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GOUT: CAUSES AND PHARMACEUTICAL ISSUES

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Abstract:

Gout is a systemic disorder which occurs due to an accumulation of urate crystal in the tissues. Urate crystals are formed when the concentration of uric acid in blood is up to the optimum level i.e; 2.4-6.0 mg/dL (Female) and 3.4-7.0 mg/dL (male) . Uric acid is the end product of purine metabolism which does not have any pathological effect it is only a waste product. Gout cause inflammation in the joints, urate crystals activate inflammation causing agents such as interleukins which shows many type of inflammation reactions. The main cause of hyperuricemia is intake of high purine diet, alcohol consumption, diuretic therapy, diabetes mellitus etc; In this article, focus is on the types of Gout, causes of Gout, pathophysiology of Gout and antigout drug therapy. The choice of specific drug therapy is to depend upon safety, efficacy, and cost.

Keywords: *Gout, Hyperuricemia, Types , Symptoms and Causes, Mechanism of action, Febuxostat.*

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INTRODUCTION:

Gout is a serious condition it happens when the urate crystals deposit urate crystals in the soft tissues or joints High concentration of uric acid level in blood above a normal level is a requirement for the formation of uric acid crystals. In spite of this fact that hyperuricemia is the only the main pathogenic defect in gout, the greatest number of people with hyperuricemia do not experience gout or even form uric acid crystals. In actuality, only 5% of people with hyperuriceamia above 9 mg/dL lead to gout.[1-2] Appropriately, it is also a conception that other factors such as genetic predisposition share in the incidence of gout. While environmental factors contribute to hyperuricaemia, renal and gut excretion of urate is central to regulation of serum urate, and genetic factors are important. Diuretics are also used to treat hypertension, for example, and they uplift the blood levels of uric acid and can increase the risk of gout. Stimulation of the NLRP3 inflammasome and liberation of interleukin 1β have crucial roles in beginning of acute gout flares. A "Lowering serum urate by target action" approach is essential for effective management of gout; Lowering the concentration of urate in serum less than 360 µmol/L prompt to dissolution of crystals and it will lead to abolishment of flares. Gout is a inflammatory disease which impact negative effects on body. It may be lethal sometimes. An allopurinol dose-acceleration approach is very powerful for achieving treatment targets, and only a few, new urate-lowering drugs are also available At global level, rates of initiation and continuation of urate-lowering therapy are very low that is why achievement of serum urate targets is limited.[3-4] In spite of number of effective treatments are available for lowering the blood-urate level [Urate-lowering therapy (ULT)], to overcome or prevent chronic joint damage and frequent gout flares, and insubstantial dosing of ULT are widely Frequent [5-6]

TYPES OF GOUT [7]

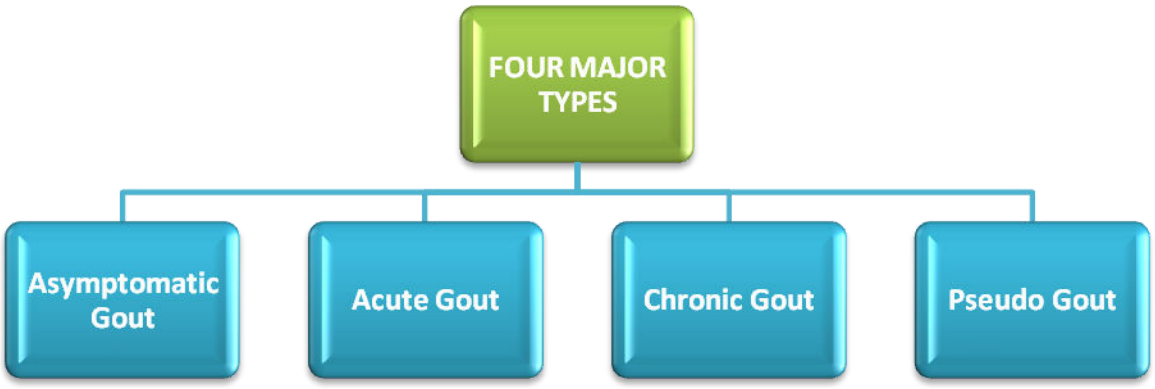


Fig. 1 Types of Gout

Asymptomatic Gout: This type of gout does not show any kind of symptoms but only increase the uric acid concentration in serum (hyperuricemia) but never develop gouty arthritis or renal failure.

Acute Gout: This is defined as rapid growth of inflammation, generally of only one joint, with painful sensation of heat and swelling. Uric acid crystals stimulate the inflammation reaction in joints or tissues around joints. It mainly involves great toe, although knees, ankles. It is revesible and completely healed.

Chronic Gout: This is discriminate by long-term joint inflammation, which causes joint pain at rest and/or on movement. After many years of acute gout it may develop and it causes many diseases such as Periphereal pain, tiffness in joints, Renal failure.

Pseudo Gout: It is a type of arthritis which cause inflammation in joints but it is due to the accumulation or deposition of calcium pyrophosphate crystals rather than urate crystals. This condition is also known as calcium pyrophosphate dihydrate (CPPD) deposition disease. In this disease mainly protect the elbow joint from permanent damage.

EPIDEMIOLOGY[8-12]

The general ubiquity of gout is 1–4% of the general population. In western countries, it occurs in 3–6% in men and 1–2% in women. In some countries,

prevalence may increase up to 10%. Prevalence rises up to 10% in men and 6% in women more than 80 years old. Annual incidence of gout is 2.68 per 1000 persons. Chances of development of gout are more 2–6 folds in man more than women. At Global level, incidence of gout increases moderately due to bad dietary habits such as fast foods, lack of exercises, intake of alcohol, increased incidence of obesity and metabolic syndrome .

RISK FACTORS FOR DEVELOPMENT OF GOUT [13-24]

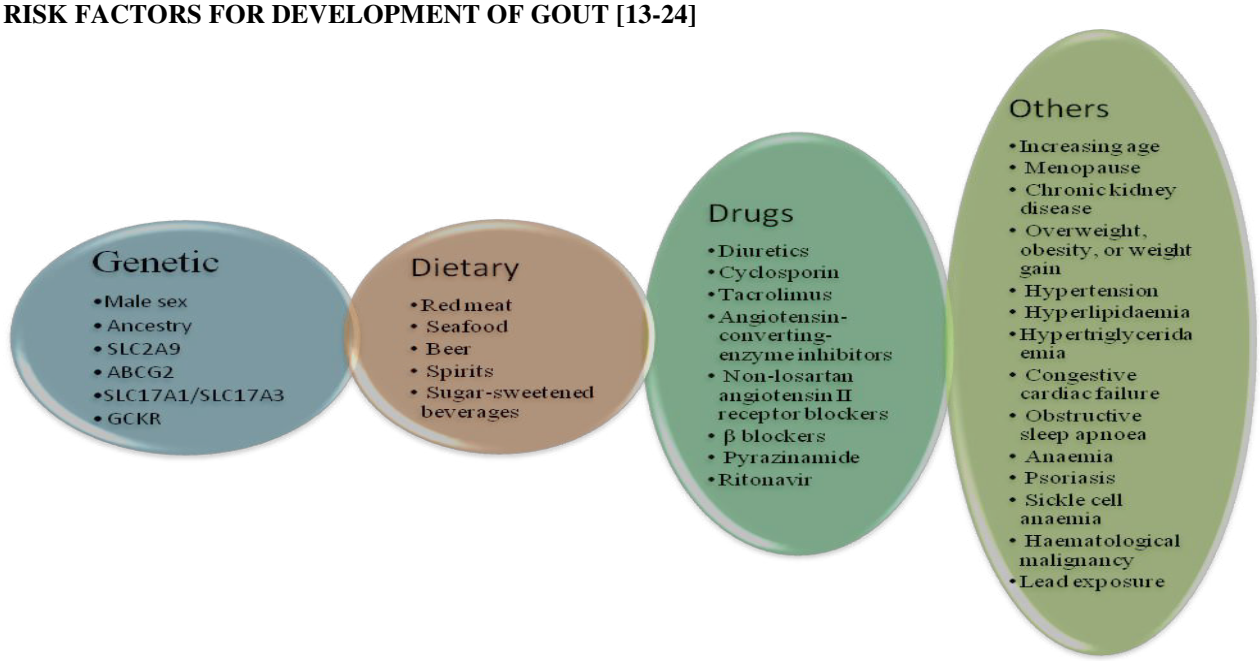
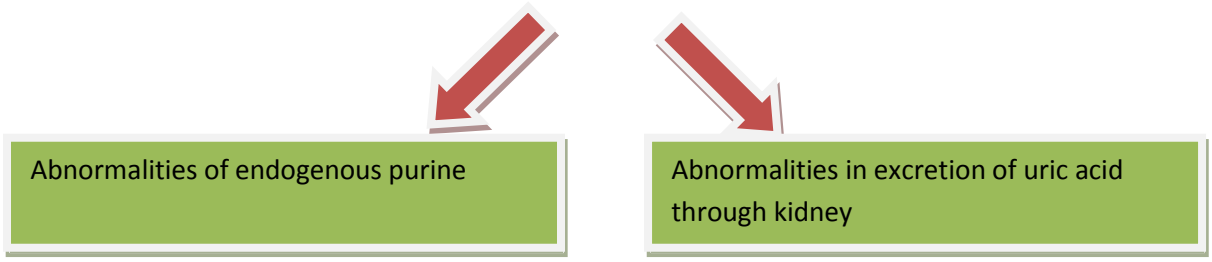


Fig. 2: Risk factors of Gout

PATHOPHYSIOLOGY [25-28]

Urate is the other name of uric acid having pKa value is 5.8 and ionized at neutral pH. It is the last product of purine metabolism in humans. The rate of production and execretion of uric acid determine the blood uric acid level in body.

Important Processes Which Cause Hyperuricemia



The serum urate concentration depends on the degradation of endogenous purines, and the renal and intestinal excretion of urate as shown in above chart. The dominating factor contributing to hyperuricaemia is under-excretion of urate. Urate is charged at a 5.8 pH which is nearby neutral and at a concentration of 6.8 mg/dl in serum, at that time crystals can form spontaneously. While, when the pH and temperature of the body decreases and salt concentration, and cartilage matrix components lead to the decrease in solubility of the urate crystals.

In this case, chances of formation of Urate stones are possible because of acidic urine and it is also known as **urolithiasis** . The serum level of urate in human considered to be 'optimum' varies among laboratories and in publications, but a range of 3.5 mg/dL (0.2 mmol/L) to 7.0 mg/dL (0.4 mmol/L) is often recited. Serum urate is usually 0.5-1 mg/dL (0.03-0.06 mmol/L) lower in women compared with men.

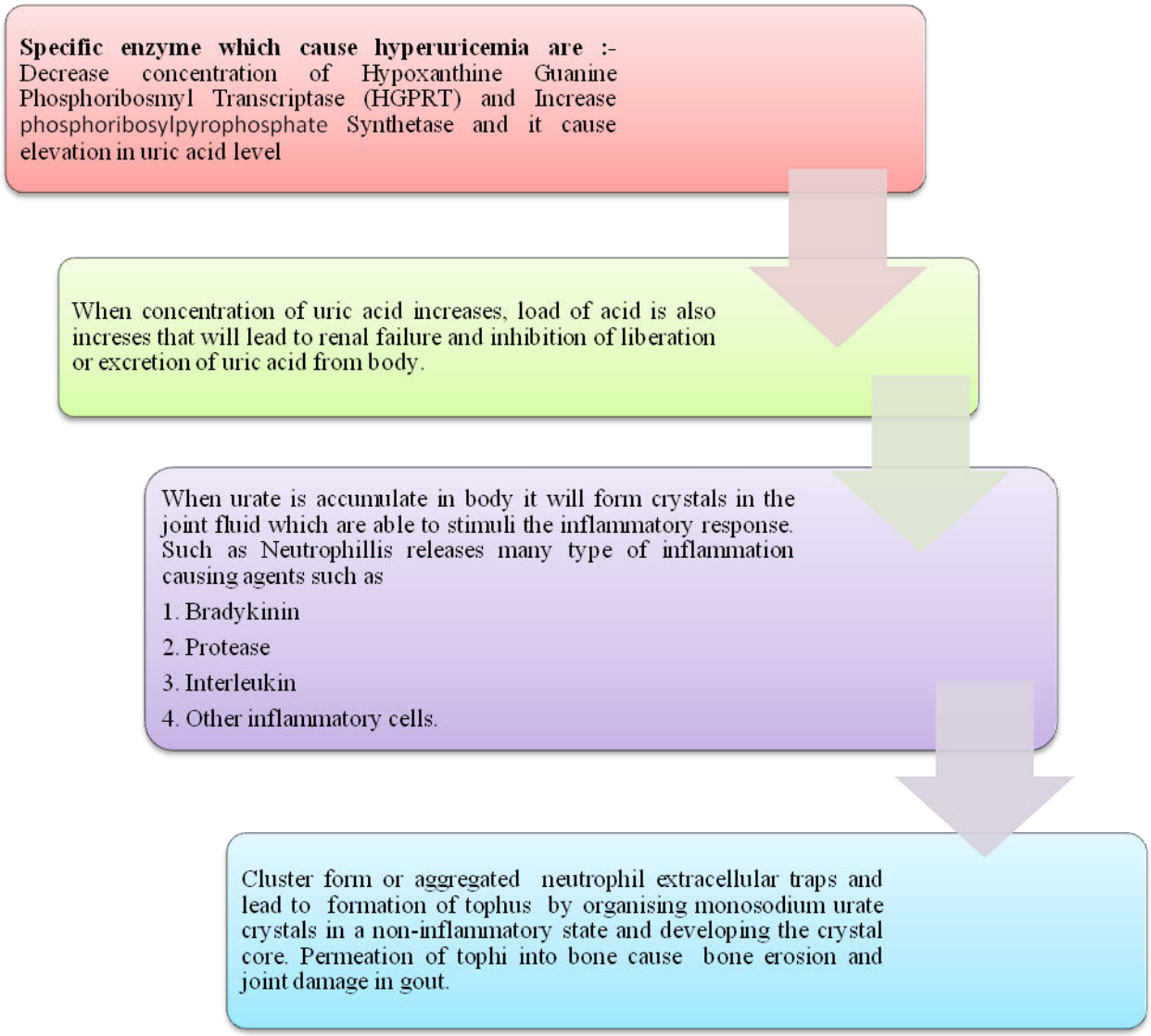


Fig. 3: Pathophysiology of Gout.

SIGN AND SYMPTOMS [29-36]

In the early stage of gout, these type of problems faced by a patient such as pain in joints, swelling, heat, redness, and difficulty in the movement of the affected joint. The initial period of mild discomfort in joint lead to severe pain after 24 h. At this stage pain of a flare is more than 7 on a scale of 0-10 and the pain is very violent which may be due to burning sensation and joint tenderness.Generally, the main site of gout is metatarsophalangeal joint but other sites of joints are also involved.

Metatarsophalangeal joints are surrounded by a thin *joint* capsule and have ligaments that support them. That's why it can cause difficulty with walking and other activities. At the night, chances of flares are most common and patient waking from sleep because of severe pain in joints. Chances of flares in humans are more in case of medical or surgical illness, loss of

DIAGNOSIS OF GOUT [38-39]

water from the body, high intake of purine-rich foods and high content of alcohol intake. Rheumatologists were reported that the presence of subcutaneous nodules (tophi) in the hands, elbows, and feet in the joint of the patients. These lesions do not show any kind of pain sensation but it

may become swell and inflamed but when these lesions are severe they cause poor grip (mainly in fingers) and also cause Akinesia (restriction involuntary movement). In history, it is reported that in the affected joint of patients tophaceous material is discharged from nodules which cause ulceration and severe infections. Inflammation in joints (synovitis), erythema, swelling, and warmth of the affected joint is the main symptoms of the gout and there is a chance of fever because of inflammation in the blood. On examination, central obesity and hypertension affirm combroid conditions.

Fig. 4: Diagnosis of Gout

ANTIGOUT DRUG THERAPY [40,41]

Table no. 1: Short- term management of Gout drugs

Drugs	Mechanism of action
NSAIDs	COX-2 inhibitors
Colchicine	➢ Inhibition of IL-1beta processing ➢ Down-regulation of tyrosine kinases and phospholipases in neutrophils ➢ Inhibition of chemotaxis, superoxide anion production, adhesion to cellular substrata, mobilization and release of lysosomal enzymes ➢ Disruption of microtubules
Corticosteroids	➢ Prevention of pro-inflammatory transcription factor activation with inhibition of inflammatory cytokines, enzymes, receptors, and adhesion molecules

Table no. 2: Drugs in development for acute Gout therapy

Drugs	Mechanism of action
Anakinra	IL-1 receptor antagonist
Rilonacept	Soluble IL-1 receptor
Canakinumab	Monoclonal anti-IL-1beta antibody

Table no. 3: Long-term management of Gout drugs

Drugs	Mechanism of action
Allopurinol	XO inhibitor
Febuxostat	XO inhibitor
Sulphinpyrazone	URAT1 inhibitor
Probenecid	URAT1 inhibitor
Benzbromarone	URAT1 inhibitor

Table no. 4 : Drugs in development for chronic Gout therapy

Drugs	Mechanism of action
Lesinurad	URAT1 inhibitor
Arhalofenate	URAT1 inhibitor
Levotofisopam	URAT1 inhibitor
RDEA3170	URAT1 inhibitor
BCX4208	Purine nucleoside phosphorylase inhibitor
Pegloticase	Pegylated uricase
Pegadricase	Pegylated uricase
DHNB	XO inhibitor

FLOW CHART OF MECHANISM OF ACTION [42]

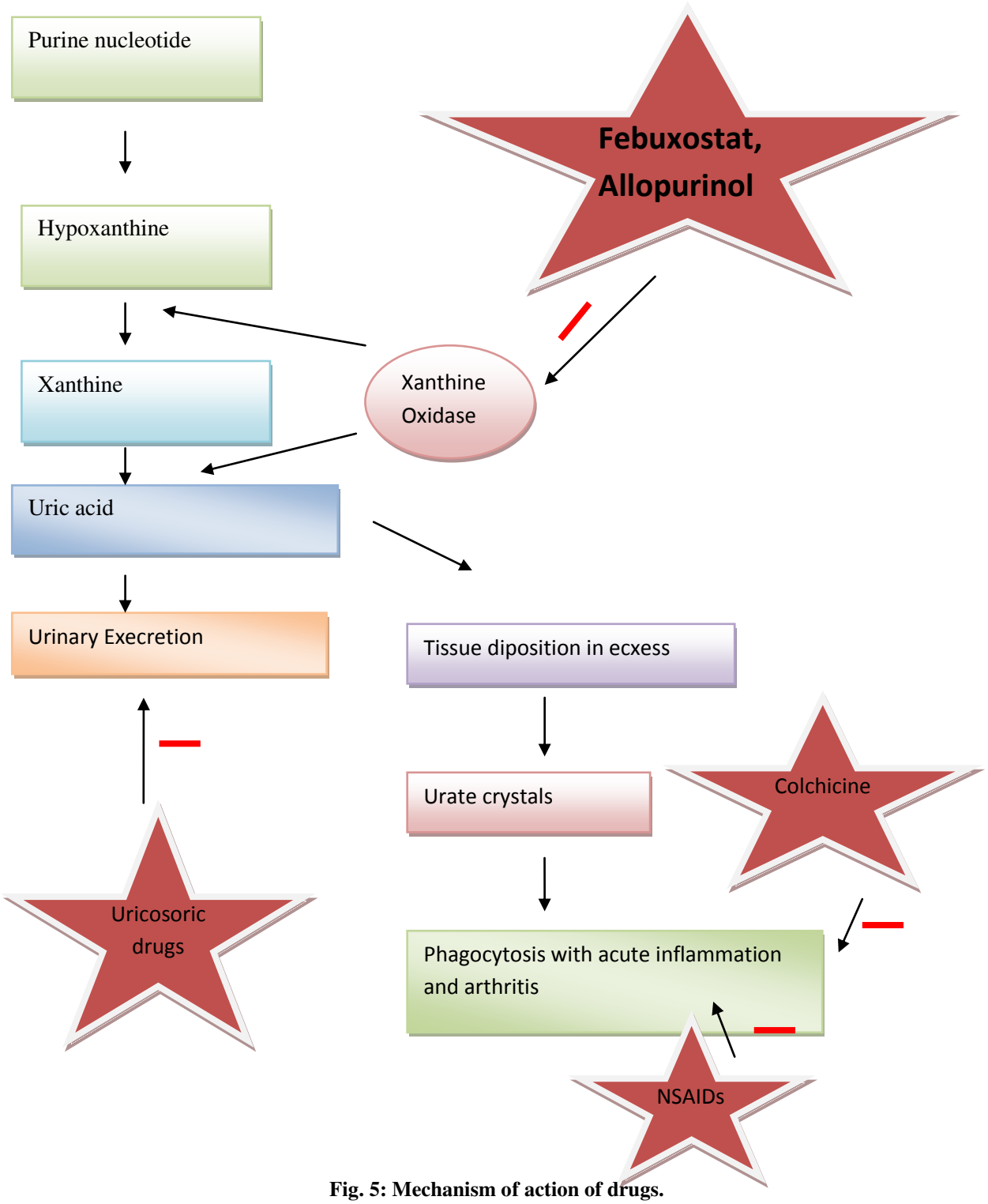


Fig. 5: Mechanism of action of drugs.

FORMULATIONS OF FEBUXOSTAT AVALABLE IN MARKET [43]

Table no. 5: Formulations of Febuxostat

BRAND NAME	COMPANY NAME	FORMULATION
ALXO	Alpic Biotech	Tablet
BUXORIC	Macleods (Procare AHT)	Tablet
EBUXO	IPCA	Film coated Tablet
EXFEB	Olcare (Excare)	Tablet
FABS	Systemic	Tablet
FABUACT	Active HC	Tablet
FABULAS	Intas	Film coated Tablet
FABULOUS	Johnlee (Vista)	Tablet
FABUZEST	Unichem	Tablet
FAYEB	Aamorb (Sioux)	Tablet
FEBARTO	Panacea	Tablet
FEBINTRA	Intra Labs	Tablet

These are some formulations available in market.

PATENTABLE FEBUXOSTAT TREATMENT [44]

Table no. 6: Patent on Febuxostat

PUBLICATION NUMBER	TITLE
WO1992009279A1	2-arylthiazole derivative and pharmaceutical composition containing the same
JPH06345724A	Cyano compound and its production
WO1999065885A1	Polymorphic modifications of 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazole-carboxylic acid and processes for the preparation thereof
US7361676B2	Solid preparation containing single crystal form
CN101474175A *	Oral solid preparation of Febuxostat with high-bioavailability and preparation method thereof
WO2011141933A2 *	Process for preparation of 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid and its pharmaceutically acceptable salts
US20110311620A1 *	Process for preparation of 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid and its pharmaceutically acceptable salts
WO2012172461A1 *	Pharmaceutical compositions of Febuxostat
EP2902016A1 *	Febuxostat tablet
WO2018001569A1 *	Pharmaceutical composition comprising a non-purine selective inhibitor of xanthine oxidase and method for the preparation thereof

*Cited by examiner

FUTURE PROSPECTIVE AND CHALLENGES [45-47]

Gout is a very popular disease now a days and number of patients suffereing from elevated uric acid level in blood. There are many medicines available in the market for acute and chronic gout but they cause side effects like NSAIDS cause liver and kidney problems if patient use it on daily basis and Xanthine oxidase inhibitors (allopurinol, Febuxostat) also cause side effects. Allopurinol cause abnormality in the kidney functions. According to research Febuxostat is better than allopurinol and has lesser side effects on body and it is safe for kidneys and it is cost effective and has low dose as compare to allopurinol rather then this febuxostat has a problem with liver which can be avoid by using transdermal delivery.According to drug profile of Febuxostat it is a BCS-II has low solubility and it is degraded by enzymes and its oral bioavaiability is 49% so these all type of problems can be overcome by a scientist. It is a future prospective for the gout management. To develop a new formulation which protect the drug from body environment and increase the efficacy and bioavailability. Recent years most of the scientists and researchers work on a nanosystem which is used as a carrier like niosomes, NLCs, nanocrystals etc; to protect and improve its efficacy.

CONCLUSION:

Gout affects the joints and its leads to Akenesia, synovitis and erythema of joints. Maintenance of the healthy lifestyle is very essential for the prevention of gout, but drug treatment is still very important in people for whom healthy lifestyle is not effective. The NSAIDs are one of the first choice drugs for any type of gout but in chronic case Xanthine oxidase (XO) inhibitors are used because they are very effective. The selection of the appropriate drug therapy is mainly dependent upon the safety, efficacy and cost of the medicine. Effective drug combinations are also given to the patient for better result. Drugs which decrease inflammation in joints may be combined with the drugs which lower the uric acid level like allopurinol and Febuxostat . The future nanosystem may also help to the patient for lowering uric acid in controlled manner. Researchers have designed a Nanocarriers which are made up of lipids that can easily cross all the membranes and reach at the target site, which helped to lowering uric acid . These Nanocarriers vesicles were selected for Febuxostat delivery because of their penetration enhancing ability. As it is less soluble in water and vulnerable to enzymatic degradation in both intestine and liver hence, its oral bioavailability is affected. So that's why new formulatios are developed to enhance bioavailability.

REFERENCES:

1. Dalbeth N, Merriman T.R., Stamp L.K. Gout Lancet. 2016; 388 (10055):2039–2052.
2. Emmerson B.T. The management of gout. New Engl J Med. 1996 ; 334 (7) :445–451.
3. Edwards NL, Sundy JS. Work productivity loss due to flares in patients with chronic gout refractory to conventional therapy. J Med Econ. 2011;14(1):10–15.
4. Singh JA, Strand V. Gout is associated with more comorbidities, poorer health-related quality of life and higher healthcare utilisation in US veterans. Ann Rheum Dis. 2008 ;67(9):1310–1316.
5. Sarawate CA, Brewer KK, Yang W. Gout medication treatment patterns and adherence to standards of care from a managed care perspective. Mayo Clin Proc. 2006 ;81(7):925–934.
6. Singh JA, Hodges JS. Opportunities for improving medication use and monitoring in gout. Ann Rheum Dis. 2009 ;68(8):1265–1270.
7. Available at: https://www.medicalnewstoday.com/articles/144827.php
8. The US National Health and Nutrition Examination Survey showed a prevalence of 2.9% in 1988–1994, and 3.9% in 2007–2008 the UK Clinical Practice Research Database generated prevalence estimates of 1.4% in 1999, and 2.5% in 2012.
9. Kuo C.F., Grainge M.J. Global epidemiology of gout: prevalence, incidence and risk factors. Nat Rev Rheumatol. 2015;11(11):649–662.
10. Zhu Y, Pandya BJ et al., Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007–2008. Arthritis Rheum. 2011; 63: 3136–41.
11. Kuo C-F, Grainge MJ et al., Doherty M. Rising burden of gout in the UK but continuing suboptimal management: a nationwide population study. Ann Rheum Dis. 2014; published online Jan 26. DOI:10.1136/annrheumdis-2013-204463.
12. Mikuls T, Farrar J. et al., Gout epidemiology: results from the UK general practice research database, 1990–1999. Ann Rheum Dis. 2005; 64: 267–72.
13. Campion EW, DeLabry LO. Asymptomatic hyperuricemia. Risks and consequences in the

Normative Aging Study. Am J Med. 1987; 82: 421–26.

14. Bhole V, de Vera M et al., Epidemiology of gout in women: Fifty-two-year followup of a prospective cohort. Arthritis Rheum 2010; 62: 1069–76.
15. Singh JA, Reddy SG et al., Risk factors for gout and prevention: a systematic review of the literature. Curr Opin Rheumatol 2011; 23: 192.
16. Zhang Y, Choi H. et al., Purine-rich foods intake and recurrent gout attacks. Ann Rheum Dis 2012; 71: 1448–53.
17. Zhang Y, Woods R, et al., Alcohol consumption as a trigger of recurrent gout attacks. Am J Med 2006; 119 (800):13–18.
18. Choi HK, Curhan G. Soft drinks, fructose consumption, and the risk of gout in men: prospective cohort study. BMJ 2008; 336: 309–12.
19. Choi JW, Ford ES. et al., Sugar-sweetened soft drinks, diet soft drinks, and serum uric acid level: the third National Health and Nutrition Examination Survey. Arthritis Rheum 2008; 59: 109–16.
20. Choi HK, Curhan G. et al., Fructose-rich beverages and risk of gout in women. JAMA 2010; 304: 2270–78.
21. Batt C, Phipps-Green AJ. et al. Sugar-sweetened beverage consumption: a risk factor for prevalent gout with SLC2A9 genotype-specifi c eff ects on serum urate and risk of gout. Ann Rheum Dis 2014; 73: 2101–06.
22. Choi HK, Curhan G. Coffee, tea, and caffeine consumption and serum uric acid level: the third national health and nutrition examination survey. Arthritis Care Res 2007; 57: 816–21.
23. Choi HK, Curhan G. et al., Intake of purine-rich foods, protein, and dairy products and relationship to serum levels of uric acid: the third National Health and Nutrition Examination Survey. Arthritis Rheum 2005; 52: 283–89.
24. Choi HK, Willett W. et al., Coffee consumption and risk of incident gout in men: a prospective study. Arthritis Rheum 2007; 56: 2049–55.
25. Choi HK, Reginato AM. et al., Pathogenesis of Gout. Ann Intern Med. 2005;143(7):499–516.
26. Feig DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. N Engl J Med. 2008;359(17):1811–1821.
27. Schauer C, Janko C, et al. Aggregated neutrophil extracellular traps limit infl ammation by degrading cytokines and chemokines. Nat Med 2014; 20: 511–17.
28. Dalbeth N, Clark B, et al. Mechanisms of bone erosion in gout: a quantitative analysis using plain radiography and computed tomography. Ann Rheum Dis 2009; 68: 1290–95.
29. Bellamy N, Downie WW. Et al., Observations on spontaneous improvement in patients with podagra: implications for therapeutic trials of non-steroidal anti-inflammatory drugs. Br J Clin Pharmacol 1987; 24: 33–36.
30. Taylor WJ, Fransen J, et al., Study for Updated Gout Classification Criteria (SUGAR): identification of features to classify gout. Arthritis Care Res (Hoboken) 2015; 67: 1304–15.
31. Grahame R, Scott JT. Clinical survey of 354 patients with gout. Ann Rheum Dis 1970; 29: 461–68.
32. Choi HK, Niu J. et al. Nocturnal risk of gout attacks. Arthritis Rheumatol 2015; 67: 555–62.
33. Dubreuil M, Neogi T. et al., Increased risk of recurrent gout attacks with hospitalization. Am J Med 2013; 126: 1138–41.
34. Aati O, Taylor WJ, Siegert RJ, et al. Development of a patient-reported outcome measure of tophus burden: the tophus impact questionnaire (TIQ-20). Ann Rheum Dis 2015; 74: 2144–50.
35. Aati O, Taylor WJ, Dalbeth N. Toward development of a tophus impact questionnaire: a qualitative study exploring the experience of people with tophaceous gout. J Clin Rheumatol 2014; 20: 251–55.
36. Zhang Y, Chen C, Choi H, et al. Purine-rich foods intake and recurrent gout attacks. Ann Rheum Dis 2012; 71: 1448–53.
37. Zhang Y, Woods R, Chaisson CE, et al. Alcohol consumption as a trigger of recurrent gout attacks. Am J Med 2006; 119: 800: 13–18.
38. Anne-Kathrin Tausche et al; Gout—Current Diagnosis and Treatment. Dtsch Arztebl Int. 2009; 106(34-35): 549–555.
39. Gaafar Ragab a , Mohsen Elshahaly b . et al., Gout: An old disease in new perspective – A review. Journal of Advanced Research, 2017; 8: 495–511.
40. Micaela Gliozzi, Vincenzo Mollace. The treatment of hyperuricemia. International Journal of Cardiology. 2016;(213): 23-27.
41. Becker MA. Hunt B. et al., Febuxostat (TMX-67), a novel, non-purine, selective inhibitor of xanthine oxidase, is safe and decreases serum urate in healthy volunteers. Nucleosides Nucleotides Nucleic Acids

2004; 23:1111.

42. K. D. Tripathi. Essentials of Medical Pharmacology 2003. Jaypee Brothers Medical Publishers (P) LTD, New Delhi. 5th edition,202-212.
43. Available at: https://portal.veoliaes.com/cims/login.jsp
44. External links
- Espacenet
- Global Dossier
- PatentScope

45. Tripura SP1*, Gaud RS. Formulation and Evaluation of Febuxostat Nanoparticles. Am. J. PharmTech Res. 2014; 4(1):1-11.
46. Singh S, Parashar P. Transdermal potential and anti-gout efficacy of Febuxostat from niosomal gel. Journal of Drug Delivery Science and Technology. 2017; 39: 348-361
47. Dalbeth N . Management of gout in primary care: challenges and potential solutions. Advance Access publication 2013: 1549-1550.