Research Article

# Clinical trial to assess the safety and efficacy of CV-HFG01 tablets in management of hyperuricemia and associated pain in gout

**Veena Deo[1], Bhushan Shrikhande[2], Gayatri Ganu[3], Ninad Naik[4]**

[1]Department of Clinical Research, Clinic Health Pvt. Ltd. Plot no 567 Great Nag Road, Baidyanath Square, Nagpur, Maharashtra, India, [2]Head of Research and Development, Clinic Health Pvt. Ltd. Plot no 567 Great Nag Road, Baidyanath Square, Nagpur, Nagpur, Maharashtra, India, [3]Managing Director - Clinical Research, Mprex Healthcare, 414, Nisarg Plaza, Bhumkar Nagar, Wakad, Pune, Maharashtra, India, [4]Consultant Physician, Atharva Ayurved Clinic, Krishna Chowk, New Sanghvi, Pune, Maharashtra, India

**Correspondence:**
Ms. Gayatri Ganu, Managing Director - Clinical Research, Mprex Healthcare, Bhumkar Nagar, Wakad, Pune - 411 057, Maharashtra, India. Phone: +91-8554912644.
E-mail: gayatri.mbgindia@gmail.com

**How to cite this article:**
Deo V, Shrikhande B, Ganu G, Naik N. Clinical trial to assess the safety and efficacy of CV-HFG01 tablets in management of hyperuricemia and associated pain in gout. Innov Pharm Pharmacother 2019;7(4):72-78.

**Source of Support:** Nil.
**Conflicts of Interest:** None declared.

## ABSTRACT

**Background:** Test product "CV-HFG01 tablet" was developed by Clinic Health Pvt. Ltd. for the management of hyperuricemia and associated pain in gout. **Aim:** The main objective of the study was to assess the safety and efficacy of "CV-HFG01 tablet" in patients with hyperuricemia and gout. **Materials and Methods:** It was an open label, single arm, prospective, and interventional clinical study conducted on 30 subjects which were advised to consume 1 tablet of CV-HFG01 twice daily orally with water for 3 months along with the ongoing treatment for gout apart from conventional drug for a hypouricemic agent. The assessment for mean decreases in serum uric acid levels from baseline; improvement of the clinical symptoms and improvement in SF-36 health survey score, patients global assessment, physicians global assessment, and performance of patient on pain visual analog scale were evaluated to determine the efficacy of the test product. **Results:** Treatment of CV-HFG01 demonstrated significant reduction in uric acid levels, pain, and stiffness in patients suffering from gout. There was a significant reduction in doses of conventional treatment by CV-HFG01 tablets. Of 30 subjects, 16 subjects were on conventional medicine for pain relief, alongside of CV-HFG01 tablets, of which 9 (56.25 %) showed reduction in doses at day 30 and 3 (18.75 %) at day 90. **Conclusion:** Thus, CV-HFG01 is safe and effective alternative in the management of gout.

**Keywords:** CV-HFG01, gout, hyperuricemia, SF-36 health survey, single arm

## Introduction

Gout is a chronic inflammatory disease that results from the deposition of monosodium urate crystals in tissues. The formation of uric acid crystals occurs with the elevation of serum uric acid (SUA) level.[1] The overall occurrence of gout in the general population is found to be 1–4% while in western countries, it is observed that 3–6% of men and 1–2% of women are suffering from gout. This occurrence increases in elders more than 80 years old up to 10% in men and 6% in women. The annual prevalence of gout is estimated to be 2.68/1000 people. The prevalence is 2–3 folds more in men than women; this variance may be due to the trait to increased renal excretion of urate by estrogen. Accordingly, despite the fact that older individuals are at an augmented risk of hyperuricemia in general, women are inexplicably affected by age due to dwindled estrogen succeeding menopause.[2,3] The prevalence of gout proliferates steadily due to deprived dietary habits such as fast foods, lack of exercise, increased frequency of obesity, and metabolic syndromes throughout the world. The risk of gout rises predominantly with augmented ingestion of purine-rich foods such as red meat and seafood which excessively increases the production of uric acid in the body. In addition, excess consumption

| Access this article online | |
|---|---|
| **Website:** www.innpharmacotherapy.com | **e-ISSN:** 2321-323X<br>**p-ISSN:** 2395-0781 |

of alcohol, sugar-sweetened foods, and beverages revealed to upsurge the uric acid levels in serum.[4,5]

The treatment for gout is commended particularly if,

- Gout assaults develop repeatedly or are very painful
- Joint impairment is evident in X-rays
- Tophi have already developed, or
- Augmented uric acid levels produced kidney stones.

The most widely commended and utilized drug for lowering uric acid is allopurinol. It limits the interruption of purines and thus diminishes uric acid levels. Another recommended drug after allopurinol is febuxostat, which is not the first-line treatment – since the clinical studies propose the upsurge risk of lethal cardiovascular diseases. Uricosuric drugs such as probenecid and benzbromarone may be used as alternative treatment preferences, which are likely to reduced uric acid level by increasing its expulsion by the kidneys. The other classes of agents used for management and treatment of gout are nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, indomethacin, naproxen, and anti-inflammatory agents such as colchicine and corticosteroids. Although these drugs have been widely used for gout treatment, they are associated with numerous side effects and adverse effects, as listed by the U.S. Food and Drug Administration in reports from research.[6,7]

Several agents acquired from herbal plants such as Triphala, giloy, neem, bitter gourd, turmeric, and ginger are known to have potentials for the management and treatment of gout. Literature reveals the *in vitro* studies conducted on flavonoids, alkaloids, essential oils, phenolic compounds, tannins, glucosides, and coumarins illustrates the prospective for anti-gout effects through xanthine oxidase inhibition. Furthermore, anti-inflammatory effects have been reported for constituents such as lignans, triterpenoids, and xanthophyll. The pre-clinical studies performed for essential oils, lignans, and tannins indicated twin effects comprising decreasing uric acid production and uricosuric action. Alkaloids, phenolic compounds, and flavonoids have been reported for its inhibition of uric acid generation and anti-inflammatory potentials.[8-10]

Numerous herbal constituents have been demonstrated to be effective in depressing uric acid levels either by targeting its generation or elimination from the body. In addition, these natural ingredients are profound to have no adverse effect unlike the synthetic agents used for the treatment of gout. Thus, presently, these natural agents must be taken into consideration for developing medications to treat gout. Hence, clinical studies for the therapeutic effectiveness of these natural agents and the fundamental mechanisms must be explored commendably.

Clinic Health Pvt. Ltd. has developed CV-HFG01 tablets for effective management of gout. It has ingredients with proven herbs with analgesic and anti-inflammatory potential and may reduce the elevated uric acid levels in gout.

**Table 1: Product description**

| S. No. | Common name | Botanical name |
|---|---|---|
| 1. | Shodhit guggul | *Commiphora mukul* |
| 2. | Harad | *Terminalia chebula* |
| 3. | Behada | *Terminalia bellirica* |
| 4. | Awala | *Emblica officinalis* |
| 5. | Guduchi | *Tinospora cordifolia* |
| 6. | Sounth | *Zingiber officinale* |
| 7. | Marich | *Piper nigrum* |
| 8. | Pippali | *Piper longum* |
| 9. | Nishoth | *Operculina turpethum* |
| 10. | Vayavidanga | *Embelia ribes* |
| 11. | Anantmool | *Hemidesmus indicus* |

## Materials and Methods

### Product description

The description of each film-coated tablet has been described in Table 1. The product was available in the pack size of 60 tablets per container with seal.

### Ethics

The study was initiated only after a written approval obtained from the Independent/Institutional Ethics Committee (IEC). The study was conducted as per approved protocol and as per Good Clinical Practice guidelines given by AYUSH in March 2013. After getting approval from the ethics committee, the study was registered on website of the Clinical Trial Registry of India (CTRI). The CTRI number of the study is CTRI/2019/04/018495, registered on 08/04/2019. Subjects were enrolled in the study only after registration of the study on the CTRI website.

### Study design

It was an open label, single arm, prospective, and interventional clinical study.

### Study objectives

The primary objective of the study was to evaluate mean percentage decrease in SUA levels. The secondary objectives of the study were to evaluate the improvement in SF-36 health survey score, patients global assessment, physicians global assessment, and performance of patient on pain visual analog scale (VAS) scale.

#### *Subject inclusion criteria*

Subjects of either sex with hyperuricemia, aged between 18 and 65 years (both inclusive) having SUA level >6.0 and <12.0 mg/dL and not taking any type of hypouricemic agents, were selected for the study. Also subjects with confirmed cases of Primary Gouty arthritis fulfilling the diagnostic criteria as recommended by the American College of Rheumatology (1977) meeting the presence of any six of the following twelve criteria: More than one attack of acute arthritis; maximal inflammation developing within 1 day of onset; monoarthritis attack; redness over effected joint; unilateral attack on the first Metatarsophalangeal (Big Toe) joint; unilateral attack involving Tarsal joint; first Metatarsophalangeal (Big Toe) joint, painful or swollen; suspected Tophi; hyperuricemia (more than 6.0 mg/dl); asymmetrical swelling within joint (X-ray); subcortical cysts without erosions (X-ray); negative culture from joint fluid during attack were included in the study. Subjects willing and able to participate in the study were included.

### *Subject exclusion criteria*

Subjects with history of any trauma or fractured joint or surgical or diagnostic intervention with reference to the affected joint (s); gout flare during screening or baseline visit, patients currently using aspirin or other NSAIDs, diuretics, other medications with known urate-lowering effects; having comorbidities such as rheumatoid arthritis and psoriatic arthritis were not included in the study. Subjects having poorly controlled hypertension (>160/100 mm of Hg); evidence of malignancy; unstable cardiovascular disease; known cases of hypothyroidism or hyperthyroidism; and history of hypersensitivity to any of the trial drugs or their ingredients and any other condition which the investigator thinks may risk the study were excluded from the study. Subjects who were pregnant or lactating woman were also not included in the study.

## Dosage and treatment duration

One tablet of CV-HFG01 twice daily orally before meal with water for 3 months along with the ongoing treatment for gout apart from conventional drug for hypouricemic agent was given to subjects. Furthermore, subjects were advised to lifestyle modifications (nutritious diet, exercise, etc.). They were called for follow-up at day 30, day 60, and day 90 after consumption of medication.

## Study assessments

### *Assessment of efficacy*

The primary efficacy was evaluated by mean percentage decrease in SUA levels from the baseline to the end of the study period, i.e., 90 days from baseline. While the secondary efficacy was evaluated by the changes in symptoms associated with gout such as pain in joint(s) (Sandhi Shula), piercing pain (Toda), tenderness, swelling (Sandhi Shotha), burning sensation (Daha), redness/erythema, warmth, and local color changes in skin (Twak Vaivarnya). The other secondary efficacy parameters were assessed by evaluating tolerability and safety of CV-HFGT01 tablets in patients with gout; quality of life on SF-36 health survey score; global evaluation for overall improvement by physician and subject; adverse events (AEs); and vitals during period of the study.

## Assessment of physician's and subject's clinical global evaluation for overall efficacy

Investigator and subject provided ratings for efficacy, whether or not it was entirely due to product treatment compared to subject's condition at admission to the study and how much had he/she changed on completion of the study.

| | |
|---|---|
| 0=Not assessed | 4=No change |
| 1=Very much improved | 5=Minimally worse |
| 2=Much improved | 6=Much worse |
| 3=Minimally improved | 7=Very much worse |

## Study procedures

Written informed consent was obtained from the interested subjects before screening for possible inclusion in the study. During the informed consent process, they were given enough time to read informed consent document which was printed in the languages best understood by them. Subjects were given freedom to ask the questions and all questions were answered by the investigator or by other study staffs. If he/she agreed to participate in the study, written informed consent for the same was obtained from him/her.

On screening visits (up to day – 5), written informed consent was obtained from subject for his/her participation in the study. Subject underwent physical and systemic examinations. Subject's medical and surgical history was taken. If any medication which the patient was currently taking, was noted, and the patient was called next day morning on empty stomach for laboratory investigations.

Subject's investigations of renal function tests were done. Subject's data regarding conventional treatment were recorded. Furthermore, subjects were advised to refrain from any Nutraceutical, Ayurvedic, Homeopathic, Siddha, Unani, etc., treatment for gout. A screening window of up to 5 days was kept, in case if there was delay in availability of test reports or in case a few tests needed to be repeated. Subjects were called on the baseline visit (day 0).

On baseline visit (day 0), subjects were recruited if he/she met all the inclusion criteria. Subjects underwent general and systemic examinations and symptom gradation. Subjects were instructed to consume CV-HFG01 tablets. Subjects were advised to follow visit schedule, i.e., day 30, 60, and 90, respectively, after consumption of CV-HGT01 tablets. Subjects were given medication packed in a single high-density polyethylene container, each containing 60 tabs. Subjects were allowed to come for follow-up either five prior or after the scheduled follow-up visit and provided subject consumed the given treatment. Subjects were called on day 30 for the first follow-up visit.

At follow-up visits (day 30 and 60), all the subjects were closely monitored for any AEs. If the subject had AE/serious AE (SAE), the details of the incidents were documented in the source document and case report form (CRF). SAE, if any, was reported to the IEC in a SAE reporting form. Rescue medication used, if any, was recorded in the CRF. Subjects were advised not to consume alcohol, caffeine, and nicotine during the study period. Subjects underwent general and systemic examinations and clinical symptom gradation. On every follow-up visit, renal function tests and symptom gradation with quality of life assessment were evaluated by collecting fasting blood samples of the subjects.

The container provided to the subject on the previous visit was collected and remaining drug was counted to check missed dosage. Subjects who missed dosing partially or completely were treated as dropouts.

At the final visit (day 90), all the subjects were closely monitored for any AEs. If subject had AE/SAE, the details of the incidents were documented in the source document and CRF. SAE, if any, was reported to the IEC in a SAE reporting form. Rescue medication used, if any, was recorded in the CRF. On day 90 visit, blood sample was collected and assessed for renal function tests and symptom gradation

with quality of life assessment. On day 90, subject's global evaluation for overall improvement and investigator's global evaluation for overall improvement were done. Subject's tolerability toward CV-HFG01 tablets was assessed. Subjects were advised not to consume alcohol, caffeine, and nicotine during the study period.

## Statistics

The primary endpoints taken under consideration were levels of uric acid. Data were analyzed by one way ANOVA followed by selective multiple comparison test. The secondary efficacy parameters, percentage change in subjective clinical signs and symptoms from baseline to each visit and end of therapy was analyzed and tested by Chi-square test. In this study, all *P* values were reported based on two-sided tests and these statistical tests were interpreted at 5% level of significance.

# Results

In the present study, 33 subjects were screened. Of 33 subjects, three did not meet inclusion and exclusion criteria as found to be deranged with liver function test, hence, were not recruited in the study. Thirty subjects were considered evaluable cases at the end of the study. There were no dropouts in the study.

## Demographic data

The mean age of the subjects of 30 completers 13 (43.33%) was females and 17 (56.66%) male subjects. Of 13 female completed subjects, the mean age of subjects was 45.30 ± 10.15 years. The age range for subjects was 34–56 years. Of 17 male completed subjects, the mean age of subjects was 48.50 ± 12.05 years. The age range for subjects was 36–60 years. The details were presented in the following Table 2.

## Efficacy assessments

### *SUA*

At baseline visit, the mean SUA level was 9.49 ± 1.01, 8.13 ± 1.19, 6.69 ± 0.59, and 4.06 ± 0.66 mg/dl at baseline, day 30, 60, and 90, respectively. Mean SUA levels were significantly reduced at day 30, 60, and 90 when compared to baseline value ($P < 0.0001$). The details were presented in Table 3.

**Table 2: Demographic details**

| Parameters | Female | Male |
|---|---|---|
| No. of cases | 13 | 17 |
| Mean | 45.30 | 48.50 |
| Standard deviation | 10.15 | 12.05 |
| Range | 34–56 years | 36–60 years |

**Table 3: Mean TSH**

| Duration | Mean serum uric acid (mg/dl) |
|---|---|
| Baseline | 9.49±1.01 |
| Day 30 | 8.13±1.19$^{<0.0001}$ |
| Day 60 | 6.69±0.59$^{<0.0001}$ |
| Day 90 | 4.06±0.66$^{<0.0001}$ |

One way ANOVA followed by selective multiple comparisons test. (It is also known as Dunnett test) <0.0001=99.9% significance. TSH: Thyroid-stimulating hormone

### *Assessment of global evaluation for overall improvement by physician*

As per global evaluation of overall improvement assessed by physician, very much improvement was observed in 27 (90%) subjects and much improvement was observed in 3 (10%) subjects at the end of the study. The details were presented in Table 4.

### *Assessment of global evaluation for overall improvement by subjects*

As per global evaluation of overall improvement assessed by subjects, very much improvement was observed in 23 (76.66%) subjects and much improvement was observed in 7 (23.33%) subjects at the end of the study. The details were presented in Table 5.

### *Tolerability of study drug by physician and subjects*

As per physician and subjects, all the subjects (100%) reported excellent tolerability to given medication. The details were presented in Table 6.

### *Profile of AEs*

The analysis reveals that 30.00% (10 subjects) of the study cases had AEs such as headache, minor cut, menstrual pain, vomiting, nausea, hyperacidity, and body ache with 15 AEs of 10 patients. These AEs were mild to moderate in nature. These AEs were resolved completely

**Table 4: Assessment of global evaluation for overall improvement by physician**

| Parameters | No. of subjects |
|---|---|
| Not assessed | 0 |
| Very much improved | 27 |
| Much improved | 3 |
| Minimally improved | 0 |
| No change | 0 |
| Minimally worse | 0 |
| Much worse | 0 |
| Very much worse | 0 |

**Table 5: Assessment of global evaluation for overall improvement by subject**

| Parameters | No. of subjects |
|---|---|
| Not assessed | 0 |
| Very much improved | 23 |
| Much improved | 7 |
| Minimally improved | 0 |
| No change | 0 |
| Minimally worse | 0 |
| Much worse | 0 |
| Very much worse | 0 |

after rescue medication was given. All the AEs were not related to medication. The results were presented in Table 7.

### *Improvement in clinical symptoms*

With the treatment of CV-HFG01 tablets, there was a significant improvement in the clinical symptoms of the subjects. The results were depicted in Tables 8-12.

Of 30 subjects, 63.33% were experiencing moderate pain in joints and 36.66% with severe pain in joints. After 30 days of treatment with test drug, there were 60% subjects reported moderate pain and 40% with mild pain in joints. Until end of the study period 30% subjects completely recovered from pain in joints and 70% still experienced with mild pain in joints. Results are demonstrated in Table 8. Value represents the number of subjects representing the assessment score. Chi-square test was used to assess the values between baseline, day 30, 60, and end of the study $P < 0.0001$ significant. Treatment with CV-HFG01 tablets reduced moderate to severe pain joints in mild to no pain in joints.

Of 30 subjects, 66.66% were experiencing moderate piercing pain in joints and 30% with severe piercing pain in joints. After 30 days of treatment with test drug, there were 63.33% subjects reported moderate piercing pain and 36.66% with mild piercing pain in joints. Until end of the study period 46.66% subjects completely recovered from piercing pain in joints and 53.33% still experienced with mild piercing pain in joints. Results are demonstrated in Table 9. Value represents the number of subjects representing the assessment score. Chi-square test was used to assess the values between baseline, day 30, 60, and end of the study $P < 0.0001$ significant. Treatment with CV-HFG01 tablets reduced moderate to severe piercing pain of joints in mild to no piercing in joints.

Of 30 subjects, 73.33% were experiencing moderate tenderness in joints and 6.66% with severe piercing tenderness in joints. After 30 days of treatment with test drug, there were 26.66% subjects reported moderate tenderness and 70% with mild tenderness in joints. Until end of the study period 46.66% subjects completely recovered from tenderness in joints and 53.33% still experienced with mild tenderness in joints. Value represents the number of subjects representing the assessment score. Chi-square test was used to assess the values between baseline, day 30, 60, and end of the study $P < 0.0001$ significant. Treatment with CV-HFG01 tablets reduced moderate to severe tenderness of joints in mild to no tenderness in joints. Treatment with CV-HFG01 tablets reduced moderate to severe pain in mild pain on VAS. Treatment with CV-HFG01 tablets significantly increased quality of life of subjects with gout.

**Table 6: Tolerability of study drugs assessed by physician and subjects**

| Assessment | No. of subjects ($n$=30) | |
|---|---|---|
| | *n* | % |
| Excellent | 25 | 83.33 |
| Good | 3 | 10 |
| Fair | 2 | 6.66 |
| Poor | - | - |

**Table 7: Profile of adverse events**

| Events | Particulars in subjects (101001030) | |
|---|---|---|
| | *n* | % |
| Headache | 3 | 10 |
| Vomiting and nausea | 2 | 6.66 |
| Menstrual pain | 4 | 13.33 |
| Hyperacidity | 3 | 10 |
| Body ache | 2 | 6.66 |
| Minor cut | 1 | 3.33 |
| No of patients | 10 | 30.00 |
| No of events | 15 | |

**Table 8: Assessment of symptoms: Pain in joints**

| Score | Baseline (%) | Day 30 (%) | Day 60 (%) | Day 90 (%) |
|---|---|---|---|---|
| 0 | 0 | 0 | 1 (3.33 | 9 (30) |
| 1 | 0 | 12 (40) | 26 (86.66) | 21 (70) |
| 2 | 19 (63.33) | 18 (60) | 3 (10) | 0 |
| 3 | 11 (36.66) | 0 | 0 | 0 |

Assessment of symptoms (*Grades-0=None, 1=Mild, 2=Moderate, and 3=Severe)

## Discussion

Purines are crucial for a range of normal physiologic functions. In humans, uric acid is the end product of purine degradation. It exists as the urate ion at physiologic pH and has a very narrow window of solubility. The enzyme xanthine oxidase is required for the conversion of xanthine to urate. Humans lack the enzyme urate oxidase (uricase), which converts urate in other species to the highly soluble compound allantoin. This may have conferred a survival advantage due to the function of uric acid as an antioxidant. Approximately 95% of urate is filtered by the glomerulus and subsequently undergoes bidirectional proximal convoluted tubule (PCT) movement with presecretory reabsorption (99%), secretion (50%), and post-secretory reabsorption (40%–50%). The movement of urate is accomplished

**Table 9: Assessment of symptoms: Piercing pain in joints**

| Score | Baseline (%) | Day 30 (%) | Day 60 (%) | Day 90 (%) |
|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 14 (46.66) |
| 1 | 1 (3.33) | 11 (36.66) | 26 (86.66) | 16 (53.33) |
| 2 | 20 (66.66) | 19 (63.33) | 4 (13.33) | 0 |
| 3 | 9 (30) | 0 | 0 | 0 |

Assessment of symptoms (*Grades-0=None, 1=Mild, 2=Moderate, and 3=Severe)

**Table 10: Assessment of symptoms: Tenderness in joints**

| Score | Baseline (%) | Day 30 (%) | Day 60 (%) | Day 90 (%) |
|---|---|---|---|---|
| 0 | 0 | 1 (3.33) | 3 (10) | 14 (46.66) |
| 1 | 6 (20) | 21 (70) | 23 (76.66) | 16 (53.33) |
| 2 | 22 (73.33) | 8 (26.66) | 4 (13.33) | 0 |
| 3 | 2 (6.66) | 0 | 0 | 0 |

**Table 11: Assessment of symptoms: VAS score**

| Baseline | | Day 30 | | Day 60 | | Day 90 | |
|---|---|---|---|---|---|---|---|
| Score | No. of subjects | Score | No. of subjects | Score | No. of subjects | Score | No. of subjects |
| 7 | 4 | 5 | 3 | 3 | 3 | 1 | 1 |
| 8 | 15 | 6 | 22 | 4 | 21 | 2 | 26 |
| 9 | 11 | 7 | 5 | 5 | 4 | 3 | 3 |

Assessment of symptoms associated with pain (*Grades-0=None, 1–5=Mild, 6–8=Moderate, and 9–10=Severe). VAS: Visual analog scale

**Table 12: Assessment of quality of life SF-36 score**

| Duration | Mean SF-36 score |
|---|---|
| Baseline | 52 |
| Day 30 | 62.93 |
| Day 60 | 72.53 |
| Day 90 | 81.76 |

SF: Short form

through several recently described anion transmembrane channels. The balance between the PCT's secretory and reabsorptive activities exerts a major influence on renal excretion of uric acid. Although the secretory capacity of the kidneys can increase with hyperuricemia, the compensation is often not enough. Therefore, in the majority (90%) of patients with primary gout, hyperuricemia results from relative renal under excretion, whereas in 10% of patients there is overproduction of endogenous uric acid. Although it is clear that hyperuricemia is the harbinger of gout, both genetic and environmental factors are recognized contributors to the development of hyperuricemia. Hypertension, the use of thiazide or loop diuretics, obesity, a high alcohol intake, and certain dietary factors all contribute in an additive manner to the risk of developing hyperuricemia and gout. These are modifiable risk factors, and targeting lifestyle and health behaviors are important not only for secondary prevention and treatment of gout but also for the overall health of the patient. Consumption of high purine meats and shellfish has been associated with an increased risk of gout, but consumption of purine-rich vegetables, such as spinach, has not. Dietary intervention has received recent attention, however, due to the association of hyperuricemia with insulin resistance. In a pilot study of men with gout, serum levels of urate and the rate of acute gouty attack significantly decreased by 17.5% and 71%, respectively, with a diet moderately restricted in calories and carbohydrates and increased proportional intake of protein and unsaturated fats. Alcohol consumption is also closely associated with gout and it is estimated that more than one-half of gout sufferers drink excessively.

Colchicine is derived from the autumn crocus and has been in widespread use since the early 1800s, first as a plant extract and later in pill form. The mechanism of action is due to the interference of tubulin dimers and subsequent leukocyte functions, including diapedesis, lysosomal degranulation, and chemotaxis. Corticosteroids can be used for patients with a suboptimal response or contraindications to either colchicine or NSAIDs and can be administered orally, intravenously, intramuscularly, or indirectly through corticotropin adrenocorticotropic hormone (ACTH). The exact mechanism of action for its efficacy in gout is unknown but may be due to the release of anti-inflammatory hormones or leukocyte modulation through ACTH receptors. The most commonly used class of urate-lowering drug is the uricostatic agents, which inhibits xanthine oxidase and leads to decreased production of uric acid. Allopurinol and its active metabolite oxypurinol reduce serum and urine uric acid levels. Side effects include rash, pruritus, cytopenias, diarrhea, and fever. A second class of urate-lowering drugs is the uricosuric agents, probenecid, and sulfinpyrazone, which acts on the renal uric acid anion transport pathway to increase uric acid excretion in urine. Uricosuric agents should be avoided in patients with a history of nephrolithiasis and are ineffective when given to patients with renal insufficiency. The major side effects include rash, gastrointestinal intolerance, and uric acid stone formation. At the present, allopurinol (a purine analog) and febuxostat (not a purine analog), which cause inhibition on xanthine oxidoreductase, are the preferred drugs with clinical application to lower uric acid production. Due to some serious side effects of allopurinol and some concern of skin and cardiovascular events for febuxostat, many attempts are made to find safer alternatives, particularly from natural sources. Natural products with medicinal value are gradually gaining importance in clinical research due to their well-known property of low incidence of adverse reactions.[11-13]

*Tinospora cordifolia* present in CV-HFG01 tablets commonly named "Guduchi" is known for its application in the treatment of various diseases the traditional medicine. Different Ayurvedic formulations containing Guduchi have been found to be active in immunomodulation and anti-inflammatory activities. Furthermore, aqueous extract of *T. cordifolia* stem parts could directly act on peritoneal macrophages to boost the nonspecific host defenses of the immune system, which could ameliorate the intoxicated effect of carbon tetrachloride on the bacterial killing capacity of peritoneal macrophages of mice. The mechanism of uric acid lowering effects could be principally contributing to xanthine oxidase system modulation.

*Operculina turpethum* present in CV-HFG01 tablets is proven anti-inflammatory and used in the formulation for various arthritis conditions including gout.

Drugs like Triphala (Amla, Behada, and Hirda) present in CV-HFG01 tablets are having a wide spectrum of pharmacological and medicinal activities such as anti-inflammatory, antiarthritic, antioxidant and free-radical scavenging, hepatoprotective, gastrointestinal motility improving and antiulcerogenic, antispasmodic, and immunomodulatory actions.

Anantmool in CV-HFG01 tablets is having anti-inflammatory and diuretic action. Vidanga with its antioxidant property brings

out the regenerative changes in the deformed joints due to hyperuricemia induced gout. Triphala works as a xanthine oxidase inhibitor like allopurinol which suppresses the production of uric acid. Anantamool has nephroprotective function which retards the urolithiasis and dissolves already formed stones in kidney while amalaki has anti-inflammatory, analgesic, antipyretic, gastroprotective, hepatoprotective, immunomodulatory, and antioxidant properties which helps reducing the local and systemic inflammatory effects of gout.

Guggulu in CV-HFG01 tablets is an oleo-gum-resin which exudes out as a result of injury from the bark of *Commiphora mukul* (Hook. ex Stocks) Engl. and *Balsamodendron mukul* (Hook. Ex Stocks); family, Burseraceae. It is a mixture of phytoconstituents such as volatile oil which contains terpenoidal constituents such as monoterpenoids, sesquiterpenoids, diterpenoids, and triterpenoids; steroids; flavonoids; guggultetrols; lignans; sugars; and amino acids. It has been used in *Ayurveda* since time immemorial for the treatment of a variety of disorders such as inflammation, gout, rheumatism, obesity, and disorders of lipids metabolism.

## Conclusion

In the present study, it was observed that CV-HFG01 significantly decreased elevated levels of uric acid in gouty patients. There was significant reduction in doses of conventional analgesics by CV-HFG01 tablets. Thus, the product CV-HFG01 holds promising potential in joint disorders and was safe and effective alternative in the management of gout. The future scope of the study will be to evaluate long-term study as a therapeutic intervention in chronic gout.

## References


1. Pisaniello HL, Lester S, Gonzalez-Chica D, Stocks N, Longo M, Sharplin GR, *et al*. Gout prevalence and predictors of urate-lowering therapy use: Results from a population-based study. Arthritis Res Ther 2018;20:143.
2. Ragab G, Elshahaly M, Bardin T. Gout: An old disease in new perspective-a review. J Aav Res 2017;8:495-511.
3. Thompson MD. Insights in public health: Hyperuricemia and gout in Hawai'i. Hawaii J Med Public Health 2018;77:121.
4. Punzi L, Scanu A, Spinella P, Galozzi P, Oliviero F. One year in review 2018: Gout. Clin Exp Rheumatol 2019;37:1-11.
5. Kuo CF, Grainge MJ, Zhang W, Doherty M. Global epidemiology of gout: Prevalence, incidence and risk factors. Nat Rev Rheumatol 2015;11:649.
6. Shekelle PG, Newberry SJ, FitzGerald JD, Motala A, O'Hanlon CE, Tariq A, *et al*. Management of gout: A systematic review in support of an American college of physicians clinical practice guideline. Ann Intern Med 2017;166:37-51.
7. Managing Gout: A Review of the Research for Adults. AHRQ; 2017. p. EHC017. Available from: http://www.ahrq.gov. [Last accessed on 2019 Feb 05].
8. Ling X, Bochu W. A review of phytotherapy of gout: Perspective of new pharmacological treatments. Pharmazie 2014;69:243-56.
9. Hao S, Zhang C, Song H. Natural products improving hyperuricemia with hepatorenal dual effects. Evid Based Complement Alternat Med 2016;1:1-5.
10. Sabina EP, Rasool M. An *in vivo* and *in vitro* potential of Indian ayurvedic herbal formulation triphala on experimental gouty arthritis in mice. Vascul Pharmacol 2008;48:14-20.
11. Poór G, Mituszova M. History, classification and epidemiology of crystal-related arthropathies. In: Rheumatology. Vol. 2. Edinburgh: Mosby; 2003. p. 1893-902.
12. Terkeltaub RA. Gout and mechanisms of crystal induced inflammation. Curr Opin Rheumatol 1993;5:510-6.
13. McLean L. The pathogenesis of gout. In: Rheumatology. Vol. 2. New York: Mosby; 2003. p. 1903-18.