Review Paper:

Modern Perspectives on Gout: From Pathogenesis to Novel Therapeutic Approaches

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Abstract

Gout, a complex form of inflammatory arthritis, has emerged as an increasingly prevalent condition affecting global populations, with significant impacts on quality of life and healthcare systems. This comprehensive review examines the intricate pathophysiological mechanisms, current pharmacological interventions and evolving treatment paradigms in gout management. The pathophysiology centers on hyperuricemia and the subsequent deposition of monosodium urate crystals in joints and soft tissues, triggered by modifiable and non-modifiable risk factors. Recent advances in understanding the role of the inflammasome (NLRP3) pathway and genetic factors have provided new insights into disease progression and potential therapeutic targets. The pharmacological management encompasses three main categories: acute attack medications (including NSAIDs, colchicine and corticosteroids), urate-lowering therapies (such as xanthine oxidase inhibitors allopurinol and febuxostat) and prophylactic treatments. Current treatment guidelines emphasize a 'treat-to-target' approach, aiming for serum urate levels below 6 mg/dL, while considering individual patient factors and comorbidities.

This review also focuses on new therapies such as Indian, Malaysian and Chinese herbal medications and innovative treatments including physiotherapy, acupuncture, joint replacement surgery and laser therapy, showing promise for treatment-resistant patients. Integrating lifestyle modifications, dietary interventions and patient education remains crucial for optimal disease management. Understanding these multifaceted aspects of gout is essential for healthcare providers to implement effective, personalized treatment strategies and improve patient outcomes.

Keywords: Hyperuricemia, Gout, Anti-inflammatory agents, Inflammasome, Novel treatment, Traditional herbal medicine.

Introduction

The most common type of inflammatory arthritis is caused by hyperuricemia, or gout[48]. Gout is a chronic illness referred to as "a disease of kings"[14]. Egyptians were the first to record this illness in 2640 BC[2]. Uric acid (UA) overproduction and/or poor excretion are the main causes of hyperuricemia (HUA) and it is a prevalent widespread metabolic illness[72]. Persistent serum UA values of more than 7 mg/dl (>420 µmol/L) in men and more than 6 mg/dl (>360 µmol/L) in women are associated with hyperuricemia[73].

Urate is expelled as uric acid, which is the end result of human's degradative metabolism of purines. The heterocyclic purine derivative uric acid (2,6,8-trioxypurine) has a molecular weight of 158 Da. Swedish pharmacist Scheele discovered uric acid in bladder stones for the first time in 1776. At the biological pH of 7.4, it is a weak acid that generates a singly-charged hydrogen or acid urate ion. Uric acid is temperature-sensitive and has relatively poor water solubility. At pH 7.4 and 37°C, the saturation point of uric acid is 392 µmol/L, or 6.6 mg/dL[10]. Allantoin, is an oxidative metabolite of uric acid, the last result of purine metabolism in all mammals (except for some primates). The uricase enzyme controls the transformation of sparingly soluble uric acid into more freely soluble allantoin[62].

In a multifunctional molybdoflavoprotein abundant in milk, kidney, lung, heart and vascular endothelium, xanthine oxidase is extensively distributed. The liver and intestines of humans have the highest specific activity for XO. This enzyme is engaged in the purine metabolism, facilitating the conversion of xanthine and hypoxanthine to uric acid. It also plays a significant role in gout and hyperuricemia[33].

Epidemiology

Hyperuricemia has become more common and incidental in recent years and their beginning age has moved earlier in life. Throughout the 1960s and 1990s, the prevalence of hyperuricemia has more than doubled and it increased gradually until at least 2016, when it reached around 21%. The global incidence rate of gout therefore rose from 1.5 to 2.5% between 1997 and 2012[21]. The incidence of this condition was 2.3% in women and 8.2% in males in a nutrition and health study done in the Taiwan[37]. Although the likelihood of developing gout rises with age, an estimated 600,000–700,000 Americans have early-onset gout (EOG), which is often regarded as the first gout episode before the age of 40[45]. This illness strikes wealthy nations more frequently than developing nations worldwide, with a fairly uneven incidence. It affects males four times more often than women; it is commonly referred to as "men's disease"[2].

Etiology

Eighty percent of urea comes from the breakdown of endogenous purines, whereas the remaining twenty percent comes from exogenous purines, including those found in diet[66]. Gout can be inherited or developed as a result of diet and genetics, however, sufferers are advised to avoid foods high in purines such as meat, fish, organs and alcohol, since they can increase blood urate levels[29]. Idiopathic and chemical flaws lead to increased purine production [such as infections with glycogen capacity], a major cause of hyperuricemia. Increased uric acid turnover and purine catabolism are associated with cytotoxic medication usage, cancer, sarcoma, myeloproliferative illnesses, lymphoproliferative disorders. Chronic hemolytic anemia is the minor cause of hyperuricemia[41].

Pathogenesis

Hyperuricemia: This is the central starting point for gout caused by two main factors:

a. Excessive production of urate

- Includes a high purine diet, fructose intake, diseases with rapid cellular turnover and alcohol consumption.
- Rare genetic causes include PRS super activity and HPRT deficiency.

b. Under-excretion of UA

- The causes include metabolic syndrome, ketones, renal illness, lactate and diuretic usage.
- Genetic reasons include urate transporter, ABCG2 variations, SLC2A9 and uromodulin mutations.

Formation of MSU (Monosodium Urate) crystals: Hyperuricemia leads to urate supersaturation which is influenced by factors like pH, temperature and joint trauma or debris, resulting in MSU crystal formation.

Acute gout: MSU crystals trigger an acute inflammatory response characterized by:

- Principal role of IL-1β via NALP3 inflammasone activation.
- Innate immune cells and other resident cells within the joint become involved.
- Release of soluble mediators of inflammation.

Resolution of the acute gout attack involves:

- Macrophage differentiation
- Anti-inflammatory signaling pathways
- Protein coating of crystals
- Anti-inflammatory cytokines.

Chronic gout and tophus formation: If hyperuricemia persists, it can lead to chronic gout characterized by:

- Activation of osteoclasts.
- Activation of macrophages and development of granulomas.
- MMP (Matrix Metalloproteinase) production[27].

Pathophysiology: The mechanism by which uric acid(UA) crystals build in the joint region, contributes to Gouty Arthritis aggravation. Lysosomal enzymes are generated, inflammatory chemokines are triggered and synovial cells take up such crystals, initiating the inflammatory response process[48]. Gouty arthritis causes mast cell, neutrophil and monocyte activation. Distinguished macrophages may store these crystals without causing an inflammatory response[7]. Mast cells play an important role in the onset of acute gouty instances via the production of IL-1 (interleukin) and histamine. This increases vascular permeability and vasodilation[17]. Neutrophil chemotaxis is mediated by monocyte and mast cell-produced chemotactic substances in addition to local vasodilation. The recruitment of endothelial cells further intensifies neutrophil migration and the inflammatory response.

As a result, there are too many neutrophils in the area[46]. 90% of neutrophil activation and acute inflammatory aggravation are caused by an increase in chemotactic substances in the synovium including interleukins, platelet-activating agents and leukotrienes, notably IL-8. Therefore, concentrating on IL-8 may be a useful tactic to stop acute gout episodes. Usually, an acute gout episode resolves on its own. After it emerges, it disappears in a few hours or days. Macrophages also help to lower the cycle of inflammation by removing cellular apoptotic remnants. Tumor necrosis factor-beta (TNF- β) is released by macrophages and inhibits IL-1, a crucial component in inflammation[63].

Repeated gout episodes lead to systemic inflammation, which is the cause of chronic gouty arthritis. Tophi growth, cartilage degradation, bone erosions and severe synovitis are indicative of chronic gout[24]. When crystals of urate are identified in the chondrocytes, synovium gets activated and release inflammatory cytokines and nitric oxide, matrix metalloproteases which contribute to cartilage deterioration and the beginning of bone erosion[23]. Key players in controlling the inflammatory response are anti-inflammatory cytokines. To treat an acute harm, two processes are involved: decreased synthesis of TNF-α and interleukin receptors on leukocytes and proteolysis of pro-inflammatory cytokines. Vasodilation and increased vascular permeability are required for macrophage extravasation into synovial fluid to eliminate inflamed regions[63].

Treatment: Colchicine, non-steroidal anti-inflammatory medicines and steroids are among the treatments used to treat gout flare-ups. In severe situations, these medications can be given combined and they work best when administered soon after the flare starts[56].

Novel treatment for gout

Physiotherapy as a Treatment for Gout: The management of physiotherapy has the potential to effectively treat gout arthritis at different stages. The symptoms of gout can be managed by physiotherapy in a variety of ways. Controlling pain, managing inflammation, decreasing fatigue, enhancing

muscle strength and flexibility and improving cardiovascular endurance are all benefits of physiotherapy. The treatment of gout benefits from two primary types of exercises: stretching exercises and strength exercises[56].

Treating Gout with Acupuncture: For the treatment of acute gout episodes, acupuncture is a highly helpful and successful method. This fundamental method is very beneficial for reducing pain and inflammation and enhancing blood circulation[39]. Acupoint injections, Chinese herbal medicine and local blocking therapy were among the other types of care used in addition to the treatment[22].

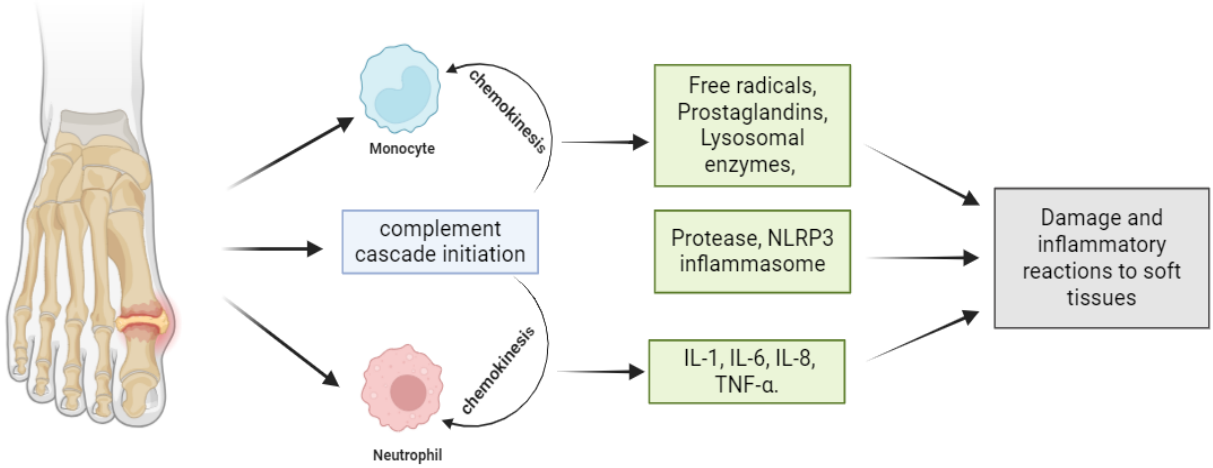

Fig. 1: The main cause of inflammation in the condition known as gouty arthritis. (NLRP3: Nod-like receptor protein 3, IL-1, IL-6, IL-8, TNF-α)

Table 1
Medications used to treat gout

Drugs	Comments
To treat acute gouty arthritis	
Colchicine	A widely distributed substance with a 10-day leukocyte lifespan, excreted through multiple pathways. It blocks crystal uptake without altering urate metabolism. Toxicity increases with P-450 inhibitors, especially in liver or kidney dysfunction[20].
NSAIDs	Though useful, its application is limited due to side effects including headaches, high potassium, kidney issues, stomach inflammation and nitrogen buildup. People with poor kidney function face higher risks[25].
Corticosteroids	Intraarticular (a single joint) and systemic (IV, IM, or oral) delivery methods are effective; however, rebound inflammation and side effects may occur[3].
To prevent acute attacks	
Colchicine	Orally effective at 0.5-1.0 mg daily, with dose adjusted to avoid diarrhea[73,75].
NSAIDs	Used when colchicine alone isn't enough and attacks happen often. Typical dose: 150-300 mg indomethacin daily or equivalent[32].
To lower serum urate concentrations	
Probenecid	Boosts urate excretion; effect reversed by salicylates. Highly protein-bound in blood. Interferes with other drug excretion. Serious side effects are uncommon, but nausea and rash affect up to 10%. Risk of kidney stones[4,15].
Sulfinpyrazone	Stronger uric acid excretion than probenecid. Also reduces blood clotting. Almost entirely protein-bound. Short-acting, but metabolites increase uric acid excretion. Salicylates decrease its effects. Risk of kidney stones[16,34,68].
Salicylate	lowers the excretion of urate; large dosages (e.g. 1 g of aspirin with 1 g of sodium bicarbonate five times a day) have uricosuric effects; clinically unsuitable for continuous usage[74].
Diflunisal	A nonsteroidal anti-inflammatory drug that relieves pain and increases uric acid excretion[19].
Benzbromarone	This long-acting uricosuric medication has limited overseas availability[59].
Allopurinol	Unique xanthine oxidase inhibitor that converts to long-acting oxypurinol. Once-daily dosing is possible. Kidney function affects oxypurinol clearance, which uricosurics can enhance[26,52,60].

Management of Gout using Joint Replacement Surgery: When gout reached a severe level, synovial fluid looked hazy and yellow, necessitating knee aspirations. A knee replacement may be required if gout damages the knee joint[6]. According to the surgeon's assessment, the tissue showed signs of infection during the procedure. There were no noticeable deposits of chalky material[12]. The infectious disease team assessed the patient and prescribed a 6-week intravenous cefazolin course. This medication was administered through a peripherally inserted central catheter. Additionally, the patient received physical and occupational therapy services at their residence. Following the operation, the patient reported less pain. When examined, there was a noticeable decrease in redness (erythema) and an improved range of motion[13].

Treatment of Gout with Laser Therapy: A novel approach for managing gout involves using Low Intensity Laser Therapy (LILT). When correctly applied, this therapeutic method has been shown to promptly and substantially alleviate the pain and inflammation linked to acute gout flare-ups. As a result, it naturally reduces or eliminates the need for medication[8]. LILT quickly decreases inflammation around the affected joints while also easing severe pain. It is believed that cells absorb visible or near-infrared light particles through structures called chromophores. These chromophores, such as cytochrome c oxidase found in mitochondria, are thought to be the key to the therapy's effectiveness[58]. Changes in cytochrome c oxidase activity lead to a boost in adenosine triphosphate (ATP) production. ATP is a crucial source of energy for cells. This increase in ATP helps to restore normal cell function, alleviates pain and promotes healing[67].

Herbal drugs: Worldwide, the use of plant-based medications for treating various illnesses is growing since these medications are considered safer than synthetic ones. India is home to abundant fragrant and medicinal plants[53]. Over 17,500 wild plant species may be found in India and 4000 have therapeutic significance[55]. Because they come from natural sources and have a history of long-term usage as folk remedies, herbal medicines are considered non-toxic or safe compared to allopathic pharmaceuticals[78].

***In vivo* experimental models for gout**

Hyperuricemia model caused by potassium oxonate: Potassium oxonate, a competitive uricase inhibitor, develops hyperuricemia in rodents. Uric acid is produced as a byproduct of purine nucleotide use. The enzyme xanthine oxidase transforms two purine nucleic acids, adenine and guanine into uric acid[61]. Humans and rats have distinct purine metabolic pathways. Purine metabolites are eliminated by the kidneys as urine and because uric acid is poorly soluble in water, it tends to accumulate throughout the body, particularly in joints.

Table 2
Indian medicinal plants used in the treatment of gout

S.N.	Plant name	Family	Part used	Phytochemical constituent	Dose
1	*Andrographis paniculata*[28,50]	Acanthaceae	Leaves	Saponins, Phenols, Tannins, Alkaloids.	50, 100, 200 mg/kg, p.o.
2	*Chrysanthemum morifolium*[44]	Asteraceae	Dried flowers	Flavonoids and Polyphenols.	25, 50 mg/kg p.o.
3	*Citrullus colocynthis*[18]	Cucurbitaceae	Fruit	Flavonoids and Polyphenols.	100 mg/kg p.o.
4	*Clerodendrum trichotomum*[30]	Lamiaceae	Leaves	Not Mentioned	450 mg/kg p.o.
5	*Gnaphalium affine*[77]	Asteraceae	Not mentioned	Flavonoids	100, 200, 400 mg/kg p.o.
6	*Mollugo pentaphylla*[35]	Molluginaceae	Whole MP plant	Carbohydrates, Saponins, Tannins, Terpenoids, Flavonoids, Steroids, Phenols, Alkaloids.	150, 300 mg/kg, p.o.
7	*Ocimum basilium*[40]	Lamiaceae	Leaves	Tannins, Flavonoids, Alkaloids, Steroids, Carbohydrates	200, 400mg/kg,
8	*Phyllanthus emblica*[54]	Phyllanthus	Fruit	Not Mentioned	200, 400 mg/kg, p.o.
9	*Sophora japonica*[31]	Fabaceae	Flower bud	Flavonoids or Polyphenols.	200, 400, 600 mg/kg, p.o.
10	*Zingiber officinale*[43]	Zingiberaceae	Roots	Alkaloids, Polyphenols.	250 mg/kg, p.o.

Table 3
Chinese medicinal plants used in the treatment of gout

S.N.	Plant name	Family	Part used	Phytochemical constituent	Dose
1	*Smilax riparia*[69]	Smilacaceae	Roots and rhizomes	Saponins	500 mg/kg p.o.
2	*Dipterocarpus alatus*[76]	Dipterocarpaceae	Branches and twigs	Polyphenol	20, 40 and 60 mg/kg p.o.
3	*Rhizoma smilacis glabrae*[36]	Liliaceae	Roots	Astilbin, isoastilbin neoisoastilbin and engeletin	10, 30, 90 mg/kg p.o.
4	*Smilax china L*[64]	Smilacaceae	Roots	Astilbin	5, 10 & 20 mg/kg p.o.
5	*Prunus mume*[70]	Rosaceae	Fruit	Neochlorogenic acid, Chlorogenic acid, Cryptogenic acid.	263, 526 mg/kg, p.o.

Table 4
Malaysian medicinal plants used in the treatment of gout

S.N.	Plant name	Family	Part used	Phytochemical constituent	Dose
1	*Artemisia vulgaris L.*[57]	Asteraceae	Leaves	Alkaloids, flavonoids, tannins, glycosides, saponins and steroids.	50, 100, 200, 400, 800 mg/kg p.o.
2	*Curcuma longa*[11]	Zingiberaceae	Roots	Polyphenols	20, 40 mg/kg p.o.
3	*Manilkara zapota*[9]	Sapotaceae	Leaves	Flavonoid	1, 3 g/kg Body weight, p.o.
4	*Marantodes pumilum*[51]	Primulaceae	Leaves and Roots	Flavonoids glycosides	50, 100, 200 mg/kg p.o.
5	*Zingiber officinale*[1]	Zingiberaceae	Roots	Flavonoid	100 mg/kg p.o.

An enzyme is present in animal uricase in place of a xanthine oxidase enzyme. Urinary acid is converted to allantoin, a water-soluble substance that facilitates its easier excretion through the urine, by the uricase enzyme, commonly referred to as uric oxidase[66]. The primary idea behind the rodent hyperuricemia model is to increase uric acid supply, to decrease uric acid excretion and to inhibit uricase. In rats, mice, rabbits, dogs and pigs, potassium oxonate is the substance that inhibits the function of uricase and causes hyperuricemia[7].

Hyperuricemia model caused by Monosodium urate (MSU): The development of MSU crystals within joints initiates gout disease. Since their discovery in joints in 1961, these crystals have been recognized as inflammation triggers. Finding MSU crystals is a key requirement for confirming a gout diagnosis[47]. MSU crystals activate neutrophils, synovial cells and monocytes-macrophages, enabling them to generate cytokines including iNOS (inducible nitric oxide synthase), TNF (tumor necrosis factor) and IL-1 (interleukin-1)[42]. Numerous chemicals are linked to the development of acute inflammation during gout flare-ups[49]. Oxidative stress from iNOS affects how synoviocytes survive by impacting mitochondrial function. It also reduces proteoglycan production in chondrocytes through PGE2, which blocks chondrocyte cell death (apoptosis)[5,38,63].

Gout, the most common inflammatory arthritis, stems from hyperuricemia (serum uric acid >7 mg/dL in men, >6 mg/dL in women) and was first noted in ancient Egypt around 2640 BC. Hyperuricemia arises from excessive uric acid production or poor excretion, affecting about 21% of the global population by 2016. Uric acid, the final product of purine metabolism, was identified in 1776 by Scheele. Insoluble at physiological conditions, it saturates at 6.6 mg/dL. Unlike other species, humans lack uricase, an enzyme that converts uric acid to soluble allantoin. Xanthine oxidase drives uric acid formation by converting hypoxanthine. High-purine diets, alcohol, genetic factors and kidney issues increase hyperuricemia risk, as do secondary factors like cancer and certain medications. Gout, more common in men (8.2%) than women (2.3%), is prevalent in affluent regions, with early-onset cases (before age 40) affecting 600,000–700,000 Americans.

Patients are advised to limit purine-rich foods like meat, fish and alcohol. Uric acid crystals in joints trigger gouty arthritis by initiating an inflammatory process involving synovial cells, mast cells, monocytes, neutrophils and macrophages. Key mediators include IL-1, IL-8 and TNF-α, which promote neutrophil activation, vasodilation and tissue damage. Acute gout episodes typically self-resolve, while chronic gout leads to cartilage degradation, bone erosions and severe synovitis due to sustained inflammation.

Potassium oxonate, a uricase inhibitor, induces hyperuricemia in rodents by raising uric acid levels and reducing its excretion. From purine metabolism, uric acid accumulates in joints, forming monosodium urate (MSU)

crystals that trigger inflammation and gout. These crystals activate immune cells to release pro-inflammatory cytokines (iNOS, TNF, IL-1), causing oxidative stress, mitochondrial dysfunction and reduced chondrocyte proteoglycan production, leading to joint damage during acute gout flare-ups.

The uricase enzyme, which transforms uric acid into the more excretable allantoin, is inhibited in the potassium oxonate-induced gout rat model to create hyperuricemia artificially. As a uricase inhibitor, potassium oxonate raises the amounts of uric acid in the blood. This hyperuricemia mimics the pathophysiological circumstances of gout by promoting the deposition of monosodium urate (MSU) crystals in joints and periarticular tissues. When the deposited crystals activate the NLRP3 inflammasome in macrophages, pro-inflammatory cytokines such as interleukin-1β (IL-1β), tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) are released, causing an inflammatory response.

Conclusion

In conclusion, gout remains a significant global health challenge, requiring an integrated approach to its management. While traditional medicinal herbs from India, Malaysia and China offer promising avenues, their therapeutic potential must be substantiated through rigorous scientific evaluation. The advent of novel treatment strategies such as physiotherapy, acupuncture, joint replacement surgery and laser therapy further enhances the ability to address this condition comprehensively. Future research focusing on synergistic approaches, combining traditional remedies with innovative treatments, holds the promise of significantly improving patient care and quality of life.

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