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Original Article

Anti-arthritic Property of Sahacharadi Kashayam Against Freund's Complete Adjuvant Induced Arthritis in Wistar Rats

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ABSTRACT

Introduction: The available modern molecular drugs for the therapy of Rheumatoid arthritis are beset with several side effects and alternative drugs are urgently needed. The present investigation was performed to evaluate the anti-arthritic activity of Sahacharadi Kashayam (SK), an Ayurvedic formulation, against Freund's complete adjuvant (CFA) - induced arthritis in rats. **Methods:** In this experimental trial, SK was administered at doses of 0.5, 1.0 and 1.5 ml/kg body weight orally to adjuvant (CFA) induced arthritic rats. The anti-arthritic activity was evaluated by using paw volume, haematological parameters and arthritic biomarkers. The efficacy of the Kashayam was compared with the standard Leflunomide (10 mg/kg) drug. **Results:** Significant reduction in paw volume and thickness by SK (0.5 ml dose) has been found and there was considerably improvement in haematological parameters and arthritic markers in CFA rats till 14 days. After 14th day SK treatment with doses (1.0 and 1.5ml), however, reoccurrence of inflammation and pathological changes were observed in rats. **Conclusion:** The study clearly indicated the anti-arthritic role of SK. Future studies, however, are warranted to provide a new approach in relation to the therapeutic dose and treatment period of SK which may eventually lead to the development of a new category of the anti-arthritic agent.

Key Words: Anti-arthritic activity, Arthritis; biomarkers, Sahacharadi Kashayam.

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INTRODUCTION

Rheumatoid Factor (RF) which is an anti-IgG factor is found in the serum of about 80% of patients with Rheumatoid Arthritis and is present in high titre frequently in patients with relatively severe disease. However, patients with other chronic inflammatory diseases may also have RF in the serum. Rheumatoid arthritis usually causes inflammation at symmetrical joints.[1] In majority of cases the proximal inter-phalangeal joints, meta-carpo-phalangeal joints of the hands and the wrists are commonly involved. Other major contenders likely to induce arthritis are, infecting agents such as herpes virus, rubella virus, Epstein-Barr virus and mycoplasma.[2]

Rheumatoid factors can form immune complexes which are taken up by the PMNs and are also thought to activate complements, both mechanisms generating inflammation. Rheumatoid arthritis is a disease with augmented mortality and significant morbidity for which effective therapeutic interventions are clearly needed. The most vital drugs currently used by Rheumatologist are anti-inflammatory, NSAID and corticosteroids. The above drugs cooperate with -ferryl haemoglobin, formed by the reaction of H_2O_2 with haemoglobin, to produce drug-derived radicals instigating oxidative damage in these systems. Today in many countries phytochemicals have replaced synthetic pharmaceuticals and it is important to emphasize that almost 30% of modern pharmaceutical preparations are obtained directly or indirectly from plants.[3]

Sahacharadi Kashayam (SK) addresses vata disorders like joint pain, osteoarthritis, rheumatoid arthritis etc. Anti-inflammatory and anti-arthritic action of this medicine helps to alleviate the various symptoms including improving the blood circulation in the affected areas, body pain and debility. This Kashayam is taken at a dose of 5 – 15 ml diluted with 15-45 ml of water twice daily before food or as directed by physician. There are no reports of any side effects of this medicine. This medicine gets its reference in Ayurvedic standard treatise Sahasrayogam. This medicine is manufactured by Arya Vaidya Sala, Kottakkal, and Sitaram Ayurveda Pharmacy etc.

The constituent plants used for preparation of Sahacharadi Kashayam are *Barleria strigose*, *Sida cordifolia*, *Tinospora cordifolia*, *Cedrus deodora* and *Zingiber officinale*. This formulation is effective in the management of vata rogas like rheumatic arthritis, numbness, back ache etc. Various properties of these medicinal plants in the formulations defined in texts of Ayurveda, like Sangrahi, Rasayana, Arshnashaka, etc., are gaining scientific validity via modern research adopting "reverse pharmacological" approach.[4] To our knowledge this is the first report on the experimental verification of the role of this Kashayam for its anti-arthritic activity against Freund's adjuvant induced arthritis.

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METHODOLOGY

Animals

Female Wistar rats of 6-8 weeks old weighed 160-180 g body were obtained from KMCH College of pharmacy, Coimbatore. All rats were kept at room temperature and allowed to accommodate in standard conditions at 12-hr light and 12-hr dark cycle in the animal house. Animals were given commercial pellet diet and water *ad libitum* freely all through the study. The experimental procedure was approved by IAEC (Institution of Animal Ethical Committee) of KMCH governed by CPCSEA, Government of India, (Proposal number: 685/po/02/a/ CPCSEA/ DATED 2015/2016).

Drug

Leflunomide was used as standard drug. The drug dissolved in 1% w/v CMC and administered orally using a gavage needle at 10 mg/kg dosage daily for 42 days.

Sahacharadi kashayam

The Kashayam is prepared out of 6.173g of *Barleria strigosa*, 6.173g of *Sida cordifolia*, 3.089g of *Tinospora cordifolia*, 1.543 g of *Cedrus deodora* and 1.543g *Zingiber officinale*. The Kashayam was obtained from Kottakal Ayurveda Sala, Chennai, India.

Induction of arthritis

Arthritis was brought about by a single intradermal injection (0.1 ml) of Freund's Complete Adjuvant (FCA) containing 1.0 mg dry heat-killed *Mycobacterium tuberculosis* per millilitre sterile paraffin oil into a pad of the left hind paw of female rats. A 26G needle was used for injection. The swelling paw were periodically examined (up to 42 days) in each paw from the ankle using Digital Vanier Callipers.[5]

Experimental design

Rats were divided into 6 groups of six animals in each group. A group receiving only vehicle, was taken as the normal control group. Arthritis was induced for another 5 sets of rats by Freund's Complete Adjuvant on the left hind paw. One set of arthritic rats were served as positive control group and treated with Leflunomide (10 mg/kg orally) from day 1 to day 42. Another three sets of arthritic rats were treated with Kashayam (0.5, 1.0 and 1.5ml/day) orally as a single dose from day 1 to day 42.

Evaluation of arthritis

Paw thickness was studied by compressing the joint by revolving the screw of micrometer screw gauge till the pain elicited as shown by leg withdrawal or squeaking. The distance covered by the screw gauge was recorded.[6] Rats were examined every three days for signs of arthritis between day 1 and 21 post CFA using scoring system. Paws were examined for severity of and loci of erythema, swelling and indurations using a 5-point scale.[7] After the treatment duration, the animals were anaesthetized by diethyl ether (inhalation) and the blood was taken from retro orbital sinus by using capillary into a centrifuge tube which contains EDTA for haematological parameters and without EDTA for serum biochemical parameters and kept in room temperature for 30 min and then centrifuged for 10min for 10,000 rpm. The following biochemical parameters were assayed.

The quantitative examination of CRP in serum was measured by latex principle enhanced immune turbidimetric assay (ITA). The concentration of CRP is determined from a calibration curve established from CRP standards of identified concentration.[8] Turbidimetric immunoassay is used for the quantitative analysis of rheumatoid factor (RF) of IgM class. The rise in turbidity parallels to the concentration of RF in test specimen.[9] Haematological parameters such as erythrocytes (RBC), haemoglobin (Hb), and leukocytes (WBC) counts were determined in blood with anticoagulant by the usual standardized laboratory method.[10]

Statistical analysis

The results were analysed using SPSS, version 22.0 (SPSS Inc., Chicago, USA). One-way ANOVA was employed for comparison among groups. The inter comparisons between the groups were made by Dunnett's multiple range tests and $p < 0.05$ was observed as statistically significant.

RESULTS

Effect of SK on paw volume

Paw oedema was determined by taking paw volume at each time interval from the 0th day onwards. Paw thickness had increased significantly ($p < 0.05$) in CFA rats after 14 days and elevation pattern ($p < 0.001$) significantly monitored till the end of the experiment (42nd day) as compared to normal (Figure 1, Table 1, Figure 2). The rats in the CFA group had significantly elevated arthritis index (on day 21, 35, 42) than the control rats.

Upon Kashayam (0.5 ml) administration from the first day for a treatment period of 42 days; rats showed significant decrease in the paw volume till the 14th day when compared with CFA rats. After 14th day of treatment, the drug treated groups showed a rise in paw volume and inflammation. Similarly, 1.0 and 1.5 ml SK treated group indicated that there is a significant increase in the paw volume after the 14th day of treatment.

When 1.5ml SK dosage group is concerned, there is a slight augmentation in the paw volume till 7th day. And a significant reduction can be found till the 14th day when compared with CFA rats. Then,

Table 1. Effect of Sahacharadi Kashayam on paw volume.

Group	Control	Only CFA	CFA + Standard	CFA + Low Dose 0.5ML	CFA + Middle Dose 1ML	CFA + High Dose 1.5ML
0th day	4.11667 ± 0.242785	3.86667 ± 0.168655	4 ± 0.293258	3.8 ± 0.157056	3.71667 ± 0.101379	3.8 ± 0.157056
7th day	4.11667 ± 0.242785	8.86833 ± 0.303704***	8.81667 ± 0.215432***	8.325 ± 0.297957***	8.19833 ± 0.299092***	8.34833 ± 0.246041***
14th day	4.11667 ± 0.242785	7.12833 ± 0.152565***	5.41 ± 0.338103^{ns}	4.77833 ± 0.966914^{ns}	5.79167 ± 0.103454^{ns}	5.55667 ± 0.174158^{ns}
21st day	4.11667 ± 0.242785	8.16667 ± 0.244495***	6.88333 ± 0.340995***	7.33333 ± 0.308401***	7.13333 ± 0.285968***	7.25 ± 0.384491***
28th day	4.11667 ± 0.242785	10.0433 ± 0.326901***	8.62 ± 0.258147**	7.84667 ± 0.427665***	8.22833 ± 0.279075*	9.23667 ± 0.540923***
35th day	4.11667 ± 0.242785	8.68667 ± 0.217603***	7.41333 ± 0.197293***	7.28667 ± 0.341083**	7.44667 ± 0.201902***	7.21667 ± 0.255365**
42nd day	4.46667 ± 0.138243	7.76667 ± 0.33632**	7.75 ± 0.319113***	7.68333 ± 0.307047***	8.11667 ± 0.193936***	8.05 ± 0.202896***

Values area expressed as mean ± SEM Statistical Significance (p) calculated by one way ANOVA. Values are expressed as mean ± SEM (n=6). [a]*p<0.05*, [b]*p<0.01*, [c]*p<0.001*, statistically significant in comparison with CFA induced rats; [#]*p<0.001* statistically significant in comparison with control group. Freund's complete adjuvant (CFA), Sahacharadi Kashayam (SK), Leflunomide (LEF).

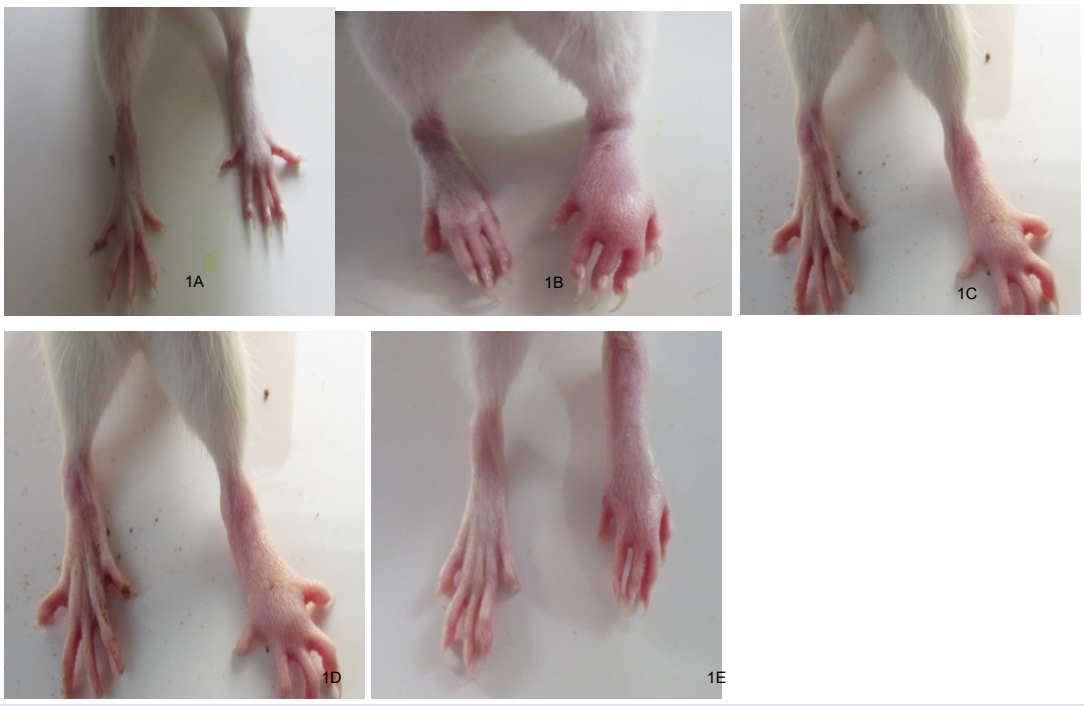

Figure 1: Paw volume changes in control and drugs treated rats in CFA model. 1A- Normal control rat. 1B – CFA induced rat; 1C – CFA +LEF; 1D – CFA + SK (0.5ml); 1E – CFA + SK (1.0ml); 1E – CFA + SK (1.5ml).

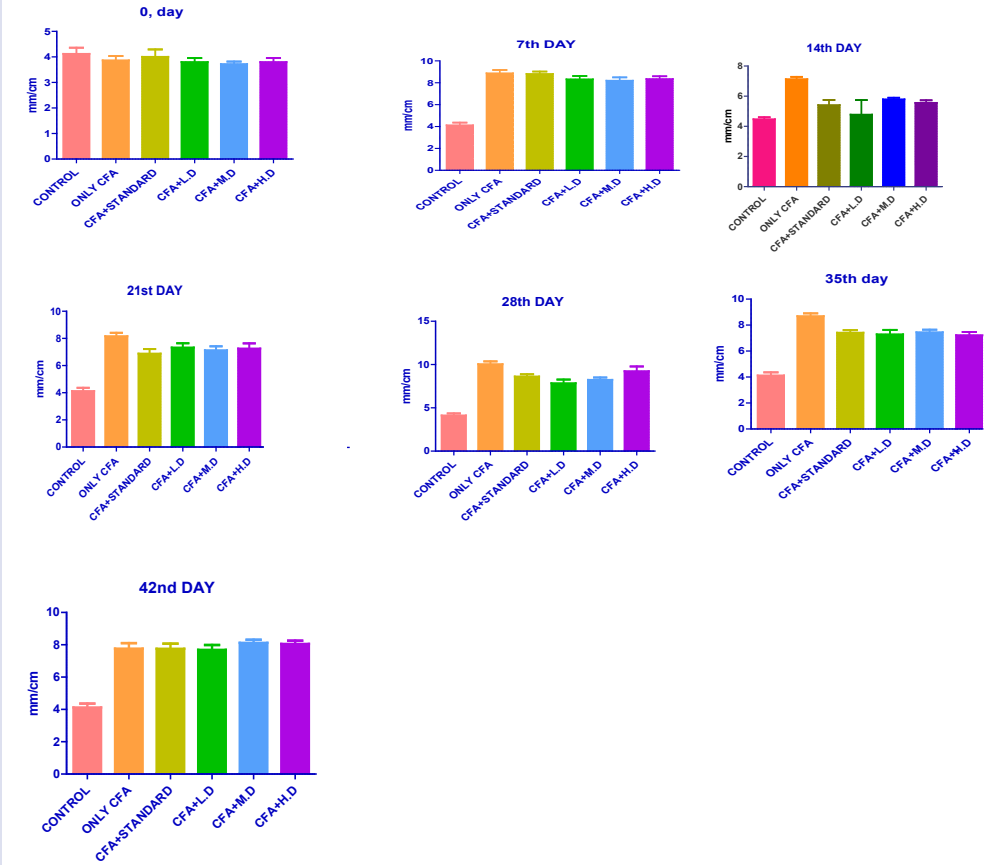

Figure 2: Indicates the Effect of anti-arthritic activity of Sahacharadi Kashayam on paw volume at different intervals.

after 14 days of treatment, a slight decrease in the paw volume can be found whereas after the 35th day of treatment, the rat group showed significant ($p < 0.001$) upsurge in paw volume. Oral treatment with standard drug increased paw volume till 7th day and reduced volume till 35th day. After 35 days of treatment, there appear to be a significant brought back of pathological changes when compared with the diseased rats. The Kashayam treatment showed augmented paw oedema and joint inflammation at 0.5ml for minimum treatment period which is depicted in Figure 1A – 1E.

Thus, it can be said that, 42 days treatment with Kashayam ($p < 0.001$) significantly augment CFA induced arthritis symptoms in SK treated group, where, 1.5 ml dosage of Kashayam showed higher paw volume and higher inflammation when compared with diseased group.

Effect of SK on serum arthritic biomarkers

Table 2, Figures 3 and 4 Indicate the effects of the experiment on C-Reactive protein and rheumatoid Factor.

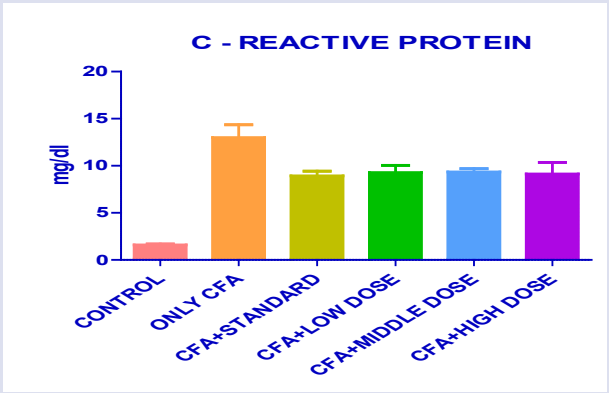

Figure 3: Levels of C-Reactive protein.

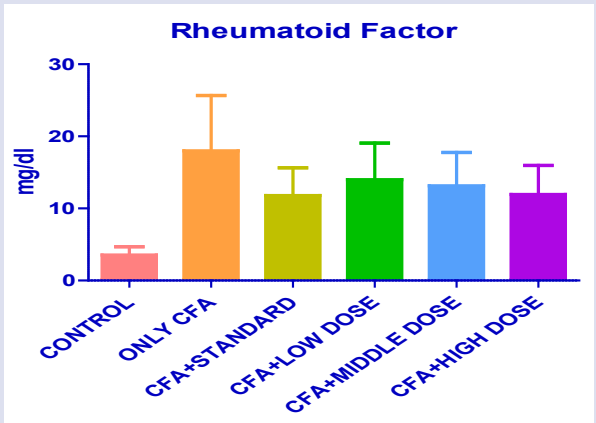

Figure 4: Levels of rhematoid factor.

Arthritic biomarkers such as C-reactive protein (CRP) and rheumatoid factor (RF) levels were clinically evaluated in rat serum. It was observed that 1.5 ml SK dosage illustrates a reduction in RFA value when compared with standard. And 0.5 ml and 1.0 ml dosage showed significant increase in RFA value. Whereas in all the three dosages, CRP value is decreased as comparable to that of CFA control, which is very much similar to that of the standard, CFA induced rats ($^{\#}p<0.001$) statistically significant in comparison with control group.

Effect of SK on haematological parameters

Changes in haematological parameters in CFA induced arthritic rats have been presented in Table 3. There seems to be a significant ($p<0.05$) increase in RBC count, haemoglobin level ($p<0.01$) and decrease in WBC count in 0.5 ml SK dosage group as compared with CFA rats. In case of 1.0 ml SK treated rat groups, these three parameters showed not much changes as compared with CFA group. In contrast to 0.5 ml SK dosage group, 1.5 ml SK treated group has shown a significant reduction in RBC count and Hb level. Oral administration of standard drug (LEF) resulted in significant increase in RBC count as well as Hb level and significant decrease in WBC count even after the CFA induction.

Effect of Sahacharadi Kashayam on haematology parameters in adjuvant induced rats is indicated in Table 3.

DISCUSSION

There a need to find out an alternative medicine which not only cures but also will have very less or no side effects. Ayurveda and Siddha systems of medicines are age old treatments for almost any type of disease. Arthritis is a common term used for many diseases that produce either inflammation of connective tissues, specifically in joints or non-inflammatory degeneration of these tissues. Perhaps the most significant inflammatory conditions to affect humanity are the diversities of arthritis and rheumatism diseases. Throughout the world herbal medicines appear to be widely accepted for treatment of these and many other diseases.

Although nonsteroid anti-inflammatory drugs (NSAIDS) and disease modifying drugs (DMARDS) could manage RA symptoms, the reported side effects from its long term use are quite detrimental. Polyherbalism has been given notable importance in Indian traditional system of medicine, due to their therapeutic efficiency. And efficiency of polyherbal formulations was described in 'Sarangdhara Samhita', an Ayurvedic literature by Sarangadharacharya, when combining the multiple herbs in a particular ratio, it will give a better therapeutic effect and reduce the toxicity. Many research articles have proved the efficacy of Ayurvedic drugs for the treatment of Rheumatoid arthritis.[11-16] In another study the GC MS analysis of Sahacharadi kashayam was reported showing the presence of the following molecules such as Heptanediamide, N,N'-di-benzoyloxy- Benzoic acid, Phenol, 2-methoxy-4-(1-propenyl), Eugenol, Tetradecanoic acid, 3-Decanone, 1-(4-hydroxy-3-methoxyphenyl)-(Gingerol), Abietic acid, 3-(6-Hydroxy-3,7-dimethyl-octa-2,7-dienyl)-4-methoxyphenol, 5H-Cyclopropa[3,4]benz[1,2-e]azulen-5-one, 1,1a,1b,4,4a,7a,7b,8,9,9a-decahydro-7b,9,9a-, Naphtho[2,3-c] furan-1(3H)-one, 3a,4,9,9a-tetrahydro-6-hydroxy-4-(4-hydroxy-

Table 2: Indicate the effects of the experiment on C - Reactive protein and rheumatoid factor.

Study Type	Control	Only CFA	CFA+LF (Standard)	CFA+ (Low Dose) 0.5 ml SK	CFA + (Middle Dose) 1 ml SK	CFA + (High Dose) 1.5 ml SK
C-Reactive Protein (mg/dL)	1.59667 ± 0.0880783	12.9967 ± 1.36014***	8.92667 ± 0.497893***	9.28167 ± 0.765996	9.33833 ± 0.357664***	9.13 ± 1.23049***
Rheumatoid Factor (mg/dL)	3.52833 ± 1.15097	17.9917 ± 7.68328	11.7883 ± 3.83725	13.9767 ± 5.07871	13.1414 ± 4.62025	11.09367 ± 4.02968

Values are expressed as mean ± SEM Statistical significance (p) calculated by one way ANOVA followed by dunnett's (n=6); $^{ns}p>0.05$, $*p<0.05$, $**p<0.01$, $***p<0.001$, calculated by comparing treated groups with control group.

Table 3: Effect of anti-arthritic activity of (42 days) of Sahacharadi Kashayam on haematological parameters.

Group	Control	Only CFA	CFA + LF (Standard)	CFA + (Low dose) SK 0.5ML	CFA + SK (Mid Dose) 1ML	CFA + SK (High Dose) 1.5ML
Rbc (x 10^6/mm^3)	5.45 ± 0.117132	4.56333 ± 0.13674**	5.61667 ± 0.14172	5.70333 ± 0.289006	4.53 ± 0.0966092**	3.77 ± 0.184065**
Wbc (x 10^3/ m^3)	10.1 ± 0.255604	13.6333 ± 0.327278***	9.93333 ± 0.256472	11.9 ± 0.386437**	13.8333 ± 0.585757***	13.6333 ± 0.331327***
Hb (g/dL)	13.3333 ± 0.350872	10.7 ± 0.406612**	13.8667 ± 0.423215	14.0667 ± 0.846431	10.6 ± 0.289828**	9.5 ± 0.324551***
Polymorphs (%)	4.33333 ± 0.210819	8.33333 ± 0.557773*	13.6667 ± 0.918937***	5 ± 0.365148	7 ± 2.28035	3.33333 ± 0.421637
Lymphocytes (%)	90.3333 ± 0.557773	85 ± 0.966092*	77.3333 ± 1.11555***	88.3333 ± 0.557773	87.6667 ± 2.01108	88.6667 ± 1.11555
Eosinophils (%)	2.66667 ± 0.210819	3.33333 ± 0.210819	3.66667 ± 0.210819	4 ± 0	2.66667 ± 0.421637	2.66667 ± 0.421637

Freund's complete adjuvant (CFA), Sahacharadi Kashayam (SK), Leflunomide (LEF). Values are expressed as mean ± SEM (n=6). $^{a}p<0.05$, $^{b}p<0.01$, $^{c}p<0.001$, statistically significant in comparison with CFA induced rats; $^{\#}p<0.05$, $^{\#\#}p<0.01$, $^{\#\#\#}p<0.001$ statistically significant in comparison with control group.

3-methoxyphenyl)-7-methoxy-, [3aR-(3aà,4à,9aá)]- and Lupeol. These molecules are known to have anti-inflammatory properties. Some other molecules such as 1-Heptatriacotanol ,Gibbane-1,10-dicarboxylic acid, 4a-(hydroxymethyl)-1-methyl-8-methylene-, 1,4a-lactone, 10-methyl ester, (1à,4aà,4bá,10á)-,3-(3-Hydroxy-4-methoxyphenyl)-l-alanine, Hexadecanoic acid, ethyl ester, n-Hexadecanoic acid were reported to have antioxidant properties. Another molecule, Heptanediamide, N, N'-di-benzoyloxy- Benzoic acid is known as Myo-neuro-stimulant.[17]

In yet another report Sahacharadi kashayam was reported to have very good antioxidant properties.[18] Many research articles have proved the efficacy of Ayurvedic drugs for the treatment of Rheumatoid arthritis.[19-21]

Chropra *et al*, 2012, have compared standardized ayurvedic formulations and hydrochloroquine sulphate (HCQS) in the treatment of Rheumatoid arthritis.[22] In one of our recent papers we have reported the efficacy of *Kodasuri verevaippu*, a Sidhha formulation,, on Carrageenan induced paw oedema and Cotton pellet induced granuloma in albino rats and the clinical efficacy of *'Kodasuri veeravaippu'(a sidhha formulation)* in patients affected by the disease *"Keelvayu"*(Arthritis).[23,24]

The constituent plants of SK are known for their contributory role in arthritis.

There are no reports on the medicinal role of *Barleria strigose.* But a closer species, *Barleria prionitis* is reported to be an excellent antioxidant and anti-inflammatory plant.[25-27] Devadaru (*Cedrus deodara* (ROXB.) LOUD, according to Susruta controls vata and kapha balance and is reported to be anti arthritic.[28] Sunthi (Ginger) (*Zingiber officinale) which* is one of the household medicines used against common cold, cough and indigestion. The medicinal values of Ginger are well documented.[29] Adel and Prakash, 2010 have reported its antioxidant properties.[30] *Sida cordifolia* is known for its anti-inflammatory and analgesic activities.[31] *Tinospora cordifolia* is a wonder drug plant with various medicinal roles.[32] Thus, it seems quite pertinent that the constituent plants do contribute to the antiarthritic properties of Sahacahradi kashayam. So, in the current study SK showed protection against arthritis at minimal dose and less treatment period when the treatment prolongs with higher dosage the reoccurrence of arthritis was noted in rat model. Therefore, the reports couldn't provide strong evidence for the antiarthritic activity of SK in the current research trials.

CONCLUSION

In conclusion, SK observes to exert beneficial effects at minimal dose and less treatment period on various pathological manifestations of Freund's Complete Adjuvant induced arthritis. But further study is needed to prove clinical effects of this Ayurvedic formulation and to reduce the reoccurrence of arthritic inflammatory changes. However, the present study authenticates the medical benefits of this Kashayam in the treatment of arthritic conditions as reported in literature.

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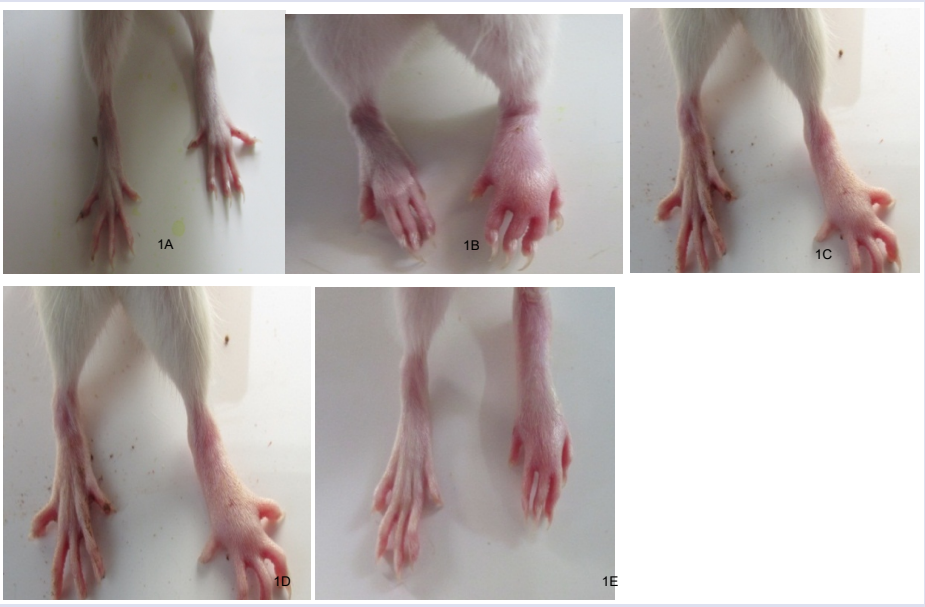
GRAPHICAL ABSTRACT



SUMMARY

Paw volume changes in control and drugs treated rats in CFA model. 1A- Normal control rat. 1B – Freund's complete adjuvant (CFA) induced rat; 1C – CFA + Leflunomide (LEF); 1D – CFA + Sahacharadi Kashayam (SK) (Low Dose-0.5ml); 1E – CFA + SK (Mid dose-1.0ml); 1E – CFA + SK (High dose-1.5ml).

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