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Natural bioactives in the management of hyperuricemia: A challenge to gout therapy

Rupa Mazumder
HOD & Professor at Noida Institute of Engineering &Technology (Pharmacy Institute), Greater Noida
Corresponding author email: rupa_mazumder@rediffmail.com

Ajay Kumar Jaysawal
Master of Pharmacy (Persuing), Noida Institute of Engineering &Technology (Pharmacy Institute), Greater Noida

Archana Sharma
Assistant Professor at Noida Institute of Engineering &Technology (Pharmacy Institute)
Email: hiarchanasharma@rediffmail.com

***Abstract*---**Hyperuricemia, also known as gout, has been identified as a well-known metabolic disorder associated with an elevated uric acid level in serum. Gout is commonly associated with various chronic disorders like hypertension, obesity, hyperlipidemia, cardiovascular disorders, and diabetes. Drugs, like nonsteroidal anti-inflammatory medications [NSAIDs] and glucocorticoids, are shown to exhibit serious side effects, when used in this therapy, although they are the first-line of treatment options available to date. Bioactive compounds have been explored for the management of hyperuricemia for their effectiveness and ability to minimize complications. Related research have reported the use of plant-based bioactives on hyperuricemia. The objective of the present review is to highlight the therapeutic effect of the naturally occurring phytochemicals and the pharmacology of the compounds involved in the same. These phytochemicals are categorized into five classes, namely alkaloids, flavonoids, saponins, and phenolic acids, that describe their anti-gout activity. Additionally, the mechanism of action by which these bioactive compounds display the hypouricemic consequences has been divided into three parts, namely, the inhibition of the production of uric acid, lowering of intestinal uric acid secretion, and enhancement of elimination of renal uric acid. Overall, the present review summarizes the utilization of plant-based bioactive for herbal remedies of hyperuricemia or gout.

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***Keywords*---**hyperuricemia, gout, bioactives, serum uric acid, xanthine oxidase.

Introduction

Gout is a disease caused due to accumulation of urate crystals in various joints and connective tissues of the body and renal interstitium causing nephrolithiasis and joint pains(Dalbeth, 2106). The incidence of gout is prevalent all over the world, with a higher degree of incidence in the Pacific areas[Kuo C.F et al, 2015]. According to the epidemiological survey, about 3% of the western population is affected by gout while the black population is found to suffer from the disease to a lesser extent. There are two types of gout:

i) Essential gout is brought about by heredity, while the
ii) Auxiliary gout occurs through infection associated with the hyperuricemic effect.

The treatment of gout has three phases:

i) Curing intense attack,
ii) Lessening the deposition of uric acid [urate] crystals to reduce gouty joint inflammation and
iii) Prophylactic treatment to subside intense flares.

Therefore, the treatment of gout has been inspired by mechanism-based therapies that reduce uric acid production, promote uric acid excretion, or depress the urate reabsorption and resist inflammation.

As previously noted, hyperuricemia can be produced by either an increase in uric acid synthesis or a decrease in uric acid metabolism in the body, with a reduction in urate excretion being one of the most common causes, accounting for around 90% of cases. As a result, lowering the body's uric acid levels may be considered an effective therapy for hyperuricemia. The production and metabolism of uric acid, on the other hand, are both complex physiological processes, and endogenous uric acid is produced by the body's metabolism of nucleic acids accounting for around 80–90% of the total uric acid levels (Kuo C.F et al, 2015). The primary enzymes that catalyze the formation of uric acid in the body are xanthine oxidase and adenosine deaminase. Xanthine oxidase has been shown to catalyze the oxidation of hypoxanthine to xanthine and xanthine to uric acid, as well as the conversion of purines from protein-rich meals to uric acid. Adenosine deaminase also catalyzes the conversion of adenosine to inosine, which is further converted to hypoxanthine and xanthine. As a result, Adenosine deaminase plays an important role in indirectly stimulating the production of uric acid (Grosser T et al., 2011). Fig. 1 depicts the uric acid catalytic process. Exogenous uric acid, on the other hand, is obtained from the consumption of purine-rich meals like shellfishes, animal guts, eggs, soy products, wheat, sugary drinks, and high-fructose diets, as previously established, increasing uric acid production, which is further linked to an increased risk of gout. Approximately 70% of uric acid is removed by the kidneys, with the remaining 30% eliminated via the intestinal

route during uric acid metabolism. In humans, the kidneys are the principal site of uric acid metabolism, with processes such as reabsorption and secretion in action (Fig. 1). Uric acid requires the excretion of multiple transporters to complete the metabolism, with the urate transporter 1 [URAT1], organic anion transporters 4 [OAT4], and glucose transporter 9 [GLUT9] primarily regulating the uric acid reabsorption and the organic anion transporters 1 [OAT1] and 3 [OAT3] regulating renal uric acid excretion.As a result, reduction of uric acid levels by blocking uric acid production and improving uric acid metabolism, thereby encouraging high-risk individual acids to adjust their dietary pattern, can help to prevent and control uric acid production. Currently available therapeutic medications for uric acid are classified as uric acid synthesis inhibitors [allopurinol, febuxostat, and so on] and uric acid excretion promoters [probenecid, benzbromarone, and others]. Although these medications can reduce uric acid levels, many of these have substantial adverse effects, including gastrointestinal problems, skin rashes, liver and renal malfunctions, and hepatotoxicity. As a result, alternative therapeutic medicines for the treatment of 10094yperuricemia must be explored.

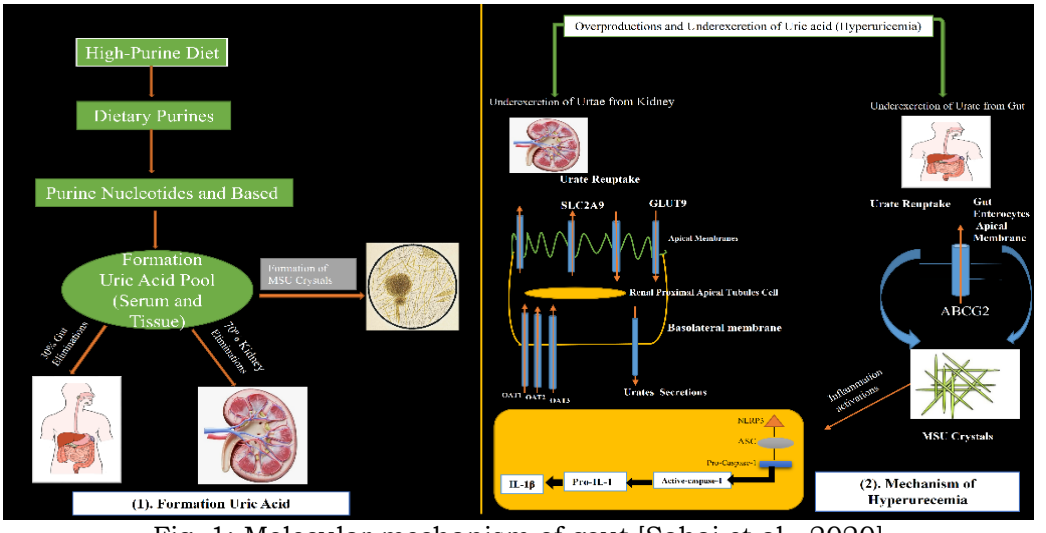

Fig. 1: Molecular mechanism of gout [Sahai et al., 2020]

Search Words: Gout, natural bioactive for gout, gout treatment, MOA of gout hyperuricemia, synthetic drug use for gout.

Epidemiology of gout

Gout can be caused by increased secretion or decreased excretion of uric acid from the kidney, resulting in hyperuricemia as a consequence.

The major causes of hyperuricemia

Expanded purine production is caused by idiopathic and chemical imperfections [e.g., glycogen capacity infections], causing hyperuricemia.

The minor causes of hyperuricemia

Purine catabolism and uric acid turnover are elevated in myeloproliferative diseases, lymphoproliferative disorders, cancer, sarcoma, chronichemolytic anemia, psoriasis, and when cytotoxic drugs are used. (Borges F el al., 2002)

Management of gout

Gout can be managed by the use of drugs from both synthetic and natural origins, as mentioned below:

Synthetic drugs used for gout management

The various categories of synthetic drugs used for the management of gout to date, along with their effects, have been enlisted in Table 1.

Table 1: Medicines used for gout management

Drugs	Comment	Source
Colchicine	It can be used to: • Treat gout flare-ups [attacks]; • Prevent increased gout flare-ups with allopurinol; and • Control the long-term disease. • Reduce the occurrence of flare-ups of symptoms of familiar Mediterranean fever [FMF], a hereditary inflammatory illness	(Spilberg I et al.,1979)(Roberge CJ et al.,1993)
NSAIDs	Indomethacin has traditionally been used to treat acute inflammation of gout, but other NSAIDs are also effective in this situation. Like all other NSAIDs, indomethacin blocks cyclooxygenase, reducing the formation of prostaglandins.	(Griffin et al.,1991)(hawkey CJ,1990][Roth, 1988)(Findling JW et al.,1980)
Corticosteroids	By short-term use of oral steroids [prednisone 3040 mg/day for 5 days] for the treatment of acute gout when non-steroidal anti-inflammatory drugs [NSAIDs] are	(Gray RG et al.,1981)(Alloway JA et al.,1993)(Groff GD & Franck WA.,1990)

	contraindicated. Steroids may also be the first-line treatment of choice.	
Probenecid	It is used for treating chronic gout or gouty arthritis that occurs due to the presence of an excess amount of uric acid in the blood. It works by excreting the excess uric acid from the body, does not cure gout, but it can prevent gout attacks after a few months of drug therapy.	(Bishop C & Rand R, 1951)(Dayton PG & Perel JM,1971)
Sulfinpyrazone	It prevents gout attacks by lowering the amount of uric acid in the blood. The drug prevents the attacks, but cannot cure them once the decrease occurs in the body.	(Dieterle W., et al, 1975)(Lecaillon JB., et al 1979)(Wilcox RG., et al, 1980)(kovalchik, 1981)
Allopurinol	It is a xanthine oxidase inhibitor, quickly metabolized to oxypurinol, a xanthineeanalog, that similarly inhibits the xanthine oxidase .The longer half-life of oxypurinol [14-28 hours] allows for its regular dosing. It causes oxypurinol excretion disorders in patients with renal failure but improves the intake of uricosuric drugs.	(Spector T, 1977)(Hande K et al., 1978)

Use of natural bioactives in the management of gout

An alternate term for "biologically active" is "bioactive" and in terms of medical dictionaries, a bioactive compound has been defined as a substance that affects and causes a reaction (Mc dougeall IA, 2009). Further, the bioactivesare phytochemicals found in foods that are capable of regulating metabolic functions and resulting in beneficial effects(Evans N, 2013)([Sutulic S ., et al, 2018).A natural product is a chemical or substance that is created by a living organism or that is found in nature. Natural products may also be synthesized chemically [semisynthesis], and they play a crucial role in challenging synthetic molecules. Natural moieties have been commercialized in a variety of ways, including in the form of cosmetics, dietary supplements, and meals made from natural components without the addition of artificial additives. The bioactive substances

include lycopene, resveratrol, saponins, and flavonoids, mostly used in the prophylactic treatment of gout, as enlisted in Table 2.

Table 2: Bioactives used for the treatment of gout

Bioactive Compounds	Dose	Comments	Ref.
Rutin	50 and 100mg/kg	Inhibits the action of xanthine oxidase, and thereby, inhibits uric acid production.	(Liu YL.,et al ,2014)(Chen Y.,et al, 2019)
Isorhamnetin	300 mg/kg	Inhibits the action of xanthine oxidase, and inhibits uric acid production	(Adachi SI.,et al, 2019)
Mulberry flavonoids	Inhibits the	Inhibits the action of xanthine oxidase, and thereby, inhibits uric acid production	(Montoro, 2005)
Morrison	40 and 80 mg/kg	Renal urate transporter has down-directed and urate emission expanded by up-managing renal Murine renal organic anion transportersto encourage the renal discharge of uric acid in mice.	(Wang CP.,et al,2010)
Puerarin	200 mg/kg	Inhibits the action of xanthine oxidase, and thereby, inhibits uric acid production.	(Mo SF., et al, 2007)
Astilbin	10 and 20 mg/kg	It is associated with promoting uric acid renal excretion by suppressing the function of glucose transporter-9, urate transporter-1 expression, and up-regulationof the expression of ABCG2, OAT1, and OAT3, in the mice model.	(Wang M.et al, 2016)
Licochalcone A	10 mg/kg	This is associated with the inhibition of uric acid reabsorption by down-regulation of OAT4 transport.	(Wang Z.,et al,2019)
Isoliquiritigenin	10 mg/kg	This is associated with the inhibition of uric acid reabsorption by down-regulation of OAT4 transport.	(Wang Z.,et al,2019)

Liquiritigenin	10 mg/kg	This is consistent with promoting renal excretion of uric acid by downregulating the expression of uric acid transporter-11 transport.	(Wang Z.,et al,2019)
Myricetin	4mg/kg	It primarily involves the inhibition of the development of uric acid by inhibiting the activities of xanthinee oxidase and adenosine deaminase.	(Zhao R., et al, 2017)
Kaempferol	150 and 300 mg/kg	Inhibits the action of xanthine oxidase, and thereby, inhibits uric acid production.	(Jiang LL., et al,2020)
Apigenin	40 and 80 mg/kg	Inhibits the action of xanthine oxidase, and thereby, inhibits uric acid production.	(Jiang LL., et al,2020)
Puerarin	100 mg/L	Inhibits the action of xanthine oxidase, and thereby, inhibits uric acid production.	(Adachi SI.,et al, 2019)
Hesperetin	20 µg/ml	Inhibits the action of xanthine oxidase, and thereby, inhibits uric acid production.	(Liu K., et al,2016)
Nobiletin	20 µg/ml	Inhibits the action of xanthine oxidase, and thereby, inhibits uric acid production.	(Liu K., et al,2016)
Acacatechin	100 µg/ml	Inhibits the action of xanthine oxidase, and thereby, inhibits uric acid production.	(Umamaheswari M.,et al,2013)
Glycitein	100 µg/ml	Inhibits the action of xanthine oxidase, and thereby, inhibits uric acid production.	(Umamaheswari M.,et al,2013)
Naringenin	100 µg/ml	Inhibits the action of xanthine oxidase, and thereby, inhibits uric acid production.	(Umamaheswari M.,et al,2013)
Galuteolin	100 µg/ml	Inhibits the action of xanthine oxidase, and thereby, inhibits uric acid production.	(Umamaheswari M.,et al,2013)

Phenolic compounds used in the treatment of gout

Flavonoids are polyphenols with a basic 2-phenylchromone structure and are found in many plants. As a result, flavonoids are found in the human diet through vegetables, fruits, grains, teas, and other plant-based foods (PtraJC & Chua BH,2010). Several clinical studies have shown that flavonoids in plant-based supplements can often reduce uric acid levels. After extracting puerarin from Pueraria lobata [Willd.], 120 uric acid patients have randomly been assigned to the control, myricetin, and puerarin groups, and changes in uric acid levels have been observed in the mentioned uric acid patients after administration of 5 ml/day puerarin and 5 ml/day myricetin injections. The results show that serum uric acid levels in the myricetin and puerarin groups have significantly been reduced [$p<0.05$], suggesting that myricetin and puerarin have significant therapeutic effects on uric acid patients (Lin S., et al, 2015).

Quercetin, a flavonol, found mostly in onions and *Sophora japonica L*, has a wide spectrum of biological activities. The impact of quercetin on uric acid-induced rats generated by potassium oxonate treatment was explored, and it has been revealed that after three weeks of administration, quercetin [10 mg/kg/d] has dramatically lowered the uric acid levels and inhibited xanthine oxidase and adenosine deaminase activities in both blood and the liver [$p<0.05$]. In addition, a clinical study has examined the effect of oral quercetin on uric acid levels in 22 healthy male volunteers with high baseline uric acid levels over 4 weeks(Xing ZH et al.,2017). Secondary metabolites, the phenolic acids, are non-flavonoid phenolic compounds, and the mechanisms of the different bioactive components are detailed in Table 3. They are an essential part of the human diet. Phytochemicals such as phenolic acids have been revealed to have xanthine oxidase and adenosine deaminase inhibitory actions in recent years and are likely to be effective in the prevention and treatment of humic acid. Chicory acid, caffeic acid, and chlorogenic acid, for example, inhibit xanthine oxidase activity. Chicory acid is obtained from the plant Cichorium intybus L. and after 21 days of dosage, chicory acid [150 mg/kg/d] has been shown to significantly reduce uric acid [$p<0.05$].Furthermore, uric acid serum adenosine deaminase and xanthine oxidase levels have been dramatically lowered [$p<0.05$], which may be connected to the suppression of the xanthine oxidase and adenosine deaminase activities. Furthermore, uric acid serum adenosine deaminase and xanthine oxidase levels have significantly been reduced [$p<0.05$], which may be related to xanthine oxidase and adenosine deaminize activity suppression. Following the administration of several doses of caffeic acid [i.e., 25, 50, and 100 mg/kg] to potassium oxonate-induced uric acid rats, uric acid levels are found to drop [$p<0.05$], refusing the Null hypothesis. Furthermore, as compared to the model control group, the BUN and serum creatinine levels have been much lower, and caffeic acid has been shown to reduce the BUN value to the usual range. In addition, in vitro studies have shown that caffeic acid can inhibit xanthine oxidase through competitive bidding to xanthine, with an IC50 value of 53.45 μM measured (Liu K.,et al,2016). Therefore, caffeic acid is thought to have a uric acid effect in lowering uric acid levels, which is one of the potential uses for the treatment of uric acid.

Mechanism of bioactive components of phenolic acid

Bioactive compound	Dose	Mechanism	References
Chlorogenic acid	50 and 150mg	Inhibition of xanthine oxidase and adenosine deaminase.	(Zhu CS., et al, 2017)
Protocatechuic acid	10 mg/kg	This is linked to thedown-regulationof URAT1by inhibiting uric acid re-absorption during the transport mechanism.	(Wang Z.,et al,2019)
Vanillic acid	166 mg/kg	This is capable of inhibiting xanthinee oxidase activity.	(Jiang LL., et al, 2020)

Alkaloids used in gout therapy

Alkaloids are a kind of nitrogen-containing organic chemicals found in a variety of species. Their impact in decreasing uric acid should not be overlooked due to their complex architectures and significant biological activity. It has recently been discovered that alkaloids not only inhibit Xanthine Oxidase and Adenosine deaminase activities but also promote uric acid excretion and block uric acid reabsorption[39]. The hypouricemic impacts and systems of activity of the alkaloids in various food sources originating from plants are summarised in Table 4.

Table 4: Mechanism of action of alkaloids used in gout therapy

Bioactive compound	Dose	Mechanism	References
Evodiamine	8 mg/kg	Inhibits action of xanthine oxidase; inhibits uric acid production	(Jiang LL., et al, 2020)
Betaine	10 and 40 mg/kg	It applies to mRNA and URAT1 and GLUT9 protein decreases and OAT1 protein and mRNA increase to enhance the excretion of uric acid.	(Liu YL., et al,2014)

Saponins class of bioactive use in gout treatment

Saponins are made primarily from land plants, but marine life also contains low levels of rapid acidity. Based on their different aglycones [Liu K.,et al,2016], saponins can be divided into two types: steroid saponins and triterpenoid saponins.Saponins have been found in recent research to reduce uric acid synthesis by reducing the action of Xanthine Oxidase and Adenosine deaminase,

as well as to promote uric acid excretion by modulating the expression of uric acid transporterse(Wang CP.,et al,2011)

Another class of bioactive use in gout therapy

Apart from bioactive substances, other ingredients [e.g., terpenoids, stilbene glycosides, coumarins] have been shown to lower uric acid. As examples, gardenoside and acetonide have been shown to have a significant hyperuricemia effect(Jie Z.,et al, 2018).Moriwaki et al. [1992] have also investigated changes in uric acid concentration following oligonol administration in six healthy persons. Two grams of oligonol per day have lowered 1h uric acid excretion and partial uric acid clearance, as well as uric acid concentrations. These other components' uric acid-lowering effects and modes of action are detailed in Table 6([Mo SF.,et al, 2007)which frameworks the uric acid - bringing down impacts and methods of activity of these different components(Jiang LL.,et al,2020).

Table 6: Mechanism of different bioactive components

Bioactive compound	Dose	Mechanism	References
Green tea polyphenols	600 mg/kg	Inhibit xanthine oxidase activities	(Widha Nugraheni., et al, 2017)
Acteoside	200 mg/kg	Suppression of serum uric acid levels inhibits the production of xanthine oxidase and downregulates the expression of uric acid transporter 1, glucose transporter 9, and mRNA.	(Huang CG.,et al, 2008)
Mulberroside A	10, 20 and40 mg/kg	To promote uric acid excretion, mRNA, glucose transporter-9, and urate transporter-1 levels are downregulated, whereas mRNA and mOAT1 protein levels are upregulated.	(Wang CP.,et al,2011)
Esculinhydrate	50 ,150 mg/kg	Xanthine oxidase inhibition	(Zhu CS.,et al,2017)
Geniposide	50 and 100 mg/kg	Promotes uric acid excretion, downregulation of uric acid transporter 1, glucose transporter 9, and upregulation of mOAT1.	(Jie., et al, 2018)
Curcumin	20 and 40 mg/kg	Serum uric acid lowering mechanism inhibits xanthine oxidase activity.	(Chen Y., et al,2019][Ac.,et al,2017)
Mangiferin	4 mg/kg	This is consistent with the down-regulation of the protein, upregulation of uric acid transporter 1, glucose	(Yang H.,et al,2015)

		transporter 9 protein expression, and ABCG2 expression to promote uric acid excretion.	

Table 7: Various bioactive formulation approaches

Bioactive	Formulation	Approaches	References
Colchicines	TDDS	Cubosomes	(Nasr M.,Et al,2020)
Cyclodextrin- colchicines	TDDS	Elastic liposomes	(Singh HP.,et al,2010)
Capsaicin	TDDS	Niosomes	(Tavano L.,et al,2011)
Curcumin	TDDS	Niosome gel	(Tavano L.,et al,2014)

Alternative treatments for gout

The various alternative means of treatment for gout have been summarised below:

For acute gout

Acute gout therapy aims to relieve pain and reduce joint inflammation as quickly as feasible. A flare-up lasts for four to eight days without any medicine. In general, anti-inflammatory medication should be initiated as soon as an acute gout flare occurs, ideally within 12 to 24 hours. Nonsteroidal Anti-inflammatory medications, glucocorticoids, and colchicine are among the first-line treatments (Nasr M.,Et al,2020), and after 24 hours, the uric acid treatment cures the symptoms of gout[Singh HP.,et al,2010]. The patient's body will react differently to each drug category depending on the physician's experience and comorbidities. Furthermore, in patients with acute gout, it is not suggested to begin treatment with medications that promote hyperuricemia, such as diuretics and low-dose acetal salicylic acid, and to raise the dose of existing therapy (Tavano L.,et al,2011)(Tavano L.,et al,2014). Comorbidities in gout patients that are incompatible with NSAIDs, colchicine, or corticosteroid treatments, may develop on occasion. Recent research indicates that interleukin-1 is a key inflammatory mediator in acute gout. Therefore, interleukin-1 antagonists are considered an alternate choice if all three conventional treatment options are contraindicated.(Navni S &Sandeep K,2018).Uric acid-lowering drugs used to treat chronic gout are not recommended for the treatment of acute gout attacks, as they can further aggravate acute gout attacks (El Tantawy WH,2021).

Table 8: Management of acute gout

Substance / group	Proposed therapy	Adverse drug effects
Nonsteroidal anti-inflammatory drugs [NSAIDs] PO	Maximum dose; 5 to 10 days or until symptoms are resolved	Renal dysfunction
Corticosteroids PO	30 to 35 mg prednisolone PO for 5 days	Cushing's syndrome metabolism disorder, hypertension/hypotension
Colchicine PO	Low-dose therapy: 2 × 0.5 mg initially, then	Gastrointestinal effects in particular

	single administration 0.5 mg after 1 hour	
Cortisone IA or IM	Single administration	Stomach acid overproduction, Cushing syndrome, disease of metabolism, hypertension/hypotension
Interleukin-1 antagonists Canakinumab SC	Single administration [150 mg SC], repeat administration after no less than 12 weeks [19]	Infections [for example, urinary tract infections and airway infections]; local skin reactions at the injection site

For chronic gout

To treat chronic gout, International Guidelines recommend lowering uric acid levels to well below the 6.8 mg/dL solubility limit. (Navni S &Sandeep K,2018)(El Tantawy WH,2021)

Table 9: Management of chronic gout

Substance / group	Proposed therapy	Adverse drug effects
Xanthine oxidase inhibitor: allopurinol	Initially 50 to 100 mg/day; elevation to the maximumusing 800 mg/day[Navni S &Sandeep K,2018)(El Tantawy WH,2021)(Lastair A.,et al,1996)	Diarrhoea, nausea, vomiting, increased liver enzymes, skin reactions [2%], hypersensitivity syndrome [0.1%]
Xanthine oxidase inhibitor: febuxostat	Primarily 80 mg/day, intensification to 120 mg/day, if necessary	Liver dysfunction, diarrhea, nausea, headache, skin rashes
UricoUric agent: probenecid	If allopurinol alone is insufficiently efficient, probenecid can be combined with allopurinol. (Schlesinger N,2004)	Irritation of gastrointestinal tract, skin reactions, anorexia
Selective inhibitor of URAT1 transporter: lesinurad	Authorized, in combination with xanthine oxidase inhibitor, for treatment-refractory cases since February 2016	Headache, influenza-like symptoms increased creatinine levels, gastro-oesophageal reflux
Uricosuric agent: benzbromarone	Not recommended by these authors due to liver toxicity	
Uricase: pegloticase	Taken off the market in July 2016(Axelord D & Preston S,1988)	Uric acid levels are reduced due to the breakdown of uric acid into allantoin, which is eliminated in the urine.

		Adverse drug effects: infusion issues, anaphylaxis, antibody formation.

Future prospective and challenges

There are many medications available in the market for acute and chronic gout, but as xanthine oxidase inhibitors have prominent side effects, intake of such medications on regular basis is not recommended. Most scientists and researchers have been working on bioactive and semisynthetic products, which can be used as carriers like niosomes, NLCs, nanocrystals, and so on, to preserve and enhance their effectiveness.

Conclusion

Gout damages the knees, leading to Akinesia, synovitis, and joint erythema. To avoid gout, the maintenance of a healthy lifestyle is extremely important, but opioid therapy is additionally vital for people with whom a healthy lifestyle isn't being possible. NSAIDs are one of the primary medications of choice for any sort of gout, but xanthine oxidase inhibitors are used because they're very effective in chronic situations. The selection of suitable drug therapy depends totally on the efficacy, effectiveness, and price of the medication. The patients are additionally offered appropriate medications for achieving improved results. Prescriptions that lessen irritation in joints need to be matched with drugs that bring down the measure of uric acids, for instance, allopurinol, febuxostat, quercetin, colchicine, and other bioactive blends. Its oral bioavailability is a smaller amount dissolvable in water and subject to enzymatic debasement in the gastrointestinal system. Many clinical trials have declared that various plant-based molecules have the property to encounter hyperuricemia.

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Abbreviation

XOD: Xanthine oxidase inhibitor, UA: Uric acid , OAT4: Organic anion transporters 4
GLUT9: Glucose transporter 9, MOA: Mechanism of action

Authors contributions
All the authors have contributed equally.

Conflicts of interests
The authors have reported no conflicts of interest

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