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REVIEW OF GOUTY ARTHRITIS: A NEW PERCEPTION FOR THE TREATMENT OF OLD DISEASES

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ABSTRACT: Gouty arthritis, an inflammatory joint disease, occurs due to the accumulation of Monosodium Urate (MSU) crystals in the joints, mainly at the metatarsophalangeal joints of the big toe. At present, the incidence and prevalence of gout are increasing globally. The various risk factors are responsible for the development of gouty arthritis, including nonmodifiable, modifiable, and genetic factors. Under physiological conditions, the purine undergoes a catabolic pathway to produce the uric acid end product excreted from the body using various uric acid transporters. The overproduction or under-excretion of uric acid leads to the pathophysiology of hyperuricemia and promotes the MSU crystals formation and deposition in joints to trigger inflammation by releasing inflammatory mediators in gouty arthritis. If chronic gout has been left untreated, the pain worsens and eventually causes cartilage degradation, bone erosion, and urolithiasis. The research studies of the antigout activity of the various secondary metabolites are manifested in this review. The inflammatory pathways involved in gouty arthritis development are being discussed to find a new therapeutic target to treat gouty arthritis better.

INTRODUCTION: In the 13th century, Randolphus of bocking was the first person who coined the term “GOUT” which is derived from the Latin word “GUTTA” (which translates into “drop”). In the olden days the disease was believed to be caused by drops of viscous hum or (liquid) dripping from the blood into the joints, this explanation currently resembles the modern scientific explanation [1]. Gouty arthritis is a type of arthropathy in which joints are painful due to the accumulation of monosodium urate crystals. It usually affects the big toe (metatarsal joint). It can also affect other joints like the ankle, knee, foot, elbow, and wrist. The needle-shaped urate crystals also deposit under the skin and form " TOPHI " lumps. There are two different types of gout. Primary gout and Secondary gout. Primary gout is not accompanied by any recognized etiology other than family history. Secondary gout is mainly due to a recognized etiology, including chemotherapy treatment for lymphoma and other risk factors.

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According to the recent reports of Global Burden of Disease Analysis among 195 countries and territories, the incidence and prevalence of gouty arthritis are increasing among the worldwide population[2]. The global health data exchange registry (GHDx) and World Health Organisation (WHO) reported 7.44 million cases of gout worldwide in 2017 (incidence, 0.097%) with a prevalence of 41.22 million cases (0.54%) and the Disability Adjusted Life Years (DALYs) was 1.28 million (0.051%) [3]. Most often, gout affects men

more than women. Previously gout has been considered a "disease of white men" as they consume red meat and drink alcohol. Hence most of the epidemiologic studies had focused on white individuals [2]. Gout is more prevalent in the obese and aging populations but it can be easily treated and prevented if the right care is taken. This disease was first identified by the Egyptians in 2640 BC. From the olden days it is believed that gout is associated with a Rich lifestyle (rich food and alcohol consumption); hence it is called as "disease of kings" [1]. The incidence of gout in India is not clear. As per the study by the international league of nations against rheumatism, a community-oriented program for control of rheumatic disease (ILAR COPCORD), in Biguvan village of India, the prevalence of gout is 0.12%. A study made in Vellore showed that the Indian urban population is more prone to gout than the rural population, and 15.8% of the affected patients are less than 30 years of age [4].

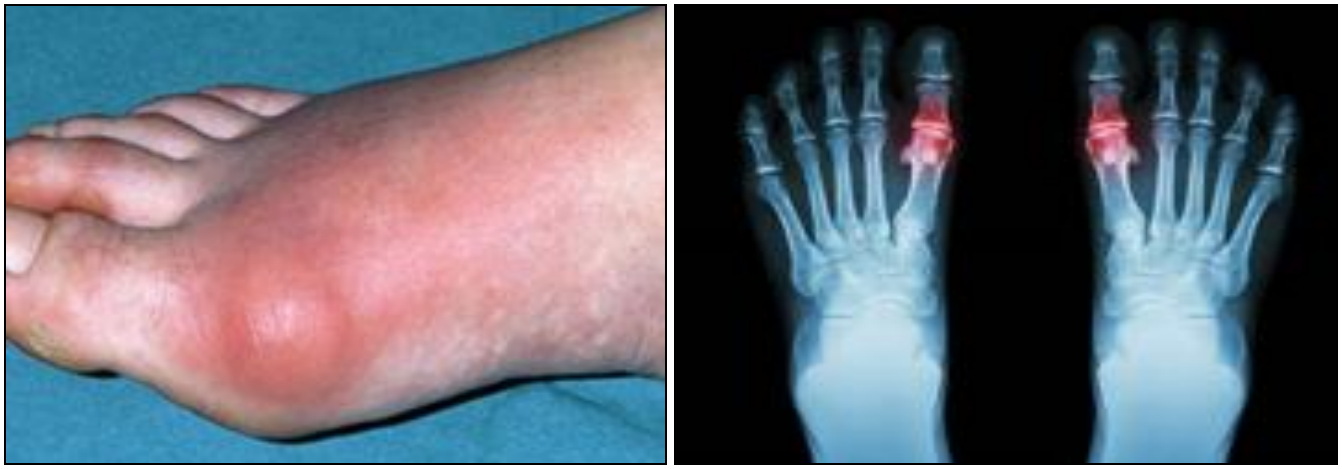


FIG. 1: SLIGHT REDNESS AT THE JOINT OF BIG TOE

Risk Factors of Gout: Two risk factors can increase the chance of developing a disease. They are nonmodifiable risk factors and modifiable risk factors. Demographic factors like age, sex, and race or ethnicity come under nonmodifiable risk factors. In contrast, dietary factors and lifestyle factors are considered modifiable risk factors. Recently, Genome-Wide Association Studies (GWAS) have reported genetic factors that include renal urate transport for developing hyperuricemia and gout [5].

Nonmodifiable Risk Factors:

Sex: The onset of gout is delayed in females more than in males. This is ascribed to enhanced renal tubular excretion of urate by oestrogen in pre-menopausal women. While in post-menopausal women, there is a higher risk of incidence of gout due to decreased oestrogen levels [5, 6].

Age: As age increases, the risk of hyperuricemia and gout also increases concomitantly. This is due to declining kidney function. According to the National Health and Nutrition Examination Survey (NHANES), the prevalence of gout or serum uric acid increase with the increasing age group [6].

Modifiable Risk Factors:

Alcohol: The relationship between excess alcohol intake and gout has been recognized. Various mechanisms have been involved in ethanol-induced hyperuricemia, including, 1) Decreased renal urate excretion due to lactic acidosis.

This occurs when ethanol metabolism leads to high NADH/NAD levels, engaging the pyruvate pathway to produce more lactate and inhibiting glucose formation (gluconeogenesis). 2) Increased purine production by stimulating the breakdown of ATP to AMP. 3) The high purine content in beer increases uric acid synthesis [7].

Purine-Rich Food: Consuming purine-rich food like red meat and seafood increases the risk of developing gout because the end product of purine metabolism is uric acid.

On the other hand, dairy products are found to be protective against gout [5, 7]. Some of the studies reported reduced serum uric levels after ingesting milk protein after considering the uricosuric effect of the protein load [5].

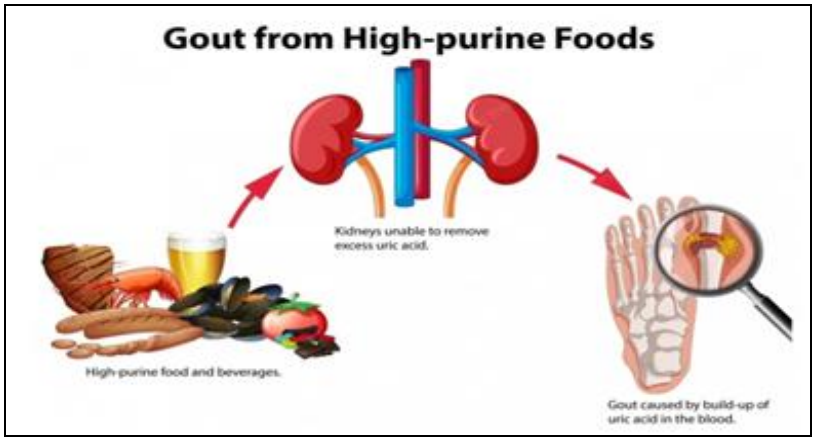


FIG. 2: HIGH PURINE-RICH FOOD AND ITS IMPACT ON GOUT

Coffee: A study was performed on Japanese males for the uric acid reduction in coffee versus green tea-consuming persons. The result showed that uric acid decreased as coffee consumption increased, but the same was not found in green tea. This may be due to caffeine-induced diuresis and the hypothesis that uric acid excretion would increase with increased renal blood flow [5]. Also, the Health Professional Follow-Up Study (HPFS) reported that drinking six cups of coffee per day was found to be protective in developing gout compared to not consuming coffee [7].

Genetic Factors: The mechanism of hyperuricemia in primary gout is mainly due to ineffective renal excretion rather than increased production. Also, it was found that the kidney excretes 70% of uric acid excretion, and the remaining 30 % is excreted into the intestine by an unknown mechanism. Hence recent studies focus on genes that regulate renal uric acid transporters [6]. SLC22A12 gene encodes urate anion transporter 1 (URAT 1), SLC2A9 encodes glucose transporter type 9 (GLUT9) and SLC22A11 gene encodes organic anion transporter 4 (OAT4) [5, 6, 7]. These are the transporter involved in the reabsorption of uric acid in the kidney. The mutation or hereditary changes in the above genes is considered as the risk factor for developing gout. A more understanding of genetic polymorphism and its relation with gout gives more perception on individuals' susceptibility to gout and also leads to more targeted therapy.

Physiology of Uric Acid Metabolism: Purines, which include adenine and guanine are the building blocks of DNA and RNA. Physiologically, uric acid is synthesized in two ways. When a purine-rich diet is ingested exogenously, the purine present in the food gets degraded into uric acid as the end product, mainly in the liver and a small amount in the intestine. And also uric acid is produced endogenously from the degradation of purines of damaged & dead cells. The formation and degradation of purine nucleotides relatively range from 300 to 400 mg per day. At first, one of the nucleotide monophosphate (adenosine monophosphate) is converted to nucleoside (inosine) in two different ways: In the first way the inosine is formed by the removal of an amino group from AMP by deaminase (deamination) followed by removal of the phosphate group from IMP by nucleotidase (dephosphorylation).

In a second way, the inosine is formed by dephosphorylation of AMP by nucleotidase followed by deamination of adenosine by adenosine deaminase. Another nucleotide, monophosphate (guanosine monophosphate) is converted to its nucleoside (guanosine) by nucleotidase. Secondly, purine nucleoside phosphorylase converts the nucleosides inosine and guanine to their respective purine base hypoxanthine and guanine. Then xanthine is formed from hypoxanthine by xanthine oxidase (oxidation) and from guanine by guanase enzyme. Finally, xanthine is again oxidized by xanthine oxidase to form uric acid [9, 10]. In most animals (other than primates) uric acid is oxidized by the uricase enzyme to the soluble form allantoin. Whereas in humans, during evolution, the gene encoding this uricase enzyme is inactivated by mutations. Hence human being lacks uricase enzyme [10].

Physiology of Uric Acid Excretion: Uric acid is excreted *via* the kidney and small intestine. Two

third of uric acid is excreted through the kidney while one-third of uric acid is excreted through the small intestine [10].

Renal Excretion of Uric Acid: The excretion of uric acid is regulated by reabsorption and secretion through various uric acid transporters located in the proximal convoluted tubule in the kidney, The transporters which are involved in the reabsorption of uric acid in the kidney are mainly URAT, OAT4 and GLUT9 and the transporters which are involved in the secretion of uric acid in the kidney are mainly ABCG2, OAT1, OAT2, OAT3 and MRP4 [10].

Extrarenal Excretion of Uric Acid: The two transporters, namely ABCG2 and GLUT9 are involved in the excretion of uric acid from blood to the intestinal lumen. The various transporters regulating urate concentration in the blood are described below [10].

Glucose Transporter 9 (Slc2a9 Gene): GLUT9 is named, Because of a similar sequence to glucose transporter and it comes under the solute carrier family (SLC). Like GLUTs, GLUT9 is not involved in transporting glucose and fructose. It is mainly involved in uric acid transport [11]. GLUT9 is encoded by the SLC2A9 gene which is located on human chromosome 4p [12]. The GLUT9 exists as two splice variants. One is GLUT9a (SLC2A9-L), and the other is GLUT9b (SLC2A9-S). The GLUT9a is situated in the basolateral membrane of the proximal tubule and GLUT9b is located at the apical or luminal membrane of the collecting duct [13]. GLUT9 is a voltage-dependent high-volume uric acid transporter with 12 transmembrane domains and is found in the kidney, liver, small intestine, and chondrocytes [12]. The research studies are finding that the mutation of the SLC2A9 gene encoding tubular GLUT9 involves a decrease in uric acid concentration (hypouricemia); this might be due to decreased reabsorption of uric acid through the kidney tubule [13]. This indicates the importance of GLUT9 in the reabsorption of uric acid through the kidney tubule. The GLUT9 is located on the apical and basolateral membrane of intestinal epithelial cells, specifically in the jejunum and ileum part of the small intestine and mediates the excretion of uric acid through the intestine [12].

Urat1 (SLC22A12): URAT1 is encoded by the SLC22A12 gene and is mainly located in the apical membrane of the proximal kidney tubules to reabsorb the uric acid by exchanging the organic anions or chloride ions and is also located in the small intestine [14]. It was initially identified in the Xenopus oocytes. URAT1 comes under the solute carrier family and is an organic anion transporter (OAT) member.

Since, the URAT1 works by exchanging the organic anions (such as lactate, citrate, α-ketoglutarate, and oxaloacetate - products of the Krebs cycle), the increased levels of organic anions in blood, invasive of certain pathophysiological conditions like alcohol poisoning (increased level of lactate) and diabetic ketoacidosis (increased level of acetoacetate & β-hydroxybutyrate), promotes the increased reabsorption of uric acid by URAT1 by exchanging with these organic anions. This leads to the development of hyperuricemia [15]. URAT1 is a tertiary active transporter and its urate reabsorption activity is influenced by secondary active transporter (Na+/organic anion (dicarboxylate) transporters) and primary active transporter (Na+/K+ ATPase) [15].

OAT4 (SLC22A11): OAT4 is situated in the apical membrane of the kidney tubule and encoded by the SLC22A11 gene. OAT4 reabsorbs the uric acid in the proximal tubule by exchanging it with a chloride ion or organic anion.OAT4 has 51 % of similar amino acid residues with URAT1 and shows weaker in vitro uric acid transportation [15].

OAT10 (SLC22A13): OAT10 is encoded by the SLC22A13 gene, and it is mainly located on the apical membrane of the proximal tubule [15]. To a smaller extent, OAT10 is also present in the intestine [11]. This also works by exchanging the dicarboxylate ions for urate reabsorption.

ABCG2(BCRP): ABCG2 transport belongs to the ATP-binding cassette family, and it is also termed as breast cancer resistance protein, because of the similarity of the ABCG2 with the developed multi-drug resistance showing breast cancer cells.ABCG2 gene is located at the gout susceptibility site of chromosome 4q.ABCG2 is initially recognized as a xenobiotic transporter in placental tissue with 1 transmembrane domain and 1 ATP binding domain

ABCG2 is situated on the apical membrane of proximal tubules of the kidney, small intestine, and liver [11]. ABCG2 promotes the excretion of uric acid by using ATP as energy. Various research studies have shown that the ABCG2 transporter is abundantly expressed in the small intestine rather than in the kidney's proximal tubule. This specifies the importance of the excretion of uric acid through the intestine *via* the ABCG2 transporter [12].

OAT1 (SLC22A6) and OAT3 (SLC22A8): OAT1 and OAT3 are the organic anion &urate transporters, encoded by the SLC22A6 gene and SLC22A8 gene, respectively. OAT1 & OAT3 have 46% & 42% amino acid residue similarity with URAT1 [15].

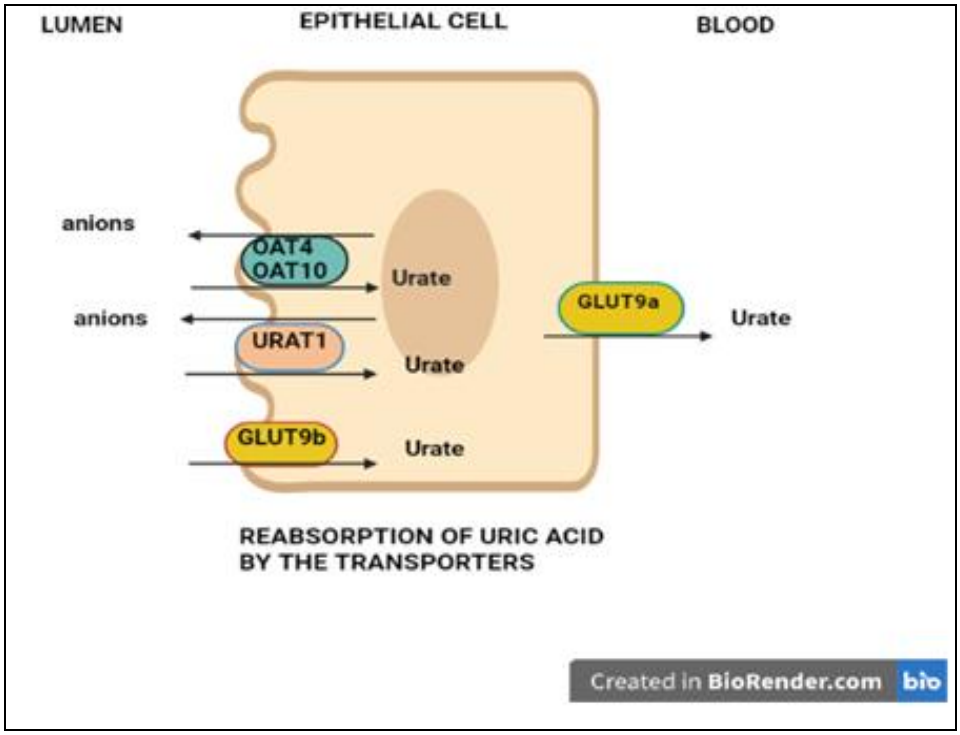
They are situated on the basolateral membrane of the proximal tubule. However, the OAT3 is situated both in the proximal tubule and the collecting duct of the kidney. Research studies about hyperuricemia prove that there is a decreased expression of both OAT1 and OAT3. This indicates the secretion of uric acid by transporting the uric acid from the renal interstitial into tubular epithelial cells [13].

MRP4 (ABCC4): The multidrug resistance protein belongs to the ATP-binding cassette family and is identified in the apical membrane of the kidney tubules MRP4 mediates the secretion of uric acid into the tubule lumen [13].

OAT2 (SLC22A7): OAT2 belongs to the solute carrier family and is encoded by the SLC22A7 gene. OAT2 transporter is expressed in various tissues, including choroid plexus, liver, placenta, skeletal muscle and kidney. OAT2 is situated at the basolateral side of the proximal tubule in the kidney and mediates the transportation of urate from blood to the proximal tubular cell [14].

NPT1, NPT4 and NPT5 (Sodium-Phosphate Co-Transporter): NPT1, NPT4 & NPT5 are the solute carrier family transporters and they are encoded by SLC17A1gene, SLC17A3 gene and SLC17A4 gene respectively. Among these, the NPT1 & NPT4 are situated on the apical membrane of the kidney's proximal tubule and mediate the urate's secretion in the kidney. Whereas, the NPT5 is situated on the apical surface of intestine epithelial cells and mediates the excretion of urate through the small intestine [15].

MCT9: MCT9 belongs to the monocarboxylate co-transporter family and is encoded by the SLC16A9 gene. It is mainly expressed in the kidney. However, the location of MCT9 in part of the kidney tubule and the mechanism of excretion of uric acid by MCT9 is still unclear [11, 14].



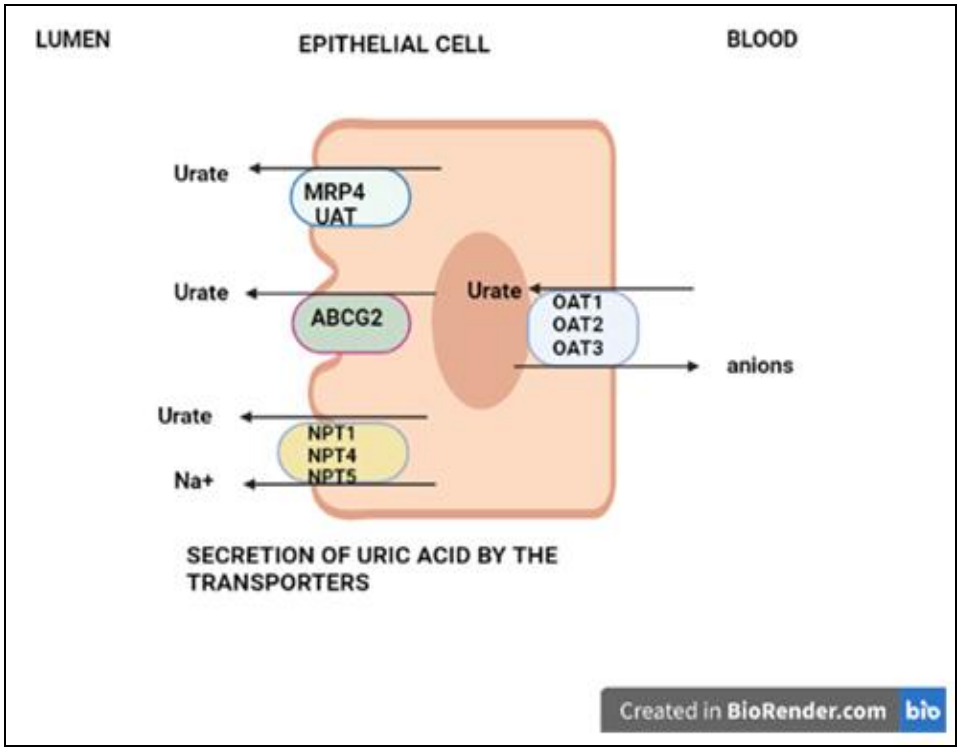


FIG. 3: URIC ACID TRANSPORTERS

Pathophysiology of Gout: Hyperuricemia is the major cause of gout which is mainly due to the under-excretion of the urate through the kidney in most cases of the patient (excretion<330 mg/dl). While in a few cases of the patient, the overproduction of uric acid leads to a hyperuricemic state (excretion>600 mg/dl) [16].

Monosodium Urate Crystal Formation and Deposition: Uric acid is a weak organic acid and it is found as a urate ion under physiological conditions. Since sodium is the principle cation, it is combined with the dissociated urate ion to form monosodium urate.

Whereas, in urine, the pH is approximately 5.75 uric acid chiefly exists in the unionized form in urine. The normal level of uric acid in human blood are 1.5 to 6.0 mg/dl in women and 2.5 to 7.0 mg/dl in men [17].

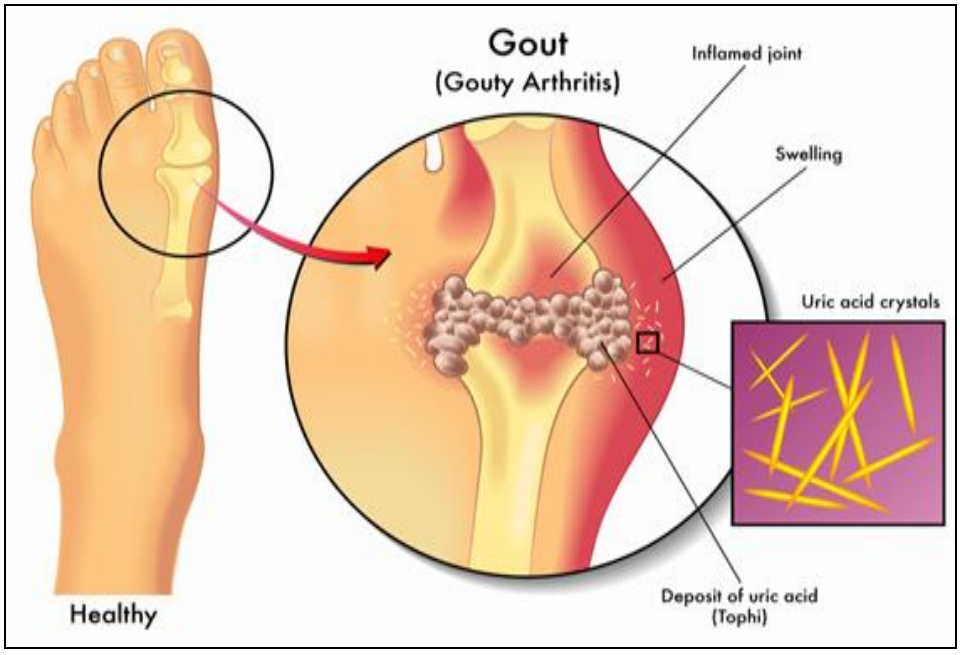


FIG. 4: MSU CRYSTAL DEPOSITION

Solubility is the main factor that is responsible for seed crystal formation (crystal nuclei), crystal growth, and deposition. The solubility of monosodium urate crystal (MSU) is affected by the following ways. Initially, when the urate concentration exceeds the normal range of solubility (6.8 mg/dl) in the serum, supersaturation of urate occurs due to the decrease in solubility. In another way, the lowering of pH and temperature causes a decrease in the urate's solubility, which tends to form a seed crystal or crystal nuclei. Various research studies have shown that crystal growth formation from the crystal nuclei or seed crystal is influenced by increased calcium ions, insoluble collagen, g-globulin, chondroitin sulphate, phosphatidylcholine, and local trauma [17]. The formed crystals are get deposited in the cool peripheral joints (metatarsophalangeal joints) of the big toe because these crystals are less soluble under cooler conditions or lowered temperatures. Subsequently, the needle-shaped sharp crystals can rub against the soft lining of the joint (Synovium) and induce pain, swelling and inflammation. This is called a "flare of gout" or an "acute attack".

FIG. 5: MICROSCOPIC IMAGE OF MONOSODIUM URATE CRYSTALS

Pathophysiology of Acute Gout: Acute gout is a paroxysmal joint inflammatory disease. The two major white blood cells are involved in developing acute gout, including Neutrophils and Macrophages (a differentiated form of monocytes). Since the neutrophils are absent in the normal joint, the entry of neutrophils into the synovium and joint fluid is activated by the interaction between residing cells (majorly synovial lining cells and mast cells) in the joint and MSU crystals. These resident cells release the proinflammatory cytokines IL-1, IL-6, and TNF α and other mediators (CXCL8), which are responsible for the expression of endothelium adhesion molecule (E selection) and drives the entry of neutrophil into the joint (18,19). Monocytes are also entered into the joints and get differentiated into macrophages. These neutrophils and M1 macrophages phagocytose the MSU crystal and release soluble inflammatory mediators like calgranulins S100A8 and S100A9, further intensifying the acute gouty inflammation [18].

The Role of Innate Immunity in Acute Gouty Inflammation: Innate immunity is the first line defense mechanism and constitutes different soluble proteins and a wide range of receptors. Since the MSU crystal is negatively charged and irregular, they non-specifically bind with different cell surface proteins and a wide range of receptors (including the FC receptor CD16, platelets, and leukocyte integrin) [18, 19]. This potentiates the inflammatory response. The innate immunity mechanism of phagocytic cells is activated by the opsonization of MSU crystals by IgG and complement components [18].

Complement in MSU Crystal-Induced Inflammation: The activation of the complement pathway by MSU crystals forms the C_5a from C_5 and C_6 –C_9 membrane attack complex. This formed complement attracts the leukocyte to initiate the phagocytosis process [18].

Toll-Like Receptors, Nlrp3 Inflammasome & IL-1β Release in MSU Crystal Induced Inflammation: Toll-like receptors are naturally proteinaceous and located on the lipid bilayer of the phagocytic cells such as macrophages and dendritic cells as a single-span membrane-spanning receptor. It plays an important role in host innate immunity by interacting with antigens. The activation of TLR_2 and TLR_4 causes the phagocytosis of MSU crystals and the release of inflammatory mediators by the phagocytic cell [18, 19]. The research study shows that one of the inflammatory mediators, IL-1β plays an important role in developing gouty inflammation. The $NLRP_3$ inflammasome mediates the processing and release of IL-1β by the response of MSU crystals [18].

Pathophysiology of Chronic Gout: If acute gout has been left untreated, flares' frequency and severity may increase and develop into chronic gout. Although gout most often affects the big toe, other joints may also be affected, including ankles,

knees, elbows, wrists, and fingers if left untreated. The MSU crystals can also be collected outside of the joints and form small macroaggregates of firm lumps near the articular cartilage called TOPHI. Under the microscope, the tophi are viewed as a macrophage and fibroblast-rich holding tank lined by a ring of fibrinogen and other proteins [18].

In chronic gout, there is an increased recurrence of the acute flares. The increase in acute flares is due to the tophus remodeling, which alters existing MSU crystals' physical or chemical state. The urate-lowering therapy (by altering the serum urate levels) or any mechanical trauma induces tophus remodeling, which causes the dissociation of crystal surface proteins are probably triggers the acute flares in chronic gout. In acute gouty arthritis, the MSU crystals activate the innate immune receptors to induce acute inflammatory responses. The stimulated innate immunity activates the adaptive immune system through antigen presentation. Since, adaptive immunity is having immunological memory or long-lasting memory, which is responsible for the recurrence of acute flares of chronic gout. The most recent studies showed that the MSU crystals can stimulate the dendritic cells, an antigen-presenting cell, and promotes the release of cytokines IL-1α/β and IL-18 that recruit the TH17 differentiated cells [18].

The uncontrolled serum uric acid levels in chronic gout further promote cartilage degradation, bone erosion & urolithiasis.

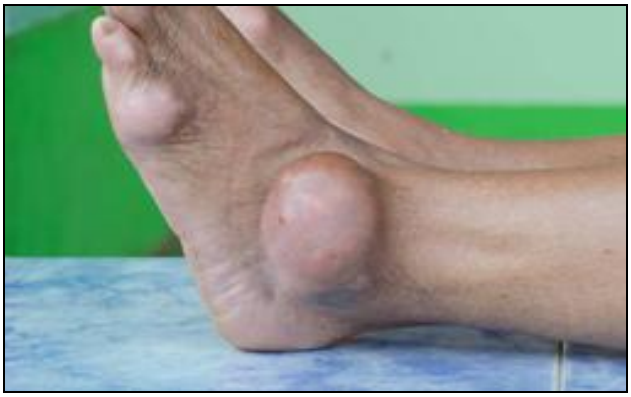


FIG. 6: TOPHUS (FIRM LUMPS OF MSU CRYSTALS MACRO AGGREGATION)

Cartilage Degradation in Chronic Gouty Arthritis: The MSU crystals are having the capacity to induce cartilage degradation by the activation of nitric oxide and MMP-3 expression in articular chondrocytes. The increased production of NO by MSU crystals can impair the chondrocyte viability & enhances the matrix catabolic activity of MMPs (matrix metalloproteins) leading to cartilage matrix degradation [18].

Bone Erosion in Chronic Gouty Arthritis: The common manifestation of chronic tophaceous gout is bone erosion. Under physiological conditions, the balanced activity between the osteoblasts (responsible for bone formation) and osteoclasts (responsible for bone resorption) maintains the integrity of the bone. Since, in chronic gouty arthritis, the MSU crystals decrease the differentiation of osteoblasts &increase the development and activity of osteoclasts, which promotes bone erosion, because of the activation of various cytokines, including the IL-1β, IL-6 and TNF-α [18].

Plants and Their Secondary Metabolites for Treatment of Gout: The various secondary metabolites from different plant species were identified, and in silico, in vivo and in vitro studies were performed to confirm their anti-gout activity. Some of the recent studies carried out on different plant species are discussed below

Wei-Di Chen *et al.* studied the anti-hyperuricemia, antigout arthritis, and analgesia activities of *Clerodranthus spicatus*, which is known as "Kidney tea" in China. The studies using in vivo methods showed that the ethyl acetate fraction has a potential antihyperuricemic effect. Further, 32 compounds were isolated by phytochemical investigation. Among the isolated compounds orthosiphol N, orthosiphol A, orthosiphol B and α-amyrin were found to be more potent than benzbromarone (a famous uricosuric drug) [20]. The edible flowers like Rosa sp., Lavandula sp., Lilium sp., *Hibiscus sabdariffa* L., Chrysanthemum sp., Matricaria sp., Gomphrena sp., Myosotis sp., and Jasminumsp were evaluated for xanthine oxidase inhibitory activity. The xanthine oxidase inhibition assay was used to determine the flower extract's antigout activity. This study illustrated that three aqueous flower extract (Rosa sp., *Hibiscus sabdariffa* L. and Malussp) has potent xanthine oxidase inhibitory activity. Their IC_{50} values, 0.10±0.15 µg/ml, 0.12±0.11µg/ml and 2.59 ±µg/ml, respectively are found to be lower than the

positive control allopurinol (IC_{50} value, 4.9±0.00 µg/ml) [21]. Traditionally *Artocarpus odoratissimus* is used by Indonesian people against gout. Nisa Naspial *et al* conducted molecular docking studies to determine the gout activity of the active component in the *Artocarpus odoratissimus* leaf. They explored that flavan-3-ol interacts with xanthine oxidase with the lowest binding energy (ΔG value -8.3 Kcal) which is lower than the reference ligands (allopurinol and hypoxanthine). For further confirmation of xanthine oxidase inhibitory activity, an *in-vitro* antigout activity test is necessary [22].

The *in-vitro* spectroscopy method and *in-silico* analysis of flavonoids present in ethanol extract of *Annona squamosa* (sugar apple) resulted that it has more potent xanthine oxidase inhibitory activity than allopurinol [23]. Kushi Jain *et al* performed antioxidant and antigout activity of *Alternanthera sessilis* and *Moringa olifera* through statistical analysis (ANOVA) and Ducan's multiple range test. The ethanolic extract of both *Alternanthra sessilis* and *moringa oleifera* has antigout activity. However, *Moringa oleifera* has more potential antigout activity than *Alternanthra sessilis* [24]. M. Nur Sidik *et al* investigate the xanthine oxidase inhibitory activity of alkaloids obtained from Alphonsea cylindrical and *Alphonsea elliptica*. Alkaloids like Kinabaline, atherospermidine, cyatholine, and N-methlouregidione were isolated by serial column chromatography.

Also, the *in-silico* docking studies showed that atherospermidine and cyathocoline are competitive inhibitors of xanthine oxidase. While the remaining two compounds are non-competitive inhibitors. The final declaration of this study is, that the Alphonsea species has the potential antigout activity [25]. The integrated *in-silico* and *in-vitro* study of Egyptian propolis led to the finding of new pharmacologically active compounds against hyperuricemia. The metabolites like Rosmarinic acid, luteolin, techtochrysin and isoferulic acid were found as more prominent virtual hits through the Glide docking study. The binding mode between the discovered hits and xanthine oxidase is revealed by molecular docking and MD simulations. Subsequently, the dose-dependent xanthine oxidase inhibitory activity of these hits is demonstrated through *in-vitro* studies. Also, the combined effect of the hits with allopurinol and febuxostat on xanthine catalytic inhibition was studied. Also, the combined effect of the hits with allopurinol and febuxostat on xanthine catalytic inhibition was studied. As a whole, this study provides a new therapeutic option from Egyptian propolis against hyperuricemia [26].

Lianzhu *et al.* carried out combined *in-vitro* and insilico molecular docking studies on two key xanthine oxidase inhibitors (Kaempferide and galangin) in galangal. According to this study, combining Kaempferide and galangin increased their binding affinity for xanthine oxidase. This is because the Kaempferide has a stronger binding affinity for xanthine than galangin and is found to be a stronger xanthine oxidase inhibitor. Hence their combination potentials the xanthine oxidase inhibitory activity [27].

The antioxidant and antigout activity of unripe *Musa balbisiana* by ultrasound-assisted extraction technology demonstrated that the ultrasonic extract with a concentration of 50 mg/L reduces the uric acid level by 10%. Hence the ultrasonic extract obtained by the UAE act as an antigout agent[28]. Eldiza Puji Rahmi *et al.* conducted *in-vitro* and *in-vivo* studies on *Marantodes pumilum* (Primulaceae) for antihyperuricemic and anti-inflammatory effects.

The various species selected are *M. pumilumvar*. alata (MPA), Varpumila (MPP), and Varlanceolata (MPL). The leaves and roots of these plants were extracted in ethanol (80%) and antihyperurecimic activity was performed by xanthine inhibition with spectrophotometric *in-vitro* assay. Then the most active extract was exposed to *in-vivo* anti-hyperuricemic effect on the hyperuricemic rat model. The results showed that the leaf extract of MPP has the highest xanthine oxidase inhibitory activity than other extracts. It also inhibited liver xanthine oxidase activity (25%) compared to allopurinol (45%). The MPP extract is found to contain myricetin, quercetin, and kaempferol [29]. The NLRP3 inflammasome is responsible for mediating the release of an inflammatory mediator like IL-1β in gout. Xueyan Zhang *et al.* investigated whether the purified biflavanoid extract (TF) from *Selaginella moellendorffi* has any effect on the activation of NLRP3 inflammasome

in gout. The main component of this extract is a flavonoid (Amentoflavone). The *in-vitro* and *in-vivo* studies resulted in gouty arthritis by the NLRP3/ASC/CASPASE -1 axis suppression [30]. While exploring the reparatory and preventive effects of oriental herb extract mixture (OHEM)[A mixture of water of *Lonicera japonica*, *Cassis obtusifolia* L., *Adenophora triphylla* var. japonica, *Rhynchosia nulubilis*, and *Glycyrrhiza glabra*] on hyperuricemia Lee J *et al.* found that OHEM has xanthine oxidase inhibitory activity. It also has many functional phytochemicals, such as polyphenols and flavonoids. Several observations, like the toxicity of OHEM, XO, and Xanthine dehydrogenase (XDH) activities in the liver tissues of rats, and assays of XO inhibitory activity, were made. The result showed that OHEM has a good effect on preventing and treating hyperuricemia [31].

Man Gong *et al.* investigate the effect of Eucommiaulmoides leaves on hyperuricemia and kidney injury induced by a high-fat/high-fructose diet in rats. The various major components of *E. ulmoides* and targets of these components were collected from different databases. And the pathway regulating uric acid metabolism was found by molecular docking. A rat model of hyperuricemia and renal injury calculated the selected targets and their efficacy. The molecular docking study resulted that iridoids and flavonoids are bound to proteins involved in inflammation and uric acid metabolism. Further, the animal study shows that the leaf extract of *E. ulmoides* decrease hyperuricemia [32]. While targeting Jatropha-derived phytochemicals to inhibit the xanthine oxidase and cyclooxygenase-2 through *in-silico* analysis for treatment of gout, it was found that the phytochemicals of *Jatropha curcas* (Jatrophone, 6-β hydroxyl-4-stigmasten-3-one,palmarumycin CPI) have a good affinity towards xanthine oxidase and cyclooxygenase-2 [33]. V. Jayavarsha *et al.* conducted a preliminary phytochemical study of the antioxidant and antigout effect of aqueous seed extract of punicagranatum, by into study. The results show that flavonoids, alkaloids, terpenoids, and steroids were present in the aqueous extract of punicagranatum. The extract has antigout potential with an IC_{50} value of 310µg/ml and an antioxidant effect with an IC_{50} of 280µg/ml. Hence the cumulative antioxidant and xanthine oxidase inhibitory activity of punicagranatum can be useful in hyperuricemic treatment [34].

Muthuswamy Umamaheshwari *et al.* conducted the *in-silico* docking studies and *in-vitro* xanthine oxidase inhibitory activity of commercially available terpenoids (bisabolol, β-caryophyllene, limonene and α-terpinene). The *in-silico* docking studies revealed that these terpenoids have very good binding interaction with xanthine oxidase. In the in vitro (enzyme-kinetic studies), it was found that bisabolol and β-Caryophyllene non-competitively inhibit xanthine oxidase while limonene and α-terpinene show competitive inhibition. Further, in vivo studies are required to develop and formulate the potent compound for gout treatment [35].

Therapeutic Strategies and Common Targets for Hyperuricemia and Gouty Arthritis: The various drugs targeting the different therapeutic targets are used to treat hyperuricemia and gouty arthritis. Colchicine was the first medicine used to treat gout by Byzantine physician Alexander of Tralles around 600 AD. In this particular topic, the common and new therapeutic targets under research are discussed to increase the drug choice and facilitate the effective treatment of gouty arthritis. Here, the therapeutic targets for huperuricemia & gout are described by considering the following pathways

- Inflammatory pathway
- Metabolic pathway
- Uric acid transporting pathway

Inflammatory Pathway: Research studies show that some inflammatory pathways are responsible for inflammation and acute flares. The drugs targeting the inflammatory mediators which are involved in these inflammatory pathways will be a good target for gouty arthritis; this includes,

- IL-17 signaling pathway
- HIF-1 signaling pathway
- TNF signaling pathway
- AGE-RAGE signaling pathway

- IL-1β – NLRP3 inflammasome pathway
- TAK-1 signaling pathway

IL-17 Signaling Pathway: The starting stage of acute gouty arthritis is associated with local inflammation, joint redness & severe pain; among them, IL-17 acts as an important proinflammatory mediator. IL-17 mediates the inflammatory pathway and immune response. Research studies show that IL-17 activates its receptors and downstream pathways like NF-κB& MAPK. This causes the release of proinflammatory mediators, such as IL-6 & TNFα to induce inflammation .this mediators, Recruits the neutrophils & induce hyperalgesia & arthritis. The released inflammatory mediators such as TNF-α & IL-1β by the activation of the NF-Kβ pathway further increase the activity of IL-17 [36].

HIF-1 Signaling Pathway: Hypoxia-inducible factor (HIF) is composed of two subunits, HIF-1α and HIF-1β. Among them, HIF-1α plays a key role in the progression of cell hypoxia stress. During the inflammation, blood flow slows down, and the oxygen consumption by inflammatory cells and antigens increases, which leads to the local environmental hypoxia and activation of HIF. This activated HIF mediates the NF –kB pathway and glycolysis pathway activation. Further glycolysis triggers the inflammatory response, especially in the macrophages which are activated by IL14 and promotes the activation of NLRP3 inflammasome and secretion of inflammatory cytokines such as IL-1β and IL-6 (36).

TNF-Signaling Pathway: Research studies show that there is a subsequent increase of TNF-α levels in MSU crystals-induced gouty joints in mice and the TNF-α inhibitor etanercept improves the clinical manifestations and laboratory results of gouty arthritis [36].

Age-Rage Signaling Pathway: The non-enzymatic synthesis of reducing sugars combined with lipids, proteins & nucleic acid produces the advanced glycosylation end products (AGEs). This AGE binds with RAGE (receptor for advanced glycation end products) and induces oxidative stress & inflammation. Research studies have shown a positive association between serum RAGE levels & serum uric acid levels in patients with hyperuricemia. So RAGE plays a critical role in developing hyperuricemia & gout disease [36].

IL-1β – NLRP3 Inflammasome: Interleukin-1β [IL-1β] is a proinflammatory cytokine that predominantly plays an important role in inflammation (in the case of gouty arthritis and several other diseases). It includes the expression of adhesion molecule (VCAM) on endothelium and leads to the transmigration of immune cells.

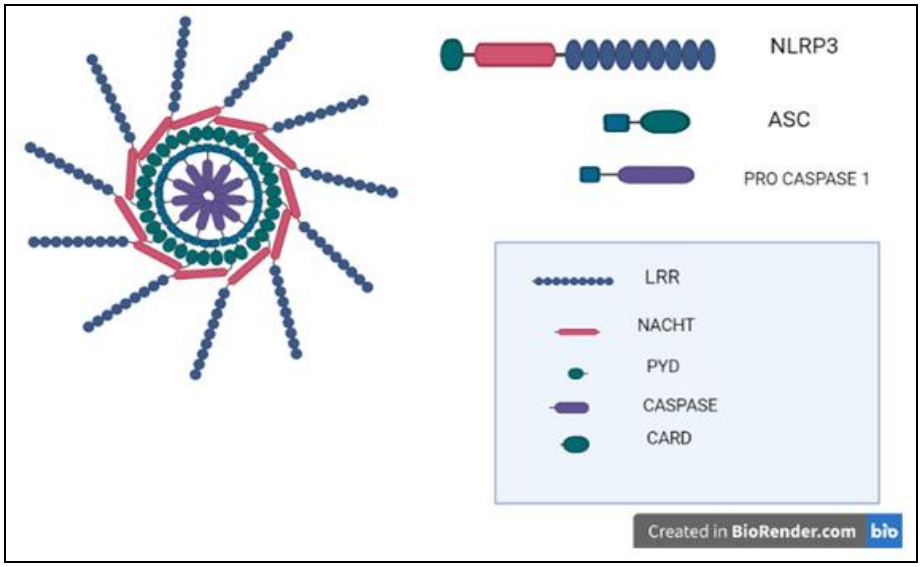


FIG. 7: NLRP3 INFLAMMASOME

It also activates other leukocytes including their cytokine production. IL-1β is also involved in various physiological processes. Since it has an important physiological role in acute or chronic inflammation and pain, it is always regulated by multiprotein complexes called inflammasomes and

one among them is the NLRP3 inflammasome. The NLRP3 inflammasome belongs to a family of intracellular pattern-recognition receptors (PRPs) called nod-like receptors (NLR). It has NLRP3 sensors, ASC adaptors, and procaspase-1. The NLRP3 sensor contains an N-terminal pyrin domain (PYD), a central NACHT domain, and a C-terminal leucine-rich repeat (LRR) domain. Adaptor apoptosis speck (ASC) contains PYD and CARD domains, and pro-caspase-1 contains caspase-1 and CARD domains. After activation, the NLRP3 undergoes oligomerization which is mediated by the centrally located NACHT domain. Subsequently the other domains ASC and procaspase-1 bind with the NLRP3 through their shared domains. Hence the prion-like complex is assembled. NLRP3 is activated by MAMPs (Microbe associated molecular patterns) or DAMPs (Damage associated molecular patterns) of exogenous or endogenous origin [37].

Mechanism Involved in NLRP3 Inflammasome Activation: Two signals are involved in the activation of the nlrp3 inflammasome. The first signal called the 'priming' signal leads to the expression of inflammasome domains. This signal is mediated by pattern recognition receptors (PRP3) or toll-like receptors and cytokine receptors (eg: TNF R, IL-1R). These receptors recognise and bind with MAMPs or DAMPs. This results in the upregulation of inactive NLRP3 and pro-IL-1β transcription through a series of transduction pathways activating nuclear factor kappa B (NF –kB), P38, and ERK regulating the transcription process. The expression of ASC and pro caspase -1 is cell-specific.

In myeloid cells, ASC and pro caspase -1 are highly expressed hence priming signal is only needed for the expression of NLRP3 and pro-IL-1β in a required amount. Whereas in alveolar epithelium there is low expression of ASC and pro-caspase-1. Hence, in this case priming signal is needed for the upregulation of all inflammasome components. The formed NLRP3 remains inactivated in association with chaperone HSP90 and co-chaperone SGT1 in the cytosol. The second or activating signal leads to the formation of the inflammasome complex and the activation of caspase-1. The activation of NLRP3 initiates the assembly of NLRP3 and ASC via various stimuli including calcium influx, potassium efflux, mitochondrial damage, and ATP .the subsequent activation of caspase-1 cleaves pro-IL-1β and IL-8 leading to the maturation and secretion of biologically active IL-1β and IL-8 which has proinflammatory activities [37, 38].

TAK-1 (Transforming Growth Factor-β-Activated Kinase-1) Signaling Pathway: Generally, MSU crystals bind to toll-like receptors and various cytokine receptors and activate the inflammasome pathway which causes inflammation. The recent research study by Anil K. Singh *et al* shows that MSU crystal also uses the alternative pathway to trigger inflammation by activating TAK -1. The research study has been done by using the chemical which inhibits the TAK-1 receptor that is activated by MSU crystals in healthy human macrophage cells and a rodent model of gout. The results have shown that the chemical completely suppresses inflammation in gout [39].

Metabolic Pathway:

Purine Nucleoside Phosphorylase: Purine nucleoside phosphorylase is an enzyme that converts the inosine and guanosine into hypoxanthine and guanine respectively in the uric acid metabolic pathway. The inhibition of purine nucleoside phosphorylase leads to a decrease in the production of uric acid level. So the purine nucleoside phosphorylase will be the better target next to the xanthine oxidase. Uldosin (BCX 4208) is the only drug that is identified as a purine nucleoside phosphorylase inhibitor understudies [40].

Xanthine Oxidase: Even though xanthine oxidase is the oldest drug target for gouty arthritis, many more drugs are still under research to increase their selectivity & efficacy. Xanthine oxidase is responsible for converting hypoxanthine into xanthin and xanthine into uric acid. Topiroxostat is a non-purine xanthine oxidase that has been exclusively approved in Japan [40].

Uricase: Uricase is the enzyme present in animals other than man and is responsible for the breakdown of uric acid into water-soluble allantoin in animals. The recombinant form of uricase is now indicated to treat gout. Pegloticase is a porcine recombinant polyethylene –glycol conjugated

uricase that was approved by FDA and is currently indicated for gouty arthritis [41].

Uric Acid Transporting Pathway: The various transporters (in the kidney and small intestine) are involved in regulating uric acid levels in the serum. Here, the various drugs studied to target those transporters are discussed.

Urat-1: The *in-vitro* experiments have shown the interaction between the urate-lowering drugs (such as probenecid, benzbromarone, losartan, and irbesartan) and URAT-1, inhibit the reabsorption of urate from the lumen of the proximal tubules [42].

OAT-10: The research studies on cyclosporine A-induced hyperuricemia shows that the increased uric acid level is due to the inhibition of OAT-10. This represents that OAT-10 will be an interesting drug discovery target [42].

OAT-4: Lesinurad, a novel drug targeting the URAT-1 and OAT-4 transporter, inhibits urate reabsorption, thus decreasing uric acid levels [43].

GLUT-9: GLUT-9 is a voltage-dependent high-volume transporter. The research studies are finding that the mutation of the SLC2A9 gene encoding GLUT-9 involves decreased uric acid levels. This denotes the importance of GLUT-9 in the reabsorption of uric acid. So the GLUT-9 will be an interesting drug discovery target [11, 12]. The transporters involved in the uric acid excretion include, the ABCG2, OAT-1, OAT-2, OAT3, MRP-4, NPT-1, NPT-4, NPT-5, MCT-9. So, further research is required. to discover new drugs that will show agonistic action on excretion transporters to facilitate the treatment of gouty arthritis [9].

CONCLUSION: Recent studies reveal that nowadays, because of the consumption of unhealthy foods among the young population under 30 are more prone to develop hyperuricemia and earlier attack of gout, which exacerbates in old age, due to the high prevalence of metabolic syndrome among those young population. However, hyperuricemia can be controlled by consuming low purine-containing health diets, if left unnoticed, there may be developed into gouty arthritis. Since various anti-inflammatory drugs (such as NSAIDs, and glucocorticoids) are available to treat acute flares and inflammation in acute gouty arthritis, that drug develops various side effects. So it is necessary to discover a new drug which is selectively targeting the inflammatory mediators involved in the development of acute flares, to avoid the long-term adverse effects produced by anti-inflammatory drugs and also further research is required to discover new drugs acting on the enzymes involved in the uric acid metabolic pathway and on the various uric acid transporters to provide better treatment in gouty arthritis.

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