acute gout and to colchicine in gout attack prophylaxis in reducing pain and risk of new gout attacks	[46]
Anakinra (Kineret)	Recombinant endogenous IL-1R antagonist protein that blocks IL-1α and IL-1β signaling via IL-1R	Phase IV	Anakinra is effective and safe for management of gout flares in difficult-to-treat patients. It is used in multiple complex scenarios (active infections, dialysis, transplantation, chronic kidney disease, polyarticular gout)	[47]
IC7Fc	Designed to improve insulin resistance and metabolic homeostasis with the design of GP130 ligand	Preclinical	T2DM, muscle atrophy	[48]
MCC950 (CRID3, CP-456773)	Specific inhibition of NLRP3 activation	Preclinical	Prevention of neurovascular remodeling and cognitive decline post-stroke in diabetic patients	[49,50]
OLT1177 (Dapansutrile)	Specific inhibition of NLRP3 activation	Phase II	Reduced joint pain and inflammation in gout flares; potential for NLRP3-related diseases	[50]

Abbreviations: GP130, glycoprotein 130; IL-1α, interleukin 1 alpha; IL-1β, interleukin 1 beta; IL-1R1, interleukin-1 receptor; IL-1RAcP, interleukin receptor co-protein; NLRP3, NOD-like receptor protein 3; T2DM, Type II diabetes mellitus.
Clinical Trials Regulation:
Phase II (Therapeutic exploratory): to collect preliminary data on whether the treatment works and additional safety data, including adverse events and optimal dosing, generally performed on a larger group of patients who have the disease or condition the medicine is intended to treat; Phase III (Therapeutic confirmatory): to confirm the effectiveness of the medicine, monitor adverse events, compare it to standard treatments, and gather comprehensive safety information, it involves a large group of patients.; Phase IV (Therapeutic use): to monitor the long-term medicine's safety and effectiveness in the general population after it has been approved and marketed.

consequence but an active contributor to disease, as demonstrated by studies where fecal microbiota transplantation significantly influenced hyperuricemic outcomes [56]. Specific bacterial taxa, including certain *Clostridiaceae* families, possess the enzymatic machinery to degrade uric acid, while probiotic lactic acid bacteria can limit intestinal purine absorption, collectively acting as a physiological buffer against serum urate elevation [57].

Parallel and equally significant dysbiosis is evident in T2DM. The diabetic gut microbiome is often marked by a depletion of beneficial *Bifidobacteria* and *Firmicutes*, alongside an enrichment of *Bacteroides* and *β-Proteobacteria* [58]. This compromised microbial architecture undermines gut barrier integrity, fuels chronic low-grade inflammation, and directly exacerbates insulin resistance. The depletion of key probiotics, particularly *Lactobacillus* and *Bifidobacterium* species, is strongly correlated with impaired glucose tolerance and aberrant energy metabolism, highlighting a direct mechanistic link to diabetic pathophysiology [59].

Given its central role in both disorders, the gut microbiota presents a compelling target for dual intervention. Research into modulation strategies has progressed along several complementary paths. Pharmacological agents, including specific antibiotics like ampicillin and neomycin, can acutely alter microbial composition and have been shown to improve glucose homeostasis in animal studies, though their long-term utility is tempered by concerns over antibiotic resistance [60]. Dietary intervention offers a more sustainable avenue; for instance, regular consumption of fermented foods such as sauerkraut, which enriches *Lactobacillus brevis*, has been linked to reduced serum uric acid levels, decreased XOD activity, and enhanced intestinal barrier function [61]. On the frontier of therapeutic innovation, faecal microbiota transplantation (FMT) aims to directly reconstitute a healthy microbiome. Proof-of-concept studies support this approach, demonstrating that interventions with defined probiotic consortia, including *Lactobacillus casei*, can lead to significant reductions in blood glucose levels in diabetic models [62].

In conclusion, the gut microbiota functions as a critical metabolic and immune interface, the dysregulation of which is intricately involved in the co-development of gout and T2DM. Moving beyond mere association, evidence from microbial manipulation studies solidifies its pathogenic role and therapeutic potential. Therefore, strategies aimed at restoring a healthy, diverse, and stable gut ecosystem – whether through diet, precision probiotics, or advanced FMT protocols – hold substantial promise as integral components of a holistic management strategy for these interconnected metabolic diseases.

5. Simultaneous treatment strategies

5.1. Pharmacological combination therapy of gout and type 2 diabetes mellitus (T2DM)

In the simultaneous treatment of gout and T2DM, the combination of pharmacological agents is one of the key strategies. For patients with both conditions, the use of uric acid-lowering drugs such as allopurinol or febuxostat, in conjunction with antidiabetic medications like metformin or pioglitazone, is recommended [63]. Uric acid-lowering drugs, including allopurinol and febuxostat, reduce uric acid production by inhibiting XOD, while antidiabetic drugs, such as metformin and pioglitazone, lower blood glucose levels by enhancing insulin sensitivity [64]. The typical dosage of allopurinol is 100–300 mg/day, and that of febuxostat is 40–80 mg/day [65]. The usual dosage of metformin is 500–2000 mg/day, and that of pioglitazone is 15–45 mg/day [63]. It is crucial to tailor the dosage of these medications to the individual patient's renal and hepatic functions. For instance, patients with renal insufficiency may require a reduced dosage of allopurinol to prevent drug accumulation and adverse reactions [63]. Similarly, the dosage of pioglitazone should be adjusted based on liver function to avoid potential hepatotoxicity.

In clinical practice, the treatment strategy is further refined according to the severity of the disease. For mild disease, a combination of allopurinol (300 mg/day) and metformin (1000 mg, twice daily) is recommended, with dosage adjustments for allopurinol based on renal function. Monitoring indicators include serum uric acid, blood glucose, and renal function. For moderate disease, febuxostat (40 mg/day) combined with pioglitazone (45 mg/day) is used, with dosage adjustments for pioglitazone based on liver function. Monitoring indicators in this case include serum uric acid, blood glucose, and liver function. In severe cases, febuxostat (40 mg/day) is combined with an insulin sensitizer, such as rosiglitazone (4 mg/day), with dosage adjustments based on both renal and liver function. Monitoring indicators encompass serum uric acid, blood glucose, renal function, and liver function. Regular blood tests are essential to closely monitor these parameters. Serum uric acid and blood glucose levels should be monitored every 1–3 months, while renal and hepatic function should be checked every 3–6

months [66]. This approach allows for the early identification of any potential issues and timely adjustment of the treatment plan, thereby optimizing therapeutic outcomes for patients with comorbid gout and T2DM [66]. Table 2 shown the medicines for the different stages of gout and diabetes.

In recent years, SGLT2 inhibitors, as a novel class of antidiabetic drugs, have not only effectively controlled blood glucose levels but also significantly reduced serum uric acid levels and the risk of gout flares [12]. For instance, SGLT2 inhibitors such as dapagliflozin and empagliflozin lower serum uric acid levels by inhibiting renal reabsorption of uric acid and increasing its excretion. In clinical trials, dapagliflozin has been shown to reduce serum uric acid levels by 0.8 ± 0.8 mg/dl in gout patients [76]. Moreover, the combination of empagliflozin with benzbromarone also significantly lowers serum uric acid levels [77]. In addition, new uric acid-lowering drugs, such as lesinurad and verinurad, which inhibit urate transporter 1 and increase uric acid excretion, offer new options for the treatment of gout [77].

The inflammatory mechanisms of gout and T2DM share commonalities, and anti-inflammatory treatment holds potential for simultaneous therapy. For gout, colchicine is an effective treatment during acute flare-ups, with a typical dosage of 1.2 mg initially, followed by an additional 0.6 mg after one hour, and then 0.6 mg twice daily until clinical symptoms subside [78]. However, colchicine is contraindicated in patients with hepatic or renal insufficiency [79]. For T2DM, anti-inflammatory drugs such as the IL-1β inhibitor canakinumab (a human monoclonal antibody used to treat certain autoinflammatory diseases), which alleviates inflammatory responses and improves insulin resistance by blocking the IL-1β signaling pathway, are used [19]. For adult patients with gouty arthritis who experience frequent gouty arthritis attacks (at least 3 attacks in the previous 12 months) and in whom non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine are contraindicated, not tolerated, or do not provide an adequate response, and for whom repeated courses of corticosteroids are inappropriate, canakinumab also can be used for symptomatic treatment. It is administered subcutaneously at a single dose of 150–300 mg every 3 months [80]. However, it should not be administered during an active infection.

IC7Fc is a designed signal protein. It is constructed by combining and modifying parts of the structures of IL-6 and ciliary neurotrophic factor [48]. It can bind to the glycoprotein 130 receptor and activate the STAT3 phosphorylation induced by IL-6. It can enhance the activity of AMPK to promote fatty acid oxidation and reduce fat accumulation. It can also specifically activate the Hippo pathway in muscle tissue to maintain muscle mass. It promotes the secretion of insulin by pancreatic β-cells to lower blood glucose levels and partially assists in stabilizing blood glucose by affecting the secretion of enteric hypoglycemic hormones. It is potentially useful for the treatment of T2DM and may also have therapeutic potential for diseases such as muscle atrophy. In animal experiments, it is mostly administered by intraperitoneal injection. It has been tested in mice and non-human primates without showing any obvious adverse events. The research team plans to advance to phase I clinical trials in humans [48].

Dapansutrile (OLT1177), with the chemical name of 3-(methylsulphonyl) propionitrile, can selectively inhibit the oligomerisation and activation of the NLRP3 inflammasome, thereby reducing the maturation and secretion of pro-inflammatory cytokines IL-1β and interleukin-18 [50]. Its clinical indications under research include knee osteoarthritis, gout, coronavirus disease, T2DM, atherosclerosis, neurodegenerative diseases (such as Parkinson's disease, multiple sclerosis), melanoma and acute radiation pneumonitis, among others [81]. At present, the gout indication is in phase IIa clinical trial, while other indications are mostly in the pre-clinical research or early – stage clinical trial exploration phase [81].

Prebiotics and Traditional Chinese medicine (TCM) formulations can improve the metabolic status of gout and T2DM by modulating the gut microbiota. For instance, inulin, a prebiotic, increases the abundance of beneficial gut bacteria such as *Bifidobacterium* and *Lactobacillus*, thereby promoting uric acid excretion and reducing serum uric acid levels, with a common dosage of 5–20 g/day [82]. TCM formulations like Liuwei Dihuang Wan also known as Six Flavor Rehmannia or Rehmannia Six Formula, improve insulin sensitivity and lower blood glucose by regulating the metabolic functions of the gut microbiota, with a typical dosage of 6–12 g/day [83]. These agents offer new avenues for simultaneous treatment of gout and T2DM by enhancing the diversity and functionality of the gut microbiota and reducing inflammatory responses.

5.2. Management and other therapy method

The effective simultaneous management of gout and T2DM extends beyond pharmacotherapy, necessitating a foundational commitment to lifestyle modification and integrative non-pharmacological approaches. These interventions target the shared pathological roots of both conditions – metabolic dysfunction, chronic inflammation, and oxidative stress – thereby providing synergistic benefits that enhance and often potentiate the effects of pharmaceutical treatments [84].

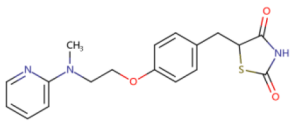
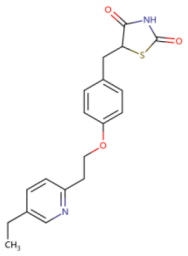
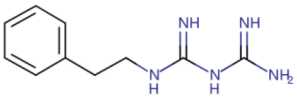
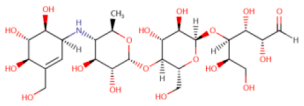
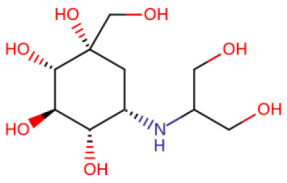
Dietary management constitutes the cornerstone of this holistic strategy. The primary objectives are to reduce exogenous purine load and fructose intake, which are key drivers of hyperuricemia, and to improve insulin sensitivity through glycemic control and weight management [85]. Patients are advised to adopt a dietary pattern low in refined sugars, high-fructose corn syrup, and high-purine animal organs and seafood [85]. Concurrently, increasing the intake of dietary fiber from whole grains, vegetables, and low-glycemic-index fruits promotes satiety, aids weight loss, and modulates postprandial glucose excursions. This dietary shift may also beneficially alter gut microbiota composition, indirectly influencing uric acid excretion and systemic inflammation [82,84]. Moderate consumption of low-fat dairy products and plant-based proteins is encouraged. Strict abstinence from alcohol, particularly beer and spirits, is critical due to alcohol's dual role in impairing renal urate excretion and promoting hepatic gluconeogenesis [85]. Furthermore, adequate hydration to maintain a daily urine output exceeding 2,000 mL is a simple yet effective measure to facilitate renal uric acid clearance [85].

Regular physical activity and structured exercise programs are equally indispensable. Aerobic exercise, such as brisk walking, cycling, or swimming, for at least 150 min per week at moderate intensity improves skeletal muscle glucose uptake via insulin-independent pathways, enhances cardiovascular health, and promotes weight reduction [84]. Incorporating resistance training twice weekly helps increase lean muscle mass, a major determinant of basal metabolic rate and long-term glycemic control. Crucially, exercise exerts potent anti-inflammatory effects, reducing circulating levels of pro-inflammatory cytokines such as IL-6 and TNF-α, which are implicated in the pathogenesis of both insulin resistance and acute gout flares [39,84].

Weight management is a central therapeutic goal that unites dietary and exercise efforts. Obesity, particularly visceral adiposity, is a strong independent risk factor for both hyperuricemia and T2DM incidence, acting as a major driver of insulin resistance and low-grade inflammation [29,84]. A sustained weight loss of 5–10% of total body weight has been shown to significantly lower serum urate levels, improve glycemic control, reduce hepatic steatosis, and decrease cardiovascular risk. This cluster of benefits underscores the profound impact of weight management, offering outcomes that are difficult to achieve by pharmacotherapy alone [9,84].

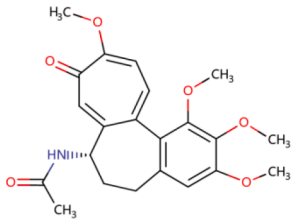
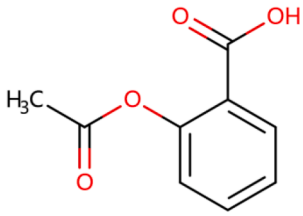
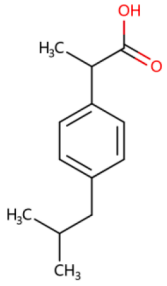
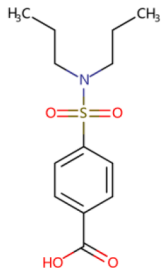
As detailed in Section 4.3, the gut microbiota represents a promising target for adjunctive therapy. The use of specific prebiotics, such as inulin or oligofructose at doses of 5–20 g/day, can selectively nourish beneficial genera like *Bifidobacterium*. This may enhance intestinal barrier function and reduce endotoxemia-linked inflammation [59,82]. Moreover, certain probiotics and traditional herbal formulations, including Liuwei Dihuang Wan, have demonstrated potential in preclinical and clinical studies to modestly lower serum uric acid and

Table 2
Medicines for the different stages of gout and diabetes.

Name	Chemical formula	Structure	Mechanism of action	Clinical trials	Classification	References
Rosiglitazone	$C_{18}H_{19}N_3O_3S$		Tissue sensitivity to insulin is enhanced via activation of PPARs in insulin-activated target tissues. Rosiglitazone, a PPARγ-selective agonist, has potent antiinflammatory effects.	Phase IV	TZDS	[67]
Pioglitazone	$C_{19}H_{20}N_2O_3S$		Tissue sensitivity to insulin is enhanced via activation of PPARs in insulin-activated target tissues. Pioglitazone decreases insulin resistance in the periphery and in the liver, resulting in increased insulin-dependent glucose disposal and decreased hepatic glucose output.	Phase IV	TZDS	[68]
Phenformin	$C_{10}H_{15}N_5$		Inhibits hepatic gluconeogenesis, enhances glucose uptake and utilization in tissues, enhances insulin sensitivity and also inhibits the release of glucagon.	Preclinical	Biguanides	[69]
Acarbose	$C_{25}H_{43}NO_{18}$		The absorption of glucose in the small intestine can be reduced and delayed by inhibiting α-glucosidase in the intestinal mucosa and slowing down the rate of starch decomposition into glucose, thus effectively lowering plasma glucose.	Phase III	α-glucosidase inhibitor	[70]
Voglibose	$C_{10}H_{21}NO_7$		The absorption of glucose in the small intestine can be reduced and delayed by inhibiting α-glucosidase in the intestinal mucosa and slowing down the rate of starch decomposition into glucose, thus effectively lowering blood glucose levels.	Phase IV	α-glucosidase inhibitor	[71]

(*continued on next page*)

Table 2 (*continued*)

Name	Chemical formula	Structure	Mechanism of action	Clinical trials	Classification	References
Colchicine	$C_{22}H_{25}NO_6$		Binding to subunits of neutrophil microtubulin alters cell membrane function, including inhibition of neutrophil migration, adhesion, and phagocytosis, and inhibits local cell production of IL-6 to achieve control of local joint pain, swelling and the inflammatory response.	Phase IV	Alkaloid	[72]
Acetylsalicylic acid	$C_9H_8O_4$		Blocks prostaglandin synthesis by inhibiting COX-1 to prevent the production of pain. Blocks the conversion of arachidonic acid to TXA2, inhibits platelet aggregation and relieves blood clots and harmful venous and arterial thromboembolism leading to diseases such as pulmonary embolism and stroke.	Phase III	NSAIDs	[73]
Ibuprofen	$C_{13}H_{18}O_2$		Non-selectively inhibits COX, reduces prostaglandin synthesis, and relieves inflammation, pain, fever, and swelling. Effective in the treatment of acute gout.	Phase IV	NSAIDs	[74]
Probenecid	$C_{13}H_{19}NO_4S$		Inhibits the renal tubular transporter, facilitating the excretion of the disease causative uric acid by blocking reuptake.	Phase IV	Anti-gout Agents/ Gout Suppressants	[75]

Abbreviations: COX, cyclooxygenase; COX-1, cyclooxygenase-1; IL-6, interleukin-6; NSAIDs, non-steroidal anti-inflammatory drugs; TXA2, thromboxane A2; TZDS, thiazolidinediones; PPARs, peroxisome proliferator-activated receptors; XOD, xanthine oxidase.
Clinical Trials Regulation:
Phase III (Therapeutic confirmatory): to confirm the effectiveness of the medicine, monitor adverse events, compare it to standard treatments, and gather comprehensive safety information, it involves a large group of patients; Phase IV (Therapeutic use): to monitor the long-term medicine's safety and effectiveness in the general population after it has been approved and marketed.

improve glucose homeostasis. These effects are likely mediated through multi-target actions on microbial ecology, host metabolism, and inflammation [83,86]. While faecal microbiota transplantation remains an investigational approach for refractory cases, it provides compelling proof-of-concept that directly reshaping the gut ecosystem can positively influence systemic metabolic parameters [56,86].

In summary, the concurrent management of gout and T2DM mandates an integrated paradigm that seamlessly combines pharmacological agents with rigorous lifestyle intervention. A structured program encompassing personalized nutrition, regular physical activity, sustained weight loss, and consideration of gut health delivers a comprehensive multi-pronged attack on shared metabolic dysregulation. This approach not only improves disease-specific outcomes but also ameliorates overall cardiometabolic risk, ultimately leading to superior long-term prognosis and quality of life for patients afflicted by this common comorbidity [84,85].

6. Conclusion

The comorbidity of gout and T2DM poses a significant burden on patient health and healthcare resources. This review article, through an in-depth exploration of the commonalities in the pathogenesis of these two diseases, particularly from the perspectives of uric acid metabolism, inflammatory responses, and gut microbiota dysregulation, proposes a variety of comprehensive simultaneous treatment strategies, offering new insights and approaches for clinical treatment.

This study not only summarises the specific traditional treatment methods for gout and T2DM but also puts forward novel treatment plans based on their shared pathophysiological mechanisms. We emphasise the therapeutic potential from the perspectives of inflammation and gut microbiota, which provides a theoretical basis for the development of new therapeutic targets and drugs. In addition, this paper highlights the importance of personalised treatment plans, which, through genetic testing and biomarker analysis, can tailor comprehensive treatment plans for patients, potentially improving treatment outcomes and prognosis.

Future research directions should focus on further exploring the specific mechanisms of action of inflammation and gut microbiota in gout and T2DM and developing new medicines that can target both diseases simultaneously. Moreover, multidisciplinary collaboration should be strengthened to optimise personalised treatment plans by integrating clinical data and basic research. The research findings of this review paper not only provide a new perspective for the simultaneous treatment of gout and T2DM but also offer important inspiration and direction for future research studies.

Ethical approval

None were requested.

CRediT authorship contribution statement

Hanfei Wang: Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **Boyu Wang:** Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **Jieying Zhang:** Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **Haibin Tong:** Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **Irma Ares:** Writing – review & editing, Investigation, Formal analysis, Data curation, Conceptualization. **Marta Martínez:** Writing – review & editing, Investigation, Formal analysis, Data curation, Conceptualization. **Bernardo Lopez-Torres:** Writing – review & editing, Investigation, Formal analysis, Data curation, Conceptualization. **María-Rosa Martínez-Larrañaga:** Writing – review & editing, Investigation, Formal analysis, Data curation, Conceptualization. **Yuanhu Pan:** Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **Jinjun Zhang:** Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **Arturo Anadón:** Writing – review & editing, Supervision, Resources, Project administration. **Xu Wang:** Writing – review & editing, Supervision, Resources, Project administration. **María-Aránzazu Martínez:** Writing – review & editing, Supervision, Resources, Project administration.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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