

Evaluating higher doses of *Shunthi - Guduchi* formulations for safety in treatment of osteoarthritis knees: A Government of India NMITLI arthritis project

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ABSTRACT

Background: Results of an exploratory trial suggested activity trends of *Zingiber officinale*-*Tinopsis cordifolia* (platform combination)-based formulations in the treatment of Osteoarthritis (OA) Knees. These formulations were "platform combination + *Withania somnifera* + *Tribulus terrestris*" (formulation B) and "platform combination + *Embllica officinale*" (formulation C). This paper reports safety of these formulations when used in higher doses (1.5–2 times) along with Sallaki Guggul and Bhallataka Parpati (a *Semecarpus anacardium* preparation). **Materials and Methods:** Ninety-two patients with symptomatic OA knees were enrolled in a 6 weeks investigator blind, randomized parallel efficacy 4-arm multicenter drug trial. The 4 arms were (I) formulation B, 2 t.i.d.; (II) formulation B, 2 q.i.d.; (III) platform combination + Sallaki Guggul; (IV) Bhallataka Parpati + formulation C. A detailed enquiry was carried out for adverse events (AE) and drug toxicity as per a priori check list and volunteered information. Laboratory evaluation included detailed hematology and metabolic parameters. Patients were examined at baseline, first and fourth weeks, and on completion. Standard statistical program (SPSS version 12.5) was used for analysis. **Results:** None of the patients reported serious AE or withdrew due to any drug-related toxicity. Mild gut-related (mostly epigastric burning) AE was reported. A mild increase in liver enzymes [serum glutamic pyruvate transaminase (SGPT), serum glutamic oxaloacetic transaminase (SGOT)] without any other hepatic abnormality was reported in 2 patients (group IV). Other laboratory parameters remained normal. The mean improvement in active pain visual analog scale (1.4, CI 0.5–2.22), WOMAC (functional activity questionnaire) pain score (1.37, CI 0.22–2.5), and urinary C-TAX (cartilage collagen breakdown product) assay was maximum (NS) in group IV. Lower dose group I showed numerically superior improvement compared with higher dose group II. **Conclusion:** The results suggested that despite higher doses, standardized Ayurvedic formulations demonstrated a good safety profile. An improved efficacy and likely chondroprotective effect was shown by group IV intervention. A confirmatory drug trial with adequate power and sample size was planned based on the learning from this trial.

Key words: Ayurveda, osteoarthritis, WOMAC, Pain VAS, chondroprotective

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INTRODUCTION

The current standard of care for Osteoarthritis (OA) knees is mostly symptomatic pain relief.^[1] There is an urgent need to develop safer and effective drugs with chondroprotective effect. Ayurveda has a tremendous potential to offer safer therapies for difficult to treat disorders such as arthritis. OA is a common disabling community ailment.^[2] Several Ayurvedic medicinal plants used to treat arthritis in clinical practice demonstrated significant biological and immunomodulation effects in clinical drug trials^[3,4] and experimental studies.^[5,6] As part of a Government "New Millennium Indian Technology Leadership Initiative" (NMITLI), we carried out several clinical and experimental investigational studies to develop and evaluate candidate

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Ayurvedic drugs to treat OA knees. Our mandate was to validate an effective and safe drug for global use.

The results of the first exploratory randomized double-blind placebo and active comparator (glucosamine) controlled drug trial to evaluate 5 selected Ayurvedic herbal formulations under the NMITLI project were recently published.^[7] The Ayurvedic formulations contained Shunthi (*Zingiber officinale*)—Guduchi (*Tinospora cordifolia*) extracts base; other extracts chosen and added were Ashwagandha (*Withania somnifera*), Amalaki (*Emblica officinalis*), and Gokshur (*Tribulus terrestris*). The formulations were administered in doses that were considered adequate by Ayurvedic experts and investigators. Although statistically significant efficacy in reducing pain (primary efficacy) as compared with placebo was not demonstrated, coded formulations “C” (Shunthi–Guduchi–Amalaki) and “B” (Shunthi–Guduchi–Ashwagandha–Gokshur) were found numerically superior for several efficacy and overall safety measures as compared with placebo and glucosamine and chosen for further validation.

In retrospect, on critical appraisal of the first study (mentioned above) we identified two principal areas for further investigation. Firstly, how safe (and effective) would be an increased optimum dose of C and B formulations? Secondly, what would be the effect of adding Sallaki Guggul (gum extract of *Boswellia species*) and Bhallataka Parpati (a traditional preparation of *S. anacardium* oil) to the selected formulations? The clinical use and experimental validation of Sallaki Guggul and Bhallataka as *Rasayana* with potent anti-inflammatory and antiarthritis properties is well documented^[8] and both were among the short listed medicinal plants for this project. This report presents results of this short-term dosing and combination study.

MATERIALS AND METHODS

Design

Ninety-two patients of symptomatic OA knees were enrolled in a randomized, investigator blind, parallel efficacy drug trial of 6 weeks duration using 4 intervention treatment arms. Two rheumatology centers participated in the study, 68 and 24 patients, respectively, were recruited in the Centre for Rheumatic Diseases, Pune, and Nizam Institute of Medical Sciences, Hyderabad. The protocol was approved by the respective institutional ethics committees. We followed the trial methodology (including patient selection, inclusion, and exclusion criteria, efficacy measures, safety evaluation and statistics, Ayurvedic plant standardization and manufacture, animal toxicity studies) used in the first NMITLI trial.^[7] Prior to signing the

informed consent, the patients were properly informed and counseled. However, some important variations and features of this trial are described.

Ayurvedic formulations

The description of the ingredients, rationale, and pharmacologic properties (including Ayurvedic), standardization and manufacture of “B” and “C” formulations were recently published.^[7] Extracts of Sallaki Guggul and Bhallataka Parpati were new additions and were individually manufactured as per Ayurvedic Pharmacopoeia and GMP guidelines and standards.^[9] Table 1 describes the compositions and dosing in each of the 4 intervention arms (Group I, II, III, and IV). All the primary formulations in each of the intervention arm had a core composition of Shunthi and Guduchi. The core composition per se and coded as “SG” was used in Group III intervention group. Patients in groups III and IV were also treated with Sallaki Guggul and Bhallataka Parpati, respectively. In brief, the daily dosage of Shunthi, Guduchi, Ashwagandha, and Amalaki, in the current study [Table 1] was 1.5–2 times higher than that used in the earlier trial.^[7] Shunthi was used as powder. Bhallataka Parpati is a popular traditional preparation of Vaidya Yashwant Govind Joshi, a senior Ayurvedic Practitioner in Pune, used to treat arthritis and allegedly considered to be safer than some of the classical Bhallataka preparations. Vaidya Joshi supervised the current study preparation, which essentially was an oil extract of Bhallataka treated with a resin of a medicinal plant called *Shorea robusta* in a systematic process to yield a dry powder (called *Parpati* in Ayurveda). Guduchi, Ashwagandha, Gokshur, and Amalaki were used in form of aqueous extracts.

The development, standardization, and manufacture of Ayurvedic formulations were same as earlier trial.^[7]

Table 1: Formulations used in each of the intervention arms

Group	Drug code and dosage regimen (no. of capsules)	Daily dose of ingredients
I	GAGS (2 TID)	Shunthi (1500 mg)+Guduchi (330 mg)+Ashwagandha (900 mg)+Gokshura (324 mg)
II	GAGS (2 QID)	Shunthi (2000 mg)+Guduchi (440 mg)+Ashwagandha (1200 mg)+Gokshura (432 mg)
III	SG (2 BID) and Sallaki Guggul (2 BID)	Shunthi (1000 mg)+Guduchi (220 mg); Sallaki Guggul (2000 mg)
IV	Bhallataka Parpati (2 TID)+SGA (2 TID)	Bhallataka Parpati (1125 mg); Shunthi (1500 mg)+Guduchi (330 mg)+Amalaki (750 mg)

Formulations coded as GAGS, SG, and SGA were first evaluated as “B,” “D,” and “C” formulations in lesser doses in an earlier trial^[7] under the NMITLI Arthritis Project. Shunthi was used as powder while Guduchi, Ashwagandha, Gokshura, and Amalaki were used as aqueous extracts

Ayurvedic experts of NMITLI project finalized the optimum doses and combinations based on personal experience, classic texts and pharmacopoeia, and consensus.

All trial material was procured and appropriately coded by Interdisciplinary School of Health Sciences under the direct supervision of senior investigator who was not part of the clinical team (BP). The safety of the interventional drugs was endorsed by the results of the acute and subacute animal toxicity studies carried out prior to the current drug trial at Agharkar Research Institute, Pune, as per OECD guidelines Serial Number 423.^[10]

The prescribed doses shown in Table 1 were taken as capsules with plain water and spaced over the wakeful hours irrespective of the meal timings. Patients were not asked to follow any specific dietary advice. They could carry on with their usual diet, physical activities, and exercises but were advised not to begin any new exercise/physiotherapy program or any other intervention (medication or otherwise) during the study period. The patients were advised to continue any other medication for a comorbid disorder (such as diabetes and hypertension) under supervision of their family doctor.

Selection of patients

Inclusion criteria

Patients fulfilling American College of Rheumatology (ACR) classification criteria of OA were included for this study. The inclusion criteria were patients of either gender, age group 40–70 years, diagnosis of OA knees based on typical history, clinical examination findings, and classical radiologic findings;^[11] pain visual analog score (VAS) ≥ 4 cm in one or both the knees while performing a weight-bearing activity during preceding 24 h; ambulant patients; who required analgesic and/or [nonsteroidal anti-inflammatory drug (NSAID), eg, ibuprofen] for pain relief were included in the study.

Exclusion criteria

Patients with nondegenerative joint diseases or other joint diseases, which would interfere with the evaluation of OA; known contraindication to any of the investigational products (especially *Bhallataka*) and medicinal plants; pregnant, lactating women, and those having childbearing potential and not following adequate contraceptive measures; nonambulatory patients or severe disabling arthritis; those who had history of intra-articular knee injection (in particular corticosteroids and hyaluronon equivalents) within the month preceding the study; patients who were undergoing treatment with methotrexate, colchicine, anticoagulants, lithium, steroids, hydantoin; patients having history of peptic ulcer or bleeding ulcer; those with evidence of severe unstable renal, hepatic,

hemopoietic, and cardiac disorder; patients participated in any trial in preceding one month; patients on antipyretics, analgesics, tranquilizers, hypnotics, excessive alcohol, or any other drug, which would interfere with pain perception and need for other drug therapy for OA, patients refused to give consent or unwilling to come for regular follow-up and any patients considered not eligible according to the investigator's discretion, were excluded from the study.

Eligible patients who gave consent were enrolled into one of the 4 intervention groups [Table 1] as per the protocol randomization schedule. All pain relieving medications, including nonsteroidal anti-inflammatory drugs were stopped prior to enrolment.

Washout period

All patients underwent a supervised maximum washout period of 5 days; lesser if the analgesic was known or pain became intolerable. Rescue analgesics were not permitted during the study period.

Efficacy variables

Endpoint evaluation visits were made at baseline and at weeks 1, 4, and 6 (completion).

Pain visual analogue score

Active pain VAS (0–100 mm on a horizontal scale) and WOMAC pain were considered to be primary efficacy measures.

Western Ontario and McMaster University's OA Index

A validated Indian version^[12] of WOMAC [Western Ontario and McMaster University's OA Index version LK3]^[13] for evaluation of knee and hip pain was used; pain (5 questions), stiffness (2 questions), and difficulty (17 questions) are scored using questions to indicate varying levels of difficulty from none to extreme (score range 0–4). Several other efficacy measures were also used—pain VAS on rest, 50 feet walking time, physician and patient global assessment (graded from asymptomatic to a very severe category) of disease, and patient's graded assessment of drug tolerability. An Ayurvedic case record form (including *prakruti*) was also completed by an Ayurvedic physician (data not presented).

Baseline symptoms and adverse events

Patients were specifically questioned as per a predetermined list of common symptoms (anorexia, nausea, vomiting, diarrhea, constipation, dysuria, skin rash, giddiness, oral mucous ulcers, dyspepsia, and abdominal discomfort and pain) based on our experiences in clinical practice and previous trials.^[3,4,14] Patients were also encouraged to volunteer information that they considered to be adverse events (AE) or a side effect (SE). A general physical

examination that included blood pressure measurements was carried out at every evaluation visit.

Investigations

The focus of investigations was on safety rather than any efficacy parameter. Laboratory variables included detailed safety data (routine hematology, biochemistry—renal, hepatic, and metabolic). However, we also investigated some efficacy markers to understand likely actions of the formulations. A serum assay for hyaluronic acid and selected inflammatory cytokines (Interleukin/IL-1 β , IL-6, and tumor necrosis factor/TNF- α) and a urinary assay to determine c-telopeptide fragment of Collagen II (C-TAX, a surrogate marker of cartilage breakdown) was carried out in patients enrolled in CRD.

Data and statistics

Data were entered centrally in CRD using a special software program designed by using a standard visual basic (for Windows) tool under supervision of trial coordinator (MS).

Sample size was not calculated as per any statistical method and no assumptions were made regarding “effect size.” An intention-to-treat analysis with the “last observation carried forward” was carried out. Significance was ascertained at $P < 0.05$ (two tail). Standard statistical software program SPSS version 12.5 was used.

Observations and results

Out of 92 recruited patients, 86 completed the study (including 72 women), 6 patients withdrew from the study after baseline randomization and were excluded from the analysis. Groups I, II, III, and IV intervention enrolled 23, 22, 22, and 19 patients, respectively [Table 1]. Median duration of illness was 4.5 years.

The interventional groups were well matched for several variables as shown in Table 2.

Safety and tolerability

Tables 3 and 4 show the number of patients with adverse events (AE) and number of AE in each of the intervention groups. All AE reported were mild and few required symptomatic remedy, which was usually as per standard Ayurvedic practice. Upper gut symptoms of discomfort, burning sensation or acid-peptic disorder related were usually treated with advise of minor dietary modifications (avoid excess salty, pungent, and spicy food) and consuming plenty of water, coconut water, and coriander. Although some patients reported skin rash and generalized itching, we did not observe a skin rash.

None of the patients withdrew due to any adverse event or

Table 2: Baseline demographics and selected efficacy measures in the intervention arms

Feature	Group I (n=23)	Group II (n=22)	Group III (n=22)	Group IV (n=19)
Female, number	18	17	18	14
Age (years), mean	58	56.4	52.1	58.2
Duration of disease (years), mean	6.2	6.9	6.2	5.2
Body mass index	27.4	28.6	29.5	26.2
Maximum pain on visual analogue scale (0–10 cm) on body weight bearing activity (walking/standing)	6.3	6.5	6.2	6.6
Time (seconds) to walk 50 feet horizontal ground	17	17.4	17.7	16.9
WOMAC pain (score 0–20)	7.9	7.6	7.6	8.9
WOMAC difficulty (score 0–68)	22.6	21.8	22.3	24.1

n = Number of subjects, WOMAC = Western Ontario McMaster’s University Questionnaire. Index score to evaluate hip and knee function in pain (score 0–20), stiffness (score 0–10) and difficulty (score 0–68) domains and a validated Indian version (WOMAC-CRD, Pune) was used in the study

Table 3: Number (percent) of patients with adverse events as per intervention arm

Adverse event	Group I (n=23)	Group II (n=22)	Group III (n=22)	Group IV (n=19)
Epigastric burning	3 (13)	4 (18)	4 (18)	1 (5.3)
Anorexia	1 (4.3)	0	1 (4.5)	1 (5.3)
Nausea	0	1 (4.5)	1 (4.5)	0
Vomiting	0	0	1 (4.5)	0
Diarrhea	1 (4.3)	1 (4.5)	1 (4.5)	0
Constipation	1 (4.3)	4 (18)	1 (4.5)	0
Skin rash/itching	0	1 (4.5)	1 (4.5)	0
Mild increase in liver enzymes	0	0	0	2 (10.5)

Table 4: Number (percent) of episodes of adverse events as per intervention arm

Adverse event	Group I (n=23)	Group II (n=22)	Group III (n=22)	Group IV (n=19)
Epigastric burning	6 (26)	4 (18.1)	5 (22.7)	1 (5.2)
Anorexia	1 (4.3)	0	1 (4.5)	1 (5.2)
Nausea	0	1 (4.5)	1 (4.5)	0
Vomiting	0	0	1 (4.5)	0
Diarrhea	1 (4.3)	1 (4.5)	1 (4.5)	0
Constipation	1 (4.3)	4 (18.1)	1 (4.5)	1 (5.2)
Skin rash/itching	0	1 (4.5)	1 (4.5)	0

drug-related toxicity. Physical examination including, blood pressure readings remained normal for all patients at every evaluation visit. Except for elevated serum liver enzymes (in particular serum glutamic pyruvate transaminase) up to 1.5 times the upper laboratory normal limit in Group IV

Table 5: Mean change (standard deviation) and improvement percentage in pain VAS and WOMAC index score in the intervention groups from baseline to 6 week completion end point

Variable	Group I (n=23)	Group II (n=22)	Group III (n=22)	Group IV (n=19)
Maximum pain on visual analogue scale (0–10 cm) on body weight bearing activity (walking/standing)	0.95 (2.04)	0.68 (1.68)	0.77 (1.7)	1.4 (1.77)
Percentage improvement in Maximum pain on visual analogue scale	12.5%	10.2%	8.6%	21.5%
WOMAC pain	1.17 (3.43)	0.32 (2.76)	0.45 (2.93)	1.37 (2.38)
Percentage improvement in WOMAC pain	7.4%	-1.2%	-3.3%	15.8%
WOMAC difficulty	1.13 (10.70)	-0.09 (7.67)	2.64 (6.83)	1.10 (10.06)
Percentage improvement in WOMAC difficulty	-4.3%	-9.9%	10.3%	0.4%

Groups compared using ANOVA, no significant difference observed. *n* = Number of subjects, WOMAC = Western Ontario McMaster's University. Questionnaire Index score to evaluate hip and knee function in pain (score 0–20), stiffness (score 0–8) and difficulty (score 0–68) domains and a validated Indian version (WOMAC-CRD, Pune) was used in the study; '↓' notation indicates worsening

(C formulation and *Bhallataka parpati*), all other laboratory parameters remained within normal limits.

Efficacy

Table 5 shows the mean change in active pain VAS and WOMAC score in each of the groups. There were no significant improvement differences between the groups for any of the variables. Significant clinical improvement for active pain VAS (95% confidence interval for mean change 0.5–2.22) and WOMAC pain score (95% confidence interval for mean change 0.22–2.5) was maximally seen in Group IV. When adjusted for age, the percentage mean change in active pain VAS from baseline to completion was maximum (41%) in Group IV. A lower dose of “B” in Group I showed numerically superior improvement (active pain VAS and WOMAC Pain) to the higher dose of “B” in Group II [Table 5]. However, except for a higher frequency of constipation reported in Group II, other AE were similar in the groups that were treated with different doses of “B.”

DISCUSSION

The primary objective of the current short-term study was to evaluate safety of higher doses of standardized *Shunthi–Guduchi* formulations meant to improve the efficacy in the treatment of symptomatic OA knees; these formulations were identified in an earlier drug trial.^[7] Despite using doses 1.5–2 times higher than previous use [Table 1], the number of AE [Table 4] and the number of patients with AE [Table 3] in the current study was strikingly low. The AE were uniformly mild and managed with standard Ayurvedic advice and did not cause any patient to withdraw during the 6-week study period. None of the patients in the current study suffered a serious AE. None of the patients consumed any analgesic during the study period.

The high doses of *Shunthi–Guduchi* formulations in the current study [Table 1] were guided by classical Ayurvedic texts but finalized through consensus of Ayurvedic experts and study investigators. It was decided to evaluate

2 higher dose regimen of “B” formulation (Group I and II) because of some discrepancy in the experts' opinion. Similarly, a higher dose of SG core platform formulation (group III) and “C” (group IV) was used in groups III and IV. Higher doses did not produce increased AE. An increased frequency of mild constipation was reported with the higher dose of “B” [Tables 3 and 4]. It is also interesting to note that in sharp contrast to the lesser dose, a higher dose of “B” did not result in a worsened overall AE profile [Tables 3 and 4] but also failed to show better improvement in pain or WOMAC scores [Table 5].

The nature of AE were mostly related to gut and ranged from mild dyspeptic symptoms to epigastric pain and burning. The number of patients and individual AE in each of the intervention arms was much less than that observed with corresponding intervention groups at eight week study period in the earlier trial.^[7] Interestingly, two patients in intervention group IV [Table 3] who were treated with a *Shunthi–Guduchi–Amalaki* formulation along with *Bhallataka Parpati* showed mild elevation of hepatic SGPT. We could not find a similar elevation of serum liver enzyme, especially with reference to corresponding formulation, during a review of the earlier trial^[7] laboratory data. However, in our earlier study on classical *Bhallatak* formulation “*Amrut Bhallatak*,” we found elevation of liver enzymes (SGOT and SGPT) in 3 out of 45 patients treated for 6 weeks in incremental higher doses.^[15]

We have also used *Bhallataka Parpati* as a monotherapy to treat rheumatoid arthritis in a 6-month controlled drug trial but did not observe elevation in serum liver enzymes.^[16] *Bhallataka* is a popular Ayurvedic medicinal plant used in several classical formulations and well known to cause severe hypersensitivity and toxicity, especially that of skin, mucosa, gut, and liver. *Bhallatak* is used very cautiously in Ayurvedic practice due to its known toxicity and hypersensitivity.^[17] The mild hepatic AE in the current study may be due to a high dose of *Shunthi–Guduchi–Amalaki* formulation administered along with *Bhallataka Parpati*. The latter needs further investigation.

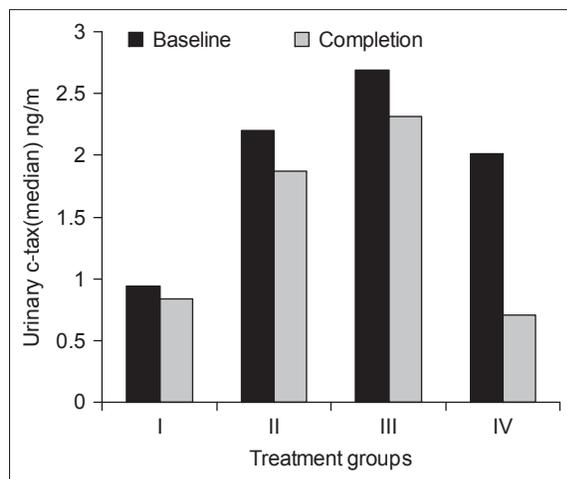


Figure 1: Urinary CTX II (C-Telopeptide Fragments of Collagen Type II) assay (median, ng/mL) as per the intervention arms

Although safety was the prime concern of the current study, it was reassuring to note improved efficacy in Group IV. Rescue medication was not allowed in the current study. It is against this background that the results shown in Table 5 assume significance. Patients with moderately severe chronic OA knees and a high extent of active pain VAS at baseline were enrolled into the current study [Table 2]. Chondroprotection is a laudable objective for any long-term medication in chronic OA.^[1] However, it is “pain” that encourages a patient of OA knees to seek quick relief, and modern medicines score high in this regard. The earlier NMITLI drug trial study allowed paracetamol as a rescue medication and demonstrated a fair degree of reduced consumption.^[7] In the current study of 6 weeks duration, using higher doses of formulations selected from the latter trial, we could manage without the rescue paracetamol and demonstrate fair–good pain relief [Table 5]. The addition of *Bhallataka Parpati* seems to have also contributed to improved pain relief. The pain relief in Group III with the addition of *Sallaki Guggul* was surprisingly modest despite a numerically best reduction in WOMAC difficulty. However, OA is a chronic disorder and a long-term relief would be more meaningful. Several laboratory markers (hyaluronic acid, cytokines, and C-TAX II) of efficacy were investigated in the current study but consistent results were only demonstrated with the urinary C-TAX II assay. It is interesting to note that although there were no significant differences, all the intervention groups showed reduction in urinary C-TAX [Figure 1] with an impressive reduction seen in group IV. The latter paved way for further validation of *Shunthi–Guduchi* formulations and *Sallaki Guggul* in particular.

There are several limitations in this study. The treatment of disease in Ayurveda is holistic and tailored to an individual and we have only focused on formulations. The sample size

was small and the duration of the study short. *Bhallataka parpati* is strictly not a classic text book Ayurvedic formulation but was chosen because of its popular use by a renowned Ayurvedic physician. Safety and tolerability is a fundamental advantage with Ayurvedic medicines and difficult to capture totally in a trial setting.^[18]

CONCLUSION

In conclusion, we have demonstrated an impressive safety profile of *Shunthi–Guduchi* formulations in the treatment of OA knees despite increased optimized doses and over and above that used in an earlier NMITLI drug trial.^[7] Although not a primary objective, the increased dose use of *Shunthi–Guduchi*-based formulation, in particular when combined with *Amalaki*, and administered in combination with *Bhallataka parpati* also seems to improve efficacy (pain relief). Addition of *Sallaki Guggul* also seems to have improved efficacy without increasing the adverse event profile. Finally, in conjunction with the previously published NMITLI trial,^[7] we strive to demonstrate the NMITLI model for a rapid (and possibly economical) and scientifically appealing clinical development of Ayurvedic formulations in chronic disorders, such as OA. The results of the current study were used to design a statistically powered drug trial for the final evaluation of *Shunthi–Guduchi*-based formulations in the treatment of OA knees.

AUTHOR CONTRIBUTION

The protocol was principally designed by AC with important inputs from GT and MS. The laboratory investigations were supervised and carried out by AV. GT and BP were largely responsible for finalizing all aspects of the Ayurvedic formulations. The trial was co-ordinated by MS. Statistical analysis was carried out by SS. This manuscript was prepared by AC, GT, and MS and all the authors vouch for its correctness and veracity. As chair of the NMITLI arthritis project, BP was responsible for its concept, rationale, and plan.

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Ayurvedic clinical evaluation methods. Several senior NMITLI experts and Ayurvedic physicians provided invaluable assistance and in particular Dr. GN Qazi, Dr. V Sumantran, Dr. Ulhas Wagh, Dr. Ashok Vaidya, Dr. Rama Vaidya, Dr. AM Mujumdar, and Dr. Pushpagandhan. Dr. Qazi was chiefly responsible for the selection of Guggul formulation used in this study.

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The Ayurvedic formulation drugs were principally developed in SHS and further standardized in Natural Remedies, Bangalore. Animal toxicity and mechanism of action studies were carried out in ARI. The drug trial protocols were principally developed and coordinated by CRD.

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