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EVALUATION OF ANTI-GOUT ACTIVITY OF TANGERETIN, A POLYMETHOXYLATED FLAVONE IN HYPERURICAEMIA AND ACUTE GOUTY ARTHRITIS RAT MODELS

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Abstract
Background: Uric acid crystals that accumulate in the joints can develop gouty arthritis, a painful and crippling form of arthritis that results in both acute inflammation and long-term joint damage. The current therapies focus on symptom relief and uric acid level lowering. Novel therapeutic strategies, however, are required since they have fewer adverse effects and greater efficacy. The purpose of this abstract is to discuss the assessment of the therapeutic efficacy of Tangeretin in potassium oxonate-induced hyperuricemia model of Wister rats. Determination of the anti-gout activity of Tangeretin in monosodium urate (MSU)-induced gout model of Wister rats. *Methods:* Information on the anti-inflammatory and antioxidant capabilities of tangeretin and its influence on gout-related pathways was gathered by conducting a thorough search of the scholarly literature. *Results*: By blocking important inflammatory mediators and pathways such nuclear factor-kappa B (NF-B) and interleukin-1 (IL-1), tangeretin has shown anti-inflammatory effects. Additionally, its strong antioxidant qualities assist in reducing oxidative stress, a factor in the aetiology of gout. Furthermore, tangeretin has the ability to alter purine metabolism, which would lower uric acid synthesis and promote its elimination. Tangeretin is emerging as a promising therapy option for gouty arthritis because of its anti-inflammatory, antioxidant, and possible uric acid-regulating effects. To assess its security, effectiveness, and ideal dosage for gout patients, more study is required, including pre-clinical and clinical trials. Tangeretin could provide a fresh and supplementary strategy to the treatment of gout, enhancing the quality of life for those who experience this excruciating ailment, if it is found to be effective.
Keywords: Tangeretin, Gouty Arthritis, Uric Acid, potassium oxonate, mono sodium urate, NF-B.

Introduction

Gouty arthritis, also known as just "gout," is a painful and perhaps crippling form of arthritis brought on by the buildup of uric acid crystals in the joints. A rapid and intense episode of pain, redness, swelling, and warmth in one or more joints characterises this kind of inflammatory arthritis. The big toe is where these assaults usually happen, although they can also affect the ankles, knees, elbows, wrists, and fingers.

A more through explanation of gouty arthritis is provided below:

Uric Acid Accumulation: Hyperuricemia, or an excess of uric acid in the blood, is the main cause of gout. Purines, which are present in some foods and are also naturally created by the body, are broken down by the body to form uric acid, a waste product. Sharp, needle-like crystals might develop in the joints as a result of an excessive blood uric acid level.

Acute Gouts: Gout is characterised by abrupt, severe bouts of pain and inflammation, sometimes known as "gout flares" or "gout attacks." These attacks can happen suddenly, generally at night, and are accompanied by excruciating pain, edoema, and joint

discomfort. The pain, which is sometimes characterised as severe, can be brought on by things like poor dietary decisions, drinking alcohol, stress, illness, or injuries.

Chronic Gout: Gout can evolve into a chronic illness, characterised by recurring gout attacks and the growth of tophi, if it is not treated. Tophi are crystal-filled lumps of uric acid that can develop in the skin and around joints. Chronic gout can cause deformities and joint degeneration over time.

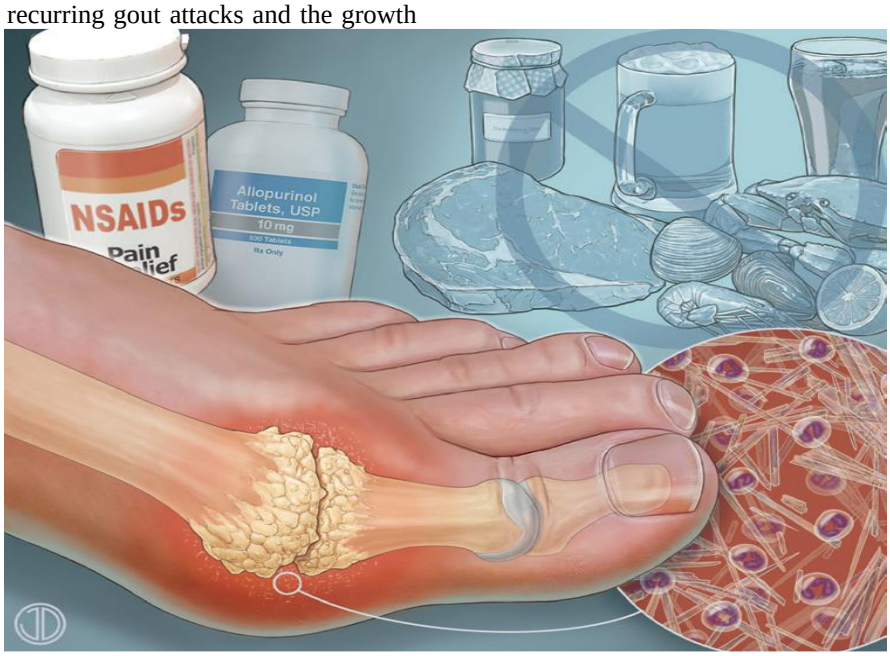


Fig.1: Showcasing gouty arthritis

Recurrent bouts of gouty arthritis can lead to the development of chronic gout and tophi, which are urate crystal deposits that cause nodules to form under the skin, in joints, and occasionally in other tissues. Joint damage and deformation may result from untreated chronic gout.

Gout risk factors: It includes genetics, age (it is more common in older people), gender (women are more susceptible after menopause), diet (high intake of purine-rich foods and alcohol), obesity, specific medical conditions (like high blood pressure and kidney disease), and certain medications.

Diagnosis: Gout is often diagnosed with a clinical evaluation, which includes a physical exam and a discussion of symptoms, in conjunction with laboratory investigations. A certain diagnostic indicator is the discovery of uric acid crystals in the joint fluid during joint aspiration. Serum uric acid levels can also be determined via blood testing.

Treatment: Gout management involves both immediate and long-term solutions. Nonsteroidal anti-inflammatory medications (NSAIDs), corticosteroids, or colchicine are frequently used to treat acute attacks in order to reduce pain and inflammation. To stop further episodes, long-term treatment seeks to reduce blood levels of uric acid. This can be accomplished by altering one's diet, adopting a healthier lifestyle (such as quitting smoking and drinking alcohol), and using drugs like allopurinol or febuxostat that assist lower uric acid production or increase its excretion [1].

Phytochemicals

The wellbeing of the world's population is greatly influenced by biodiversity, which makes a substantial contribution to human welfare and development. Around 80% of the world's population still relies on herbal remedies, and many modern medications have their roots in medicinal plants, according to reports from the WHO. Natural ingredients have long been used as the basis for medicinal medications. Some well-known examples include digitalis (derived from foxglove), ergotamine (from contaminated rye), quinine (from cinchona), and salicylates (from willow bark). Using a combination of molecular, botanical, phytochemical, and biological methods, drug discovery from natural sources requires a multidisciplinary approach. As a result, the development of drugs based on medicinal plants is still a crucial area that has not yet been fully investigated, where a thorough search might undoubtedly yield significant leads for a number of pharmacological targets. Ironically, unscientific

resource exploitation is a situation that is being seen all around the world as a result of the potential benefits of plant-based therapies [2]. For their possible effect on gout, the following class of phytochemicals has been studied:

Flavones

One of the crucial subgroups of flavonoids are flavones. As glucosides, flavones are abundantly distributed in leaves, flowers, and fruits. Major sources of flavones include celery, parsley, red peppers, chamomile, mint, and ginkgo biloba. This subclass of flavonoids includes the compounds luteolin, apigenin, and tangeritin. The polymethoxylated flavones tageretin, nobiletin, and sinensetin are abundant in citrus fruit peels.

They have a ketone in the fourth position of the C ring and a double bond between positions 2 and 3. While hydroxylation in other sites, primarily in position 7 of the A ring or 3′ and 4′ of the B ring, may occur, most flavones from vegetables and fruits have a hydroxyl group in position 5 of the A ring [3].

Tangeretin

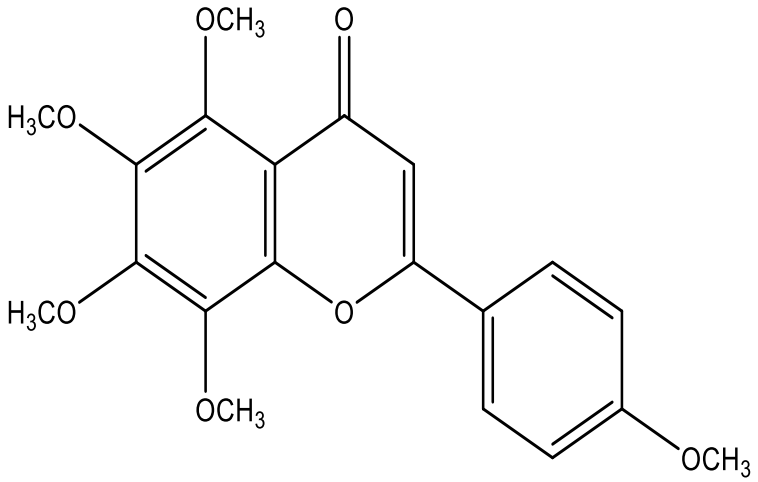


Fig. 2: Chemical structural of tangeretin (4',5,6,7,8-Pentamethoxyflavone)

Tangeretin is a polymethoxylated flavone (PMF), which is a naturally occurring substance. It is a member of the flavonoid family of substances, which is commonly present in a variety of fruits and vegetables. A yellowish, crystalline substance with a bitter flavour called tangeretin. Water barely dissolves it, but organic solvents like ethanol, methanol, and dimethyl sulfoxide (DMSO) make it soluble. Because it is not readily absorbed and used by the body when taken orally, tangeretin is renowned for its limited bioavailability. Its medicinal potential may be limited as a result; hence different methods are being considered to increase its bioavailability [4].

For instance, the PMF tangeretin is abundantly present in plants of the genus Citrus. Citrus reticulata and Citrus sinensis L. Osbeck are a couple of the tangeretin-rich plants. Tangeretin accumulates more in flavedos than in leaves among citrus varieties. Tangeretin is extracted from Citrus jambhirifruit extracts of crushed dry peel. Additionally, tangeretin was found in the peels of the citrus fruit bergamot. Citrus species such as Citrus unshiu, Citrus reticulata,Citrus tachibana, Citrus depressa, Citrus paradisi (grapefruit), and Citrus poonensis have also been found to contain tangeretin [5].

Fig. 3: Tangeretin powder

Scientific research has been sparked by a variety of biological behaviors that tangeretin displays. Its potential anti-inflammatory, anticancer, anti-antioxidant, and neuroprotective effects have all been researched. Tangerine has also demonstrated positive effects on lipid metabolism, lowering cholesterol levels, and preventing platelet aggregation.

Tangeretin's precise mechanisms of action are currently being uncovered. It is thought to work through a number of different biochemical routes, including the activation of antioxidant enzymes, control of gene expression, alteration of cell signalling pathways, and inhibition of enzymes associated in the development of cancer and inflammation. When ingested in moderate doses from dietary sources like citrus fruits, tangeretin is usually regarded as safe. As with any substance, harmful consequences could result from excessive consumption or supplementation. Because tangeretin supplements have a limited bioavailability, it is advised to speak with a healthcare provider before beginning any new supplementation regimen [6, 7]. Tangeretin demonstrates a few traits that could help with gout management.

Inflammation in the afflicted joints is a hallmark of gout. Anti-inflammatory activities of tangeretin have been demonstrated; as a result, reducing joint inflammation and gout symptoms may be made possible. Tangeretin has antioxidant properties that can help combat the negative free radicals created when gout flares up. Tanneretin may help lessen inflammation and perhaps even relieve gout symptoms by lowering oxidative stress. Xanthine oxidase is an enzyme that contributes to the formation of uric acid. The amount of uric acid in the body can be decreased by inhibiting this enzyme. According to certain research, tangeretin may have xanthine oxidase inhibitory activity, which could reduce uric acid synthesis and shield against gout attacks.

It's significant to note that there has only been a small amount of study on the function of tangeretin in gout, and the majority of these studies have used animal models or laboratory settings. To learn more about the efficiency and safety of tangeretin for treating gout in people, additional study, including clinical studies, is required [8].

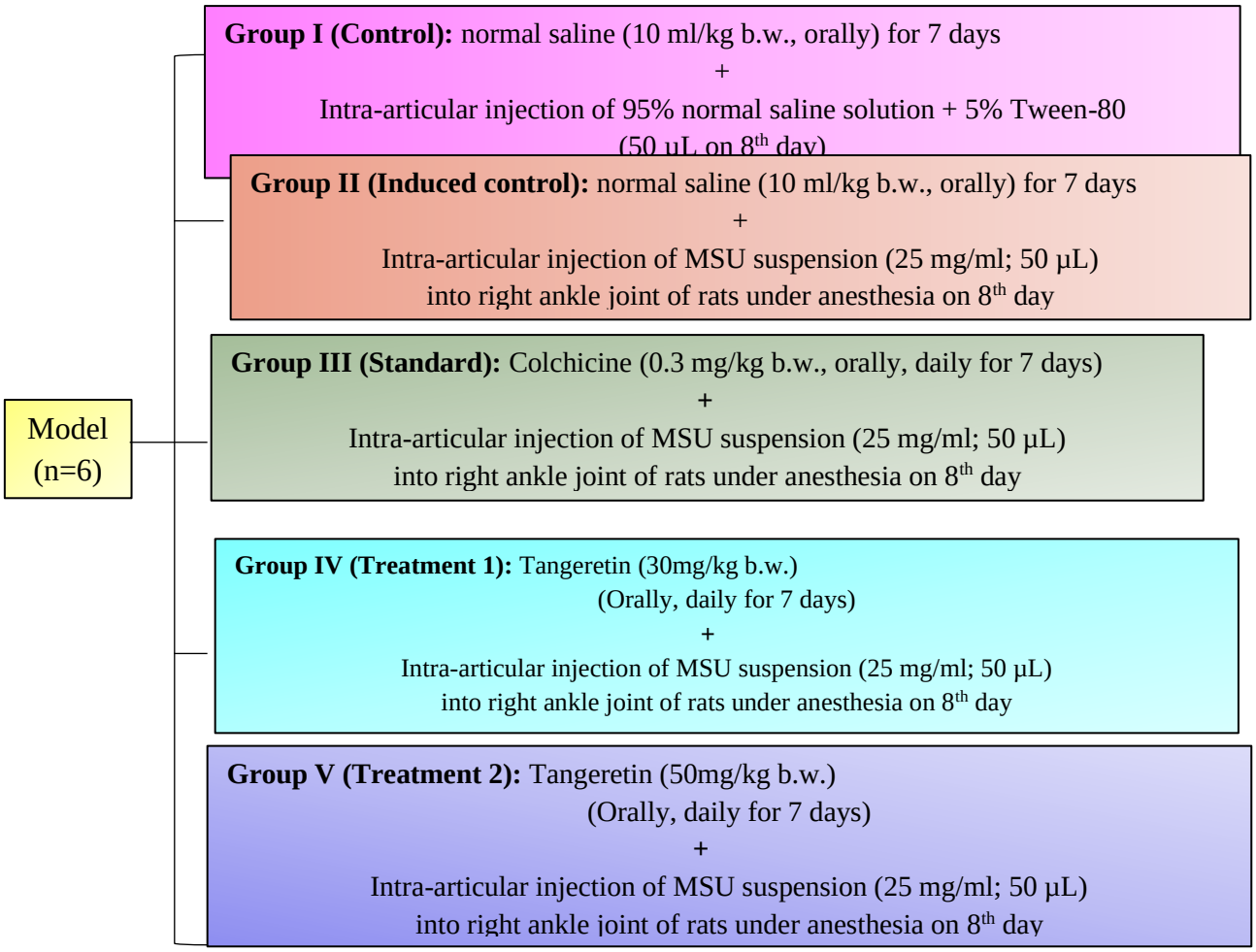
Material and Methods

Animals used

Male Wistar rats (8 weeks old, weighing around 180 to 220g) were obtained from the Institutional animal house facility. They were caged in standard laboratory conditions in an environment of regulated temperature (23 ± 1°C) and humidity (55%). They were subjected to an alternate 12 hours of light and dark cycle for the entire experimental period. All rats had access to a standard diet of pellets along with water ad libitum. All experiments were conducted with earlier consent from IAEC following CCSEA guideline.

Establishment of a Rat Acute Gouty Arthritis Model [9]

Group division



Establishment of the acute gouty arthritis model was roughly considered successful if there was observe swelling 2 h after MSU injection.

Swelling Degree Measurement

Paw oedema was marked using a pen after administration of MSU crystal and the enhanced thickness was measured at different time points at 0, 2, 6, 12, 24,36 and 48 h using vernier caliper. Oedema in right ankle joint was estimated as difference with the basal value and represented as Swelling degree (%) = [thickness test value (mm)- thickness basal value (mm)]/thickness basal value (mm) × 100% [9].

Collection of blood samples

On the 8th day, rats were sacrificed by cervical dislocation. Blood was collected by cardiac puncture, kept at 25°C or RT for half an hour and centrifuged (3000 RPM, 4°C, 10 min) to isolate the serum from it. Thereafter the serum collected was preserved in −80°C for biochemical estimation [9].

Collection of synovial fluid samples

To obtain synovial fluid, the hair present above the right ankle joint was cleansed and an incision was made in the joint capsule laterally using a scalpel. Then, the joint cavity was flushed multiple times with normal saline to acquire the synovial fluid samples. The samples were subjected to a 20 min centrifugation (1000×g, 4°C) and the supernatants collected were preserved at −80°C till further use [9].

Biochemical estimations

The amount of creatinine (Cr), uric acid (UA)and urea nitrogen (UN) present in serum and urine were estimated by the colorimetric method using different commercial assay kits obtained from Jiancheng Biotechnology Institute, Nanjing, China following manufacturer's instructions [9].

Estimation of creatinine (Cr)

Alkaline Picrate method was used to estimate the creatinine in serum and urine samples. Firstly, for sample preparation, urine or serum was diluted in distilled water in the ratio 1:50. Then, the sample was deproteinized by pipetting 0.2ml of sample and 2ml of Picric acid reagent in a clean and dry test tube. After that, it was mixed properly and centrifuged at 2500-3000 rpm for 10 mins to get a clear supernatant. Then, 3 clean and dry test tubes were taken and marked as Blank, Standard and Test respectively. To the test, 1.1ml of supernatant and 0.1ml of buffer reagent was poured. In standard, 1ml of picric acid reagent, 0.1ml of creatinine standard and 0.1ml of buffer reagent was added and in blank, 1ml of picric acid reagent, 0.1ml of distilled water and 0.1ml of buffer reagent was added. All the test tubes were mixed properly and left at room temperature for 20 minutes precisely. The absorbance of the standard and test samples was studied against blank and amount of creatinine was calculated [9].

Estimation of uric acid (UA)

Uricase/PAP method was used to estimate the uric acid in serum and urine samples. Initially, working reagent was prepared by mixing 0.8ml of Buffer reagent and 0.2ml of enzyme reagent. Then, 3 clean and dry test tubes were taken and marked as Blank, Standard and Test respectively. To the test, working reagent of 1ml and 0.02ml of sample was poured. To the standard, working reagent of 1ml and 0.02ml of uric acid standard was added. To the blank, working reagent of 1ml and 0.02ml of distilled water was added. All the test tubes were mixed properly and incubated at 37°C for 5 minutes. The absorbance of the standard and test samples were studied against blank in 30 minutes and amount of uric acid in serum was calculated [9].

Estimation of urea nitrogen

Urea can be hydrolyzed by urease to produce NH4+ and CO2. In alkaline medium, NH4+produces blue substance with phenolic chromogenic agent. The production of blue material is proportional to the urea content which is observed through a spectrophotometer at a wavelength of 640 nm. Mod. Berthelot method was used for it. Before performing the assay, urine or serum was diluted with distilled water. Then, 3 clean and dry test tubes were taken and marked as Blank, Standard and Test respectively. To the test, 1ml of buffer reagent, 0.1ml of enzyme reagent and 0.01ml of sample was poured. To the standard, 1ml of buffer reagent, 0.1ml of enzyme reagent and 0.01ml of urea standard was added. To the blank, 1ml of buffer reagent, 0.1ml of enzyme reagent and 0.01ml of distilled water was poured. All the test tubes were mixed properly and incubated at 37°C for 5 minutes. Then, 0.2ml of Chromogen reagent was added to all the 3 test tubes. They were mixed properly and incubated in a similar manner. The absorbance of the standard and test samples was studied against blank in 60 minutes and amount of urea present was calculated [9].

Estimation of inflammatory cytokines

The content of inflammatory cytokines such as ICAM-1, IL-1β and IL-6 in the serum was determined by employing commercial enzyme-linked immunosorbent assay kits (Enzyme-linked Biotechnology Co., Ltd., Shanghai, China) as per the manufacturer's instructions [9].

RESULTS & DISCUSSION

Effect of Tangeretin on the degree of joint swelling in MSU induced acute gouty arthritic rats

The data illustrated in Table 5.1 depicts that intra-articular injection of normal saline did not induce any joint swelling in animals belonging to control group. However, a single dose of intra-articular MSU injection produced a significant degree of swelling in the right ankle joint of animals after 2 hours of injection ($P<0.001$). The swelling in the ankle joint was observed to increase with time and found at its peak at 12 hours after which it showed a gradual decrease with time. However, it was significantly elevated with respect to control group ($P<0.001$) at various time points. Therefore, the results indicated successful establishment of MSU-induced gouty arthritis. 0.3mg/kg of Colchicine was taken as positive control and it was noted to interfere with joint swelling after 2 hours of its administration. Results showed that the degree of joint inflammation significantly reduced after treatment with Colchicine with respect to induced control group (Group II) ($P<0.001$). Upon treatment with varying doses of Tangeretin, i.e., 30 and 50mg/kg b.w. respectively, the degree of joint inflammation was observed to reduce significantly ($P<0.001$) as compared to Group II in a dose-dependent fashion.

The acute gouty arthritis animal model was established in mice and rats by stimulating the synovial membrane along with the surrounding tissues by injecting MSU suspension into ankle joint (intra-articular injection) of experimental animals. [10] The knee joint of the hind limb can also be used for the induction of acute gouty arthritis. [11] In the current study, MSU suspension was administered via intra-articular route of ankle joint cavity which was found to be an effective model in producing acute gouty arthritis that was analogous to human acute gouty arthritis. The accumulation of MSU in the synovial fluid causes infiltration of macrophages and neutrophils in the synovium upsurging an acute arthritic phase [12]. The acute inflammation subsides due to effect of drug administration and its transformation to chronic inflammation takes place with additional infiltration of lymphocytes, initiation of

hyperplasia and loss of synovial epithelium [13]. In the current study, the anti-inflammatory potential of Tangeretin was noted after administration of its varying doses (30 and 50mg/kg respectively) that reflected the acute changes in degree of inflammation of the ankle joints.

Table 7.1 The effects of Tangeretin on the degree of joint swelling in rats with MSU-induced acute gouty arthritis

Parameters	Group I	Group II	Group III	Group IV	Group V
2h	2.325 ± 0.184	9.617 ± 0.303 a***	5.913 ± 0.251 b***	6.553 ± 0.222 b***, c^{ns}	6.272 ± 0.299 b***, c^{ns}
6h	2.508 ± 0.213	17.380 ± 0.572 a***	8.313 ± 0.350 b***	10.458 ± 0.402 b***, c**	9.007 ± 0.321 b***, c^{ns}
12h	2.543 ± 0.216	22.155 ± 0.495 a***	9.882 ± 0.416 b***	12.003 ± 0.310 b***, c**	10.093 ± 0.372 b***, c^{ns}
24h	2.480 ± 0.194	17.618 ± 0.362 a***	7.302 ± 0.291 b***	9.185 ± 0.344 b***, c**	8.360 ± 0.279 b***, c^{ns}
36h	2.553 ± 0.295	15.513 ± 0.370 a***	5.452 ± 0.377 b***	8.487 ± 0.297 b***, c***	7.575 ± 0.229 b***, c***
48h	2.570 ± 0.232	10.357 ± 0.234 a***	2.750 ± 0.306 b***	4.847 ± 0.200 b***, c***	3.788 ± 0.386 b***, c^{ns}

Where (n=6) Group I: Control, Group II: Induced control [MSU suspension (25 mg/ml; 50 µL)], Group III: Standard[Colchicine (0.3 mg/kg b.w) + MSU suspension], Group IV: Treatment [Tangeretin (30mg/kg b.w) + MSU suspension] Group V: Treatment [Tangeretin (50mg/kg b.w)+ MSU suspension] Comparisons: a= Group II with group I; b = Group III, IV and V with group II and c = Group IV and V with Group III. Significant: $^{ns}P>0.05$; $*P<0.05$; $**P<0.01$; $***P<0.001$. [MSU: Monosodium urate].

Effect of Tangeretin on expression levels of chemokines and pro-inflammatory cytokines in serum and synovial fluid in MSU-induced gouty arthritic rats

Evaluation of three major cytokines (IL-1β, IL-6 and ICAM-1) was done to investigate the anti-inflammatory potential of Tangeretin on synovial fluid and serum obtained from MSU-induced acute gouty arthritic rats. The results conveyed a significant ($P<0.01$) elevation in the cytokine levels of gouty arthritis bearing animals as compared to normal animals. Post treatment with gradual dose of Tangeretin (30 and 50mg/kg b.w. respectively) revealed significant restoration ($P<0.01$) of levels of IL-1β, IL-6 and ICAM-1 in both synovial fluid and serum of gouty arthritis bearing experimental animals.

An elevation in blood uric acid level stimulates the deposition of monosodium urate crystals in joint cavities. This accumulation initiates the activation of inflammatory cytokines which further causes monocytes, neutrophils and macrophage accumulation [14, 15]. Such response stimulates the production of various pro-inflammatory cytokine during acute gouty arthritic attacks, i.e., interleukins (IL-6 and IL-1β) which causes inflammasome activation and membranolysis. Further, intracellular adhesion molecule-1 (ICAM-1) expression is elevated which has a pivotal role in leukocytic transportation across endothelial and epithelial barriers [16-17]. The results obtained from MSU-induced gouty arthritis model supported the anti-inflammatory and anti-gout potential of Tangeretin as it successfully relieved joint swelling by increasing production of IL-1β, IL-6 and ICAM-1 which are reported initiators and progressors of acute-gouty arthritis.

Table 7.2 The effects of Tangeretin on the expression levels of chemokines and pro-inflammatory cytokines in the serum and synovial fluid of MSU-induced acute gouty arthritis rats

Parameters	Group I	Group II	Group III	Group IV	Group V
Serum ICAM-1 (ng/mL)	3.841 ± 0.514	5.987 ± 0.172 a***	2.514 ± 0.148 b***	3.425 ± 0.170 b***, c^{ns}	4.184 ± 0.287 b**, c**
Serum IL-1β (pg/mL)	2.457 ± 0.325	5.541 ± 0.152 a***	2.925 ± 0.842 b**	3.291 ± 0.225 b**, c^{ns}	2.617 ± 0.114 b***, c^{ns}
Serum IL-6 (pg/mL)	12.541 ± 1.541	22.148 ± 0.954 a***	11.740 ± 0.842 b***	13.205 ± 0.921 b***, c^{ns}	12.054 ± 0.752 b***, c^{ns}
Synovial fluid ICAM-1 (ng/mL)	10.125 ± 0.171	11.941 ± 0.385 a*	9.428 ± 0.542 b***	10.254 ± 0.251 b*, c^{ns}	9.842 ± 0.417 b**, c^{ns}
Synovial fluid IL-1β (pg/mL)	7.241 ± 0.852	12.458 ± 0.732 a***	6.285 ± 0.447 b***	8.204 ± 0.517 b***, c^{ns}	7.958 ± 0.374 b***, c^{ns}
Synovial fluid IL-6 (pg/mL)	33.251 ± 0.841	39.845 ± 1.787 a*	32.147 ± 1.742 b**	34.149 ± 0.948 b*, c^{ns}	33.891 ± 0.804 b*, c^{ns}

Where (n=6) Group I: Control, Group II: Induced control [MSU suspension (25 mg/ml; 50 µL)], Group III: Standard[Colchicine (0.3 mg/kg b.w) + MSU suspension], Group IV: Treatment [Tangeretin (30mg/kg b.w) + MSU suspension] Group V: Treatment [Tangeretin (50mg/kg b.w)+ MSU suspension] Comparisons: a= Group II with group I; b = Group III, IV and V with group II and c = Group IV and V with Group III. Significant: nsP>0.05; *P<0.05; **P<0.01; ***P<0.001. [MSU: Monosodium urate, ICAM-1: Intercellular Adhesion Molecule 1, IL-1β: Interleukin-1β, IL-6: Interleukin-6].

Conclusion

The current study demonstrated that Tangeretin helped in the reduction of join swelling and restoration of elevated levels of pro-inflammatory cytokines and chemokines (IL-1β, IL-6 and ICAM-1) of MSU-induced acute gouty arthritis in Wistar rats.

Tangeretin also showed potent hyperuricemic effects by stabilization of abnormal kidney function parameters (uric acid, creatinine and urea nitrogen) and pro-inflammatory cytokines and chemokines (IL-1β, IL-6 and ICAM-1) of potassium oxonate-induced hyperuricemia in Wistar rats.

Tangeretin also possessed potent enzyme inhibition activity as it inhibited the major enzyme, xanthine oxidase (XOD) that is involved in uric acid production which is the major mechanism behind advancement of acute-gouty arthritis condition.

Overall, Tangeretin showed potent anti-hyperuricemic and anti-gouty arthritis action on in vivo study.

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