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Research Article

Chrysin as a Natural Flavonoid for Gout Management: Mechanistic Insight and Therapeutic Perspectives

Pabitra Panigrahi [1*], Rohit Saini [2], Jitendra Singh Yadav [3], Sachin Rathod [4]
[1-4] Pharmaceuticals, Shree Dhanvantary Pharmacy College, Kim, Surat, Gujarat, India

Corresponding Author: *Pabitra Panigrahi

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Abstract

Gout, a disease of king, is a chronic inflammatory and metabolic disorder caused by hyperuricemia and urate crystal deposition, leading to severe joint inflammation and pain. Conventional therapies such as allopurinol, febuxostat, NSAIDs, and colchicine are effective but associated with significant adverse effects, including hepatotoxicity, gastrointestinal intolerance, cardiovascular risks, and drug interactions. Chrysin (5,7-dihydroxyflavone), a natural flavonoid obtained from honey and propolis, has anti-hyperuricemic, anti-inflammatory, and antioxidant properties, so it is a promising alternative for gout. Chrysin reduces uric acid levels primarily through xanthine oxidase inhibition and modulation of renal urate transporters, and suppresses inflammatory pathways including NF-κB and NLRP3 inflammasome, as a result decreasing inflammatory cytokines such as IL-1β, IL-6, and TNF-α. Preclinical studies demonstrate that chrysin significantly lowers serum uric acid, reduces joint swelling, and improves inflammation. However, its clinical application is limited by poor solubility and low oral bioavailability. Advanced drug delivery systems such as nanoparticles and liposomes have shown potential to improve their pharmacokinetic profile. Overall, chrysin represents a promising natural therapeutic candidate for gout management, warranting further clinical investigation.

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INTRODUCTION

Gout is a most common chronic inflammatory and metabolic disorder characterized by hyperuricemia and deposition of monosodium urate crystal in joint and surrounding tissue, causing acute pain and inflammation [1, 2] Historically gout is known as "Disease of king" due to its association with life style, pathogenesis of gout is linked to hyperuricemia which is the primary etiological factor for crystal deposition. This link was first suggested by Antoni Van Leeuwenhoekn early 350 years ago when he identified uric acid crystal in gouty tophus [3]. Hyperuricemia is defined as increasing level of serum uric acid. At 37 c and pH 7, the saturation concentration of serum uric acid level is 6.8 mg/dl. If serum uric cross saturation level, then serum uric acid converted into mono sodium urate crystal. [4]The prevalence of gout ranges from1-4% and severity is found to 0.1-0.35 of the population. It is more common in men as compared to women with male to female ratio of about 3.1-10.1 in India, the bone and joint decade (BJD) COPCORD survey (2006-2011) reported a gout prevalence of 0.05% [5]. In the recent decade, the incidence and prevalence of gout have been increased significantly. Prevalence of gout reaching approximately 11-13% and incidence of gout about 0.4% among individual aged over 80 years. Further, gout happened more frequently among certain population like ethnic minority in USA, Han Chinese, New-Zealand maori and other Asian ethnic group [6].

Different conventional therapies such as allopurinol, febuxostat, NSAIDs, colchicine and corticosteroid for the management of gout are widely used. However, several limitations restrict the effectiveness of the therapies [7]. Allopurinol is the first-line urate-lowering treatment for the gout patient which inhibit XO that responsible for uric acid production. Fontana *et al*. carried out a study involving eleven patients suspected of experiencing allopurinol-induced liver injury. Their findings revealed a link between hepatotoxicity and the HLA-B*58:01, HLA-B*53:01**,** and HLA-A*34:02 alleles [8]. Long-term use of allopurinol may lead to an elevation in thyroid-stimulating hormone (TSH) levels**,** potentially indicating the development of subclinical hypothyroidism [9]. Febuxostat is a non-purine xanthine oxidase inhibitor (XOI) that exhibits greater selectivity and potency compared to allopurinol. Febuxostat is contraindicated in patients receiving azathioprine or mercaptopurine therapy, as inhibition of xanthine oxidase can elevate the levels of these drugs, potentially leading to severe toxicity and myelosuppression [10]. NSAIDs have well-known adverse effects affecting the gastric mucosa, renal system, cardiovascular system. Diclofenac seems to be the NSAID with the highest reported increase in adverse cardiovascular events [11]. The main limitation of colchicine in the management of gout is narrow therapeutic index. The gastrointestinal tract is most often affected by adverse reactions, with diarrhoea being the most frequent (23%), followed by vomiting (17%) and nausea (4–17%). Other reported effects include central nervous system symptoms like fatigue and headache, as well as metabolic or endocrine issues such as gout and throat pain [12].

Flavonoids are obtained from natural edible oil and honey and less adverse effect to human-being. Natural flavonoids have the potency to reduce the uric acid production [13] clinical and scientific interest rise in natural flavonoid especially in chrysin due to their strong anti-inflammatory activity and potent xanthine oxidase inhibition, making them potent alternative gout hyperuricemia and related inflammatory condition [14, 15]. Recent publications show chrysin can inhibit XO, decrease the production of uric acid, prevent NLRP3 inflammasome activation, and control inflammatory cytokines. It is also relevant to gout pathology. Mechanism of Chrysin Anti-inflammatory mechanism: Animal studies show chrysin reduces joint swelling, inhibits prostaglandin and cytokine secretion, and decreases COX-2, IL-6, and TNF-α production. Xanthine oxidase inhibition: Chrysin acts as a potent competitive XO oxidase inhibitor and helps to decrease the production of uric acid [16].

This review aim to summarize the current knowledge on gout caused due to hyperuricemia and examine the therapeutic potential of chrysin as a natural flavonoid for the management of gout by summarizing it's mechanical role in xanthine oxidase inhibition, anti-inflammatory and anti-oxidant pathway and modulation of key molecular target such as NF-kB and NLRP3.This review critically analysing available preclinical evidences pharmacokinetic and bioavailability limitation safety profile and advanced formulation strategies, In order to highlights the potential of chrysin as a safe effective adjunct or alternative therapeutic candidate and to identify future research direction for it's clinical translation in gout management.

Chrysin: Chemical and Pharmacological Background

Chrysin is a naturally occurring flavonoid found in various plant sources such as honey, propolis and blue passion flower. The chrysin content is 0.10 mg/kg in honeydew and 5.3 mg/kg in forest honeys [17]. Propolis commonly referred to as **"**bee glue**,"** is a resinous material gathered by honeybees from different plant sources. Studies showed that the chrysin content in propolis is as high as 28 g/l [18, 19]. concentration range of chrysin was found to be 0.012–0.120 mg/mL, with an average recovery rate of 99.41% from the leaves of passion flower [20].

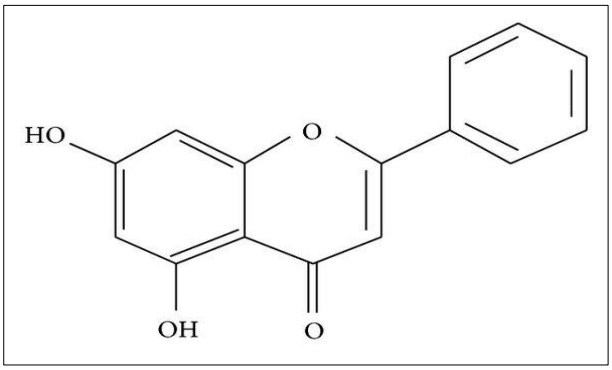

Fig 1: Chemical Structure of chrysin

Unlike many other flavonoids, chrysin's therapeutic potential is still underexplored in current research due to its poor absorption and low bioavailability. Growing research highlights the pharmacological potential of chrysin, which exhibits strong anti-inflammatory, antioxidant, and anticancer properties by

promoting apoptosis across various human and animal cell types. [21, 22].

Anti-inflammatory effect

Chrysin plays a vital role in reducing immune-related inflammation by limiting the damage caused by macrophages, neutrophils, and other inflammatory mediators. The study has been shown that chrysin lower the levels of pro-inflammatory mediators such as TNF-α, NF-κB p65, IL-1β, IL-17A, IFN-γ, IL-12, and IL-6.Chrysin effectively inhibits NF-κB and PPAR-γ, leading to downregulation of pro-inflammatory enzymes including COX-2, MPO, iNOS, prostanoids, and phospholipase A2 [23]. Chrysin was used to treat human osteoarthritis (OA) chondrocytes followed by IL-1β stimulation for 24 hours [24]. Qi *et al*. found that chrysin (10–60 μg/mL) suppressed LPS-induced iNOS expression and inhibited JAK-STAT phosphorylation, STAT1/3 translocation, and the release of TNF-α, IL-6, MCP-1, and ROS in RAW264.7 cells. By blocking ROS-mediated JAK-STAT signaling, chrysin effectively reduced LPS-induced inflammation [25]. Intraperitoneal administration of chrysin significantly reduced cigarette smoke-induced inflammation, lowered MPO expression and cytokine release, and decreased phosphorylation of p38 and ERK [26].

Anti-oxidant effect

Chrysin-loaded solid lipid nanoparticles (SLNs) at doses of 5 mg/kg and 10 mg/kg significantly enhanced antioxidant activity and non-antioxidant enzyme levels in the hippocampus affected by amyloid-β25–35 (Aβ25–35). Additionally, chrysin reduced lipid peroxidation, acetylcholinesterase activity, and neuronal damage, thereby preventing memory impairment [27].Another study demonstrated that oral administration of chrysin in rats protected against age-related memory loss by increasing the levels of superoxide dismutase, catalase, and glutathione peroxidase. It also reduced reactive oxygen species, inhibited Na (+), k(+)-ATPase activity, and prevented the decline of brain-derived neurotrophic factor (BDNF) levels in aged mice [28]. Chrysin treatment was found to alleviate cisplatin-induced lipid peroxidation and xanthine oxidase activity while restoring glucose-6-phosphate dehydrogenase and quinone reductase levels. It also reduced the expression of i-NOS, COX-2, NF-κB, and TNF-α, thereby protecting against hepatic tissue damages [29, 30]. Administration of chrysin at doses of 20 and 40 mg/kg body weight protected the liver and kidneys of Wistar rats from oxidative stress by inhibiting cytochrome P450 2E1, alcohol dehydrogenase, and xanthine oxidase and it also reduced serum levels of aspartate aminotransferase, alanine aminotransferase, creatinine, urea nitrogen, and lactate dehydrogenase [31].

Anti-cancer effect

Cancer is a global health issue characterized by the uncontrolled growth and spread of abnormal cells that can invade and spread to other parts of the body [32]. Chrysin treatment enhanced antioxidant levels and reduced lipid peroxidation, helping maintain the balance between oxidants and antioxidants during carcinogenesis [33]. Chrysin suppresses tumour growth by inducing apoptosis through activation of the Notch1 signalling pathway in both *in vitro* and *in vivo* models [34]. The main mechanisms of chrysin involve inhibiting cell proliferation, triggering apoptosis, and reducing inflammation [35]. Notably, chrysin supplementation alters the expression of β-arrestin-2, a key signalling molecule, which in turn affects multiple cellular signalling pathways [36]. It was concluded that chrysin may slow down tumour development rather than completely prevent its formation.

Pathophysiology of Gout and Potential Role of Chrysin

Hyperuricemia urate crystal deposition

Hyperuricemia which means elevated level of uric acid in blood that was resulting from excess production or insufficient excretion of uric acid [37]. Uric acid represents the end product of both endogenous and dietary purine metabolism. At a physiological pH of approximately 7.4 within the extracellular environment, nearly 98% of uric acid exists in its ionized form, known as urate [38]. Due to the high sodium content in the extracellular fluid, urate predominantly exists as monosodium urate, which has a limited solubility of around 380 μmol/L. When urate levels rise above this threshold, the likelihood of monosodium urate crystal formation and deposition increases [39]. When UA (uric acid) crystals are deposited in the joint area, gouty arthritis inflammation begins. Lysosomal enzymes are produced and inflammatory chemokines are activated when these crystals are taken up by synovial cells, initiating the inflammatory process [40]. The release of mast cells, monocytes, and the activation of neutrophils are linked to gouty arthritis [41].

Role of xanthine oxidase (XO) in uric acid production

Xanthine oxidase (XO) is an essential enzyme in purine metabolism that facilitates the sequential hydroxylation of hypoxanthine to xanthine and subsequently to uric acid, while simultaneously producing reactive oxygen species such as superoxide radicals and hydrogen peroxide [42].Human xanthine oxidase (XO) activity is believed to play a role in the onset of coronary artery and gout-related disorders, as it contributes to oxidative damage within body tissues [43].

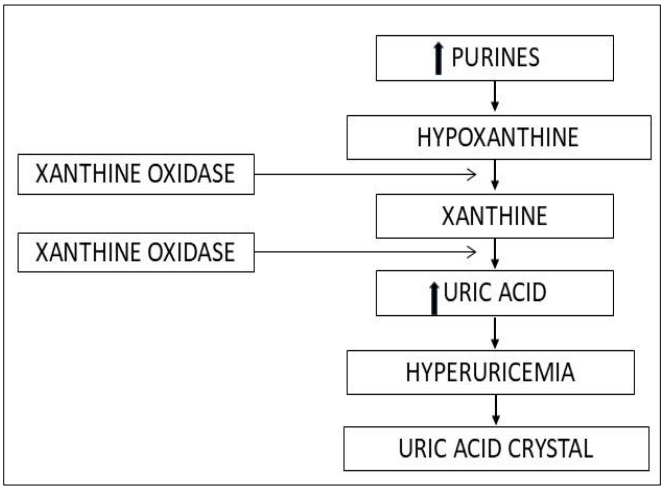

Fig 2: Enzymatic pathway of purine to uric acid end product

Activation of NLRP3 inflammasome and IL-1β pathway in gouty inflammation

An essential factor in the development of acute gout inflammation is the NLRP3 (Nod-like receptor protein) inflammasome. When it comes to acute gout joint inflammation, ASC (adaptor molecule apoptosis-associated speck-like protein containing a CARD) plays a crucial role as a mediator between the NLRP3 protein and pro-caspase-1 protease [44]. Martinon *et al*. Toll-like receptors TLR2 and TLR4 trigger the NLRP3 inflammasome when monocytes consume MSU crystals. Pro-caspase-1 protease is hydrolysed and changed into active caspase-1 protease by the ASC adaptor protein [45]. causing active caspase-1 to cleave pro-inflammatory IL-1 β and mature IL-1 β, which ultimately causes a severe inflammatory response in gout patients [46].

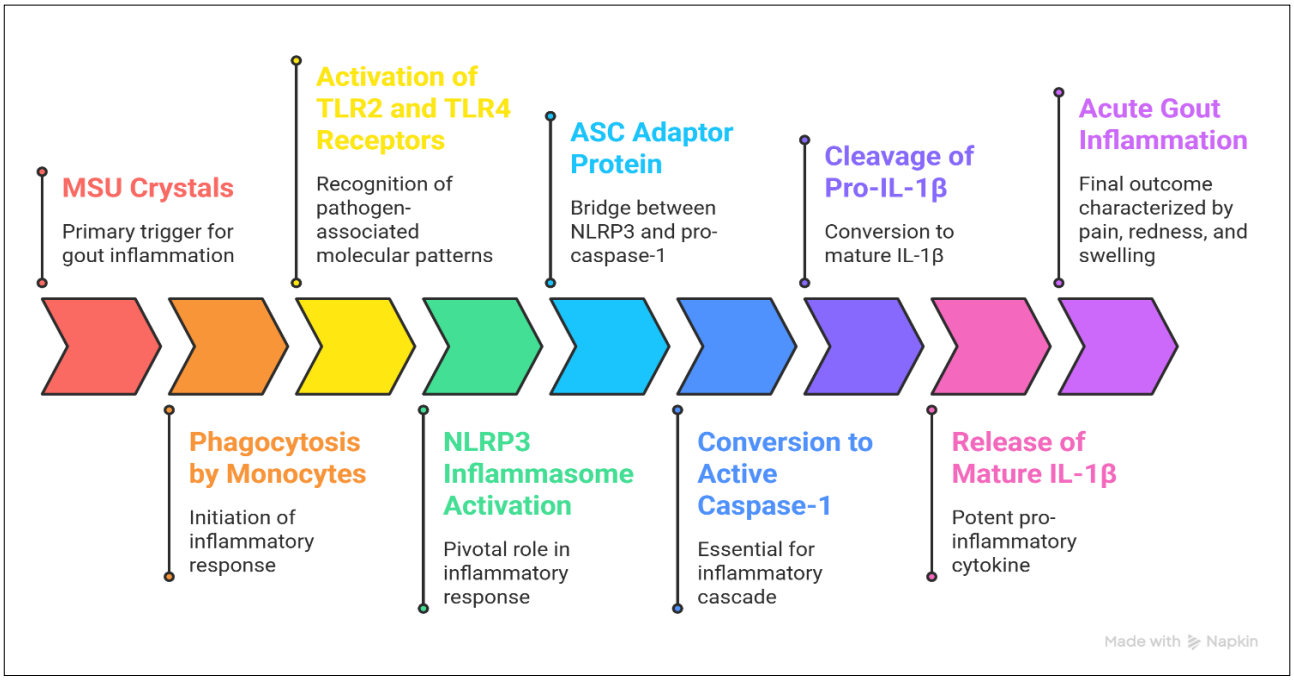

Fig 3: MSU Crystal triggered NLRP3 inflammasome pathway in gout

Potential targets of chrysin

XO inhibition → reduction in uric acid

Xanthine oxidase is an enzyme responsible for conversion of hypoxanthine to xanthine and then xanthine to uric acid. Chrysin primarily target gout through inhibition of xanthine oxidase, which results into decreased production of uric acid. Hence chrysin compete to bind the active site of xanthine oxidase that result into blocking the conversion of xanthine to uric acid [14-15].

NF-κB suppression → anti-inflammatory effect

Chrysin exhibits anti-inflammatory effect by suppressing the NF-kB (Nuclear factor kapp B). Chrysin block IkB kinase (Ikk), leading to enhanced stability of IkB, at this time chrysin trap the NF-kB in the cytoplasm where NF-kB is inactive. As a results inhibition of inflammatory cell infiltration and decreased production of inflammatory mediators including TNF-α, IL-1β, IL-6 that results in enhanced anti-inflammatory effect [47].

NLRP3 modulation → reduction in crystal-induced inflammation

Chrysin decrease the expression of NLRP3, Caspase and proteins as a result, inhibition of release crystal induced key inflammatory mediators including IL-1β and IL-18. This results into decrease of inflammation and pain related symptoms caused due to gout, so action of chrysin on NLRP3 cascade is an important mechanism for crystal induced gout inflammation [48].

Antioxidant activity → prevention of oxidative damage

Chrysin exhibits anti-oxidant activity by acting on scavenging ROS, increasing endogenous antioxidant enzyme and inhibit lipid peroxidation as a result prevention cellular damage by chrysin [49].

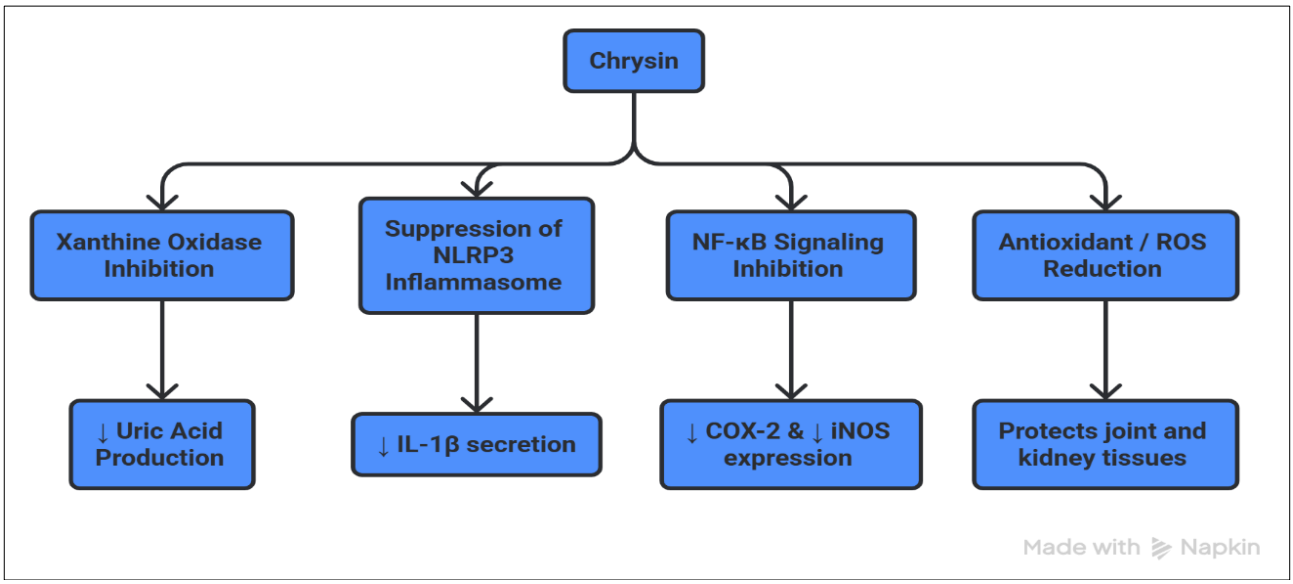

Fig 4: Schematic representation shows molecular target chrysin in gout

Preclinical Evidence of Chrysin in Hyperuricemia and Gout

***In vitro* studies: XO inhibition assays**

In-vitro study confirms that chrysin is a potent inhibitor of XO, the activity is measured using enzyme inhibition assay. The IC50 value of chrysin is approximately 1.26µm which is lower than allopurinol-2.93µm that indicate chrysin have strong inhibitory potential. Chrysin is reversible competitive inhibitor of xanthine oxidase enzyme, chrysin bind active site of enzyme and prevent binding XO enzyme as a result uric acid production. Molecular docking simulation states that chrysin interact with key amino acid in the active cavity of xo. Such as Leu648, Phe649, Glu802 and other effective blocking catalytic centre. Kinetic analysis demonstrates that chrysin competes with the substrates (xanthine) for the enzyme active site. The use of UV-visible absorption, fluorescence titration, circular dichroism and molecular in this assay provide chrysin has potency to inhibit XO [14].

Animal models:

Different animal models of hyperuricemia and gouty arthritis have been published, for *in vivo* evaluation of hyperuricemia and anti- inflammatory of the compound. The administration of MSU-crystals into various anatomical structures to induce crystal-induced inflammation has been proposed

Potassium oxonate-induced hyperuricemia

Potassium oxonate is a competitive uricase inhibitor, which cause hyperuricemia in rodents [50]. The last byproduct of purine nucleotide breakdown is uric acid. The xanthine oxidase enzyme helps convert two purine nucleic acids, adenine and guanine, into uric acid. The enzyme xanthine oxidase is responsible for the purine nucleotide catabolism pathway in humans [51].

The purine metabolic pathway differs significantly between humans and rodents. In humans, the final metabolites of purine degradation are eliminated primarily through the kidneys as urine. However, due to the low aqueous solubility of uric acid, it has a tendency to accumulate and deposit in body tissues, particularly within the joints. In contrast, most experimental animals possess the enzyme uricase instead of relying solely on xanthine oxidase. Uricase, also known as urate oxidase, catalyses the conversion of uric acid into allantoin, a highly water-soluble compound that is readily excreted in urine [52]. Hyperuricemia in rodents can be experimentally induced by impairing uric acid elimination or by inhibiting uricase activity. Potassium oxonate is widely used for this purpose, as it effectively suppresses uricase function and induces hyperuricemia in animal species such as rats, mice, rabbits, dogs, and pigs [51].

In the experimental hyperuricemia animal model, potassium oxonate was administered to induce elevated serum uric acid levels and to evaluate the anti-hyperuricemic activity of the test compounds. All animals, except those in the normal control group, received potassium oxonate at a dose of 250 mg/kg, dissolved in 0.9% normal saline, via the intraperitoneal route 1 hour prior to oral administration of the test drugs, once daily for three consecutive days. One hour after the final drug administration, the animals were anesthetized using a combination of ketamine and xylazine at doses of 100 mg/kg and 20 mg/kg, respectively. Blood samples were then collected from the abdominal aorta. The collected blood was allowed to clot at room temperature for approximately 1 hour, followed by centrifugation at 2500 rpm for 10 minutes. The separated serum was stored at −20 °C until further analysis of uric acid levels [53].

MSU crystal-induced gouty arthritis

The formation of monosodium urate crystals represents the initial and most critical event in the development of gout. These crystals play a key role in initiating inflammatory cellular responses. The deposition of monosodium urate crystals in synovial joints was first reported in 1961, and their presence is considered essential for the definitive diagnosis of gout [54]. MSU crystals activate synovial cells such as monocytes,

macrophages, and neutrophils, leading to the release of pro-inflammatory mediators including interleukin-1, tumour necrosis factor, and inducible nitric oxide synthase [55]. These mediators are major contributors to the acute inflammatory response observed during gout flares [56]. Increased iNOS activity promotes oxidative stress, which can impair synoviocyte survival by disrupting mitochondrial function [57]. In addition, it inhibits chondrocyte proteoglycan synthesis through prostaglandin E2-mediated regulation of chondrocyte apoptosis [58].

Monosodium urate crystals were prepared by dissolving uric acid in 800 mL of distilled water containing 9 mL of 0.5 N sodium hydroxide, while maintaining the pH at 8.9 at 60 °C. The solution was kept overnight at very low temperature to allow crystallization. The formed crystals were then washed, dried, and the needle-shaped crystals obtained were suspended in sterile saline for further use [59]. Experimental animals such as mice, rats, or rabbits were randomly divided into five groups: control, colchicine standard, and three test dose groups. Colchicine was administered once daily for five consecutive days. One hour after the final treatment, normal saline was injected into the control group, while a 50 µL suspension of MSU crystals (25 mg/mL) was injected intra-articular into the other four groups under anaesthesia at the medial side of the right ankle joint [15].

Inflammation was assessed by measuring paw thickness using a Vernier caliper at predetermined time intervals over a period of three days. After 72 hours, the animals were sacrificed by cervical dislocation. Blood samples were collected from each animal, and serum was separated. A 10% tissue homogenate was prepared from the liver and spleen using ice-cold 0.01 M Tris–HCl buffer at pH 7.4. The resulting tissue homogenates, along with serum samples, were used for the estimation of lysosomal enzymes, lipid peroxidation, antioxidant status, and the inflammatory mediator tumour necrosis factor [15].

Reported outcomes

In animal model, chrysin shown beneficial effect on gout and hyperuricemia which includes lowering serum uric acid, reducing paw swelling/edema and suppressing inflammatory cytokines such as IL-1β, TNF-α, and IL-6.

- **↓ serum uric acid-**
  Oral administration of chrysin (50–150 mg/kg) in high-fructose-induced hyperuricemic rats significantly for 28 days reduced serum uric acid levels. Chrysin decrease serum uric acid level by inhibiting xanthine oxidase enzyme and enhance the uric acid renal excreation by modulating various transporter protein like URAT1, GLUT9, OAT1, ABCG2 [15].
- **↓ paw edema/swelling-**
  In Complete Freund's Adjuvant (CFA) induced Arthritis in a Pre-Clinical Rodent Model, Treatment with chrysin 50 and 100 mg/kg significantly reduced the arthritis score and paw/ankle swelling [15].
- **↓ inflammatory cytokines (IL-1β, TNF-α, IL-6).**
  Complete Freund's Adjuvant (CFA) induced rodent model demonstrated that Chrysin significantly reduced serum and tissue levels of TNF-α, IL-6, and IL-1β in Complete Freund's Adjuvant-induced arthritis in rats [15].

Comparison

Chrysin has been evaluated in several animal models alongside with convectional gout therapeutic agent such as allopurinol, febuxostat, and anti-inflammatory agents like indomethacin. The following key comparative findings are obtained below:

chrysin (50–150 mg/kg) significantly reduced serum uric acid and improved renal uric acid excretion comparably to allopurinol (10 mg/kg) in high-fructose- or potassium oxonate-induced hyperuricemic rats. Both chrysin and allopurinol/febuxostat decrease xanthine oxidase activity; however, chrysin additionally activates renal urate transporters to enhance urinary uric acid excretion, whereas allopurinol and febuxostat lack this dual mechanism of action [15]. In MSU crystal–induced gouty arthritis models, chrysin produced a marked reduction in paw edema and inflammatory cell infiltration, comparable to that observed with indomethacin, a standard NSAID used in acute gout. Furthermore, both chrysin and the standard drug significantly lowered pro-inflammatory cytokines including IL-1β, TNF-α, and IL-6, along with a reduction in oxidative stress in inflamed tissues [15].

Table 1: Comparison of chrysin with others Standard drug

Drug	Uric Acid Reduction	Anti-inflammatory	Paw Edema Reduction
Chrysin	High	High	High
Allopurinol	Very High	Moderate	Moderate
Febuxostat	Very High	Low	Low
Indomethacin	Nope	Very High	Very High

Synergistic and Combination Strategies

Chrysin with other flavonoids (quercetin, luteolin)

Chrysin exhibits enhanced therapeutic potential when used in combination with other flavonoids such as quercetin and luteolin, demonstrating notable synergistic effects. The combined treatment of chrysin and quercetin shows synergistic anticancer activity against MCF-7 and MDA-MB-231 cells. This combination suppresses cell proliferation, induces cell cycle arrest in MDA-MB-231 cells, and promotes apoptotic cell death [60]. Similarly, the combination of chrysin and luteolin produces synergistic anticancer effects by enhancing apoptosis through caspase activation and inhibiting cancer cell migration. The combined treatment also modulates apoptotic signalling by increasing the expression of pro-apoptotic proteins such as BCL-2. In addition, this flavonoid combination significantly reduces inflammatory cytokine levels and oxidative stress markers, thereby attenuating excessive inflammatory responses [61].

Chrysin-loaded nanocarriers for enhanced bioavailability

Chrysin loaded nano carrier have been demonstrated to enhance low bioavailability, due to poor water solubility, rapid metabolism and elimination. Various types of nano-carriers are present. Such as polymer-based nanoparticle polymer micelles, lipid-based nanoparticle (solid lipid nano particle, Nanostructure lipid carrier) has shown promising improvement in solubility and stability, controlled release and absorption of

chrysin. Polymer based chrysin nano particle enhance drug release, improving stability, half-life and also shown increased Cmax and AUC as compared free chrysin [62]. Lipid based nanocarriers provide high entrapment efficiency (≈80–90%), controlled drug release and enhance oral bioavailability. Polymeric micelles such as chrysin folate conjugated micelles improve oral bioavailability by water solubility [63]. Novel delivery system such as nano-emulsion & self-nano emulsifying drug delivery system improve that enhances local bioavailability and permeability in GI tract.

Pharmacokinetic and Bioavailability Concerns

Poor Solubility & Rapid Metabolism

A pharmacokinetic study of chrysin in humans shows that oral bioavailability of chrysin was estimated to be less than 1%. The study also stated that 90% chrysin eliminated through faces and rest was eliminated through urine. High faecal elimination of chrysin due to its low aqueous solubility [64]. Studies show that chrysin undergoes both phase-I and phase-II metabolism. In phase-I, chrysin is metabolized by CYPs and produces metabolites like 5,6-dihydroxy flavones & 5,7,4-trihydroxy flavone. In phase-II, chrysin is metabolized by UGTs and SULTs and metabolites like Chrysin-7-O-glucuronide & Chrysin-7-O-sulphate. The study suggests that metabolism in the GI tract and in the liver is one of the reasons to cause low oral bioavailability of chrysin. These two factors cause extremely low oral bioavailability and restricting therapeutic potential of chrysin [65].

Approaches to overcome:

A variety of Nano-formulation for chrysin including liposomes, liposomes, nanoparticle and solid dispersion have studied to overcome from low solubility and rapid metabolism.

Nano-formulations

Liposomal preparations are an exciting technique to improve the poor aqueous solubility, short metabolism and low bio-availability of chrysin. Liposomes improve apparent solubility of chrysin and protect it from fast phase II conjugation followed by its transformation into a lipid vehicle. This improves chrysin stability and bioavailability. Most common vesicles that have been reported are phosphatidylcholine- and cholesterol-based vesicles which are prepared via thin–film hydration. To further prolong the circulation time, PEGylated liposomes has been used for decreasing reticuloendothelial clearance. Studies have shown that chrysin's antioxidant, anti-inflammatory, and anticancer activities are significantly enhanced with liposomal encapsulation due to improved intracellular delivery and continuous release. Modified systems like bile-salt enriched bilosomes and surface-coated liposomes provide many additional benefits. For instance, improved stability in the GI system, enhanced permeability and better encapsulation efficiency are all additional advantages [66]. In general, liposomes can be seen as a versatile and biocompatible delivery platform that can overcome the major biopharmaceutical limits of chrysin. They have the potential use as oral, topical and systemic therapeutic delivery systems.

You can also improve the bioavailability of chrysin with other solid formulations. For example, polymeric NPs or protein-based NPs can reduce the particle size of chrysin. This way, it protects chrysin from rapid metabolism and allows controlled or targeted release. For example, methoxy-poly (ethylene glycol)-β-polycaprolactone (mPEG-PCL) NPs, which contained chrysin and had a size of around 77 nm were able to substantially improve anticancer efficacy *in vitro* and *in vivo*. Indeed, using a mouse xenograft model, NP-chrysin with a medicinal dose via injection gave a similar tumour inhibition effect as that of free chrysin but at a greatly reduced dose, implicating that the NP formulation improved delivery efficacy and therapeutic index [67]. Likewise, chitosan-based chrysin NPs (via ionic gelation) not only improved solubility and sustained release but also improved the antibiofilm activity of chrysin against Staphylococcus aureus [68].

The solid dispersion of chrysin is an excellent way to enhance its aqueous solubility and oral bioavailability as a crystalline drug can be transformed into an amorphous solid dispersion in a hydrophilic carrier matrix. As an example, Wang and co-workers created a solid dispersion of chrysin using Plasdone® S630 through the solvent evaporation technique. An optimized drug–polymer mass ratio of 1:6 was discovered, which resulted in >90% cumulative drug release in both acidic and neutral media. Furthermore, the authors found the AUC (Area Under Curve) of the drug in rats during oral administration via a chrysin suspension to be 41-fold higher than that of a chrysin suspension. This formulation has an acceptable storage stability and can offer a significant improvement in antihyperlipidemic effects in a hyperlipidemic rat model. This means that solid dispersion can overcome the solubility limited absorption of chrysin, thus reducing its dose [69].

Another study stated that solid dispersions of combining chrysin with Brij® L4 and aminoclay led to a 13–53-fold increase in its solubility, rapid and complete dissolution (~60% in 1 h, ~83% in 8 h), and conversion to the amorphous state, as shown by X-ray diffraction, ultimately significantly improving its *in vivo* absorption and its effect as an absorption enhancer [70].

Prodrugs and structural modification

To counteract chrysin's rapid phase II metabolism (especially glucuronidation/sulfation at the 7-OH) and its poor aqueous solubility, researchers have developed prodrugs by chemically masking the hydroxyl group. One notable example is a carbamate-based prodrug (called C-1), where the 7-OH of chrysin is derivatized into a bi-piperidine carbamate, leading to a ~47-fold increase in water solubility and markedly improved metabolic stability. *In vivo*, this prodrug shows significantly enhanced oral bioavailability (F ≈ 24%) and a much longer half-life ($t_{1/2}$ ≈ 16.7 h) compared to free chrysin, and also exerts stronger therapeutic effects in a non-alcoholic fatty liver disease (NAFLD) mouse model [71].

Other than prodrugs, structural derivative of chrysin have been synthesized to improve its pharmacokinetics or enhance specific bioactivities. A broad review of synthetic strategies (etherification, esterification, C–C coupling, rearrangements) shows how different modifications at the 5-, 7-, and other

positions can modulate activity, solubility, and metabolic stability [72]. For instance, a series of 23 derivatives made via alkylation and bromination showed much stronger α-glucosidase inhibitory activity than chrysin itself, with some compounds (e.g., 2f) having IC_{50} values as low as 0.08 µM [73]. Similarly, CPD 6 a novel chrysin derivative demonstrates potent anti-inflammatory effects in both acute and chronic skin inflammation models.

Safety and Toxicological Profile

General safety in animal studies.

Preclinical animal data indicate that chrysin has a relatively wide safety margin when administered orally at conventional experimental doses, and it often shows protective effects against drug- or toxin-induced organ damage in rodents; multiple *in vivo* studies report hepatoprotective, cardioprotective and neuroprotective actions at doses commonly used in pharmacology experiments (typically 1–100 mg/kg), with no adverse findings at these ranges in short-term studies. Comprehensive reviews of chrysin's pharmacology summarize abundant rodent studies where chrysin produced beneficial biochemical and histological outcomes and had no overt toxicity at study doses, supporting its candidacy as a safe bioactive flavonoid in preclinical models [74].

Acute and sub-chronic toxicity testing provides more quantitative limits: an OECD-style toxicological evaluation in rats determined an oral LD_{50} of roughly 4,350 mg/kg, and identified a NOAEL near 500 mg/kg with a LOAEL at 1,000 mg/kg, where renal and hepatic histopathological changes were observed at the highest tested doses indicating that toxicity mainly appears only at very high exposures. Separate recent multi-endpoint studies of chrysin formulations (including oil-in-water systems and engineered nano-systems) found oral LD_{50} values >2,000 mg/kg and generally no treatment-related gross abnormalities in acute settings, but the authors stress that sub-chronic and chronic studies are still limited and that formulation type can modify biodistribution and therefore the toxicological profile [75]. For humans, daily intake of 0.5–3.0 g of chrysin has been deemed safe based on *in vitro* and *in vivo* studies, highlighting a broad safety margin [65].

Hepatic & renal safety — comparison with allopurinol

As above, animal evidence generally shows no intrinsic hepatotoxicity or nephrotoxicity at pharmacologic doses of chrysin and, often reproducible organ-protective effects in chemically or surgically induced liver/kidney injury models (lower oxidative markers, preserved histology) [74]. Acute toxicology gives a large margin between effective doses and LD_{50}, and sub-chronic data show tolerability up to several hundred mg/kg [75].

Allopurinol is an established xanthine-oxidase inhibitor used clinically for gout; however, it carries known, sometimes serious hepatic and renal safety considerations. Hepatotoxicity is a recognized (albeit uncommon) adverse effect that can present as asymptomatic transaminase elevation or, rarely, as severe drug-induced liver injury often within a hypersensitivity syndrome [76]. Allopurinol can also cause allopurinol hypersensitivity syndrome (AHS/DRESS/SJS–TEN) in which hepatic dysfunction and acute kidney injury are cardinal and potentially fatal features [77]. Oxypurinol is the active metabolite of allopurinol is renally cleared, so accumulation in CKD increases risk and mandatory to dose adjustment. Overall, while generally safe when dosed appropriately, allopurinol carries a distinct and non-negligible risk profile for severe hepatic/renal adverse events in susceptible patients [78].

Long-term use considerations

The long-term safety profile of chrysin has primarily been studied in rodents. A 90-day oral toxicity study in Sprague–Dawley rats determined the LD_{50} value of chrysin to be 4350 mg/kg whereas NOAEL (No Observable Adverse Effect Level) and LOAEL of chrysin was found to be 500 and 1000 mg/kg, respectively at this dose, the animals started to show lower body weight, higher liver weight and changes in biochemical parameters like ALT, AST, bilirubin, creatinine, GGT. Also, there was a rise in oxido-nitrosative stress in the liver and kidney, along with histopathological lesions which indicated organ damage at high repeated doses. [75]Different studies using 25–150 mg/kg for weeks show hepato- and nephroprotection against poisonings like paracetamol, methotrexate, cisplatin, paclitaxel, pesticides, and acrylamide through various pathways like antioxidant and anti-inflammatory [79]. Reviews conclude that nutritional or therapeutic exposures are generally safe, while toxicity is mainly associated with supraphysiological doses capable of generating peroxidase-derived reactive metabolites. [79]High-concentration mechanistic concerns—including suppression of de novo DNA synthesis and antioxidant-to-pro-oxidant switching in peroxidase-rich environments [80]. Human dietary exposure is low, and short-term supplementation studies using 300–625 mg/day show no major safety concerns, though robust long-duration clinical data remain limited [65]. Practical long-term use should remain well below the rodent LOAEL and closer to the NOAEL-scaled human equivalent (a few hundred mg/day), with regular monitoring of hepatic enzymes, renal markers, oxidative stress biomarkers, haematology, and histopathology, particularly when using high doses or high-bioavailability systems.

Future Prospectives

Chrysin has demonstrated significant potential in gout management through its ability to inhibit xanthine oxidase, modulate urate transporter, and suppress inflammatory pathways like NLRP3 and NF-kB. Chrysin shows promising therapeutic effect in combination therapy with convectional urate lowering, anti-inflammatory agent and it also potentially improving efficacy while reducing side effect. Clinical translation of chrysin remain limited due to lack of well-designed human studies. Future research should focus on conducting trails to establish its efficacy, optimal dosage and long-term safety. Further studies on pharmacokinetics, toxicity, and herb-drug interaction of chrysin are essential. Overall, appropriate formulation strategies and clinical validation chrysin could emerges as a safe and effective alternative for gout management.

CONCLUSION

Chrysin shows as a promising natural flavonoid for gout management, having strong preclinical evidence demonstrating its efficacy in reducing serum uric acid through xanthine oxidase inhibition, and suppression of NLRP3 and block NF-κB inflammatory pathways often chrysin matching standards like allopurinol, febuxostat, and indomethacin in dual uricosuric, anti-inflammatory, and antioxidant actions that reduce oxidative stress during gout flares. Chrysin having critical limitations in human clinical data and poor oral bioavailability (<1%) due to low solubility and rapid phase I/II metabolism, so advanced nano-formulations such as nanoparticles, liposomes, and solid dispersions offer a viable path forward by enhancing bioavailability up to 41-fold, provide sustained and minimizing systemic risks. Chrysin having a favorable toxicology profile (NOAEL ~500 mg/kg in rats, LD50 >4,000 mg/kg). Overall, chrysin represents a potential safe and effective alternative for gout treatment, but further clinical studies are required to confirm its therapeutic efficacy.

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About the corresponding author

Pabitra Panigrahi is a scholar in the Department of Pharmaceuticals at Shree Dhanvantary Pharmacy College, Kim, Surat, Gujarat, India. His academic interests include pharmaceutical sciences, drug development, and healthcare research. He is dedicated to advancing knowledge through research, innovation, and contributing to scientific and academic excellence in the field.