

Evaluating the Anti-arthritic Activity of *Sandamarutha Rasa Chenduram*

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ABSTRACT

Background: Rheumatoid Arthritis (RA) is a chronic autoimmune inflammatory disorder characterised by synovial inflammation, cartilage destruction, oxidative stress and progressive joint deformity. Anti-rheumatic drugs provide symptomatic relief, but prolonged use is associated with adverse effects. *Sandamarutha Rasa Chenduram* (SRC) is a traditional Siddha mercury-sulphur formulation indicated for inflammatory disorders, but experimental evidence for its anti-arthritic activity is limited. **Objectives:** To evaluate the anti-arthritic, anti-inflammatory and antioxidant effects of SRC in rats. **Materials and Methods:** In the Complete Freund's Adjuvant (CFA)-induced arthritis model, Wistar albino rats ($n=6$ per group) were allocated to five groups: normal control, arthritis control, diclofenac (4 mg/kg, p.o.), and SRC (30 and 90 mg/kg, p.o.). Treatment was started on the day of CFA injection and continued for 21 days. Paw thickness, arthritis score, haematological parameters, Rheumatoid Factor (RF), serum TNF- α and IL-6, and synovial tissue antioxidant markers (SOD, CAT, GSH and LPO) were assessed. In the cotton pellet-induced granuloma model (four groups, $n=6$ per group), SRC was compared with vehicle and indomethacin (10 mg/kg, p.o.) for exudate weight, granuloma weight and serum cytokines. **Results:** SRC reduced paw thickness and arthritis score in a dose-dependent manner; values at 90 mg/kg were numerically close to those of diclofenac. SRC significantly shifted WBC, RBC, ESR and RF towards normal values and lowered TNF- α and IL-6 levels. SOD, CAT and GSH were increased and LPO was reduced. In the granuloma model, SRC inhibited exudate formation (32.11% and 71.79%) and granuloma tissue formation (43.42% and 72.67%) at 30 and 90 mg/kg, respectively. **Conclusion:** Under the conditions of this study, SRC showed anti-arthritic, anti-inflammatory and antioxidant effects in rats. Histopathological, radiological and clinical studies are needed to confirm its efficacy and safety.

Keywords: Anti-arthritic activity, CFA-induced arthritis, Cotton pellet granuloma, *Sandamarutha Rasa Chenduram*, Siddha medicine.

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INTRODUCTION

Rheumatoid Arthritis (RA) is a progressive systemic autoimmune disease characterised by synovial hyperplasia, pannus formation, cartilage destruction and irreversible joint damage, leading to reduced quality of life (Chauhan *et al.*, 2026). Its pathogenesis involves immune dysregulation, oxidative stress and pro-inflammatory cytokines. TNF- α and IL-6 play important roles in sustaining synovial inflammation, osteoclast activation and cartilage erosion, and excessive generation of reactive oxygen species contributes to tissue injury and progression of chronic arthritis (Jahid *et al.*, 2023). Conventional treatment

includes Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), corticosteroids and Disease-Modifying Anti-Rheumatic Drugs (DMARDs), which give symptomatic relief, but long-term use can cause hepatotoxicity, nephrotoxicity, immunosuppression and cardiovascular complications. This has increased interest in alternative treatments with fewer adverse effects (Nithyashree & Deveswaran, 2020).

The Siddha system of medicine uses formulations of herbal, mineral, metallic and animal origin for various ailments (Kannan *et al.*, 2017). Among the 32 types of internal medicines, chenduram is a class of mineral preparations, typically sulphides or oxides of metals or minerals, obtained by processes such as frying, calcination, grinding, direct flaming and sublimation (S. R. Pholtan Rajeev, 2019). *Sandamarutha Rasa Chenduram* (SRC), prepared by grinding, is traditionally indicated for pain and inflammatory conditions. Siddha research commonly follows a reverse pharmacological approach, in which experimental evidence is generated for formulations already in clinical use



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(Madhavan, 1994). The present study therefore evaluated the anti-arthritic effect of SRC in experimental models.

Complete Freund's Adjuvant (CFA)-induced arthritis and cotton pellet-induced granuloma are widely used models for anti-arthritic and anti-inflammatory screening, as they reproduce several features of chronic synovitis, inflammatory cell infiltration, granuloma formation and oxidative stress-mediated damage (Kumar *et al.*, 2016). We evaluated the anti-arthritic, anti-inflammatory and antioxidant effects of SRC in Wistar albino rats using these two models, together with its effects on inflammatory cytokines, haematological parameters and oxidative stress markers.

MATERIALS AND METHODS

Test drug

Sandamarutha Rasa Chenduram is a Siddha mineral formulation prepared from purified mercury (Suddha Rasam) and purified sulphur (Suddha Gandhagam). Herbal juices were used only for triturating (grinding) during processing and are not ingredients of the final product. All the procedures are done in Department of Gunapadam practical laboratory.

Ethical approval

The study was screened by the Institutional Research Review Board (IRRB), National Institute of Siddha, Tambaram Sanatorium, and reviewed and approved by the Institutional Animal Ethics Committee of Sri Lakshmi Narayana Institute of Medical Sciences (approval number SLIMS/05-12/IAEC/2025-26).

Experimental animals

Wistar albino rats (*Rattus norvegicus*) weighing 140-160 g were obtained from an authorised breeder (Mass Biotech, Chengalpattu) and housed at the animal facility of Sri Lakshmi Narayana Institute of Medical Sciences, Puducherry, in accordance with CPCSEA guidelines. The animals were housed in polypropylene cages with corn cob bedding, fed with standard pellet diet (Chompaka Feeds and Foods, Bengaluru) and given Reverse Osmosis (RO) water *ad libitum*. Cages and water bottles were cleaned weekly.

Grouping and acclimatization

All animals were individually numbered and randomly allocated to the experimental groups. Grouping was performed by the investigator and no blinding was applied. Each animal was identified by marking the head, body and tail with picric acid solution, which allows individual monitoring and accurate recording of observations and body weight (Menčík *et al.*, 2018).

Preparation and administration of drugs

SRC was suspended in a vehicle consisting of honey and distilled water mixed in equal proportion (1:1, v/v). Diclofenac sodium and indomethacin were suspended in the same vehicle. All treatments were given orally once daily by gavage at a volume of 10 mL/kg. Control groups received the vehicle alone.

CFA-induced arthritis

Arthritis was induced by a single injection of 0.1 mL CFA emulsion (5 mg/mL) into the subplantar region of the right hind paw (Li *et al.*, 2018). CFA induces a chronic, immune-mediated polyarthritis that resembles several features of human RA.

Thirty Wistar albino rats were divided into five groups of six animals each ($n=6$). Group I (normal control) received the vehicle only. Group II (arthritis control) received CFA and vehicle. Group III (reference control) received CFA and diclofenac sodium (4 mg/kg, p.o.). Groups IV and V received CFA and SRC at 30 and 90 mg/kg, p.o., respectively. Treatment was started on the day of CFA injection (day 0) and continued once daily for 21 days. Paw thickness and arthritis score were assessed on days 0, 3, 7, 14 and 21 after CFA injection.

Paw thickness

The thickness of the injected hind paw was measured with a Vernier caliber on days 0, 3, 7, 14 and 21.

Arthritis score

The injected hind paw was scored on a 0-4 scale (Table 1) adapted from Brand *et al.* (2007). Scoring was done by the investigator without blinding.

Blood and tissue collection

At the end of the 21-day treatment period, rats were fasted overnight and anaesthetized with pentobarbitone sodium (60 mg/kg, i.p.). Blood was collected by retro-orbital puncture into separate tubes: EDTA tubes for RBC and WBC counts, 3.8% sodium citrate for ESR (4 parts blood to 1 part citrate), and plain tubes for serum. Serum was separated by centrifugation at 3000 rpm after clotting and stored at -80°C until RF, TNF- α and IL-6

Table 1: Arthritis scoring scale (adapted from Brand *et al.*, 2007).

Score	Clinical appearance of the paw
0	Normal; no erythema or swelling
1	Erythema and mild swelling confined to the tarsals or ankle joint
2	Erythema and mild swelling extending from the ankle to the tarsals
3	Erythema and moderate swelling extending from the ankle to the metatarsal joints
4	Erythema and severe swelling encompassing the ankle, foot and digits

were estimated. The animals were then euthanized by excess anaesthesia, and the synovial tissue of the inflamed paw was dissected out, homogenised (10%, w/v) in ice-cold 0.05 M sodium phosphate buffer (pH 7.4) containing 1.15% KCl and centrifuged at 6000 g for 20 min at 4°C. The supernatant was stored at -80°C for antioxidant estimations. Protein content of the supernatant was determined by the method of Lowry *et al.* (1951).

Haematological parameters

Total RBC count. Blood was drawn to the 0.5 mark of the RBC pipette and RBC diluting fluid to the 101 mark (1 in 200 dilution). The contents were mixed by gentle rotation for 3 min (Ghai, 2013). After discarding the first few drops, the mixture was charged into a Neubauer chamber under a cover slip and the cells were allowed to settle for 2 min. Cells were counted in 80 small squares under high power. RBC count (cells/cmm) = dilution $\times$ 50 $\times$ N, where N is the number of cells counted.

Total WBC count. Blood was drawn to the 0.5 mark of the WBC pipette and WBC diluting fluid to the 11 mark (1 in 20 dilution) and mixed for 3 min. The chamber was charged as above, and cells were counted in 64 small squares under low power. WBC count (cells/cmm) = 50 $\times$ N.

ESR. Citrated blood (4 volumes of blood with 1 volume of 3.8% sodium citrate) was drawn into a Westergren pipette up to the 200 mm mark and held vertically in a Westergren stand at room temperature, away from vibration and direct sunlight. The height of the plasma column above the settled red cells was read after 1 hr and expressed as mm/h.

Rheumatoid factor and inflammatory cytokines

Serum RF was measured with a commercial rat RF ELISA kit according to the manufacturer's instructions and expressed in IU/mL.

Serum TNF- α and IL-6 were quantified by sandwich ELISA using commercial rat-specific kits, following the manufacturer's protocol. In brief, standards and samples were added to microplate wells pre-coated with the capture antibody and incubated, so that the cytokine bound to the immobilised antibody. After washing, a biotin-conjugated detection antibody was added, followed by washing and incubation with streptavidin-Horseradish Peroxidase (HRP). After a final wash, TMB substrate was added, and the colour reaction was stopped with the acid stop solution supplied in the kit. Absorbance was read at 450 nm in a microplate reader. Concentrations were calculated from a standard curve and, for both cytokines, are expressed in ng/mL.

Antioxidant estimations in synovial tissue homogenate

Lipid Peroxidation (LPO). LPO was estimated as thiobarbituric acid-reactive substances by the method of Ohkawa *et al.* (1979). Tissue supernatant (0.2 mL) was mixed with 0.2 mL of 8.1% sodium dodecyl sulphate, 1.5 mL of 20% acetic acid (pH 3.5) and 1.5 mL of 0.8% aqueous thiobarbituric acid; the volume was made up to 4 mL with distilled water and heated at 95°C for 60 min. After cooling, 1 mL of distilled water and 5 mL of n-butanol-pyridine mixture (15:1, v/v) were added, shaken vigorously and centrifuged at 4000 rpm for 10 min. The absorbance of the organic layer was read at 532 nm. Values were calculated against a malondialdehyde standard (1,1,3,3-tetramethoxypropane) and expressed as nmol/g tissue.

Superoxide Dismutase (SOD). SOD was assayed by the method of Kakkar *et al.* (1984). The assay mixture contained 0.05 mL of sample, 0.3 mL of sodium pyrophosphate buffer (0.025 M, pH 8.3), 0.025 mL of phenazine methosulphate (186 μ M) and 0.075 mL of nitroblue tetrazolium (300 μ M). The reaction was started with 0.075 mL of NADH (780 μ M), incubated at 30°C for 90 sec and stopped with 0.25 mL of glacial acetic acid. The chromogen was extracted into 2 mL of n-butanol by vigorous shaking,

Table 2: Effect of *Sandamarutha Rasa Chenduram* on paw thickness (mm) in CFA-induced arthritis in rats.

Group	Treatment	Day 0	Day 3	Day 7	Day 14	Day 21
I	Normal control, vehicle (10 mL/kg, p.o.)	5.22 $\pm$ 0.38	5.30 $\pm$ 0.39	5.28 $\pm$ 0.35	5.37 $\pm$ 0.41	5.29 $\pm$ 0.40
II	Arthritis control, CFA	5.37 $\pm$ 0.50	9.83 $\pm$ 0.72	11.42 $\pm$ 1.08	12.52 $\pm$ 1.19	12.83 $\pm$ 1.20
III	CFA + diclofenac (4 mg/kg, p.o.)	5.29 $\pm$ 0.41	7.40 $\pm$ 0.63*	6.67 $\pm$ 0.62***	5.83 $\pm$ 0.51***	5.09 $\pm$ 0.48***
IV	CFA + SRC (30 mg/kg, p.o.)	5.29 $\pm$ 0.49	7.93 $\pm$ 0.62	8.98 $\pm$ 0.82*	7.08 $\pm$ 0.61**	6.04 $\pm$ 0.54***
V	CFA + SRC (90 mg/kg, p.o.)	5.30 $\pm$ 0.51	6.27 $\pm$ 0.58**	6.08 $\pm$ 0.52***	5.89 $\pm$ 0.57***	5.32 $\pm$ 0.53***

Values are mean $\pm$ SEM (n= 6). * p <0.05, ** p <0.01, *** p <0.001 vs arthritis control.

Table 3: Percentage inhibition of paw thickness by Sandamarutha Rasa Chenduram in CFA-induced arthritis in rats.

Treatment	Day 3	Day 7	Day 14	Day 21
CFA + diclofenac (4 mg/kg, p.o.)	24.72	41.59	53.43	60.33
CFA + SRC (30 mg/kg, p.o.)	19.32	21.37	43.45	52.92
CFA + SRC (90 mg/kg, p.o.)	36.22	46.76	52.96	58.53

Table 4: Effect of Sandamarutha Rasa Chenduram on arthritis score in CFA-induced arthritis in rats.

Group	Treatment	Arthritis score
I	Normal control, vehicle (10 mL/kg, p.o.)	0
II	Arthritis control, CFA	3.91±0.26
III	CFA + diclofenac (4 mg/kg, p.o.)	2.04±0.19***
IV	CFA + SRC (30 mg/kg, p.o.)	2.83±0.24**
V	CFA + SRC (90 mg/kg, p.o.)	1.47±0.13***

Values are mean ± SEM (n= 6). **p<0.01, ***p<0.001 vs arthritis control.

allowed to stand for 10 min and centrifuged, and the absorbance of the butanol layer was read at 560 nm against a butanol blank. One unit of enzyme activity was defined as the amount of enzyme that inhibits chromogen formation by 50% in 1 min under the assay conditions.

Catalase (CAT). CAT was assayed by the UV method of Aebi (1984). The 3 mL reaction mixture contained 50 mM phosphate buffer (pH 7.0) and 0.1 mL of tissue supernatant, and the reaction was started by adding hydrogen peroxide to a final concentration of 10 mM. The decomposition of H₂O₂ was followed at 240 nm at 25 °C, and the time taken for the absorbance to fall from 0.450 to 0.400 (corresponding to decomposition of 3.45 µmol H₂O₂ in the 3 mL mixture) was recorded. Activity was expressed as µmol H₂O₂ decomposed/min/mg protein.

Reduced Glutathione (GSH). Tissue supernatant (0.25 mL) was deproteinized with an equal volume of ice-cold 5% trichloroacetic acid and centrifuged at 3500 rpm for 10 min. To the clear supernatant, 0.2 M phosphate buffer (pH 8.0) and 0.5 mL of DTNB (0.6 mM in 0.2 M phosphate buffer, pH 8.0) were added, mixed, and the absorbance was read at 412 nm (Ellman, 1959).

Cotton pellet-induced granuloma

Twenty-four Wistar albino rats were divided into four groups of six animals each (n= 6) and randomly allocated after individual numbering. Group I (vehicle control) received the vehicle only. Group II (reference control) received indomethacin (10 mg/kg, p.o.). Groups III and IV received SRC at 30 and 90 mg/kg, p.o., respectively. 30 min after the first dose, animals were anaesthetized with pentobarbitone sodium (60 mg/kg, i.p.) and sterilised cotton pellets weighing about 10 mg were implanted subcutaneously, bilaterally, in the axillary region. Treatment continued once daily for 7 days. On the 8th day, animals were anaesthetized, blood

was collected by retro-orbital sinus puncture, and the pellets with surrounding granuloma tissue were excised and freed of extraneous tissue. Serum was separated by centrifugation at 3000 rpm for cytokine estimation (TNF-α and IL-6, as described above). The wet weight of each pellet was recorded and the pellet was then dried in an incubator at 60°C for 18 hr to constant weight. Exudate weight was calculated as wet weight minus dry weight. Granuloma weight was calculated as dry weight minus the initial weight of the pellet. Percentage inhibition of exudate and granuloma formation was calculated relative to the vehicle control (Winter & Porter, 1957).

Statistical analysis

Data are expressed as mean ± SEM. Differences between groups were analysed by one-way ANOVA followed by Dunnett's test using GraphPad Prism. p<0.05 was considered statistically significant.

RESULTS

CFA-induced arthritis

Results are shown in Tables 2-6. CFA injection increased paw thickness from about 5.4 mm to 12.8 mm by day 21 in the arthritis control group. SRC reduced paw thickness in a dose-dependent manner. On day 21, paw thickness was 6.04 mm and 5.32 mm in the 30 and 90 mg/kg SRC groups, compared with 5.09 mm in the diclofenac group and 12.83 mm in the arthritis control group (Table 2). Inhibition of paw swelling on day 21 was 52.92% and 58.53% for SRC 30 and 90 mg/kg, and 60.33% for diclofenac (Table 3). The arthritis score was lower in all treated groups (Table 4).

Arthritis control rats showed higher WBC, ESR, RF, TNF-α and IL-6 and lower RBC than normal control rats. Treatment with SRC shifted these values towards those of the normal control, with the larger effect at 90 mg/kg (Table 5). The antioxidant enzymes SOD, CAT and GSH were reduced and LPO was raised in arthritis control rats; SRC increased SOD, CAT and GSH and reduced LPO (Table 6).

Cotton pellet-induced granuloma

Results are shown in Tables 7-9. SRC reduced exudate weight by 32.11% (30 mg/kg) and 71.79% (90 mg/kg), compared with 75.43% for indomethacin (Table 7). Granuloma dry weight was reduced by 43.42% and 72.67% at 30 and 90 mg/kg, and by 76.37% with indomethacin (Table 8). Serum TNF-α and IL-6 were lower in all treated groups than in the vehicle control (Table 9).

Table 5: Effect of *Sandamarutha Rasa Chenduram* on haematological parameters, rheumatoid factor and serum cytokines in CFA-induced arthritis in rats.

Group	Treatment	WBC ($\times 10^3$ /cmm)	RBC ($\times 10^6$ /cmm)	ESR (mm/h)	RF (IU/mL)	TNF- α (ng/mL)	IL-6 (ng/mL)
I	Normal control	8.29 $\pm$ 0.72	6.58 $\pm$ 0.52	5.17 $\pm$ 0.46	0.59 $\pm$ 0.03	0.021 $\pm$ 0.001	0.23 $\pm$ 0.02
II	Arthritis control	17.37 $\pm$ 1.06	3.93 $\pm$ 0.29	18.42 $\pm$ 1.67	27.24 $\pm$ 1.82	0.133 $\pm$ 0.01	1.63 $\pm$ 0.12
III	CFA + diclofenac (4 mg/kg)	12.57 $\pm$ 1.17*	5.88 $\pm$ 0.57**	8.93 $\pm$ 0.71***	4.84 $\pm$ 0.27***	0.040 $\pm$ 0.002	0.44 $\pm$ 0.03
IV	CFA + SRC (30 mg/kg)	13.08 $\pm$ 1.26	5.42 $\pm$ 0.51*	10.23 $\pm$ 0.87**	10.22 $\pm$ 0.83***	0.096 $\pm$ 0.007	0.93 $\pm$ 0.07
V	CFA + SRC (90 mg/kg)	10.27 $\pm$ 0.94**	6.09 $\pm$ 0.58**	8.90 $\pm$ 0.72***	3.94 $\pm$ 0.33***	0.042 $\pm$ 0.003	0.41 $\pm$ 0.03

Values are mean $\pm$ SEM ($n=6$). * $p<0.05$, ** $p<0.01$, *** $p<0.001$ vs arthritis control. Highlighted cells: significance marks to be added from the statistical output.

Table 6: Effect of *Sandamarutha Rasa Chenduram* on antioxidant parameters in synovial tissue in CFA-induced arthritis in rats.

Group	Treatment	SOD (units/mg protein)	CAT (μ mol/min/mg protein)	GSH (units/mg protein)	LPO (nmol/g tissue)
I	Normal control	4.83 $\pm$ 0.35	1.48 $\pm$ 0.12	6.72 $\pm$ 0.36	0.59 $\pm$ 0.04
II	Arthritis control	2.31 $\pm$ 0.24	0.24 $\pm$ 0.02	3.29 $\pm$ 0.32	1.48 $\pm$ 0.12
III	CFA + diclofenac (4 mg/kg)	4.56 $\pm$ 0.36***	1.19 $\pm$ 0.10***	5.10 $\pm$ 0.46**	0.63 $\pm$ 0.04***
IV	CFA + SRC (30 mg/kg)	4.06 $\pm$ 0.40***	0.97 $\pm$ 0.06***	5.04 $\pm$ 0.40**	0.93 $\pm$ 0.0***
V	CFA + SRC (90 mg/kg)	4.60 $\pm$ 0.39***	1.21 $\pm$ 0.01***	5.98 $\pm$ 0.44***	0.60 $\pm$ 0.05***

Values are mean $\pm$ SEM ($n=6$). ** $p<0.01$, *** $p<0.001$ vs arthritis control. Highlighted cells: values to be checked against the raw data.

Table 7: Effect of *Sandamarutha Rasa Chenduram* on exudate weight and percentage inhibition of exudate in cotton pellet-induced granuloma in rats.

Group	Treatment	Wet weight of pellet (mg)	Dry weight of pellet (mg)	Exudate weight (mg)	Inhibition of exudate (%)
I	Vehicle control (10 mL/kg, p.o.)	158.75 $\pm$ 9.85	46.49 $\pm$ 3.75	112.27 $\pm$ 8.37	-
II	Indomethacin (10 mg/kg, p.o.)	46.21 $\pm$ 3.45***	18.63 $\pm$ 1.07***	27.59 $\pm$ 1.91***	75.43
III	SRC (30 mg/kg, p.o.)	106.50 $\pm$ 7.33*	30.34 $\pm$ 2.56*	76.22 $\pm$ 6.16**	32.11
IV	SRC (90 mg/kg, p.o.)	52.31 $\pm$ 4.39***	20.63 $\pm$ 1.61***	31.67 $\pm$ 2.43***	71.79

Values are mean $\pm$ SEM ($n=6$). * $p<0.05$, ** $p<0.01$, *** $p<0.001$ vs vehicle control.

DISCUSSION

In the CFA-induced arthritis model, SRC reduced paw thickness and arthritis score in a dose-dependent manner. At 90 mg/kg, paw thickness, arthritis score and percentage inhibition were numerically close to those of diclofenac (4 mg/kg), but SRC and diclofenac were not compared statistically, so equivalence cannot be claimed. Treatment was started on the day of CFA injection, so

the findings reflect protective, early-intervention activity and do not show an effect on established arthritis.

SRC treatment was also associated with lower WBC, ESR, RF, TNF- α and IL-6 and higher RBC counts than in arthritis control rats. These changes were partial: at 90 mg/kg, RF (3.94 vs 0.59 IU/mL), WBC (10.27 vs 8.29 $\times 10^3$ /cmm) and TNF- α (0.042 vs 0.021 ng/mL) remained above the normal control values. TNF- α and

Table 8: Effect of Sandamarutha Rasa Chenduram on granuloma dry weight and percentage inhibition of granuloma in cotton pellet-induced granuloma in rats.

Group	Treatment	Initial pellet weight (mg)	Dry weight of pellet (mg)	Granuloma dry weight (mg)	Inhibition of granuloma (%)
I	Vehicle control (10 mL/kg, p.o.)	11.61±0.93	46.49±3.75	34.87±2.14	-
II	Indomethacin (10 mg/kg, p.o.)	10.37±1.01	18.63±1.07***	8.24±0.73***	76.37
III	SRC (30 mg/kg, p.o.)	10.66±0.97	30.34±2.56*	19.73±1.34**	43.42
IV	SRC (90 mg/kg, p.o.)	11.09±1.07	20.63±1.61***	9.53±0.81***	72.67

Values are mean ± SEM (n= 6). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs vehicle control.

Table 9: Effect of Sandamarutha Rasa Chenduram on serum inflammatory mediators in cotton pellet-induced granuloma in rats.

Group	Treatment	TNF- α (ng/mL)	IL-6 (ng/mL)
I	Vehicle control (10 mL/kg, p.o.)	0.176±0.013	1.530±0.146
II	Indomethacin (10 mg/kg, p.o.)	0.060±0.002***	0.372±0.03***
III	SRC (30 mg/kg, p.o.)	0.098±0.006**	0.891±0.005***
IV	SRC (90 mg/kg, p.o.)	0.072±0.006***	0.477±0.002***

Values are mean ± SEM (n= 6). ** $p < 0.01$, *** $p < 0.001$ vs vehicle control. Highlighted cells: SEM values to be checked against the raw data.

IL-6 are key mediators in RA, so lower levels are consistent with an anti-inflammatory effect. The higher SOD, CAT and GSH and lower LPO in synovial tissue indicate reduced oxidative stress in the inflamed joint. Because only these markers were measured, mechanisms such as immunomodulation or effects on NF- κ B and Nrf2 signalling remain hypotheses to be tested.

In the cotton pellet model, SRC reduced exudate weight and granuloma tissue formation, with the 90 mg/kg dose giving percentage inhibition (71.79% and 72.67%) close to that of indomethacin (75.43% and 76.37%); these were not compared statistically. The results suggest activity against both the exudative and proliferative components of inflammation in this model.

Other Siddha herbo-mineral formulations have also been reported to reduce paw swelling and inflammatory responses in experimental arthritis, including Rasa Chendooram in CFA-induced arthritis (Sabarmathi *et al.*, 2019) and Arumuga Chenduram in collagen-induced arthritis (Ramamurthy *et al.*, 2020), and the polyherbal Siddha drug Avuri Karpam reduced granuloma formation in the cotton pellet model (Manikgantan and Kumar, 2023). The present findings are in line with these reports.

LIMITATIONS

This study has several limitations. Joint histopathology and radiological assessment have not yet been done, so structural protection of the joint is not shown. Treatment started at the time of arthritis induction, and the study does not model treatment of established disease. Grouping and scoring were not blinded,

and the sample size was small (n= 6 per group). Safety data come from the authors' unpublished acute, sub-acute and sub-chronic studies; as SRC contains mercury, further safety evaluation is needed before clinical use.

CONCLUSION

Under the conditions of this study, SRC showed dose-dependent anti-arthritis, anti-inflammatory and antioxidant effects in CFA-induced arthritis and cotton pellet-induced granuloma in rats. Histopathological and radiological confirmation, studies in established arthritis, and clinical studies are needed to evaluate its efficacy and safety.

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ABBREVIATIONS

ANOVA: Analysis of Variance; **CAT:** Catalase; **CFA:** Complete Freund's Adjuvant; **CPCSEA:** Committee for the Purpose of Control and Supervision of Experiments on Animals; **DMARDs:** Disease-Modifying Antirheumatic Drugs; **DTNB:** 5,5'-Dithiobis-(2-nitrobenzoic acid); **EDTA:** Ethylenediaminetetraacetic Acid; **ELISA:** Enzyme-Linked Immunosorbent Assay; **ESR:** Erythrocyte Sedimentation Rate; **GSH:** Reduced Glutathione; **HRP:** Horseradish Peroxidase; **IAEC:** Institutional Animal Ethics Committee; **IL-6:** Interleukin-6; **i.p.:** Intraperitoneal; **IRRB:**

Institutional Research Review Board; **KCl**: Potassium Chloride; **LPO**: Lipid Peroxidation; **NF- κ B**: Nuclear Factor Kappa B; **Nrf2**: Nuclear Factor Erythroid 2-Related Factor 2; **NSAIDs**: Nonsteroidal Anti-Inflammatory Drugs; **p.o.**: Per Oral; **RA**: Rheumatoid Arthritis; **RBC**: Red Blood Cells; **RF**: Rheumatoid Factor; **RO**: Reverse Osmosis; **ROS**: Reactive Oxygen Species; **SEM**: Standard Error of the Mean; **SOD**: Superoxide Dismutase; **SRC**: Sandamarutha Rasa Chenduram; **TCA**: Trichloroacetic Acid; **TMB**: Tetramethylbenzidine; **TNF- α** : Tumour Necrosis Factor Alpha; **WBC**: White Blood Cells.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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