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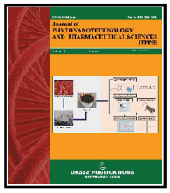

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# Management of Acute Gout: Review of the treatment framework

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**Abstract**

Gout, a condition characterized by the accumulation of monosodium urate crystals in the joints, is associated with hyperuricemia. It is linked to multiple etiologies such as genetics, diet and comorbidities and progresses from asymptomatic hyperuricemia to acute flares and, if untreated, to chronic gout. Gout flares are marked by sudden, severe joint pain and inflammation, requiring timely intervention. Effective management of gout requires a combination of acute symptoms relief and prevention of future flares. Anti-inflammatory agents such as NSAIDs, colchicine or glucocorticoids are pivotal in treating acute attacks. Recently, canakinumab, an IL-1 inhibitor, has been approved for treating gout flares, representing a significant advancement in therapy. Alongside drug treatments, non-pharmacological approaches, such as dietary and lifestyle modifications, play an important role in managing gout and its symptoms. These modifications help prevent recurrent attacks and reduce the severity of symptoms over time. Personalized treatment plans are crucial for achieving optimal outcomes. Medicinal plants are increasingly being adopted due to their natural origin and historical evidence of efficacy and safety with various plants shown to have xanthine oxidase inhibition activity for use in treatment of gout. The individualized approach to therapy is critical, as treatment needs may vary based on the patient's condition, comorbidities, and response to medications. It is important to combine traditional treatments with newer therapies and lifestyle modifications, to provide a holistic approach to acute gout management and improve the patient's quality of life.

## 1. Introduction

Gout, known as the 'Disease of Kings (Fenando *et al*., 2023), is a type of inflammatory arthritis distinguished by the build-up of monosodium urate (MSU) monohydrate crystals in the joint fluid and other tissues. It is affiliated with hyperuricemia, characterised by serum urate levels of 6.8 mg/dl or more (Mikuls, 2022). Hippocrates from ancient Greece was the first one to describe gout. Gout is caused by multiple factors such as genetics, concomitant diseases and diet. Irrespective of the cause, the outcome is increased levels of uric acid in serum, which eventually, leads to clinical gout (Fenando *et al*., 2023). MSU crystals are formed when levels of urate increase, deposition of these crystals in and around various joints, indicates gout onset. The symptoms of gout develop in four stages- asymptomatic hyperuricemia, formation of MSU crystals, intermittent and chronic gout (Zhang *et al*., 2022). Gout manifests as pain, tenderness and inflammation of peripheral joints leading to the formation of tophi (Clebak *et al*., 2020). Gout's incidence and prevalence differ depending on the population studied and the research methodology, incidence ranges from 0.58-2.89 per 1,000 person-years and prevalence from <1% to 6.8%. Males have a higher prevalence of developing gout than females, but this difference reduces with age as reducing levels of estrogen produces a uricosuric effect (Zhang *et al*., 2022). Gout occurs in 2 clinical phases. The first phase is distinguished by spontaneously resolving intermittent acute attacks, occurs for 7-10 days, and has asymptomatic periods between the attacks. The second phase occurs when hyperuricemia is insufficiently treated and is characterized by the presence of chronic tophi and often involves polyarticular attacks. Gout flares are very painful and considerably disabling. It affects single joints usually but multiple joints can also be involved. If left untreated, the flares can resolve independently within weeks, especially in the early stages. However, with treatment improvement symptoms are resolved faster (Mikuls, 2022). The goal of treating acute flares is mainly to reduce pain, inflammation and other symptoms. With the long-term goal being the prevention of future flares (Fenando *et al*., 2023). Though, pharmacological management is the primary approach for treating gout, non-pharmacological approaches (Abhishek and Doherty, 2018) are also recommended because an unhealthy diet, hyperglycemia and adiposity can cause the development of gout (Zhang *et al.,* 2022). Although, there exists a good understanding of molecular causes of hyperuricemia and inflammation in gout. There are significant gaps in the standard of care provided to gout patients. Despite healthcare providers' experience, some shortcomings are still present in patient education and medication adherence to gout therapy (Khanna *et al*., 2012). During this time of significant advances, we must commit to following a rational approach to the management of gout (Burns and Wortmann, 2011).

### 1.1 Acute gout attack

It is also called gout flares. It is an early presentation of gout and is marked by abrupt onset of inflammation and severe pain in joints

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that peaks within 24 h of the attack. Gout flare-ups often elicit local inflammation presented as an erythematous, swollen, warm joint. Fever, malaise and fatigue are the systemic features of joint inflammation (Fenando *et al*., 2023; Rymal and Rizzolo, 2014). Gout flares are usually monoarticular. In most cases (50% of cases), it involves the initial site of the first metatarsophalangeal (MTP) joint and other sites of involvement are talar, subtalar, ankle and knee. 10-40% of cases involve multiple joints, and polyarticular gout flares, usually in patients suffering from long-standing diseases (Rymal and Rizzolo, 2014). Other than joints, tendons and bursa can also be affected. The initial attack eases within 3-14 days, even without treatment, but further attacks will be prolonged. A second attack occurs within a year in about 60% of patients and 3 years in 80% of patients. The attacks may be precipitated by local trauma, changes in eating patterns, weight loss or weight gain, use of diuretics and starting of urate-lowering drugs (Fenando *et al*., 2023).

## 2. Therapy

The main objective of acute gout treatment is to hasten the relief from pain, inflammation and disability (Mikuls, 2022). Therapy must be initiated within 24 h of the onset of symptoms. The therapy duration should be at least a week to 10 days to prevent rebound flare-ups (Fenando *et al*., 2023). The first-line treatment for acute gout attack management is non-steroidal anti-inflammatory drugs (NSAIDs), colchicine and glucocorticoids (systemic). Non-pharmacological measures include ice application, rest of the affected joints and dietary modifications such as following a low-fat, low-purine diet (Mikuls, 2022).

### 2.1 General principles of therapy

- The faster the therapy is initiated for gout flare, the more prompt and thorough resolution of symptoms occurs.
- The period of gout flare therapy varies from days to weeks, which varies depending on when therapy is initiated.
- When patients are on urate-lowering therapy and gout flare occurs, then continue the ULT without any interference because there is not any benefit in temporary cessation.
- Prophylaxis of gout flares using anti-inflammatory agents can be continued in the starting months of ULT (Fenando *et al*., 2023).

### 2.2 Selection of agents

The first-line treatment for gout flares such as colchicine, NSAIDs and glucocorticoids should be initiated immediately after the starting of symptoms. The selection of an agent for early flare therapy depends on the patient's comorbid conditions and the agent familiarity of the prescriber. The initial choice of agents also depends on the patient's experience, successful use, and ease of access to medication. Expert guidelines increasingly favor the recommendation of glucocorticoids as a first-line treatment for gout flares (Khanna *et al*., 2012; Qaseem *et al*., 2017; Richette *et al*., 2017).

### 2.3 Non-steroidal anti-inflammatory drugs

NSAIDs are the first-line treatment or the choice of treatment as there is good evidence of efficacy in acute gout unless their use is contraindicated (Clebak *et al*., 2020; Stamp and Chapman, 2013). The only 3 NSAIDs approved for use in acute gout treatment are : (i) Naproxen, (ii) Indomethacin, and (iii) Sulindac. Other available NSAIDs are also considered effective due to similar pharmacokinetics at recommended doses (Rymal and Rizzolo, 2014; Coburn and Mikuls, 2016). Indomethacin historically was the preferred choice (Hainer *et al*., 2014), but now it is not preferred due to its toxicity. Aspirin is not used to treat gout flares as kidney accumulation of uric acid will be induced by low-dose salicylates. Despite this effect, it is recommended to continue low-dose aspirin for cardiovascular prophylaxis during acute gout treatment (Yü and Gutman, 1959; Yü *et al*., 1963; Caspi *et al*., 2000; Segal *et al*., 2006; Zhang *et al.,* 2014). The risk-benefit ratio for NSAIDs must be assessed for the patients before initiation of therapy; the adverse reactions of NSAIDs include risk of bleeding, GI distress, oedema and hypertension (Rymal and Rizzolo, 2014). Multiple NSAIDs must not be used concurrently for treatment in patients and interviewing the patients about their medications will help avoid such unintended use (Gaffo, 2023).

### 2.4 COX-2 selective inhibitors

Celecoxib will be used in patients who are intolerant to traditional NSAIDs or to prevent adverse GI effects (Fenando *et al*., 2023; Rymal and Rizzolo, 2014). Since both COX-1 and COX-2 inhibitors have interconnected physiological functions, the COX-2 inhibitors do not have any major advantage over the traditional NSAIDs regarding renal toxicity (Stamp and Chapman, 2013). The dose and frequency NSAIDs and COX-2 inhibitors are given in the following Table 1.

**Table 1: NSAIDs and COX-2 inhibitors dose and frequency for acute gout**

| NSAIDs (oral) | Dose | Frequency |
|---|---|---|
| Naproxen | 500 mg | BD |
| Indomethacin | 50 mg | TID |
| Celecoxib | Initial dose- 200-400 mg followed by 200 mg | BD |

#### 2.4.1 Duration of therapy

Treatment with NSAIDs is most effective when it is initiated within 48 h of symptoms development. Reduction in dose of NSAIDs can be done when there is a significant reduction in symptoms, but dosing frequency should be maintained. Discontinuation of NSAIDs can be done in a few days after the clinical signs and symptoms are resolved completely (Gaffo, 2023). Usually, recommended doses of NSAIDs are given for the initial three days of treatment and then the dose is tapered corresponding to the patient's progress (Fernando *et al*., 2023). Anti-inflammatory therapy with NSAIDs is done for duration of 5-7 days, if treatment is initiated within 12-36 h of symptom development. A delay in starting the treatment can make the flares less responsive and will require a longer course of therapy (Gaffo, 2023).

#### 2.4.2 Contraindications

NSAIDs are the first line treatment of acute gout unless their use is contraindicated, the contraindications include:

- Cardiovascular disease (uncontrolled hypertension or heart failure)
- Chronic kidney disease (creatinine clearance of less than 60 ml/min per 1.73 square meters)
- NSAID allergy

- Active duodenal or gastric ulcer
- Cerebrovascular disease
- History of gastric bypass
- History of gastrointestinal bleeding
- Pregnancy (Fenando *et al*., 2023; Clebak *et al*., 2020)

### 2.4.3 Efficacy of NSAIDs

There are a few high-quality randomized trials assessing NSAIDs efficacy in gout flares. A randomized open-label trial consisting of 399 participants having gout flares compared oral naproxen 750 mg followed by 250 mg, thrice a day for one week with a low dose of colchicine 0.5 mg thrice a day for four days; after a week there was not any variation in pain intensity, but there were reduced adverse effects with naproxen (Roddy *et al*., 2020).

## 2.5 Colchicine

Colchicine, an anti-inflammatory drug used in the prevention and therapy of acute gout attacks (Rymal and Rizzolo, 2014; Coburn and Mikuls, 2016). Oral colchicine was approved in 2009 by the FDA for acute gout (Mikuls, 2022). Colchicine, a tricyclic alkaloid, interrupts various inflammatory response pathways. Its main mechanism of action is the polymerization of cytoskeletal microtubules, which is important in the functioning of neutrophils (Yang, 2010). Tubulin is the primary target for colchicine action. Colchicine acts by binding to unpolymerized tubulin and forms a complex of colchicine-tubulin, which regulates the following by forming complexes:

- Functioning of microtubule
- Function of cytoskeleton
- Cell proliferation
- Expression of the gene
- Signal transduction
- Chemotaxis
- Neutrophil secretion of granule contents

The complex decreases neutrophil adhesion by suppressing the redistribution of E-selectin in the endothelial membrane. On oral administration, colchicine will be readily bioavailable for cellular uptake because of its lipophilic nature and it is cleared by hepatic elimination (Fernando *et al*., 2023).

### 2.5.1 Trial data on colchicine

- For centuries colchicine has been used to treat gout flares and some existing studies show that it is as effective as NSAIDs. A randomized open-label clinical trial involving 399 participants suffering from gout flares showed that colchicine and naproxen had equal efficacy in reducing pain (Roddy *et al*., 2020).
- In another randomized clinical trial, colchicine significantly reduced pain compared to placebo. A dose of 1.2 mg of colchicine was started at the onset of the flare, followed by 0.6 mg an hour later (low-dose regimen) and had more efficacy than placebo in pain reduction by 50% or more 24 h later (37.8% and 15.5% response rates, respectively).
- Studies show that this low-dose regimen had similar efficacy as the high-dose regimen, *i.e.,* 1.2 mg initial dose and then 0.6 mg/h for 6 h, but had fewer adverse gastrointestinal effects (Mikuls, 2022) like diarrhoea and emesis (Gaffo, 2023). The low-dose regimen saw a 40% absolute risk reduction in adverse effects. However, the study lacks information on follow-up treatment of residual pain beyond 32 h after the flare (Coburn and Mikuls, 2016). Treatment of acute gout flares with colchicine should be initiated within the first 24-36 h from the onset of symptoms, as it is less effective when given beyond 72-96 h after the onset of symptoms (Rymal and Rizzolo, 2014; Hainer *et al*., 2014).
- A total of 1.8 mg colchicine is administered on the first day of therapy, with 1.2 mg and 0.6 mg after one hour. After the resolution of the flare, the dose of colchicine is modified to 0.6 mg twice a day for two days.
- In patients already on colchicine prophylaxis during the flare, this regimen is used till the flare is treated and then we can resume their usual prophylactic dose (0.6 mg once or twice a day).
- If two or three doses of low-dose colchicine fail to alleviate gout flares, an alternative anti-inflammatory agent such as NSAIDs or glucocorticoids must be added to the treatment regimen (Yang, 2010; Terkeltaub *et al*., 2010; Colchicine and other drugs for gout, 2009).
- Traditionally, a dose of 0.6 mg was used every 12-24 h (Coburn and Mikuls, 2016).
- The European Alliance of Associations for Rheumatology recommends a maximum of 3 doses of 0.5 mg per day of colchicine for acute gout. The US FDA approves a total dose of not more than 1.8 mg on the first day of gout flare (Fenando *et al*., 2023).

### 2.5.2 Dosage modifications

The doses are modified in high-risk groups, it is recommended to not use more than 0.3 mg on the day of the flare and subsequently, this dose is not repeated for the next 3-7 days or more in such patients. The guidelines to be followed while prescribing colchicine to high-risk patients are:

- Patients with advanced kidney or hepatic impairment (CrCl of <30 ml/min or Child-Pugh C cirrhosis), who are receiving any interacting medications, should not take colchicine regardless of their recent medications.
- Patients who were prescribed colchicine for prophylaxis within the past 14 days, with normal renal and hepatic function, should only take the medication, if they have not used a medication that is a potent CYP3A4 inhibitor or is a P-glycoprotein inhibitor within the last 2 weeks.
- Patients who were prescribed colchicine for prophylaxis within the past 14 days, with renal and hepatic impairment, should only take the medication, if they have not used a medication that is a moderate CYP3A4 inhibitor within the last 2 weeks (Fenando *et al*., 2023).

### 2.5.3 Adverse effects and toxicities

Adverse effects of colchicine include common GIT symptoms like diarrhea, abdominal cramping and pain, nausea, vomiting and other

effects like myotoxicity and myelosuppression such as leukopenia, thrombocytopenia and aplastic anemia. In patients experiencing paresthesia, numbness and/or weakness, colchicine-induced neuromyopathy, a complication of chronic therapy, is suspected especially in individuals with reduced CrCl. Severe toxicities are rare in short courses of colchicine but can occur in high-dose regimens. The severe toxicities that can occur are as listed:

- Cytopenia
- Rhabdomyolysis/myopathy
- Peripheral neuropathy
- Hepatic failure
- Severe cutaneous eruption

Intravenous colchicine administration is strongly advised against as it poses a risk of serious adverse effects, including death (Fenando *et al*., 2023; Gaffo, 2023).

#### 2.5.4 Contraindications and drug interactions

It is suggested to contraindicate colchicine use in individuals with kidney or hepatic impairment if they have recently, within the last 2 weeks, used medications that inhibit CYP3A4 and P-glycoprotein efflux pump, as they may further reduce colchicine clearance by interfering with its metabolism. This includes clarithromycin, azithromycin, ketoconazole, verapamil and antiretroviral drugs. The combination of these drugs with colchicine increases the possibility of myelosuppression and can cause fatal pancytopenia (Hung *et al*., 2005). Patients with any degree of kidney or hepatic insufficiency receiving a P-glycoprotein inhibitor or drugs that reduce CYP3A4 are contraindicated for colchicine use (Yang, 2010; Terkeltaub, 2009). According to the FDA, caution must be taken while using colchicine along with less potent CYP3A4 inhibitors such as amiodarone, diltiazem, grapefruit juice, *etc.*

### 2.6 Glucocorticoids

When patients do not respond to NSAIDs or colchicine after three days of therapy (Gaffo, 2023) or are contraindicated to these treatments, then glucocorticoids are the first-line treatment. The three forms of glucocorticoids-intraarticular, oral and parenteral are employed in the therapy of gout. Glucocorticoids are administered intra-articularly for monoarticular flares and orally for polyarticular flare-ups. They have similar efficacy to other agents used in gout flare treatments with no greater chances of adverse effects in most patients (Fenando *et al*., 2023).

#### 2.6.1 Intra articular glucocorticoids

They are recommended for use when gout flare is limited to one or two joints in the patient (Gaffo, 2023) and are preferred for use in such cases over parenteral glucocorticoids due to lower risk of adverse effects (Zhang *et al*., 2021). The published evidence about glucocorticoids intra-articularly in gout therapy is limited to small, open-label trials (Fernández *et al*., 1999).

#### 2.6.2 Oral glucocorticoids

They are recommended for use when gout flares affect multiple joints in the patient. Prednisolone's initial dose is 30-40 mg once daily or in divided doses twice daily till the resolution of the flare begins and the taper dose over the next 7-10 days (Alloway *et al*., 1993; Zeng *et al*., 2021). In a clinical trial comparing oral prednisolone 30 mg for 5 days Vs a combination of indomethacin and intramuscular injection of diclofenac 75 mg. There was no significant difference in pain reduction and they had similar efficacy (Man *et al*., 2007).

#### 2.6.3 Parenteral glucocorticoids

Patients who are not able to take the medication orally or are not candidates for intraarticular injection of glucocorticoid, intramuscular or intravenous glucocorticoids are suggested for such patients. The usual dose of IV methylprednisolone is 20 mg twice a day, gradually reducing the dose and when improvement begins transition to oral prednisone (Fenando *et al*., 2023). Meta-analysis of a few randomised trials shows that parenteral glucocorticoids have similar efficacy as other therapies for gout flares (Zeng *et al*., 2021). Rebound flares commonly occur after discontinuation of glucocorticoid; hence, to reduce the risk the doses are tapered over 10-14 days after the resolution of symptoms or provide preventative treatment (Hainer *et al*., 2014), such as initiating low-dose adjunctive colchicine during tapering. It is recommended to extend the tapering of doses up to 14-21 days in individuals exhibiting rebound flares.The frequent adverse effects of moderate-high doses include hyperglycemia, oedema, hypertension and mood changes. Frequent and repeated dosing of glucocorticoids should be avoided to limit such adverse effects. Other alternative treatment approaches must be selected in individuals suffering from uncontrolled diabetes, hypertension, and known glucocorticoid intolerance (Fenando *et al*., 2023).

### 2.7 Interleukin-1 inhibitors

Interleukins-1(IL-1) inhibitors are suggested for use in the treatment of gout flares when the first-line treatments such as NSAIDs, colchicine and glucocorticoids are contraindicated, intolerant or ineffective in the patients (Gout: diagnosis and management, 2022). IL-1, a proinflammatory cytokine, highlights the pivotal role it plays in the inflammatory reaction to MSU crystals, making it a target for the treatment of gout (Sivera *et al.,* 2014; Martinon *et al*., 2006). IL-1 antagonists are effective in the pathogenesis of various autoinflammatory diseases, offering evidence for their possible role in the inflammatory process of gout (Dinarello, 2011). In humans, blocking of IL-1 helps block the inflammatory cascade; therefore it prevents gout flare-ups and manages the manifestation of acute refractory gout (Sivera *et al*., 2014; Tran *et al*., 2013). IL-1 inhibitor's major adverse effects include injection site reactions and infections. The main limitation of their extensive use is their cost (Stamp and Chapman, 2013). The three IL-1 inhibitors used in gout are canakinumab (FDA-approved), anakinra and rilonacept (off-label use in gout).

#### 2.7.1 Canakinumab

A human monoclonal anti-IL-1β antibody available as a subcutaneous injection (Rymal and Rizzolo, 2014). It acts by binding to IL-1β and reduces inflammatory activity by obstructing its interaction with the IL-1 receptor. Canakinumab injection may be required every 2 months due to its long plasma half-life (26 days) (Schlesinger, 2014). Two randomized trials involving 456 gout flare patients demonstrated that canakinumab 150 mg showed greater pain reduction in 72 h compared to triamcinolone acetate, intramuscular (So *et al*., 2010). In a 2021 meta-analysis, it was noted that canakinumab was better in reducing pain and joint tenderness comparatively to the other anti-inflammatory interventions on day 2 (Afinogenova *et al*., 2022).

Canakinumab is an approved drug in Europe to treat gout patients experiencing at least 3 flares in a year that cannot be managed using other therapies (Schlesinger *et al*., 2012; Janssen *et al*., 2019). On 25th August 2023, the US FDA approved canakinumab (Ilaris) to treat gout flares in adult patients intolerant, contraindicated or provide inadequate response to NSAIDs and/or colchicine or patients for whom repeated courses of glucocorticoids are inappropriate. The recommended dose of ILARIS for gout flares is 150 mg administered subcutaneously in adult patients, in patients who need re-treatment, a minimum of 12-week interval is required before a new dose administration.

### 2.7.2 Anakinra

A recombinant human IL-1 receptor antagonist, produced by recombinant-DNA technology using an *E. coli* bacterial expression system. It differs only by a single methionine residue at its amino acid terminus from the native human IL-1 receptor antagonists. It is used as a 100 mg/day SC injection and is preferred due to its short plasma half-life (4-6 h) (Fenando *et al*., 2023; Gaffo, 2023; Schlesinger, 2014). Some randomised trials have shown that anakinra is effective for the treatment of gout flares, although, it poses an increased risk of rebound flares. A randomized trial involving 88 patients with crystal-proven gout flare, anakinra was compared to the standard therapies such as colchicine, naproxen and oral glucocorticoids. Anakinra, 100 mg given for 5 consecutive days showed similar short-term improvements in pain, tenderness and swelling like that of the comparator (Janssen *et al*., 2019). Another different randomized trial involving 165 patients suffering from gout flare who could not be treated with NSAIDs or colchicine, it was found that 100-200 mg of anakinra used daily provided similar pain reduction as 40 mg of triamcinolone, single intramuscular injection, after 24-72 h (Saag *et al*., 2021).

### 2.7.3 Rilonacept

It is a fusion protein which acts by binding to IL-1β. It prevents IL-1 from binding to the cell surface receptors and thus from inducing inflammation. It has a plasma half-life of 8.6 days, requiring a single weekly injection (Schlesinger, 2014). The FDA committee recognizes that rilonacept has a moderate treatment effect in gout flare prevention and suggested that the trials should include gout patients who are intolerant or are contraindicated to NSAIDs or colchicine or those with decreased renal function. Further efficacy and long-term safety studies are necessary for the use of rilonacept in gout flares; therefore, it is not recommended as an alternative treatment for gout patients who are resistant to conventional gout therapy. The FDA emphasizes that there exists a role for IL-1 inhibitors in managing gout (Tran *et al*., 2013).

## 3. Medicinal plants used to treat gout

The increasing reliance on medicinal plants for treating various ailments stems from their perceived safety and accessibility compared to synthetic drugs, which often come with significant side effects. For instance, drugs like glucocorticoids can cause hyperglycemia, oedema and hypertension. In contrast, herbal medicines are regarded as safer due to their natural origin and long-standing use in traditional practices. This shift toward plant-based treatments reflects a growing preference for natural alternatives over allopathic medications, especially in countries like India, which boasts a rich diversity of over 17,500 wild plant species, including 4,000 with recognized medicinal value (Kapoor *et al.,* 2017).

**Table 2: Medicinal plants with reported xanthine oxidase inhibitory activity**

| S.No. | Plant name | Family | Part used | Xo inhibition %(100 µg/ml) | $IC_{50}$ in µg/ml | Reference |
|---|---|---|---|---|---|---|
| 1. | *Adenanthera pavonina* | Fabaceae | Leaves | 47.15 | - | Apaya and Chichioco, 2011 |
| 2. | *Antigonon leptopus* | Polygonaceae | Leaves | 59.0 | - | Apaya and Chichioco, 2011 |
| 3. | *Averrho acarambola* | Oxalidaceae | Flowers | 2.46 ± 0.6 | - | Merriman and Dalbeth, 2011 |
| 4. | *Chammomila recutita* | Asteraceae | Flowers | - | 87.6 | Havlik *et al.,* 2010 |
| 5. | *Daucus corata* | Umbelliferae | Roots | - | Ã200 | Havlik *et al.,* 2010 |
| 6. | *Equisetum arvense* | Equistaceae | Roots | 33.13 ± 4.00 | | Owen and Johns, 1999 |
| 7. | *Capsicum annum* | Solanaceae | Fruits | - | Ã200 | Havlik *et al.,* 2010 |
| 8. | *Coriandrum sativum* | Apiaceae | Fruits | - | Ã200 | Havlik *et al.,* 2010 |
| 9. | *Crocus sativum* | Iridaceae | Whole plant | - | Ã200 | Havlik *et al.,* 2010 |
| 10. | *Tecoma stans* | Bignoniaceae | Whole plant | 41.1 ± 1.3 | - | Gobindappa *et al.,* 2011 |

## 4. Non-pharmacological therapy

The non-pharmacological approaches include lifestyle, nutritional and behavioural modifications. They are used as an adjunct to drug therapy as these modifications are not effective enough on their own to treat or prevent gout (Fenando *et al*., 2023; Mikuls, 2022).

- Obese or overweight patients are advised to achieve ideal weight.
- Moderate physical exercises are recommended but avoid vigorous physical exercise and trauma to joints (Jordan *et al*., 2007).
- Avoid or limit alcohol consumption and recommend aiming for a minimum of 3 alcohol-free days in a week (Fenando *et al*., 2023; Jordan *et al*., 2007).
- Inclusion of low-fat yogurt or skimmed milk (low-fat dairy products), cherries, soybeans, vegetables and plant-sourced proteins are recommended in the diet (Clebak *et al*., 2020).
- It is recommended to follow dietary approaches to stop hypertension (DASH) and Mediterranean diets (Zhang *et al*., 2022) but avoid diets like the atkinsdiet and 'Crash diets' (Jordan *et al*., 2007).

- Restrict consumption of high-fat foods particularly trans fatty acids (fast food, butter and cream products) and food rich in purine (red meat, organ meat, seafood) (Fenando *et al*., 2023; Zhang *et al*., 2022).
- Avoid or limit the consumption of beverages high in sugars and containing high-fructose corn syrup (Fenando *et al*., 2023).
- Ice pack application and resting the affected joint serve as an adjunct to pharmacological therapy for pain reduction (Clebak *et al.,* 2020; Jordan *et al.,* 2007).

## 5. Conclusion

Acute gout attack management requires early and appropriate therapy to prevent progression and recurrence of the condition. The mainstay of therapy used are NSAIDs, colchicine or glucocorticoids. The selection of agents for therapy is personalized for each patient according to their needs, comorbidities, tolerance to the agent and significant consideration given to the adverse effects and contraindications. Novel agents used in gout such as IL-1 inhibitors (canakinumab) are used as the agent of choice when patients are not candidates for the mainstay therapy. Known for its vast repository of medicinal and aromatic plants, India exemplifies the global trend of exploring herbal remedies for sustainable and less toxic healthcare solutions for gout. Non-pharmacological measures such as modifications of diet and changes in lifestyle complement the drug interventions. Therefore, a customized and comprehensive approach including both pharmacological and non-pharmacological interventions is essential for the effective treatment and prevention of acute gout attacks.

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## Conflict of interest

The authors declare no conflicts of interest relevant to this article

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