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Review Article

Nanotechnology and Natural Remedies: A Comprehensive Review on Role of Curcumin Nanoparticles in Gout Management

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ABSTRACT

Gout, a chronic inflammatory arthritis driven by hyperuricemia and monosodium urate crystal deposition, remains a significant clinical challenge due to limitations in current pharmacological therapies, including adverse effects and poor patient compliance. Curcumin, a natural polyphenol derived from Curcuma longa, exhibits potent anti-inflammatory and antioxidant properties with potential therapeutic implications for gout. However, its clinical translation is hindered by poor solubility, low bioavailability, and rapid metabolism. Nanoparticle-based delivery systems have emerged as a promising strategy to enhance the pharmacokinetic and pharmacodynamics profile of curcumin. This review explores the pathophysiology of gout and highlights curcumin's molecular mechanisms of action, including the inhibition of NF-κB signalling and modulation of pro-inflammatory cytokines. It further discusses recent advancements in curcumin nanoformulations, such as polymeric nanoparticles, liposomes, and solid lipid nanoparticles-and their preclinical efficacy in gout models. Nanoparticle-mediated delivery not only improves curcumin's solubility and stability but also enables targeted delivery to inflamed tissues, potentially reducing systemic toxicity. While current findings are promising, further clinical investigations are essential to validate the safety, efficacy, and therapeutic viability of curcumin nanoparticles in gout management. This review underscores curcumin nanotechnology as a novel and viable adjunct or alternative to conventional gout therapies.

Keywords Anti-Inflammatory, *Curcuma longa*, Hyperuricemia, Nanoformulations, NF-Kb, Pro-Inflammatory Cytokines.

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INTRODUCTION

Gout is a common medical problem whose prevalence is increased with increasing age and reaches 9% in men and 6% in women of age 80 years and older (Bochu and Ling, 2014). Gout is an inflammatory joint disease characterized by Hyperuricemia, which means elevated uric acid level in the blood, which later leads to the deposition of urate crystals in the joints and kidneys, followed by painful inflammation, gouty arthritis, and uric acid nephrolithiasis (Kapoor *et al*., 2017a). In this, the plasma urate level gets elevated to 15-40 mg/dl (normal-2-8mg/dl), and uric acid is the product of purine metabolism, having low solubility, especially at low pH. In some cases, treatment of leukaemia, lymphomas with chemotherapy and radiation enhances the production of uric acid, and long-term use of drugs like thiazides, furosemide, levodopa, and ethambutol leads to reduced excretion of uric acid from the kidney, and this is called Secondary Hyperuricemia. Xanthine Oxidase (XO) is responsible for oxidation of hypoxanthine to xanthine and finally xanthine to uric acid. Over activity of this enzyme and increased intake of dietary food rich in nucleic acids (e.g. meat, leguminous seeds) impair renal excretion of uric acid and result in hyperuricemia and gout (Tripathi, 2008).

Elevated serum uric acid can also lead to risk of Hypertension, kidney stones, Non-Alcoholic Fatty Liver Disease (NAFLD), Chronic kidney disorder, Cardiovascular disorders, etc. (Kuo *et al*., 2015; Saag and Choi, 2006). At a low level, uric acid can be considered an antioxidant. Uric acid is thought to exert a protective antioxidant effect, particularly in the plasma and interstitial fluid. This is an evolutionary perspective because it was believed that primates especially Homo sapiens, had lost the ability of breakdown of uric acid by various genetic mutation and this leads to loss of Uricase (UA oxidase) activity, which is an enzyme causes breakdown of uric acid into allantoin. Uricase

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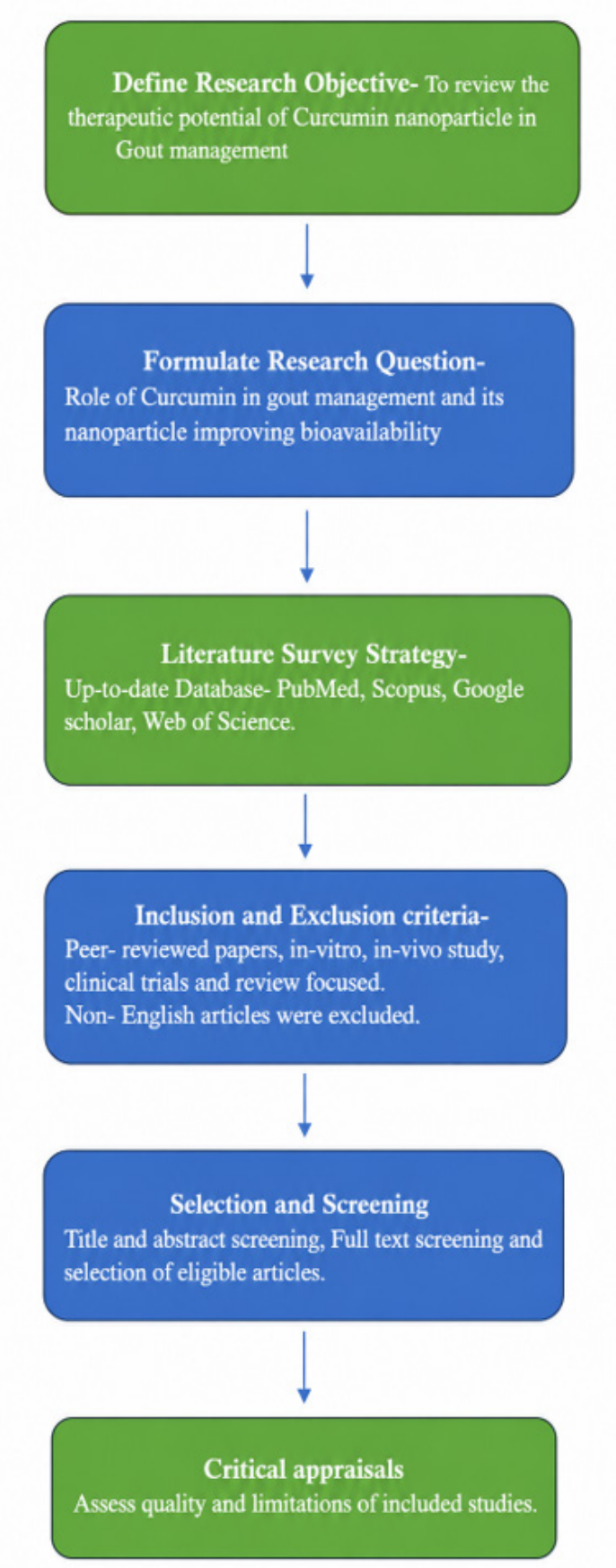
mutation occurs perhaps later to compensate for the loss of other key enzymes, like ascorbic acid (Vitamin C), which is a potent antioxidant. As Uric acid is a weaker antioxidant than Vitamin C, it is required in higher concentration to compensate for the absence of endogenous Vitamin C (Ames *et al*., 1981; Sautin and Johnson, 2008).

Conventional treatment strategies include treatment of gout either by reducing the production of uric acid (XO inhibitors) or increasing uric acid excretion (uricosuric drugs). New agents such as uricase analogue and biological cytokine inhibitors have also been used for the treatment of gout (Kapoor *et al*., 2017b). Gout can be considered as an inflammatory response. There are some receptors like Toll-like receptor 4 (TLR4) that acts as a signalling receptor for inflammatory responses, mediating both innate and acquired immunity. Damage to the kidney is due to the release of cytokines and chemokines such as Tumour Necrosis Factor alpha (TNF α) and Interleukin (IL) by initiating a complex signalling cascade. Toll-like Receptor 4 (TLR4)-mediated signalling pathway can also amplify the inflammatory response by activating the Nucleotide-Binding Oligomerization Domain (NOD)-like receptor pyrin domain-containing 3 (NLRP3) inflammasome (Zhang and Yang, 2023).

The use of plant-based drugs for the treatment of Hyperuricemia has been increasing worldwide as they are much safer than the drug of chemical origin. India is rich in medicinal and aromatic plants. Some countries like India, Malaysia, in the Asian continent, are rich emporiums and veritable repositories of medicinal and aromatic plants, they have approximately 3000-4000 plants having medicinal values (Abu *et al*., 2018). The biological activities of medicinal plants rely on the presence of valuable phytochemicals, for example, flavonoids, tannins, saponins, and alkaloids, etc. Currently, very few literatures are available that show the medicinal plants in the region having anti-gout activity (Ashiq *et al*., 2021).

METHODOLOGY

This review article has covered all the studies regarding anti-gout and anti-inflammatory property of curcumin and its Nano technological approaches to enhance the bioavailability, chemical and physical stability etc. For the study we had used up-to-date databases such as, Google Scholar, PubMed, Scopus, Web of Science etc. The keywords used in our articles are, "Curcuma longa", "Curcuminoids", "anti-inflammatory", "Hyperuricemia", "anti- gout", etc. We have taken reference from 118 articles and 1 book chapter and the criteria for selecting them is based on "studies reported in English, as language is the barrier". We have taken information from all the articles in summarized from and made a flow chart of our working methodology.



LITERATURE REVIEW

Auberson *et al*., (2018) has evaluated SLC2A9 (GLUT9) mediates urate reabsorption in the mouse kidney and explained that Uric Acid (UA) is a metabolite of purine degradation and is involved in gout flairs and kidney stones formation. GLUT9 (SLC2A9) was previously shown to be a urate transporter *in vitro. In vivo*, humans carrying GLUT9 loss-of-function mutations have familial renal hypouricemia type 2, a condition characterized by hypouricemia, UA renal wasting associated with kidney stones, and an increased propensity to acute renal failure during strenuous exercise. Mice carrying a deletion of GLUT9 in the whole body are hyperuricemic and display a severe nephropathy due to intratubular uric acid precipitation. However, the precise role of GLUT9 in the kidney remains poorly characterized. We developed a mouse model in which GLUT9 was deleted specifically, along the whole nephron in a tetracycline-inducible manner (subsequently called kidney-inducible KO or kiKO). Overall, these results indicate that GLUT9 is a crucial player in renal handling of urate *in vivo* and a putative target for uricosuric drugs.

Kiyani *et al*., (2019) has evaluated Turmeric Nanoparticles as Anti-Gout Agent: Modernization of a Traditional Drug. Turmeric has assisted in the control of inflammation and pain for decades and has been used in combination with other nutraceuticals to treat acute and chronic osteoarthritis pain. Recently, the effect of turmeric, turmeric extract, or Curcuminoids on musculoskeletal pain, either by themselves or in conjunction with other substances, has been reported. The aim of this study was to develop and characterize Turmeric Nanoparticles (T-NPs) for various parameters, both *in vitro* and *in vivo*. Uric acid levels were significantly reduced after the treatment with T-NPs. indicating that T-NPs show superior potential against gout management. Thus, T-NPs can be developed as an efficient antigout agent with minimum toxicities.

Zhang *et al*., (2021) has evaluated anti-inflammatory activity of curcumin-loaded tetrahedral framework nucleic acids on acute gouty arthritis. Gouty arthritis is a very familiar inflammatory arthritis. Controlling inflammation is the key to preventing gouty arthritis. However, colchicine, the most highly represented drug used in clinical practice, has strict contraindications owing to some severe side effects. Curcumin (Cur), a natural anti-inflammatory drug, has demonstrated good safety and efficacy. However, the rapid degradation, poor aqueous solubility, and low bioavailability of Cur limit its therapeutic effect. To strengthen the effectiveness and bioavailability of Cur. Cur loaded tetrahedral framework nucleic acids (Cur-TFNAs) were synthesized to deliver Cur. Therefore, we believe that Cur-TFNAs have great prospects for the prevention of gout and similar inflammatory diseases.

Asif *et al*., (2023) has done synthesis, characterization and evaluation of anti-arthritic and anti-inflammatory potential of curcumin loaded chitosan nanoparticles. The current study was conducted to fabricate, and optimize curcumin loaded chitosan and Sodium- Tripoly Phosphate (STPP) Nanoparticles (NPs) to improve the bioavailability of curcumin. NPs were fabricated employing the Ionic gelation method. Four formulations were developed based on the selected variables like STPP and chitosan concentration, rotations per minute (rpm), temperature, and pH of chitosan solution. NPs were characterized for morphology, drug-polymer compatibility, yield, particle size, encapsulation efficiency, release behavior, anti-inflammatory and anti-arthritic activity compared to curcumin and standard drug. The study concluded that curcumin-loaded chitosan and STPP NPs formulated successfully by the Ionic gelation method, which increased curcumin absorption leading to a reduced dosing rate and improved patient compliance.

Javed *et al*., (2024) has evaluated Anti-gouty arthritis and anti-inflammatory effects of curcumin nanoparticles in monosodium urate crystals induced Balb/C mice. These crystal depositions result in joint swelling and increased concentration of serum uric acid in blood. The commercially available drugs lower serum uric acid levels and reduce inflammation, but these standard therapies have many side effects. This study aimed to investigate anti-gout and anti-inflammatory properties of Curcumin Nanoparticles (CNPs). For this purpose, CNPs were prepared by dissolving curcumin into dichloromethane. Then, gout was induced by injecting Monosodium Urate crystals (MSU) in the ankle joint and in the intra-peritoneal cavity which caused ankle swelling and increased blood uric acid level. Thus, the study concluded that CNPs can be developed as an efficient anti-gout agent with minimal side effects.

Yang *et al*., (2024) has reviewed Targeting Toll-Like Receptor4 (TLR4) and the NLRP3 inflammasome: Novel and emerging therapeutic targets for hyperuricemia nephropathy. The clinical manifestation of hyperuricemia, known as hyperuricemia nephropathy, is relatively common. Its pathophysiology is largely based on chronic inflammation in circulatory and renal tissues. Toll-Like Receptor 4 (TLR4), a subclass of innate immune receptors, detects both pathogen-associated molecular patterns (PAMPs) and Damage-Associated Molecular Patterns (DAMPs), initiating inflammatory and immune responses that lead to the release of pro-inflammatory cytokines interleukin 1 beta (IL-1β) and tumour necrosis factor alpha (TNF-α). These cytokines are pivotal in renal inflammation, especially in conditions like hyperuricemia, acute renal injury, ischemia-reperfusion injury, and acute renal failure. TLR4 and NLRP3 inflammasome are anticipated to be novel markers and therapeutic targets for assessing treatment efficacy and prognosis in hyperuricemia nephropathy. This paper provides a comprehensive overview of the structural composition and biological functions of TLR4 and NLRP3 inflammasome and systematically reviews their relevance in the pathogenesis of hyperuricemia nephropathy.

Etiology and Pathogenesis of Gout

Urate Production- Purine Biosynthesis

Gout has very complex pathogenesis and its modern relevance is understood by a rise in its prevalence (Zhu *et al*., 2011). Now, gout is considered as one of the most common forms of inflammatory arthritis. Pathogenesis of gout follows two distinct processes (a) formation of uric acid in the form of urate, at a level sufficient to drive the precipitation of monosodium urate into crystalline form, (b) inflammatory responses due to accumulation of crystals (Keenan *et al*., 2017). Purine is the breakdown product of uric acid. It is a heterocyclic compound composed of pyrimidine and imidazole rings. In mammals it is found in the form of DNA and RNA, Adenosine Triphosphate (ATP), Adenosine Monophosphate (AMP), Adenosine Diphosphate (ADP), Cyclic AMP, Guanosine Triphosphate (GTP) and Cyclic Guanosine Monophosphate (cGMP) (Haskó *et al*., 2008). Purine Biosynthesis starts from the ribose-5-phosphate in the presence of enzyme Phosphoribosyl Pyrophosphate (PRPP) synthase, which catalyses addition of a pyrophosphate moiety to form the adduct PRPP. At the same time, another enzyme glutamine-phosphoribosyl pyrophosphate amido transferase catalyses interaction of PRPP with glutamine to form 5-phosphoribosyl amine, which later serves as the backbone for biosynthesis of Purine. The end product of this reaction is Purine Inosine Monophosphate (IMP), which later converts into AMP or GMP. Both PRPP synthase and Glutamine-PRPP-Amido transferase inhibit or slow down the biosynthesis of purine because it directly increases the substrate load for urate formation and increases the serum urate level as well (Olivera, 2003).

Uric acid Metabolism

Due to evolutionary constraints in terms of energy expenditure, in case genes get deleted or damaged by internal mechanisms, it is prudent to have mechanisms/self-corrective pathways that minimize purines from catabolism once they get committed and cannot be recovered back. Such pathways are termed as purine salvage and are almost always linked with purine biosynthesis feedback control. The central enzyme responsible for purine salvage, HGPRT1 (Ashihara *et al*., 2011). Deficiency of hypoxanthine/guanine phosphoribosyl transferase causes impaired purine salvage and generation of uric acid (Vasiliou *et al*., 2013). Partial deficiency of HGPRT1 also known as Kelley-Seegmiller syndrome, is present with hyperuricemia but no neurologic symptoms (Kelley *et al*., 1969), On the other hand complete deficiency of HGPRT1 is known as Lesch-Nyhan syndrome, which is an X- linked recessive disorder characterised by high level of serum urate, nephrolithiasis, gout flares, mental retardations etc. and some hereditary defects of energy metabolism such as glucose-6 phosphate deficiency will contribute to hyperuricemia (Lesch and Nyhan, 1964). In most cases, an increase in cell turnover can cause secondary urate overproduction, among erythropoietic diseases causing hyperuricemia, autoimmune diseases, sickle cell diseases, and haemolytic anaemia are included (Reynolds, 1983). Patients with lymphopoietic and myelopoietic disease, including leukaemia, lymphomas, myelodysplastic syndrome, myeloid metaplasia, Waldenström's macroglobulinemia, are also at increased risk of hyperuricemia (Hooey *et al*., 1965).

Excretion and Underexcretion of Uric Acid

Kidneys are the primary organs for the excretion of uric acid. In the body, uric acid is completely or partially unbound to the plasma protein, which causes ultrafiltration via the glomerulus. Decrease in glomerulus function causes a decrease in urate excretion and promotes the serum urate level. After ultrafiltration, urate in the proximal tubule undergoes various steps (a) reabsorption, in which 80-90% of urate is reabsorbed, (b) secretion, in which the reabsorbed urate is transferred back to the tubule lumen, where only 10% of total filtrate is excreted (So and Thorens, 2010; Wright *et al*., 2010). In most cases, underexcretion is the main cause of hyperuricemia, hereditary defects of renal tubule, hyperuricemic nephropathy such as medullary cystic kidney disease, are characterised by early hyperuricemia and chronic kidney disorders and are considered to be the primary cause of renal urate underexcretion (Bleyer and Hart, 2006). Secondary causes include (a) age and sex, classic studies documented that children have low serum urate level, at it increases during puberty in males, but in females the level is low during her menstrual cycles, (b) systemic illness, include glomerular insufficiency and other chronic renal conditions, (c) medications, medication like diuretic, levodopa, ethambutol, (d) diet, purine rich diet (meat, leafy green vegetables), fructose, alcohol etc (Cea Soriano *et al*., 2011; Krishnan, 2009).

This underexcretion causes accumulation of uric acid in the joints in the form of crystals, which leads to activation of pathways by the classic pathway by an immunoglobulin-independent, C-reactive protein-dependent pathway (Fields *et al*., 1983; Giclas *et al*., 1979). Urate crystals can bind to the antibodies, especially IgG and transmit inflammatory signalling by activating inflammatory cells such as neutrophils. Complement activation mediated by the urate crystal may also result in the production of soluble complement membrane attack complexes, which may, in turn, stimulate nearby cells to cause an inflammatory response. Other proteins that might be relevant, including fibronectin and kininogen, might also attach to or be absorbed by the urate crystal (Terkeltaub *et al*., 1983; Tramontini *et al*., 2004).

Inflammatory cells are activated in such a manner that several mechanisms have been activated (a) crystal recognition via toll-like receptors, (b) interactions between urate crystals and cholesterol rafts in the cell membrane, and (c) phagocytic mechanism (Liu *et al*., 2005). There are numerous intra-cellular signalling associated with inflammatory responses such as PI3K, REK, JNK, p38 mitogen-activated protein kinase, phospholipases

C and D, depending upon the type of cell activation of these molecules results in different phenotype alterations including production of cytokines and lipid mediators, induction of phagocytosis, superoxide generation (Abramson *et al.*, 1982; Di *et al.*, 1991). Urate crystals can make macrophages produce IL-1β, and this IL-1β is responsible for producing gouty inflammations. The NLRP3 inflammasome, which is also referred to as NALP3, CIAS1, or cryopyrin, is a multi-molecular cytosolic complex that has a central role of producing IL-1β but also IL-18 and IL-33. The pro form of IL-1β is cleaved into activated IL-1β by the inflammasome-associated enzyme caspase-1, which may also assist in the secretion of IL-1β and subsequently leads to the production of Tumor Necrosis Factor (TNF) at the cell surface (Martinon, 2010).

Current Treatment Strategies for Gout

In gout, accumulation of urate crystals leads to activation of various inflammatory pathways and signalling. Currently, for the primary anti-inflammatory management of gout, Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), corticosteroids, colchicine, etc. bluntly dampen the inflammatory responses in a cost-effective manner (Gliozzi *et al.*, 2016). Additionally, the evidence supporting some of these treatments has been constrained by insufficient evaluation in randomized, controlled, double-blind clinical trials, largely due to the inherent self-limiting nature of acute gout flares. The recent identification of etoricoxib as an effective COX-2-selective inhibitor for acute gout has introduced a new treatment strategy, though the cardiovascular safety of COX-2 inhibitors is still being examined (Terkeltaub, 2003).

Apart from the above-mentioned drugs, Xanthine oxidase inhibitors, Uricosuric, and uricase agents are the potent drugs against hyperuricemia. Xanthine oxidase inhibitors are the first line drug for gout. As per FDA guidelines, the starting dose for the administration of allopurinol is 100mg and maximum dose is 800 mg daily. The selective xanthine oxidase inhibitor Febuxostat does not have purine-like structure like allopurinol, but is metabolized primarily by glucuronidation and oxidation in the liver (Chao and Terkeltaub, 2009). Febuxostat has been authorized for use at daily doses of 40 mg and 80 mg in the USA, and up to 120 mg daily in Europe. In clinical practice, to manage drug costs, febuxostat is primarily prescribed for patients who have hypersensitivity to allopurinol, cannot tolerate it, or have experienced treatment failure, including those for whom uricosuric therapy is either not suitable or has been ineffective (Becker *et al.*, 2005a).

Uricosuric drugs such as probenecid and benzbromarone are second line drugs for the treatment of gout, the mechanism involves increasing renal excretion of uric acid by primarily inhibiting the urate anion absorption by proximal renal tubule epithelial cells. They are used with xanthine oxidase inhibitors, since the latter decrease urinary uric acid excretion (Perez *et al.*, 2002a; Reinders *et al.*, 2007). In patients who do not respond to xanthine oxidase inhibitors and uricosuric drugs, uricase agents were used as they have potential to treat tophi and this therapy has been developed and optimized for the prevention and treatment of Tumour lysis syndrome (Sundy and Hershfield, 2007).

Curcumin: Overview

Curcuma longa Linn, belonging to the family of *Zingiberaceae*, is a member of the ginger family, which is the highest yielding variety of turmeric, which is natively associated with South and Southeast Asia. Curcumin is the focal component of turmeric, used in pharmaceuticals, cosmetic, and food industries. Curcumin is used in the treatment of arthritis, Alzheimer's, gastric problems, etc., (Aggarwal *et al.*, 2013; Araújo and Leon, 2001). Curcumin is a small polyphenolic compound with a molecular weight of 368.37 g/mol and a melting point of approximately 183°C. Its IUPAC name is 1,7-bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione. Structurally, curcumin consists of two ferulic acid-like units connected by a methylene group, bridging what would otherwise be carboxylic acid groups (Iqbal *et al.*, 2003). Intra-molecular hydrogen atom transfer occurs at the beta di-ketone chain of curcumin that leads to keto-enol tautomerism in curcumin. The concentration of keto-enol tautomer may vary due to the temperature, pH, aromatic ring substitution, solvent polarity (Bertolasi *et al.*, 2008; Cornago *et al.*, 2008). Curcumin is poorly soluble in water due to its hydrophobic nature, and readily soluble in organic solvents such as ethanol, acetone, isopropanol, and moderate solubility in hexane, cyclohexane, tetrahydrofuran, etc., but its solubility is slightly improved in basic conditions (Priyadarsini, 2009). Curcumin breaks down more quickly at physiological pH levels or higher, indicating that its degradation is influenced by pH. This characteristic poses a major challenge for its use as a therapeutic agent. However, curcumin remains completely stable in the acidic environment of the stomach, despite its poor water solubility (Wang *et al.*, 1997a) (Table 1).

Pharmacological Properties of Curcumin

Anti-inflammatory actions

Curcumin has been used as a potent anti-inflammatory agent in the Asian continents. Inflammation is generally caused by the introduction of microbial infection and tissue injury to the living cells, which leads to the destruction of host tissues (Gupta *et al.*, 2013). As per some *in vitro* studies, curcumin shows its anti-inflammatory activity by reducing the inflammatory responses by Tumour Necrosis Factor-α- alpha(TNF-α) (Kim *et al.*, 2007).

Immunomodulatory effects

The Immune system plays a significant role in our body to fight against certain foreign microbes, normalizing and regulating the immune system, resulting in a reduction of inflammatory responses. Curcumin has been found to reduce the production of several proinflammatory cytokines, such as TNF, IL-1, IL-2,

IL-6, IL-8, IL-12, and various chemokines. This effect is believed to occur primarily by suppressing the activity of the NF-κB transcription factor (Jagetia and Aggarwal, 2007) (Figure 1).

Antioxidant activity

Reactive oxygen species are the highly reactive oxygen-derived species having an unpaired valence electron (Teleanu *et al*., 2022) Mitochondria is the primary source for the production of reactive oxygen species, where oxidative phosphorylation for the production of ATP takes place. By increasing the effects of superoxide dismutase, catalase and glutathione curcumin can reduces mitochondrial oxidative stress (Sathyabhama *et al*., 2022).

Antibacterial activity

Despite of being poorly water soluble, limited bioavailability and pharmacokinetic profile, curcumin shows high antibacterial activity (Adamczak *et al*., 2020). Its mechanism involves inhibition of bacterial quorum sensing, by targeting the DNA and proteins they interfere with the cellular processes of the microbes, damage to the cell membrane (Trigo *et al*., 2021) (Table 2) (Figure 2).

Diabetes Mellitus

Diabetes Mellitus is a metabolic disorder characterised by hyperglycaemia, which means high blood sugar level (Sena-Júnior *et al*., 2020).

Challenges in Curcumin's clinical application

Curcumin has been used in several antimicrobial studies due to its low side effects, despite their wide range of traditional applications they have not been impactful in pharmaceutical due to their low bioavailability, photo-degradation, hydrophobic nature, chemical instability, rapid metabolism and short half-life (Karthikeyan *et al*., 2020). Degradation of curcumin is least at lower pH (between 1 to 6), and at alkaline or neutral pH it gets degraded to feruloyl methane and ferulic acid. Hence they would be stable in intestine and stomach (Wang *et al*., 1997b). Poor systemic bioavailability of curcumin is a challenge for its oral delivery, which is due to its insolubility in water. It has been studied that oral administration of 500mg/kg of curcumin in rats gives maximum serum level of 0.06±0.01 μg/mL, whereas when the same dose is given intravenously its shows the maximum serum level of 0.36±0.05 μg/mL (Shehzad *et al*., 2010).

Figure 1: Turmeric (Curcumin).

Systemic Bioavailibility Of Curcumin After Oral Administration

Enhancing Solubility to Increase the Bioavailability of Curcumin

Though solubility enhancement is one of the major area of interest in curcumin dissolution, two different strategies can be used to enhance the bioavailability (a) reducing the size of curcumin molecule, to increase the surface area (b) use of surfactants, hydrophobic carriers and formation of inclusion complexes etc., (Ipar *et al*., 2019a; Jamwal, 2018). Novasol, a patented formulation by AQUANOVA AG (Tabanelli *et al*., 2021) is formulated when a surfactants like Tween-80, exceeds the crucial micellar concentration in aqueous solution. In a study micellar curcumin containing 7% curcumin powder and 93% of tween-80, been tested oh healthy volunteers to access the bioavailability in three small clinical trials and the data showed great increase in bioavailability (Schiborr *et al*., 2014) (Table 3).

Cyclodextrins inclusion complexes or the hydrophilic carriers such as Poly Vinyl Pyrronilone (PVP) might be the good options for improving the solubility problem in curcumin. Cyclodextrins comprise of oligosaccharides, made up of non- reducing chiral glucose connected to a ring structure. Curcumins water dispersibility is due to the hydrophilic vectors present in Poly Vinyl Pyrrolinone (PVP) (Jäger *et al*., 2014; Jamwal, 2018; Purpura *et al*., 2018) Few clinical trials has been performed for testing the bioavailability of innovative curcumin formulations, namely (a) Cavacurmin, a gamma cyclodextrin based compound (b) Curcumin, consisting of 63-75% PVP, 1-3% antioxidants, 10-40% cellulose derivatives. The reduction in the particle size tends to increase the surface area and allows rapid dissolution of the curcumin to increase the bioavailability (Ipar *et al*., 2019b). Mesoporous silica nanoparticles have wide range of application in biomedicines due to their large surface area, biocompatibility, elevated drug loading capacity, adjustable surface functionalisation etc., (Tripathi *et al*., 2024). The stability of the nanoparticle does not effects the particle size, rather it concludes that small nanoparticle are more soluble than the larger ones which gets aggregated rapidly and also exhibits greater dispersibility, hence reducing the size causes targeted delivery of nanoparticle (Perrault *et al*., 2009). There are certain patented curcumin formulations had been in clinical trials by reducing the particle size (a) Biocurc, comprise mainly of curcumin (6.17%w/w), labrasol (5.39%w/w) and, (b) Gelucire, comprising

Table 1: (List of Drugs Used for Treatment and Management of Gout).

Class	Drugs	Mechanism	References
Nonsteroidal anti-inflammatory	Ibuprofen (400-800 mg) Naproxen Sodium Indomethacin (25-50 mg)	Inhibits the Cyclooxygenase, prevents inflammation	(Van Durme *et al*., 2021)
Xanthine oxidase inhibitor	Allopurinol(200mg) Febuxostat (40-120 mg)	Blocks Xanthine oxidase enzyme, responsible for the production of uric acid	(Becker *et al*., 2005b)
Uricosuric drugs	Probenecid Benzbromarone	Increases renal excretion of uric acid by inhibiting urate anion absorption	(Kramar and Müller, 1973; Perez-Ruiz *et al*., 2002b)
	Colchicine	Inhibits tubulin, and disrupts inflammatory pathways	(Schlesinger *et al*., 2006)

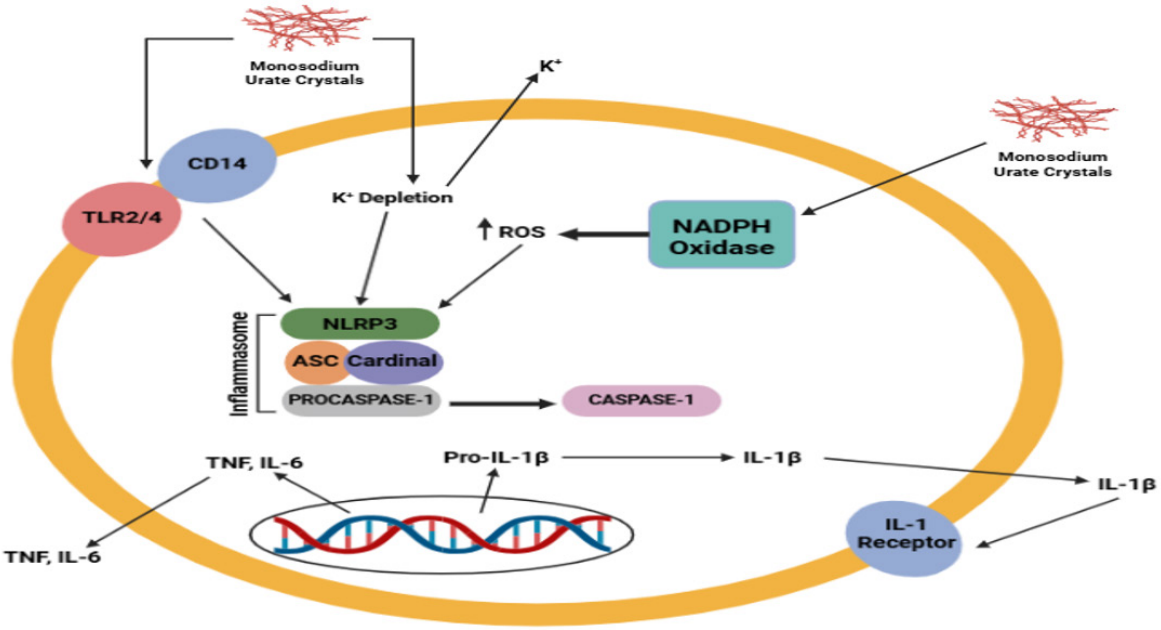


Figure 2: Activation of inflammasome due to accumulation of monosodium urate crystals.

of PEG 400 (55.55%w/w), HPC (1.64%w/w), a preliminary study has evaluated the oral bioavailability on 20 healthy humans, it showed that despite of low plasma level of curcumin, the pharmacokinetic modelling revealed that curcumin is rapidly moving from central compartments to the peripheral tissues, that explains their therapeutic efficacy (Pawar *et al*., 2012).

Methods of Preparation of Different Curcumin Nanoparticles

With ongoing evolution of nanotechnology, in a novel drug delivery system, nanoparticles have their own significance. Formulation of nanoparticles will open the paths for new approaches which will lead to enhancement of solubility, bioavailability, pharmacological activity, physical and chemical stability. Therefore, several techniques are being used and developed for the development, as well as amplifying the activity of curcumin nanoparticles (Rajalakshmi and Dhivya, 2018).

Coacervation Techniques is a method used for the synthesis of curcumin nanoparticles; in this method, a polymer is dissolved in several organic solvents (e.g., ethyl acetate or acetonitrile, dichloromethane) and the hydrophobic herbal drug like curcumin is dissolved directly within the polymeric solution and is allowed to homogenize properly. The nanoparticles are collected by centrifugation. Hazardous solvents cannot be used, an inexpensive method, it requires a large amount of solvent at a time (Chirio *et al*., 2011).

Spray drying method is a technique in which the curcumin and a desired polymer are mixed together in a solvent and a mixture of solvents, having a drug concentration 10% (w/w). After some time, the solvent is allowed to evaporate by the flow of hot air (Vasconcelos *et al*., 2007)Later, it results in the formation of the amorphous drug, which gets crystallised partially during processing (Paradkar *et al*., 2004).

Nanoprecipitation method is also termed as the Solvent displacement method, in this method a polymeric solution is prepared by suspending the desired polymer in a solvent and then the herbal drug is added to it. The prepared drug-polymer solution is dipped in the water with continuous stirring and results in precipitation. Later, the solvent is being evaporated by the hot air flow (Bhujbal *et al*., 2021a).

Solvent evaporation method involves two steps: (a) preparation of a solution consisting of polymer and herbal drug, (b) evaporation and dispersing the solvent used for dissolving the herbal drug, which results in the formation of a solid mass (Bhujbal *et al*., 2021b). After the emulsion is formed it is converted into a nano-suspension due to evaporation of the solvent (Verderio *et al*., 2013). This method requires low temperature for evaporation, and thermal deposition can be prevented. The disadvantages are (a) solvents are expensive, (b) selection of the proper solvent, evaporation is a time-consuming process(Chiou and Riegelman, 1969).

Single emulsion method is a conventional method of curcumin nanoparticle formulation. In this method curcumin nanoparticles are dispersed in a solvent at high-speed homogenization and ultrasonication. Later the solvents are evaporated by continuous magnetic stirring at room temperature. The solidified nanoparticles are ultrasonicated, washed with distilled water to remove impurities, and lyophilized(Rao and Geckeler, 2011).

Microemulsion is an ideal method for the modelling of nanoparticles. The surfactants to be used are hydrophilic in nature for oils and hydrophobic in nature for water. Microemulsion can be formed by adding surfactants with herbal drugs along with oil and water with continuous stirring, it results in the formation of a turbid solution with small droplets (Antonietti, 2003; Duong *et al*., 2020). Certain parameters that may affect the Microemulsion techniques are temperature, variation in pH, etc (Healy *et al*., 1976)

Ultrasonication is a technique that is employed for the hydrophobic drugs. During synthesis, the herbal drug is dissolved in an organic solvent, and the resulting solution is then added into the polyelectrolyte solution under Ultrasonication process, and after some time, the nanoparticle is synthesized (Zheng *et al*., 2010).

Thin film hydration method is a technique in which the herbal drug and the surfactants to be used are allowed to mix with organic solvents under sonication conditions. The solvent is allowed to evaporate and distilled water is added in sonication conditions to form a nanosuspension, which is centrifuged to obtain nanoparticles (Moorthi *et al*., 2012a).

Emulsion Polymerization method is a fast and readily adaptable technique for the synthesis of curcumin nanoparticles. There

Table 2: (Systemic Bioavailability of curcumin on its oral administration).

Model (Dose)	Pharmacokinetic Data	References
Rat (400 mg)	Trace curcumin in portal blood, not in heart blood	(Rao *et al*., 1970)
Rat (2% of diet)	Plasma – 12Nm	(Piper, 1998)
Rat (50 mg/kg)	Plasma – 0.2927±0.065 µg/mL	(Shoba *et al*., 1998)
Rat (2 g/kg)	Modest serum concentration	(Ammon *et al*., 1993)
Human (36-180 mg/day)	Despite of 29 days treatment undetectable in serum plasma	(Sharma *et al*., 2001)
Human (2 g/kg)	Undetectable or very low serum plasma concentration	(Holder *et al*., 1978)

Table 3: Inhibitory effect of Turmeric Flavonoid and Nano-Curcumin on Xanthine oxidase and Uric Acid Production.

Agent	Concentration	Inhibitory effect on Xanthine oxidase	Effect on uric acid production
Nano-Curcumin	5 µg/mL	Moderate inhibition	Decreases uric acid production
Nano-Curcumin	10 µg/mL	Increased inhibition	Decreases
Nano-Curcumin	15 µg/mL	High inhibition	Decreases production of uric acid
Nano-Curcumin	25 µg/mL	91% inhibition(highest)	Significant reduction in uric acid levels
Xanthine oxidase	N/A	Key enzyme in uric acid production	Target to reduce uric acid and oxidative stress
Turmeric Flavonoids	Not specified	Potent Xanthine oxidase inhibitor	Reduction in serum uric acid level

are two types of emulsion techniques, named as organic and continuous phase, that are used for the synthesis of nanoparticles (Lowe and Temple, 1994; Vauthier *et al*., 2003). In this method, the synthesis also involves the dissolving of surfactant in the pure water under ultrasonication and the curcumin is dissolved in the organic solvent for making the solution and after sometimes this solution is added to the surfactant to form curcumin nanoparticles (Moorthi *et al*., 2012b).

Antisolvent precipitation method is a technique for synthesis of hydrophobic drugs. In this method, curcumin is dissolved in the organic solvents and then the solution is mixed with deionized water with continuous stirring. Among the different methods of synthesizing curcumin nanoparticles, ionic gelation and antisolvent precipitation are the most efficient and desirable. Although both methods have some drawbacks, they are best suited for improving the solubility and stability of curcumin, which is naturally poorly soluble. The ionic gelation process is based on polymer crosslinking with the drug, while antisolvent precipitation is controlled by parameters like stirring rate, time, and temperature. Moreover, the microemulsion method is especially valuable when curcumin nanoparticles are to be used in drug delivery. More studies are needed to investigate new synthesis routes to further optimize curcumin nanoparticle formulations (Kakran *et al*., 2012).

Ionic gelation method is the most convenient and simple method for the synthesis of nanoparticles. In this technique, poorly

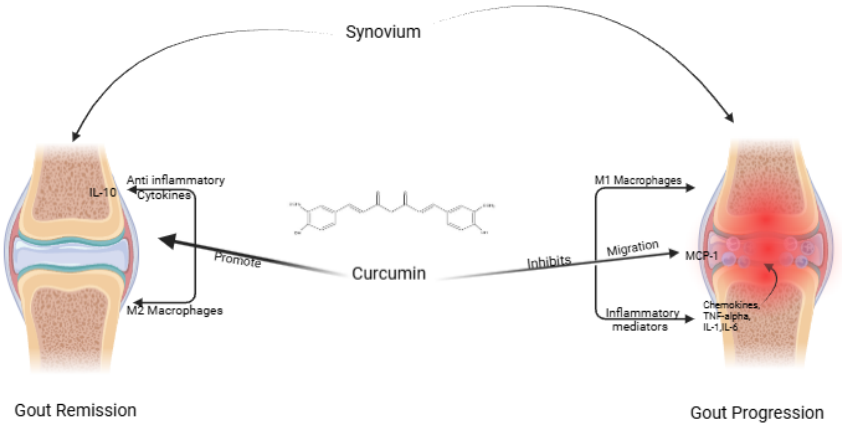


Figure 3: Mechanism of Curcumin in Modulating Gout Progression and Remission.

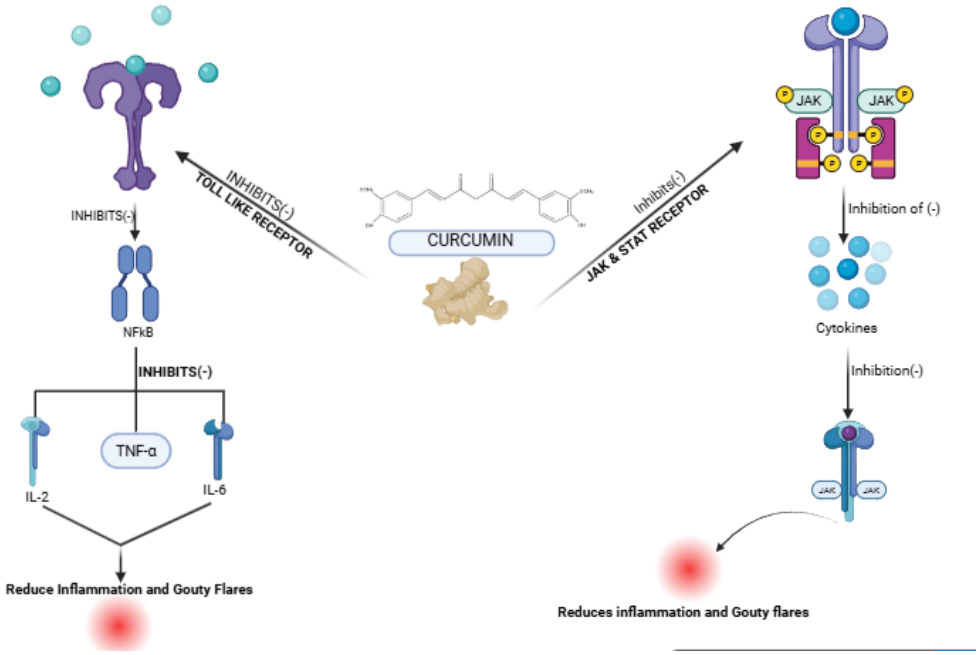


Figure 4: Mechanistic pathways of curcumin in reducing inflammation and gouty flares.

water-soluble drugs like curcumin are added to the organic solvents and then this solution is dissolved in a polymeric solution with constant stirring. This polymer improves the solubility and stability of curcumin nanoparticles by forming a crosslink between the drug and itself (Avadi *et al*., 2010).

Fessi method is a technique for synthesis of curcumin nanoparticle in which curcumin is dissolved with suitable solvent under sonication condition. The solution is then added to pure water along with some surfactants with continuous stirring (Bhawana *et al*., 2011).

Examples of Curcumin nanoparticles

- Curcumin loaded Niosome.
- Curcumin loaded liposomes.
- Curcumin loaded Dendrimer.

Role of Curcumin and its Nanoparticles in Gout Management

Gout and Rheumatoid arthritis are called as arthritic disease and are characterized by loss of immunological tolerance to autoantigens, chronic inflammations and overproduction of antibodies by its own (Yang *et al*., 2022). Gout can be characterized by accumulation of Monosodium Urate Crystals (MSU) in the joints, tendons and other soft tissues and those drugs used for the treatment of these disease are expensive and they may have serious adverse effects (Maity *et al*., 2021). Curcumin can be used in the treatment of Gout and Arthritic disease and it's seen that patient receiving curcumin (500mg) for gout had significantly reduced Erythrocyte Sedimentation Rate (ESR) (Chandran and Goel, 2012).

It was found that curcumin has ability to reduce the severity of gout and arthritic diseases, which includes joint destruction, oedema, pannus formation, synovial hyperplasia by reducing infiltration inflammasome by decreasing IL-6, IL-1 and TNF-alpha etc., (Manca *et al*., 2015) (Figure 3). Curcumin loaded- solid nanoparticles could significantly reduce joint hyperalgesia and decrease paw withdrawal threshold in rat, NLRP3 inflammasome seems to be involved in the development of several arthritic diseases and gout. NLRP3 inflammasome leads to the downregulation of the inflammatory cytokines (Arora *et al*., 2015; Fan *et al*., 2018; Zhang *et al*., 2018). Moreover, it's been studied that curcumin cognate AI-44 by inhibiting NLRP3 inflammasome activation and targeting cathepsin B, is a novel drug for the treatment of gouty arthritis. It inhibits the interaction between cathepsin B and NLRP3 and prevents the activation of NLRP3 inflammasome (Li *et al*., 2019). Liposome encapsulated dimethyl curcumin can also be used for the treatment of gout as it almost reduces neutrophils, eosinophils, lymphocytes, monocytes etc. Some study shows that MSU loaded curcumin causes cytotoxicity and apoptosis while reducing IL-1, IL-6, TNF- alpha, PGE-2 and some other inflammatory cytokines (He *et al*., 2023; Sun *et al*., 2018).

A study suggested, there is an impact of xanthine oxidase on inhibiting the production of uric acid and nano-curcumin has inhibitory effect on xanthine oxidase. Nano-Curcumin has shown inhibition of xanthine oxidase at different concentration like 5 mcg/mL, 10 mcg/mL, 15 mcg/mL but it has shown highest inhibitory effect of 91% at concentration of 25 mcg/mL The inhibitory effect on xanthine oxidase by nano-curcumin leads to decrease the production of uric acid (Dulaimy *et al*., 2023). Xanthine oxidase plays a crucial role in treatment of hyperuricemia by decreasing the uric acid production and reducing vascular oxidative stress associated with elevated uric acid level (Kostić *et al*., 2015). Turmeric is rich in flavonoids and there active metabolites are potent xanthine oxidase inhibitor and they shows some great results in lowering serum uric acid level (Kunnumakkara *et al*., 2023).

FUTURE DEVELOPMENT IN GOUT TREATMENT

Current advancement focuses on different approaches for the treatment, prevention of gout and arthritic diseases. The treatment involves patient to engage themselves and encourage them to follow healthy lifestyles. Without proper treatment it can leads to deterioration of joints and compromises patient's quality of life (Peng *et al*., 2023). Some studies show that women are more prone to Gouty arthritis in comparison to men, due to their reduced oestrogen, especially in postmenopausal women. Different approaches like urate- lowering therapies, management of acute attacks, management of inflammatory pains are taken (Qi *et al*., 2024). Various studies suggested that different animal model were used to investigate inflammatory mechanism responsible for cartilage and skeletal worsening. The research shows that different approaches such as potassium oxonate introduction, administration of MSU, diet have been used for the induction of hyperuricemia (Patil *et al*., 2021).

Nanotechnology has come up with an advancement in the treatment of gout, due to the small size and larger surface area they offer enhanced drug delivery. There are certain advantages such as targeted drug delivery, improves bioavailability of herbal drugs, enhances drug solubility and precise drug delivery (Zhu *et al*., 2023).

In future the management of gout lies on individualised treatment approaches, such as IL-1β antibody targeting molecule and canakinumab. Some research shown that CRISPAR CAS 9 approach can also manipulate UA metabolism and cures gout (Yadav *et al*., 2022). Gene therapies, especially targeting NLRP3 could be the most prominent but have some limitations. Future research and advancement in the treatment of gout includes different models on ncRNA, new chemicals etc., (Liu *et al*., 2023). Artificial intelligence and machine learning are reorganizing, treatment and management of gout from data analysis form

different biomarker research, clinical trials and genetic studies. Future treatments may include biologics, gene therapies and advanced machines all together. Digital health technologies are helping patients by improving patients care, patient's knowledge that leads to patient better treatment adherence. The fast progress in the in the different fields can lead to management of gout and improves the quality of life of patient.

CONCLUSION

Nanotechnology has transformed medicine by amplifying the therapeutic merits of naturally available products. An eminent example is curcumin, one of the highly used bioactive phytochemicals derived from turmeric. It is a potent ant-inflammatory, antioxidant, and analgesic agent; hence, it is a strong candidate for the treatment of inflammatory diseases such as gout. However, the clinical usefulness of curcumin has been limited because of its poor solubility, Low bioavailability and large metabolism. To overcome these limitations, various nanoparticle delivery systems like curcumin nanoparticles have been developed to improve stability, bioavailability, and targeted delivery to infected sites. Curcumin nanoparticles have a few advantages over standard curcumin formulations. Sustained release, increased cellular uptake, and improved bioavailability are seen together, optimizing the therapeutic action of curcumin. These studies show that curcumin nanoparticles dramatically inhibit inflammation by modulating key inflammatory pathways, throwing out of pro-inflammatory cytokines, and blocking oxidative stress since these all play a very important role in the pathogenesis of gout (Figure 4). The nanoparticles have also been brought to light for their effectiveness against joint damage and pain, thus providing a natural, safer alternative than conventional anti-gout medications usually associated with unwanted side effects.

In conclusion, the amalgamation of nanotechnology with conventional medicines, such as curcumin nanoparticles, poses as a new hopeful therapeutic approach to gout management. Although preliminarily positive, much work remains in conducting clinical trials for optimum formulation, evaluation of long-term safety, and defining standardized dosing regimens. Developments in nanomedicine stand to assist in taking this route into the clinic, thus providing a more efficient, natural, and sustainable means in managing gout.

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ABBREVIATIONS

MSU: Monosodium urate; Cur: Curcumin; **NPs:** Nanoparticles; **NOS:** Non-reactive Oxygen; **NF-kB:** Nuclear factor- kappa B; **IL-1β:** Interleukin-1 beta; **IL-6:** Interleukin-6; **IL-10:** Interleukin-10; IL-2: Interleukin-2; **IL- 14:** Interleukin-14; **TNF-α:** Tumour Necrosis Factor- Alpha; **TLR:** Toll like receptors; **NLRP3:** Nod like receptor pyrin domain containing 3; **PEG:** Polyethylene glycol; **PLGA:** Poly lactic co-glycolic acid; **PVA:** Polyvinyl alcohol; **LPS:** Lipopolysaccharides; **UV:** Ultraviolet; **XO:** Xanthine Oxidases; **SD:** Sprague Dawley **i.p.:** Intraperitoneal.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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AUTHORS CONTRIBUTION

Harsh Mishra contributed to the collection and assembly of data, literature search, and preparation of the manuscript draft, critical review in the article and final approval of the article. Ms. Ridhi contributed to the conception and design of the study, data analysis and interpretation, and critical review of the manuscript. Both authors participated in the development of the manuscript, approved the final version, and agree to be accountable for all aspects of the work.

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