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GOUT: UNVEILING THE COMPLEX INTERPLAY BETWEEN PATHOPHYSIOLOGY, EPIDEMIOLOGY, GENETICS, AND THERAPEUTIC OPTIONS - A COMPREHENSIVE REVIEW

Sethuramani A.[1]*, Ajith P.[2], Chandrasamy M.[2], Raxshiya Smily J.[2], Safia farvin S.[3] and Sedhulakshmi K.[3]

[1]Assistant Professor, Department of Pharmacognosy, College of Pharmacy, Madurai Medical College, Madurai, Tamil Nadu, India.
[2]Department of Pharmacognosy, College of Pharmacy, Madurai Medical College, Madurai, Tamil Nadu, India
[3]College of Pharmacy, Madurai Medical College, Madurai, Tamil Nadu, India.

***Corresponding Author: Sethuramani A.**

Assistant Professor, Department of Pharmacognosy, College of Pharmacy, Madurai Medical College, Madurai, Tamil Nadu, India. **Email ID:** mpharm76@gmail.com

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ABSTRACT

Gouty arthritis, one of the earliest known diseases, was first identified by the Egyptians around 2640 BC. Known as 'the unwalkable disease' by Hippocrates, gout is linked historically to the consumption of rich foods and alcohol, grossing it the name 'the disease of kings'. Gout results from monosodium urate (MSU) crystals accrued due to elevated serum uric acid (SUA) levels. Although hyperuricemia is the primary cause, only a marginal with high uric acid levels ripens gout. Hyperuricemia ascends from amplified fabrication or declined seepage of uric acid, allied with circumstances like metabolic syndrome and cardiovascular disease. Pathophysiology of gout encompasses genetic insights with SLC2A9 and ABCG2 and, metabolic causes like an interruption of the xanthine oxidase enzyme activation and synthesis, and inclined levels of triglycerides are in concert with momentous roles. Common treatments include NSAIDs, corticosteroids, and medications to reduce uric acid levels, though these have side effects. There is growing interest in herbal medicines for gout, as some plants can act as xanthine oxidase inhibitors with fewer side effects.

KEYWORDS: Gouty Arthritis, Hyperuricemia, Monosodium Urate Crystals, Purines, Colchicine, Nonsteroidal Anti-inflammatory Drugs (NSAIDs), Urate-lowering Therapy, Inflammatory Arthritis, Genetic Factors, Phytochemicals.

INTRODUCTION

Gouty arthritis is one of the oldest recognized diseases, first identified by the Egyptians around 2640 BC. Podagra is an acute form of gout that affects the big toe's metatarsophalangeal joint was later described by Hippocrates in the fifth century BC, who famously called it 'the unwalkable disease.' Historically, gout has been remitted by the intake of dietary purines and unwarranted levels of alcoholic beverages, habits that were once the privilege of the wealthy. This association has led to gout being known as the 'disease of kings'.[1] The uric acid deposition in joints has been affirmed in mummified Egyptian remains from Philae, dating back roughly 4000 years. Nonetheless, Hippocrates is thought to have presumed the first exact portrayal of gout around 400 BCE. At that time, it was commonly believed that physical diseases were caused by an imbalance of the four primary humors in the body: black bile, yellow bile, blood, and phlegm. Hippocrates theorized that gout was caused by an excessive accumulation of one of these humors in the joints.[2]

The history of treating gout has been intricate. Colchicine was initially used to address gout around 500 BCE, primarily for its purgative effects rather than its anti-inflammatory benefits. Colchicum autumnale, also called meadow saffron, came from Colchis on the Black Sea and was well-known as a laxative.[3]

In 1763, Viennese physician Baron von Storck began using colchicum extract to treat acute gout. Around the same time, French military officer Nicholas Husson created a colchicum-based remedy known as 'Eau Medicinale' for treating various ailments, including gout. Roughly 30 years later, Pelletier and Caventou isolated the active compound colchicine, leading to its broader use. It is believed that Benjamin Franklin, who suffered from gout, brought the product to America in the late 1700s. By the late 1800s, high-dose salicylates were acknowledged as an effective treatment for acute gout. From 1948 to 1963, the development of corticotropin (ACTH), prednisolone, and allopurinol significantly improved gout treatment options.[4]

Gout

Gout is a systemic condition caused by the accumulation of monosodium urate (MSU) crystals in body tissues. These crystals form when serum uric acid (SUA) levels exceed a certain threshold. Although hyperuricemia is the primary cause of gout, not everyone with elevated uric acid levels develops the condition or experiences uric acid crystal formation. Only approximately 5% of individuals with uric acid levels above 9 mg/dL ultimately develop gout.[5]

Hyperuricemia is a metabolic condition caused by either increased production or reduced excretion of serum uric acid (SUA). Imbalances in SUA levels have been associated with several diseases, including gout, metabolic syndrome (MetS), cardiovascular disease, diabetes, hypertension, and kidney disease.[6]

UA is an enzymatic end product of purine metabolism in humans.[7] Purines are a class of molecules utilized by all body cells for numerous critical biochemical functions. They are produced through a complex process called the de novo synthetic pathway, undergo various interconversion steps, and are eventually broken down and eliminated as uric acid.[8]

Epdimeology

In general, gout affects 1–4 percent of the population. It impacts 1% to 2% of women and 3–6% of men in countries in the West. The prevalence might increase by up to 10% in some nations. For men and women over 80, the prevalence rises to 10% and 6%, respectively. Gout affects 2.68% of people per year. Men experience it two to six times more frequently than women. The global incidence of gout is steadily increasing as a result of improper eating habits, especially consuming fast food, not doing physical activity, and rising rates of obesity and metabolic syndrome.[9]

(A) The all-age prevalence for gout in 2019 in 204 countries and territories.

(B) Net drift of gout prevalence from 1990 to 2019 in 204 countries and territories.[10]

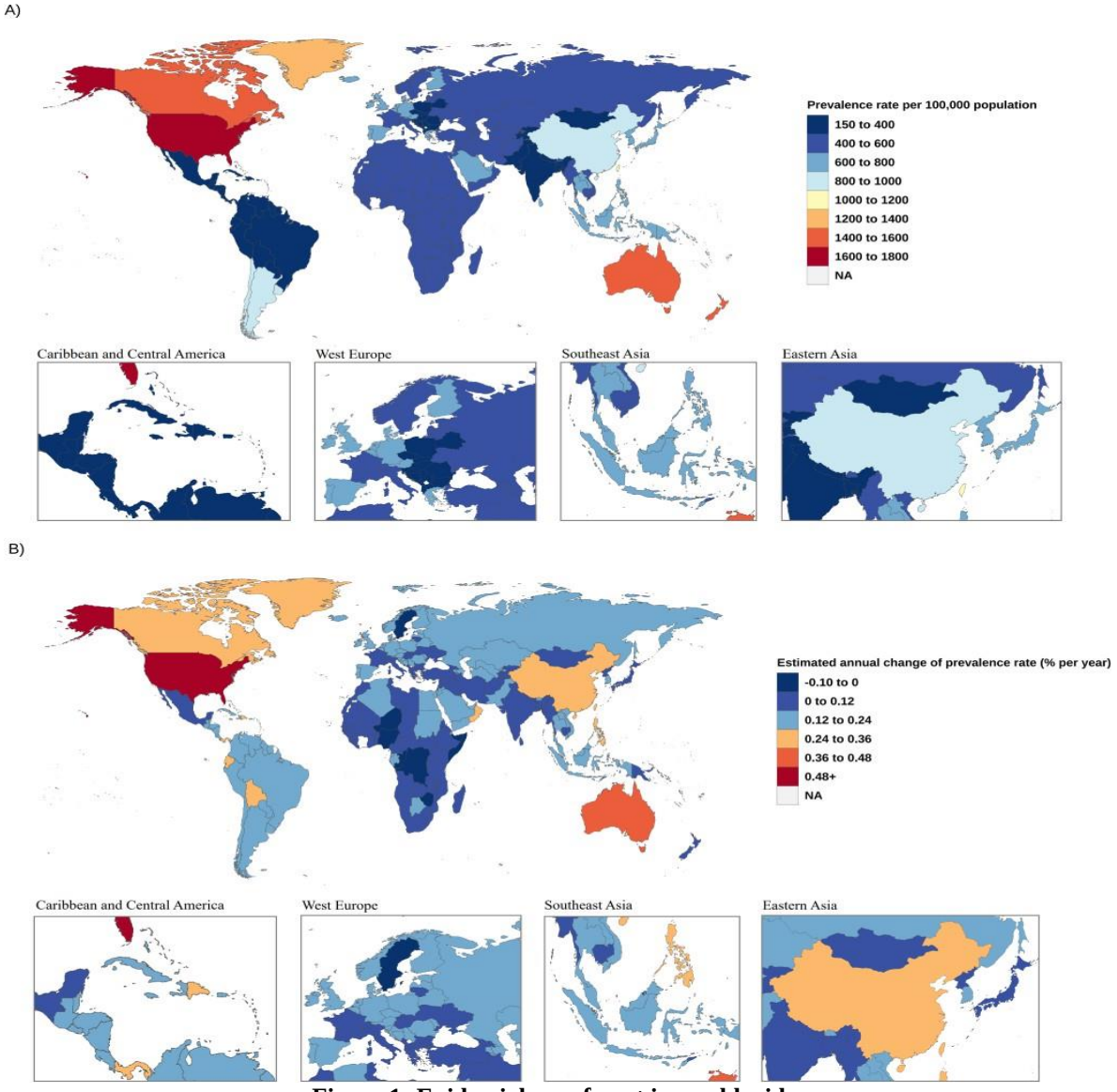

Figure 1: Epidemiology of gout in world wide.

Uric acid

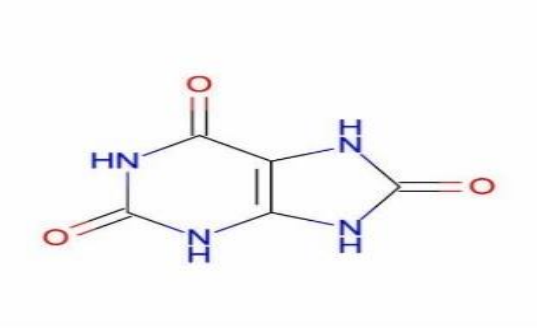

Figure 2: Structure of uric acid.

Uric acid, also known chemically as 7,9-dihydro-1H-purine-2,6,8(3H)-trione and with a molecular mass of 168 Da, is produced as a result of the breakdown of purine nucleotides, specifically adenine and guanine. This metabolic process primarily occurs in organs like the liver, intestines, muscles, kidneys, and vascular endothelium, marking the end product of purine metabolism derived largely from animal proteins. Both active and dying cells contribute to this process by breaking down their nucleic acids, adenine and guanine, which undergo deamination and dephosphorylation to produce inosine and guanosine. These compounds are further metabolized by the enzyme purine nucleoside phosphorylase into hypoxanthine and guanine, respectively. Hypoxanthine is then oxidized by xanthine oxidase to form xanthine, and guanine also converts to xanthine through similar enzymatic processes.[11]

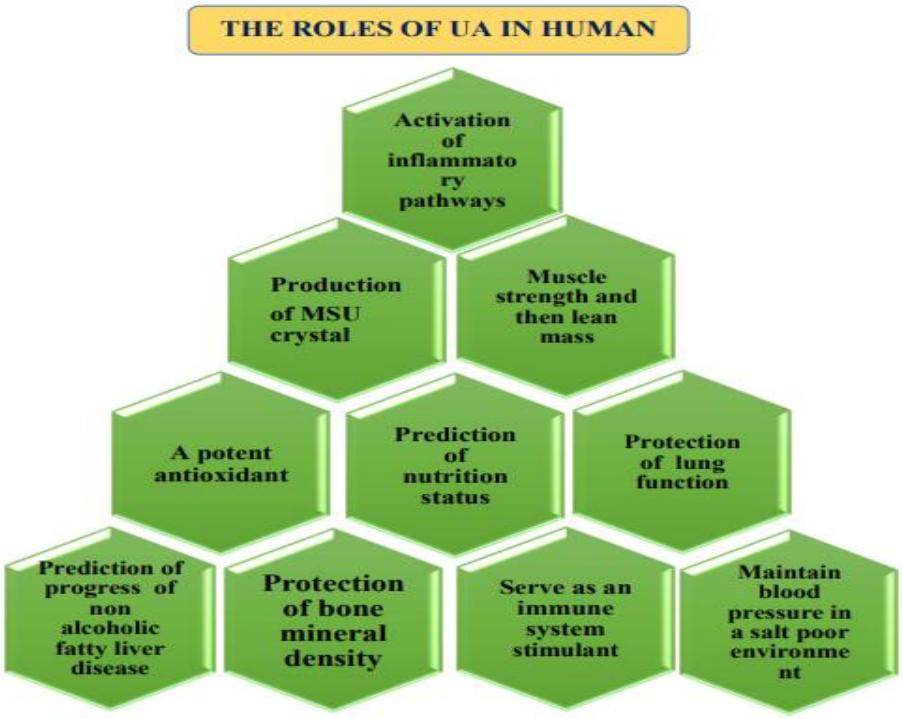

Figure 3: Roles of UA in Humans.

Underlying factors for the gout

Hyperuricemia, or substantial blood levels of uric acid, is the main etiological factor for gout. Most foods and beverages, like alcohol, liver, red meat, geese, and shellfish, feature substantial quantities of a chemical called purines. Uric acid is the result of the body's breakdown of such molecules. Urine usually comes from the kidneys after uric acid dissolves in the blood. The tissues underlying the joints can undergo acute pain and inflammation if the body produces too much uric acid or does not clear it out sufficiently. Uric acid can accumulate and crystallize into needle-like particles in this scenario.[12]

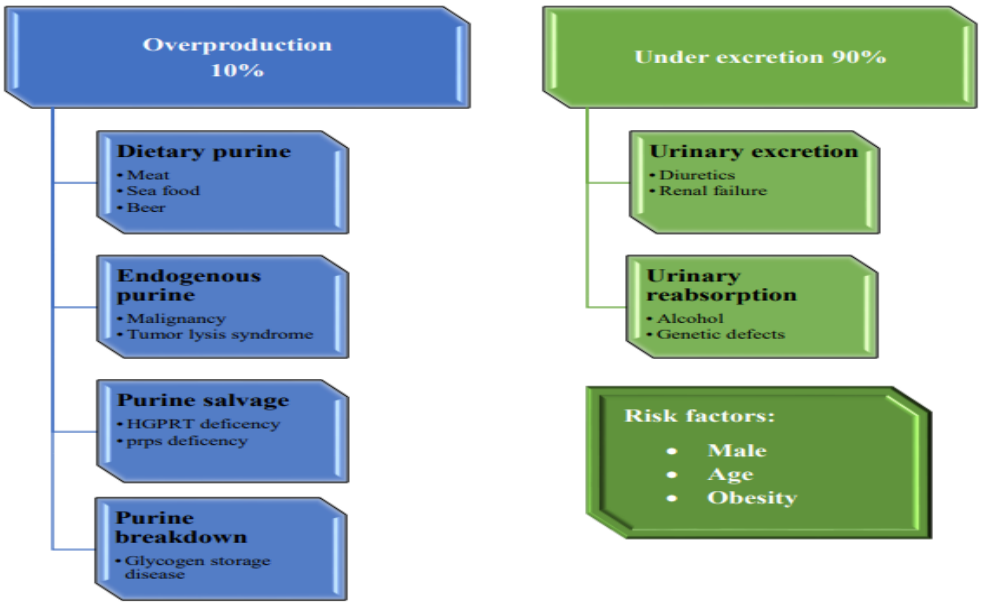

Figure 4: Various underlying factors of gout.

Stages of gout[13]

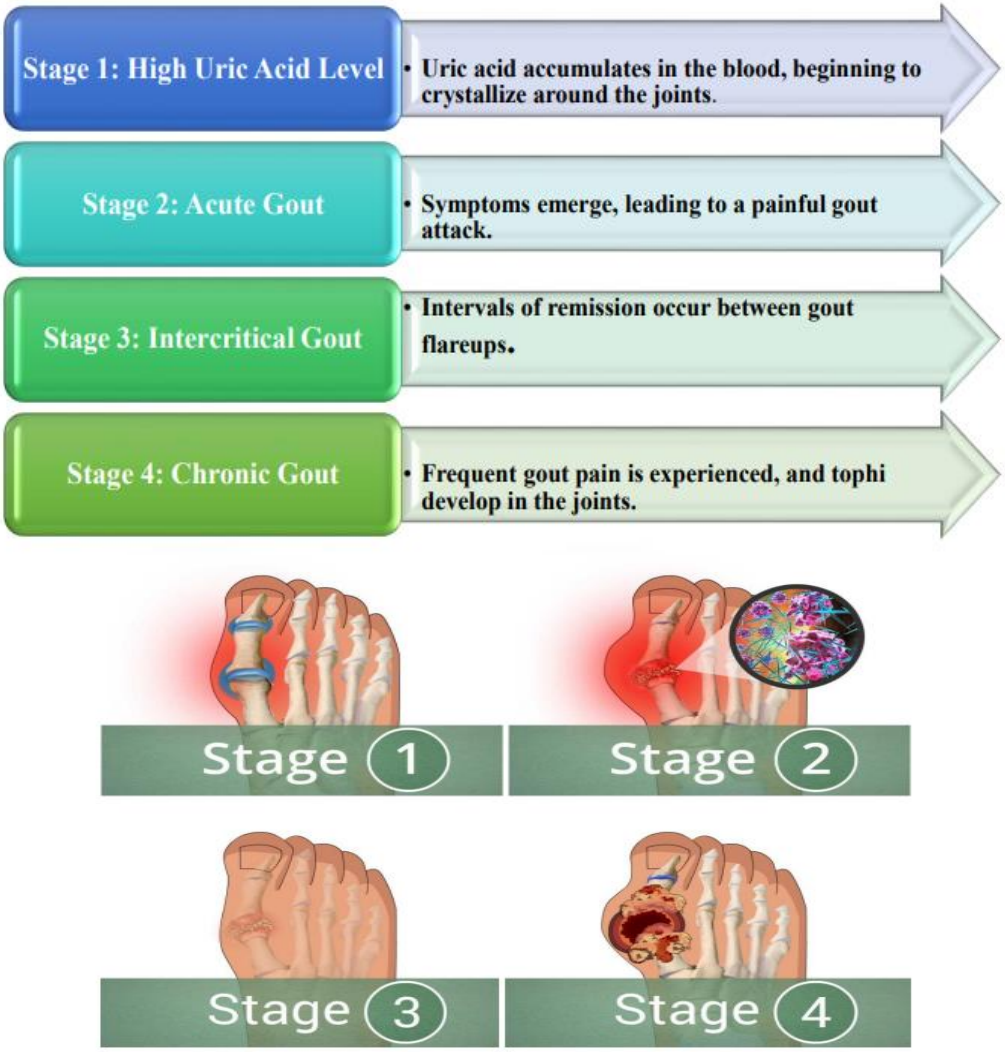

Figure 5: Stages of gout.

Pathophysiology of gout

The ionized form of uric acid that circulates throughout the body is called urate. With a pH of 5.8, uric acid is a weak acid by itself. The phenomenon of urate crystal deposition in tissues is initiated when the normal limit of serum uric acid is exceeded. Increased blood uric acid levels, or hyperuricemia, are pathological when they are greater than 6.8 mg/dL.[12]

Monosodium urate (MSU) crystals, the end by-product of purine metabolism in humans, accumulate in the joints, soft tissues, and bones, resulting in gout, a type of inflammatory arthritis. This disease may present in a number of ways, including urolithiasis, tophaceous gout (identified by an elevated level of tophi), acute gout recurrence (acute arthritis), chronic gouty arthritis (chronic arthritis), tophaceous gout (characterized by the formation of tophi), impaired renal function, and urolithiasis (kidney stones).

The pathophysiology of gout involves a complex series of interconnected processes.

- Various genetic and metabolic factors contribute to the development of hyperuricemia in the bloodstream.
- Metabolic, physiological, and other characteristics are responsible for the formation of MSU crystals. Soluble inflammatory factors, cellular components, innate immune processes, and the properties of MSU crystals themselves drive an acute inflammatory response.
- Immune mechanisms are then engaged to resolve the acute inflammation caused by MSU crystals. Chronic inflammatory processes, along with the impact of immune cells and crystals on osteoblasts, chondrocytes, and osteoclasts, lead to cartilage degradation, bone erosion, joint damage, and the formation of tophi.[14]

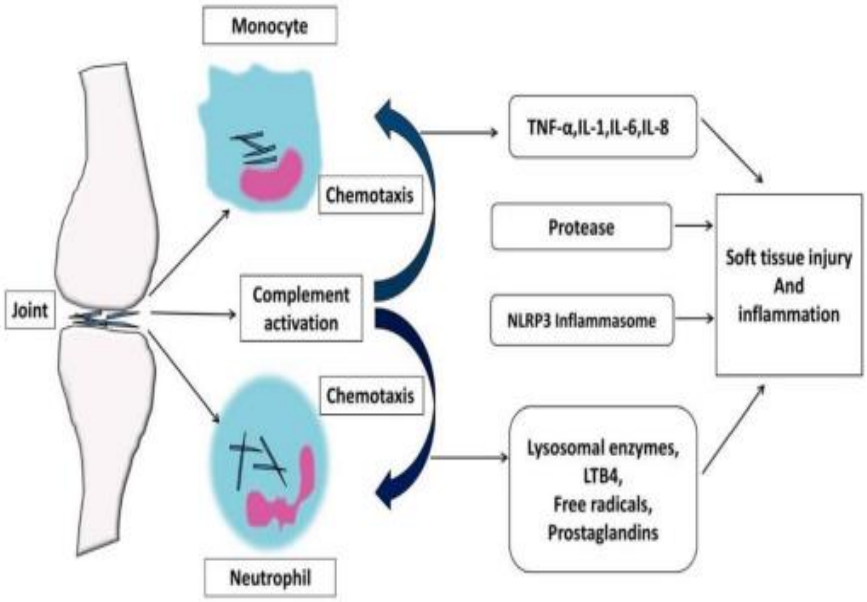

Figure 6: Pathophysiology of gout.

Molecular mechanisms of gout

In gouty inflammation, leukocytes are activated by monosodium urate (MSU) crystals, initiating a complex inflammatory response. This process occurs in two distinct stages: the priming phase and the crystal-mediated phase. During the priming phase, the expression of inflammasome components and pro-inflammatory cytokines, such as IL-1β and IL-18, is upregulated. Priming signals include endogenous molecules like C5a, GM-CSF, and TLR ligands, as well as exogenous factors like long-chain saturated fatty acids from the diet. In the crystal-mediated phase, the NLRP3 inflammasome oligomerizes, leading to the cleavage and secretion of IL-1β and IL-18. This results in the recruitment of neutrophils to the inflammed tissue, which release additional cytokines, chemokines, and inflammatory mediators, thereby sustaining the inflammation. Furthermore, inflammasome-independent mechanisms, such as necroptosis and microRNA regulation, also play roles in gouty inflammation. The interaction between MSU crystals, inflammatory mediators, and immune cells underpins the pathogenesis of gout.[15]

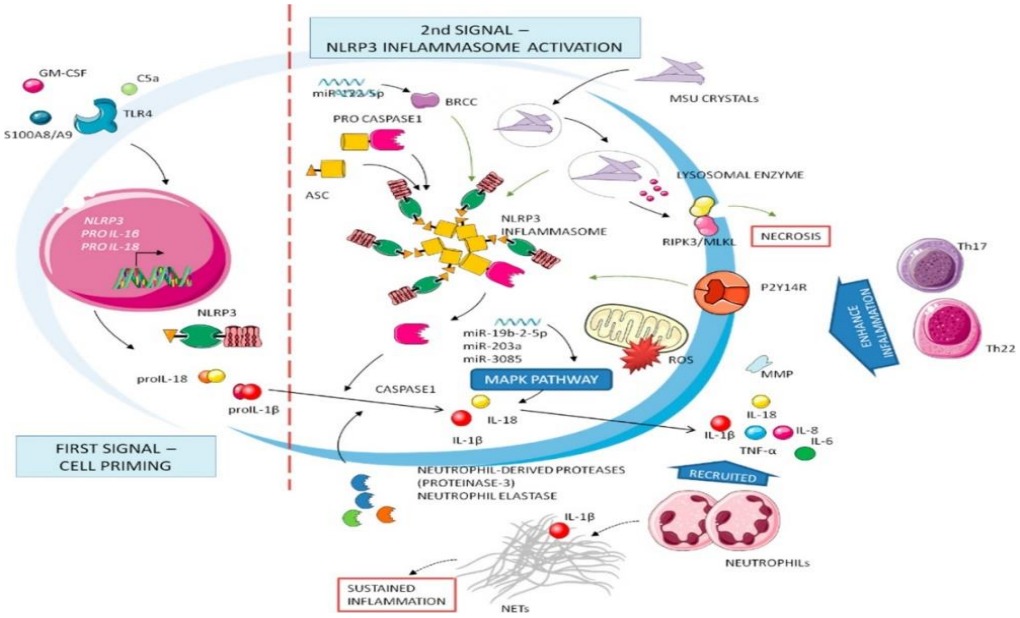

Figure 7: Molecular mechanisms of gout.

A complex network of molecular mechanisms is implicated in gout. Inflammation has been defined by two stages: The first signal (**left**) and the second signal (**right**). Cell priming production of precursors of cytokines and inactive inflammasome molecules needs the subsequent activation step after Signal 2. IL-1β is critical to the upregulation of inflammatory processes.

Genetic mechanism of gout

The familial and hereditary nature of gout has long been recognized. However, it was only in the past decade that several genes involved in rare metabolic and kidney diseases were identified as being associated with the pathogenesis of gout. Many of the identified loci include genes encoding for the urate transporter and for urate metabolism.[16] Among these, solute carrier family 2 (*SLC2A9*) and ATP-binding cassette superfamily G member 2 (*ABCG2*) have multiple variants associated with serum urate levels and, overall, the increased risk of gout. Moreover, *ABCG2* has an established key role in the onset and severity of gout.[17]

In the last decade, advances in genotyping technologies have facilitated the identification of genes involved in initiating the inflammatory response to MSU crystals. These genetic associations yield additional findings on inflammatory regulation and shared pathways in the pathogenesis of gout. Furthermore, investigations on genes involved in auto-inflammatory diseases, such as the *MEFV* gene of familial Mediterranean fever, have obtained heterogeneous results of association with gouty inflammation.[18,19]

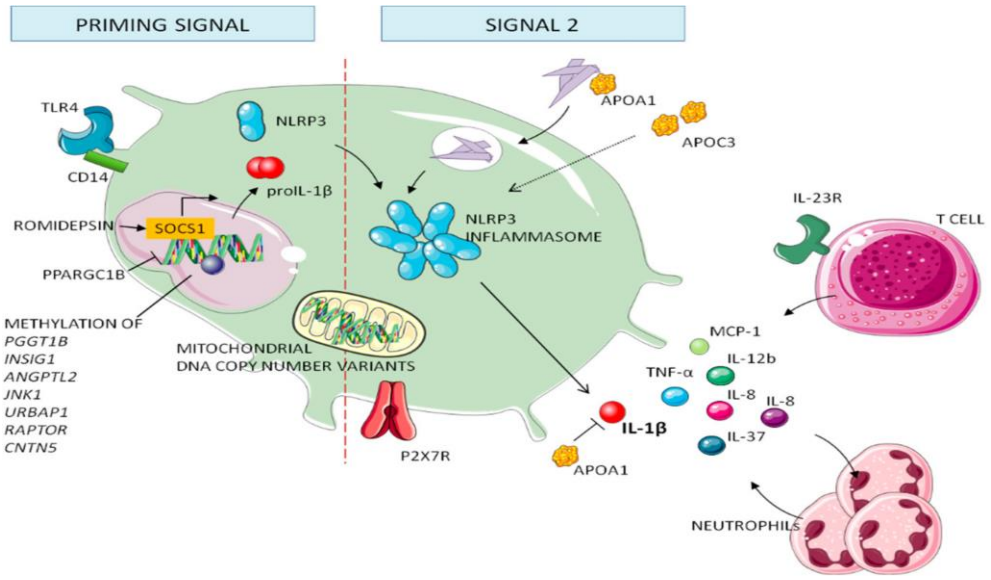

Figure 8: Genetic mechanism of gout.

Common comorbid medical disorders, Conditions and Symptoms for hyperuricemia (Gout)

A serum urate (SU) concentration of 6.8 mg/dL in excess is also known as hyperuricemia and is viewed as an indication for the development of gout. Genetic Mendelian randomization research that found a significant relationship between gout and genetic serum urate scores offers reliability to this argument. The relationship revealed in this crystalline arthritis with different comorbidities may be clarified through elevated serum urate levels.[20]

Table 1: Conditions related with gout.

System	Examples of Disorders, Condition, and Symptoms
Neurological	Alzheimer's disease, Vascular dementia Parkinson's disease.
Cardiovascular	Hypertension, Coronary heart disease, Atherosclerosis, Stroke, Heart failure, Peripheral vascular disease, Atrial fibrillation, Thromboembolism.
Metabolic	Diabetes, Metabolic syndrome, Osteoporosis
Ophthalmological	Macular degeneration
Renal/genitourinary	Chronic kidney disease, Nephrolithiasis, Erectile dysfunction.
Rheumatological	Osteoarthritis

Common treatment for gout

Prescription drugs are usually part of the treatment. These medications can help regulate the symptoms, prevent recurrence, and minimize the risk of adverse effects such as kidney stones and tophi, which refer to the formation of white growths in the affected areas attributed to uric acid crystals. Corticosteroids, which additionally diminish inflammation, and nonsteroidal anti-inflammatory medications are common therapies. These lessen unease and swelling in the gout-affected areas. Certain medications lessen the body's production of uric acid and enhance the kidneys' capacity to eliminate it. An acute gout attack reaches its peak 12–24 hours after it starts if treatment is not received. Without therapy, a person should heal in 1-2 weeks, but there may be a lot of pain during this time.[12]

Conventional treatment Strategies and Associated side effects

Treatment of gout involves either reducing the production of uric acid (XO inhibitors) or increasing uric acid excretion (uricosuric drugs). New agents, such as uricase analogs and biological cytokine inhibitors, have been used for the treatment of gout. Allopurinol, a commonly used XO inhibitor, has various adverse effects, such as hypersensitivity syndrome, Stevens-Johnson syndrome, renal toxicity, and fatal liver necrosis. Gastric and renal adverse effects are common with the long-term use of anti-inflammatory agents. Selective COX-2 inhibitors are less toxic than non-selective nonsteroidal anti-inflammatory drugs (NSAIDs), but renal side effects are similar to conventional NSAIDs. Fatal hypersensitivity syndrome, gastric disturbances, and nephrotic damage are associated with the use of urate-lowering drugs such as XO inhibitors and uricosuric agents. Nausea, vomiting, severe diarrhea, and kidney damage are common with the use of colchicine. Cytokine inhibitors are highly effective with very few side effects, but these drugs are extremely expensive when compared with traditional treatment.[21]

Impact of medicinal plants

The use of plant-based drugs for the treatment of various ailments is increasing worldwide as they are considered much safer compared to synthetic drugs. India is a veritable and rich emporium of medicinal and aromatic plants.[22] India has more than 17,500 wild plant species, and out of these, 4000 have medicinal value.[23] The market sales and research activities of herbal products are growing steadily.[24] As compared to allopathic drugs, herbal medicines are claimed to be non-toxic or generally regarded as safe because they are obtained from natural origin and their reported long-term use as folk medicine.[25]

Phytochemicals used for the management of gout

Phytochemicals, in particular, have been widely reported as hyperuricemic agents both *in vivo* and *in vitro* with minor side effects. The integrative, multi-targeted, and multi-factorial actions of phytochemicals may prove essential in reducing SUA levels, dissolving MSU crystals, and combating HUA and gout.[26]

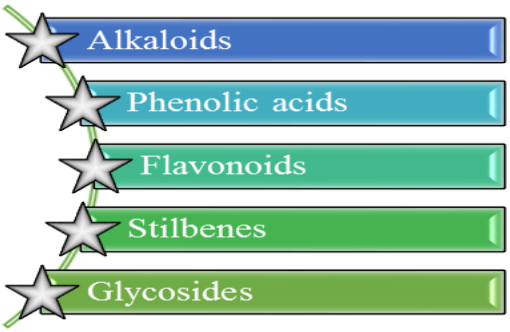

Figure 9: Phytochemicals used for management of gout.

Herbs acting on antihyperuricemia[27]

Figure 10: Various herbs having Anti-hyperuricemia.

Various types of Plants and Its species are used in the treatment of hyperuricemia[28]

Table 2: Types of Plants and Its Species for the treatment of hyperuricemia.

Si. no	Plant name	Parts used	Phytoconstituents	Reference
1	*Adenanthera pavonina* (Red sandalwood) Family: Fabaceae	Leaves	These are chemical compounds present in this plant adenanthera pavonina like O-acetylrthanolamine, octacosanol, dulcitol, glucosides, betasitosterol, stigmasterol glucoside.	[29]
2	*Alliumcepa aggregatum* (onion) Family:Amaryllidaceae	Tuber	organosulfur, allylsulfides, flavonoids, flavanols, Salk (en) ylcysteinesulfoxides, cycloalliin, selenium, thiosulfinates, and sulfur, seleno.	[30,31]
3	*Barleria prionitis* (porcupine flower) Family: Acanthaceae	Whole plant	Alkaloids, terpenes, flavonoids, glycosides, lignin's, phenolic, saponins etc. The leaves and flowering tops parts have been compounds were reported to highly in potassium salts. The leaves were reported to contain balarenone, pipataline, lupeol, prioni side suutell are in, melilotic acid, syringic acid, vanillic acid, p-hydroxybenzoic acid, 6-hydroxyflavones, Luteolin-7-	[32]

			O-β-D-glucosisde, β-sitosterol, scutellarein7-neohesperidoside, apigenin7-O- glucoside.The aerial parts to contain barlerinoside, verbascoside, shanzhiside, methylester, barlerin, acetylbarlerin, methoxy diserroside, lupulinoside.	
4	*Camellia sinensis* (Green tea) Family: Theaceae	Whole plant	These are chemical compounds present in this plant contain Catechins, caffeine, theobromine, gallic acid, fibre, ampelopsin, epicatechin, theanine (amino acid).	[33]
5	*Erythrina indica* (Indian coral tree) Family: Fabaceae	Bark	The chemical constituent's presence of alkaloid, carbohydrate, amino acids, tannins, steroids, flavonoids. It also contains several phenolic metabolites, such as pterocarpans, isoflavones, flavanones and chalcones, It also contains sterols like capesterol, β-sitosterol, β-amyrin, erythratine.	[34,35]
6	*Erythrina stricta* (Coral tree) Family: Fabaceae	Flower, root, bark	Flower parts contain 11-acetyl erysotrine, erythratidinone. Following compounds are present in this plant root like Erythrabsysin II, erystagallin A, erythrabyssin I, 5-hydroxysophoranone, sandwicensin, sophoradiol, soyasapogenol, 8-oxoerythrinine, alkyl trans ferulates and a mixture of β-sitosterol and stigmasterol.	[36,37]
7	*Glycyrrhiza uralensis* (Chinese liquorice) Family: Leguminosae	Roots	The plants indicated presences of Saponins, flavonoids, coumarin, alkaloids, polysaccharides, sitosterol, and amino acids, glycyrrhetinic acid. Root: Triterpene glycoside and consists of one molecule of 18β-glycyrrhetinic acid and twomolecules of glucuronic acid (18β-glycyrrhetinic acid-3-O-β-D-glucuronopyranosyl-(1→2)-beta-D-glucuronide).	[38]
8	*Hedyotis diffusa* (Snake-needle grass) Family: Rubiaceae	Aerial part	These are chemical compounds presences of Triterpenes, flavonoids, anthraquinones, phenolic acids and their derivatives, sterols, alkaloids, volatile oils, polysaccharides, cyclotides, coumarins and alkaloids.	[39]

9	*Justicia gendarussa* (Karunochi) Family: Acanthaceae	Folium	Justicia gendarussa leaves contains shows the presence of alkaloids, flavonoids, triterpenoid, carotenoids, phenolic compounds, sugar and starch. aromatic amine like 2-(2'-amino-benzylamino) benzyl alcohol and their respective methyl ethers, 2-amino benzyl alcohol, stigmasterol, lupeol, 16-hydroxylupeol, ß-sitosterol, aromadendrin, ß -Sitosterol-ß-D-glycoside, and male antifertility compound like gendarusin A and gendarusin B were also isolated from the plant, betasitosterol, lupeol, an alkaloid, friedelin and aromatic amines.	[40,41]
10	*Petroselinum crispium* (Parsley) Family: Apiaceae	Leaves	The plants indicated presences of Flavonoids, carbohydrates, coumarins, essential oils, 1R-αpinene, β-pinene, β-phellandrene, styrene, 3-benzodioxole, 4- methoxy-6-(2- propenyl), 1,3-benzodioxole, 4,7-dimethoxy-5- (2-propenyl).	[42,43]
11	*Manikara zapota* (sapota) Family: Sapotaceae	Leaves, peels, seeds	These compounds contains shows the presence of carbohydrate, calcium, phosphorus, iron, thiamin, riboflavin, niacin, vitamin C, vitamin A.	[44,45]
12	*Vitex negundo* (Nocchi) Family: Lamiaceae	Leaves, root	These are compounds presences of contains volatile oil, triterpenes, diterpenes, sesquiterpenes, lignan, flavonoids, flavones, glycosides, stilbene derivative. δguaiene, guaia-3,7-dienecaryophyllene epoxide, ethyl hexadecenoate, α-selinene, germacren-4-ol, caryophylleneepoxide, (E)-nerolidol, β-selinene, α-cedrene, germacrene D, hexadecanoic acid, p-cymene and valencene, viridiflorol, β-caryophyllene, sabinene, 4-terpineol, γterpinene, caryophyllene oxide, 1-oceten-3-ol, globulol.	[46,47]

CONCLUSION

In the end, gout is a well-researched illness with a lengthy historical background that dates back to antiquity and is frequently connected to the opulent lifestyles of the privileged. The main cause of the illness is hyperuricemia, which leads to monosodium urate (MSU) crystals accumulating in tissues and joints, causing severe discomfort and inflammation. Gout has a heterogeneous pathophysiology involving immunological, metabolic, and genetic factors. Not every

individual with high uric acid levels gets gout, even if hyperuricemia is a major risk factor; this suggests that other genetic and environmental variables may also be involved.

Gout has traditionally been treated with an assortment of pharmaceutical interventions, including corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), and urate-lowering medications like allopurinol, in addition to natural remedies like colchicine. However, these therapies often result in serious adverse effects, making research into complementary and alternative therapies essential.

Recent research investigations have demonstrated the potential of phytochemicals and herbal remedies to treat gout and hyperuricemia, providing potentially effective therapeutic options with fewer adverse effects. The review underlines the significance of conventional therapy in the ongoing exploration for effective gout remedies, as seen by the utilization of various plants and their constituents.

In summary, even though significant progress has been made in understanding and treating gout, more research is still needed to fully understand the disease's genetic, molecular, and environmental causes, as well as to investigate potential alternative treatments. This will provide more individualized and successful management techniques, enhancing the quality of life and outcomes for patients.

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