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# A PILOT STUDY TO CLINICALLY EVALUATE THE EFFICACY AND SAFETY OF A HERBOMINERAL PREPARATION 'VATNIVRITI' IN PATIENTS WITH PRIMARY ASYMPTOMATIC HYPERURICEMIA

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## ABSTRACT
In lieu of the fact that Ayurveda is an effective and safe option in many diseases, its role in primary asymptomatic hyperuricemia has also been illustrated in Indian literature. Aims and objectives: The present study is planned to investigate the clinical efficacy and safety of a herbomineral medicine 'Vatnivriti' in treating primary asymptomatic hyperuricemia. Methods: An open label prospective study was conducted at Shri Ashutosh Maharaj (SAM) ayurvedic treatment centre, Nurmahal, Punjab. 60 patients in the age group 24–65 years having primary hyperuricemia and generalized body pains with serum uric acid levels more than 7mg/dl without any co-morbid illness but with a strong family history of gout were enrolled, out of which 56 patients completed the study. Patients were treated with Capsule Vatnivriti 500 mg twice a day with milk. Results: Primary efficacy end point (serum uric acid level less than 6mg /dl) was achieved in 53.57% patients at week 6 and 82.10% of patients at week 12. Percentage change in mean uric acid levels was 23.68 ±13.10 at week 6 and 32.34±13.82 at week 12 with a statistically significant difference from baseline value($P<0.0001$). At week 12, percentage decrease in mean uric acid levels was significantly higher by 10.868±13.485 from week 6 ($p<0.0001$). Complete relief of pain was observed in 48 patients while 8 patients showed reduction in pain severity as determined by Numeric Rating Scale. Only 2 patients complained of nausea. Conclusion: Vatnivriti offers an efficacious and safe combination of natural products for the treatment of hyperuricemia.

**KEYWORDS:** Hyperuricemia, Gout, Uric acid, Vatnivriti.

## INTRODUCTION
Hyperuricemia is an elevated uric acid level in the blood. Serum uric acid concentrations greater than 6 mg/dl for females, 7 mg/dl for men, and 5.5 mg/dl for youth (under 18 years old) are defined as hyperuricemia.[1] Almost 10% of adults experience hyperuricemia once in life time.[2] The results of nationally representative samples of United States' adults suggest that the prevalence of hyperuricemia has increased substantially over the past 2 decades.[3] High prevalence of hyperuricemia is also evident in Asian countries with Approximately 25.8% prevalence in India.[4] Symptomatic Hyperuricemia often presents as gout and nephrolithiasis due to precipitation of uric acid crystals in joints and tissues. More than two thirds of hyperuricemic individuals are reported to have asymptomatic hyperuricemia without any signs or symptoms of crystal deposition.[5]

Asymptomatic hyperuricemia is a common biochemical abnormality characterized by serum uric acid concentration above the saturation limit without any clinical manifestations of urate deposition.[6-8]

Under excretion (90%) and over production of uric acid (10%) are the causes for raised levels of uric acid in plasma.[2] Under excretors of uric acid either have primary idiopathic hyperuricemia or secondary hyperuricemia resulting from identified contributing factors, such as a comorbid diseases or drugs. Overproduction occurs primarily as a result of increase in the amount of dietary purine intake available for conversion to urate which leads to hyperuricemia.[9]

Experts recommend lifestyle changes, dietary modifications, and weight loss as primary management strategies for asymptomatic hyperuricemia.[10] It is not

recommended to treat every patient of asymptomatic hyperuricemia pharmacologically unless serum uric acid is more than 12 gm/dl or hyperuricemia is associated with risk factors like strong family history of gout, nephrolithiasis and acute uric acid nephropathy.[2,8] In such high risk patients, hyperuricemia if not controlled, can lead to crystallization of monosodium urate deposits in joints and renal system resulting in gout, nephrolithiasis and acute uric acid nephropathy. ntreated hyperuricemia in such patients can also lead to multiple comorbidities including lipid abnormalities, hypertension, chronic kidney disease, coronary artery disease, diabetes stroke, parkinsonism and preeclampsia which necessitates the treatment with drugs lowering uric acid levels to reduce future risk.[12-17]

Conventional management of hyperuricemia includes either the use of xanthine oxidase inhibitors like allopurinol and febuxostat or uricosuric drugs like probenecid, benzbromarone or sulfinpyrazone. Limited number of allopathic antihyperuricemic drugs possess lack of complete effectiveness, adverse effects, drug interactions and precautionary use in renal failure patients.[3,18-21]

Ayurvedic medicines offer an advantage of being not only highly efficacious but also safe to use. Indian medicine system is highly accepted and practiced not only in India but internationally too. In Ayurveda, hyperuricemia which is also known as Vaat-rakta is disease of functionally impaired vaat (vitiated) which invades blood and joints.[22-24] Indian literature has already illustrated the antihyperuricemic effects of many herbal preparations but the data on their efficacy and safety is limited because of limited number of systematic and planned clinical studies done so far. Vatnivriti capsule is a remedy which has been formulated taking into consideration the drawbacks of conventional treatment regimens and found to be an efficacious and safe treatment option for decreasing uric acid levels in hyperuricemia. Hence our study is a pilot project to generate valid clinical data to provide evidence for efficacy as well as safety of herbal drug Vatnivriti in patients with serum uric acid levels >7mg/dl with positive family history of gout.

## MATERIALS AND METHODS

It was a prospective, open label, interventional pilot study done over a period of 12 weeks. Approval was taken by the ethics committee before starting the study. Informed consent was taken from each patient for voluntary participation in the study. Serum uric acid of patients who visited the outpatient department with nonspecific pain in body [without any clinical presentation of gout] but with strong family history of gout were analyzed. 60 eligible patients who were having serum uric acid ≥ 7mg /dl were prescribed Capsule Vatnivriti 500 mg twice a day with milk. Patients were included irrespective of their age, sex, occupation, social status, and ethnicity.

Serum uric acid measurement was done by automated analyzer in the laboratory of the study centre. Exclusion criteria were pregnant and lactating females, significant hepatic or renal dysfunction, hypersensitivity, urolithiasis or any other co morbid condition. All the patients were motivated for dietary modifications like decreased intake of alcohol, foods rich in purine [organ meats, asparagus, cauliflower, dried peas and beans, mushrooms, oatmeal, spinach and wheat bran] and drinking plenty of water. Clinical and biochemical assessment was done at 0 week, 6 weeks and 12 weeks during follow up visits. Follow up visits were done for assessment of efficacy end points and adverse effects if any.

Primary efficacy end point was percentage of subjects achieving serum uric acid less than 6 mg/dl at 6 weeks and 12 weeks. Drug efficacy was also assessed by measuring percentage change in uric acid from day 0 to week 6 and week 12. Intensity of generalized body pains was assessed by using Numeric Rating Scale (NRS) as mild, moderate and severe as per the numerical value marked from 0-10 on NRS by each participant at 6 weeks and at 12 weeks respectively.[25] Adverse effects were also monitored on follow up visits both clinically or by laboratory parameters. Patients were followed up every month for next 6 months for monitoring the sustainability and safety of the study drug. Results were statistically analyzed at the end of the study by descriptive analysis, paired student t test and chi square tests.

### Drug, dosing and administration

Vatnivriti capsule is a herbomineral preparation which is prepared by SAM ayurvedic treatment centre's own Sanjeevika pharmacy by standardized manner after mixing the appropriate amount of each component as given below.

Each 500 mg capsule contains
Yogaraj guggulu (250mg)
Arogyavardhini vati (60mg)
Kaishore guggulu (60mg)
Chandraprabha vati (60mg)
Shudh kuchla (50mg)
Moti pishti (20mg)

## RESULTS AND DISCUSSION

60 patients of primary hyperuricemia with uric acid≥7 mg/dl and nonspecific body aches along with positive family history for gout and without any co morbid illness were selected to be followed up after giving the study drug. Out of total 60 such patients, 4 patients were excluded due to lack of follow up. Hence data from 56 patients was analyzed statistically to demonstrate efficacy and safety of study drug.

Subjects (f: m=14:42) enrolled were in the age group 24-65 years with mean age of 40.14±12.47 years. 4 (16.66%) patients were non vegetarians. Mean Body mass index (BMI) of the patients as calculated by their height and weight measurements was 26.50±4.62 kg/$m^2$.

Mean baseline serum uric acid was 7.921±1.022 mg/dl ranging from 7 to 11 mg/dl.

After administration of study drug, primary efficacy end point (serum uric acid level less than 6mg /dl) was achieved in 53.57% of patients at week 6 and 82.10% of patients at week 12, demonstrating substantial and duration dependent uric acid lowering effect of Vatnivriti. [Figure 1] Mean Serum uric acid at 0 week, 6 weeks and 12 weeks was 7.921± 1.022, 5.971± 0.846 and 5.260± 0.812 mg/dl respectively [Table 1]

A statistically significant decrement in uric acid levels was observed at week 6 and week 12 as compared to baseline values [Figure 2]. Percentage change in mean serum uric acid levels was recorded as 23.68 ±13.10 at week 6 and 32.34±13.82 at week 12 as compared to baseline uric acid (P<0.0001). Uric acid lowering effect was significantly more at week 12 as compared to week 6 with percentage change in mean uric acid levels to 10.86±13.48 (p<0.0001). [Table2]

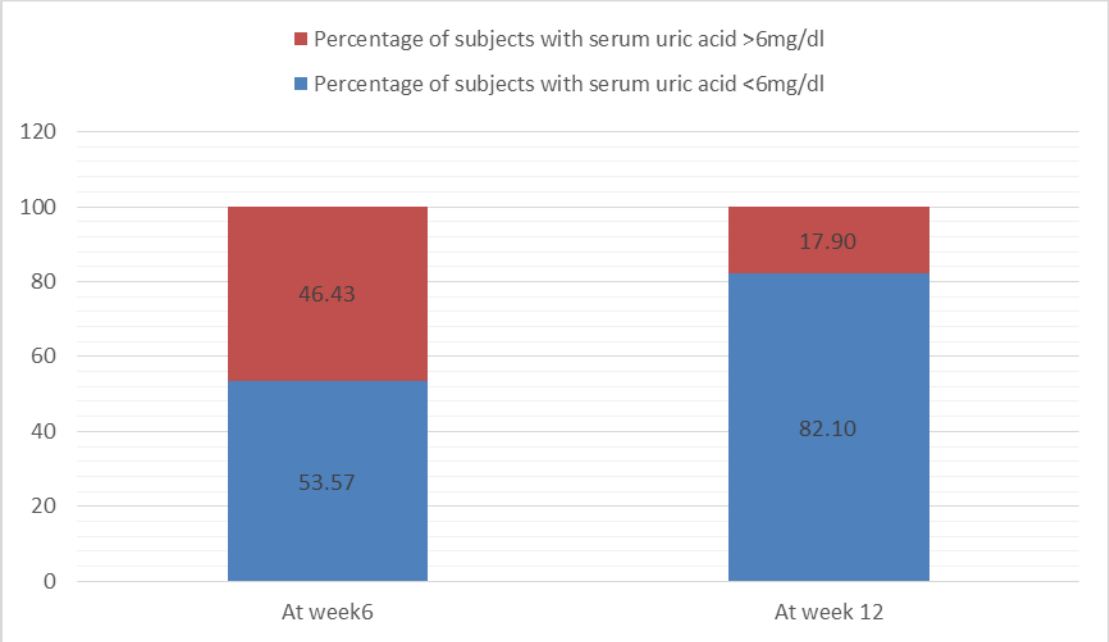


**Figure 1: Primary efficacy parameter at week 6 and week 12.**

**Table 1: Serum uric acid values at follow up visits.**

| | Mean serum uric acid(mg/dl) (mean ±S.D) | Minimum value(mg/dl) | Maximum value(mg/dl) |
|---|---|---|---|
| Week 0 | 7.921±1.022 | 7 | 11 |
| Week 6 | 5.971±0.846 | 4.2 | 7.2 |
| Week 12 | 5.260±0.812 | 3 | 7 |

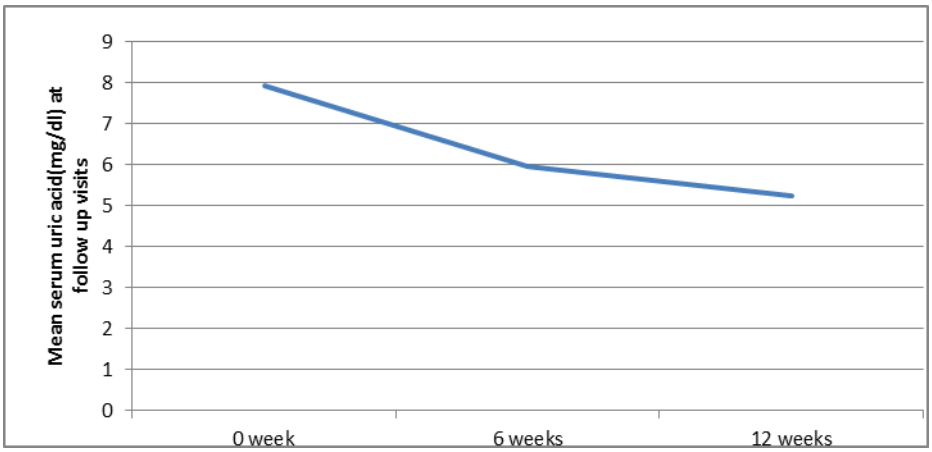


**Figure 2: Decreasing trend of mean serum uric acid at follow up visits.**

**Table 2: Percentage change in mean serum uric acid levels at each visit.**

| Time intervals | Percentage change in mean serum uric acid (Mean± S.D) | P Value |
|---|---|---|
| 0-6 weeks | 23.68±13.10 | <0.0001 |
| 0-12 weeks | 32.34±13.82 | <0.0001 |
| 6-12 weeks | 10.86±13.48 | <0.0001 |

Complete relief of pain was observed in 36 patients [64.3%] while 20 patients [35.7%] showed reduction in pain severity at week 6 whereas 48 patients [85.7%] had complete pain relief and 8 patients [14.3%] showed reduction in pain severity at week 12. Nausea was the only demonstrable adverse effect in 2 patients.

Clinical studies on efficacy of herbal drugs in hyperuricemia are lacking so ours is one such study which has demonstrated considerable therapeutic efficacy and safety of herbomineral preparation 'Vatnivriti capsule' in hyperuricemia. Different components of this herbal preparation possess characteristic properties which are beneficial in treating a patient with vitiated Vata and hence effective in decreasing higher uric acid levels.

Yogaraj guggulu and Kaishore guggulu are the commonly used ayurvedic formulations of guggulu (Commiphora mukul) which have been found to be beneficial in bones, joints and connective tissue disorders because of anti-inflammatory and analgesic action.[26-28] Yograja guggulu is a classical polyherbal preparation including 31 herbal and mineral ingredients with proven anti-inflammatory and analgesic action. Chandraprabha vati is another classical polyherbal preparation including 37 herbal and mineral ingredients effective in treatment of pain and inflammation.[29] Arogyavardhini vati, a widely used health promoting ayurvedic preparation has been added to the preparation as it improves overall health by balancing all the three doshas.[30] Moti pishti which is a herbomineral preparation has been added in the preparation because of its usefulness in various diseases due to vitiated Vata and its cooling properties.[31,32] Kuchla shudh [Nux vomica] is known for its analgesic and anti-inflammatory activity due to its major alkaloids (brucin and brucin N-oxide) and this is attributed to the inhibition of inflammatory mediators like prostaglandin E2 (PGE2) and increased content of 5-hydroxytryindole-3-acetic acid (5-HIAA).[33,34]

Results of our study demonstrated lowering of uric acid to < 6 mg/dl in 53.57% patients at week 6 and 82.10% patients in week 12 whereas 'Zafar et al' demonstrated uric acid <6mg/dl in 46.4% patients in allopurinol group and 14.2% patients taking combination of allopurinol and fenofibrate at day 90.[35] Another randomized trail demonstrated subjects attaining <6 mg/dl were 48%, 65%, 69% and 22% with 80 mg, 120 mg, 240 mg febuxostat and allopurinol respectively at 3 monthly intervals.[9] 'Becker et al' demonstrated 53% subjects attaining <6 mg/dl with febuxostat 80 mg, 62% with 120 mg febuxostat and 21% with allopurinol at 3 monthly interval.[36] In our study, percentage change in mean serum uric acid levels was recorded as 23.68 ±13.107 at week 6 and 32.34±13.821 at week 12 as compared to baseline uric acid (P<0.0001) whereas percentage change in serum uric acid has been observed as 32.2% after allopurinol use and 20.2% with combination of allopurinol and fenofibrate at day 90 in another similar study.[35] Hence our study drug has been found to be non-inferior in attaining primary efficacy end point than the conventional drugs.

In present study, improvement in nonspecific body aches over 12 weeks was also seen using the study drug with only nausea as the demonstrable adverse effect in 2 patients. Other studies demonstrate headache, diarrhea, upper respiratory tract infections, arthralgia, altered liver function tests, connective tissue signs and symptoms and cardiovascular adverse effects with conventional antihyperuricemic agents like allopurinol and febuxostat.[9,35-38]

Limitations of our study are small sample size, lack of controls and non-inclusion of gout patients to actually evaluate the efficacy of Vatnivriti in gout. Reason for these shortcomings is the preliminary nature of this study. Present study has been done as a pilot project by the SAM Ayurvedic Treatment centre so as to generate data to further evaluate efficacy and safety of Vatnivriti capsule through exploratory trials. In future, randomized controlled studies are planned with large number of patient population with clinical presentation of gout so as to mark this drug better as compared to existing drugs in hyperuricemia and gout.

## CONCLUSION

Vatnivriti capsule is highly efficacious natural antihyperuricemic agent causing substantial and sustained lowering of serum uric acid levels with minimal adverse effects. Hence it can prove to be a better alternative to conventional remedies in future.

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