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RESEARCH ARTICLE

Safety and efficacy of *Curcuma longa* extract in the treatment of painful knee osteoarthritis: a randomized placebo-controlled trial

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Abstract *Curcuma longa* Linn. is widely used for the treatment of disorders associated with inflammation and was evaluated for its safety and efficacy in the treatment of painful knee osteoarthritis (OA). This was a randomized, single blind, placebo-controlled trial. Total of 120 patients (37 males and 83 females) with primary knee OA received either placebo (400 mg twice daily) or NR-INF-02 (500 mg twice daily) or glucosamine sulphate (GS) (750 mg twice daily) alone or combination of NR-INF-02 and GS for 42 days. The efficacy was assessed during treatment period, on day 21 and day 42. The decrease in severity of pain symptom and function of affected knee as primary efficacy outcome measure was assessed by Visual Analog Scale (VAS) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scale, respectively. The clinical examination of affected joint was measured by an orthopaedic specialist and using a Clinician Global Impression Change (CGIC) scale. The analysis of post-treatment scores following administration of NR-INF-02 using VAS, WOMAC, and CGIC at each clinical visit showed significant decrease ($p < 0.05$) compared to placebo. NR-INF-02 treated group showed a significant ($p < 0.01$) decrease in use of rescue medication, along with clinical and subjective improvement compared to placebo. The tolerability and acceptability profile of NR-INF-02 was better during the trial period. The study demonstrates safety and efficacy of NR-INF-02 as a useful treatment option for patients with primary painful knee OA.

Keywords *Curcuma longa* Linn. · Osteoarthritis · Visual Analog Scale (VAS) · Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) · Clinician Global Impression Change (CGIC) · Placebo-controlled clinical trial

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Introduction

Osteoarthritis (OA) is one of the most common types of arthritis. A community survey in rural and urban parts of India shows its prevalence to be 17–60.6 % (Sharma et al. 2007). OA is reported to affect 20 million people in US alone and the number is expected to increase to 66–100 % over the next two decades (Felson 2008).

The treatment options for OA include pharmacological, non pharmacological, and surgical. The most frequently used pharmacological agents include analgesics (Felson 2006) viz., acetaminophen, NSAIDs like naproxen, salicylates, ibuprofen, selective COX2 inhibitor (celecoxib), and glucosamine, chondroitin sulphate, capsaicin, intra-articular injections of hyaluronic acid, steroids, etc. The side effects of analgesics vary from mild gastritis to gastric ulcers, bleeding and perforation (Fries et al. 1991).

The use of oral glucosamine is well established in the treatment of OA over decades. Glucosamine as a precursor of glycosaminoglycans forms a major component of the joint cartilage. It is therefore hypothesized that supplemental glucosamine may help rebuild cartilage and relieve the symptoms of arthritis (Felson 2006; Clegg et al. 2006).

Usage of alternative therapies, such as acupuncture and medicinal herbs, are on the rise since there are risks and

limitations associated with commonly used NSAID group of drugs. According to Ahmed et al. (2005), 60–90 % of OA patients are reported to seek treatment with complementary and alternative medicine (CAM). Many herbal drugs have been investigated for their utility in the treatment of OA and also found to be safe. *Curcuma longa*, one of the herbal preparations, is shown to be effective in the management of OA (Khanna et al. 2007). Curcuminoids, a component of *Curcuma longa*, has been extensively studied for the treatment of different types of arthritis (Jurenka 2009). However, there are no reports on anti-inflammatory and analgesic activity of polar fraction especially polysaccharides containing *Curcuma longa* extract.

Hence, the present placebo-controlled, randomized trial was designed to investigate efficacy and safety of polysaccharide rich *Curcuma longa* extract (NR-INF-02) for its analgesic and anti-inflammatory property in patients with knee OA and to compare the same with placebo, glucosamine sulphate (GS) alone, and its combination with GS.

Methods

The investigational product NR-INF-02, an extract from rhizome of *Curcuma longa* Linn., developed and registered as Turmacin™ by Natural Remedies Pvt. Ltd, Bangalore, India was used as a trial medication. This was supplied as oral gelatin capsules each 500 mg of active NR-INF-02 containing 12.6 % w/w polysaccharides as determined by high pressure liquid chromatography (HPLC) described by Gomis et al. (2001).

This was a randomized, single blind, placebo-controlled, comparative study carried out by the Division of Clinical Pharmacology at the outpatient Department of Orthopedics, of a tertiary care hospital. Approval from Institutional Ethical Review Board (IERB) was obtained. The study was carried out according to the principles of the International Conference on Harmonization (ICH) and Good Clinical Practice (GCP) as well as World Health Organization (WHO) and Indian Council of Medical Research (ICMR) guidelines for controlled trials on pharmaceutical products, 2006. The trial was registered at Clinical Trial Registry of India [CTRI/2010/091/001251]. Written and informed consent was obtained from each patient at screening before the initiation of study-related procedures. The power of the study was 87 % with a sample size of 30 in each of the four groups ($N = 120$ excluding drop outs) to detect the difference of 45 % reduction in pain scores using VAS scale compared to placebo.

Patients of both genders were included in the trial if they were above 40 years of age with clinical evidence confirming diagnosis of knee OA. The duration of pain was at least 6 months on majority of days during the preceding months and showing radiological evidence (tibiofemoral osteophytes of at least 1 mm and Kellgren and Lawrence grade 2 or 3) (Kellgren and Lawrence 1957) of OA Grade 2 [definite osteophytes, definite narrowing of joint space] and Grade 3 [moderate multiple osteophytes, definite narrowing of joints space, some sclerosis, and possible deformity of bone contour]. Patients with concurrent medical or arthritic conditions confounding evaluation of the knee OA, primary predominant patella-femoral disease, history of clinically significant trauma/surgery to the affected knee, and co-existing disease that could preclude the successful completion of the trial were excluded from the trial.

A specially designed proforma was used to collect demographic data such as, age, sex, weight, height, etc. The disease data, duration, and severity of the OA including co-existing disease conditions such as controlled diabetes mellitus, hypertension, and data on drug treatment, on oral, and topical use of NSAIDs were recorded.

The subjects enrolled for clinical trial were allocated to either one of the treatment groups viz., placebo, NR-INF-02, GS, combination of NR-INF-02 and GS using computer-generated simple randomization sequence. The unique integer random numbers were then considered (box containing either placebo or NR-INF-02 or combination) for allocation of treatment with trial medication generated at Natural Remedies Pvt. Ltd., Bangalore, India. The trial subjects and orthopedic consultant were blinded, during the entire trial period except study investigator (single blind) who was aware of treatment intervention. The trial procedure was explained to patients in their respective language before randomization and enrollment procedure.

The treatment schedule of various study groups and doses are mentioned in Table 1. The dose of NR-INF-02 was administered based on the pre-clinical studies, wherein NR-INF-02 showed significant anti-inflammatory and analgesic activity at 90 mg/kg rat body weight (unpublished data). The dose for glucosamine was arrived on the basis of previous published literature (Herrero-Beaumont et al. 2007).

The assessment of primary outcome measure among study patients was carried out on day zero, 21 and 42 for severity of OA pain using Visual Analogue Scale (VAS) which was scored between 0 and 100 [‘0’ = no pain to ‘100’ = most severe pain].

WOMAC scale (Bellamy 1989), validated in previous study and modified for Indian use [CRD Pune version] (Likert Version-3.0), was used for functional assessment with 24 questions (Q) to grade the pain (Q1–5), stiffness (Q6–7), and physical functional difficulty (Q8–24) pertaining to the affected knee joint/joints. The patient response was graded qualitatively (0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = extreme) with a maximum score of 96 (Chopra et al. 2004).

Table 1 Treatment schedule with trial medications in patients with knee OA

Pt. group no.	Treatment groups and doses	Morning (No. of capsules)	Night (No. of capsules)	Total dose/day in mg
I	Placebo (Microcrystalline cellulose)—400 mg/capsule	1	1	800
II	NR-INF-02 (500 mg/capsule)	1	1	1,000
III	GS (375 mg/capsule)	2	2	1,500
IV	NR-INF-02 (500 mg/capsule) + GS (375 mg/capsule)	1 + 2	1 + 2	1,000 + 1,500

The Clinician Global Impression of change (CGIC) was employed to assess improvement in patients' overall condition and was rated based on the clinical examination on day 21 and 42. The scale range was from 0 to 7 ['0' = no pain and '7' = worst pain]. Assessment through clinical examination was carried out by the designated orthopedic consultant for presence or absence of joint tenderness, crepitus, limitation of movement, subluxation of joint, and muscle wasting.

Tablets, acetaminophen (paracetamol) 2,000–4,000 mg per day, were allowed as rescue medication in patients of all groups. Patients were instructed to withhold rescue medication 24 h prior to clinical examination of knee joint at each clinic visit. The use of other drugs from NSAID group and narcotic analgesics were not permitted. The assessment of compliance to medications was carried out by directing study patients to record number of times study medications taken on a calendar given to each patient. This secondary outcome measure was assessed by recording number of acetaminophen (paracetamol) tablets used as rescue medication by each patient and was entered in Case Report Form (CRF) at each clinic visit. The total number of rescue medications consumed was then calculated for each individual group. The acceptability of test medications by study patients wherever available was recorded at the end of study period and graded as 0–3 (0 = Not acceptable, and 1–3 as acceptable—1 = good, 2 = better, and 3 = best).

The data on frequency of occurrence of adverse events as a measure of assessment of safety in each trial group was recorded throughout the study period and categorized based on organ system involved. The causality was evaluated using WHO guidelines.

Statistical analysis

Data were analyzed using one-way ANOVA to compare the baseline values for demographic, anthropometric, and clinical characteristics. The Chi square test was used for the analysis of categorical variables and repeated measure ANOVA for the primary efficacy and safety parameters, i.e., clinical assessment from day 0 to day 42, and when found significant Bonferroni's post hoc test and mixed model analysis to assess the effect of pharmacological intervention among the groups as per intension to treat [ITT] principle. p value less than 0.05 was considered as statistically significant.

Results

Of the 157 screened, 120 eligible patients were randomized into the study [Fig. 1]. There was no significant difference in the demographic, anthropometric, and clinical characteristics between the four study groups except gender wise distribution ($p = 0.03$) and the intake of NSAIDs for OA ($p = 0.019$) (Table 2).

The reduction in VAS, WOMAC, and CGIC at baseline, first follow-up and second follow-up are presented in Table 3. Overall, there was a significant reduction in VAS, WOMAC, and CGIC scales over the treatment period. There was a significant interaction effect between the four study groups and time for VAS, WOMAC, and CGIC scales ($p < 0.01$). Significantly greater reduction was observed in the VAS pain scores in patients who were administered NR-INF-02 and GS alone compared to placebo and combination of NR-INF-02 with GS groups ($p < 0.05$). However, no significant difference was observed between NR-INF-02 and GS alone. Reduction in the WOMAC scores was significantly higher in the NR-INF-02 compared to placebo and combination of NR-INF-02 with GS groups ($p < 0.05$) with no significant difference observed with group treated with GS. NR-INF-02 alone and combination of NR-INF-02 with GS showed significant reduction ($p < 0.05$) for Clinicians Global Impression of Change (CGIC) compared with placebo and GS alone with greater effect being observed for NR-INF-02 group.

There was a significant reduction in the number of patients complaining of joint tenderness from initial 29 patients to 4 patients at the end of the study [86.2 % reduction] in the NR-INF-02 treated group compared to other groups ($p < 0.01$). However, for the joint crepitus, a significant difference was seen in NR-INF-02 and also its combination with GS at the end of the study period. Significant decrease was obtained when patients were assessed for joint effusion, terminal limitation of joint movement across all treatment groups compared to placebo (Table 4).

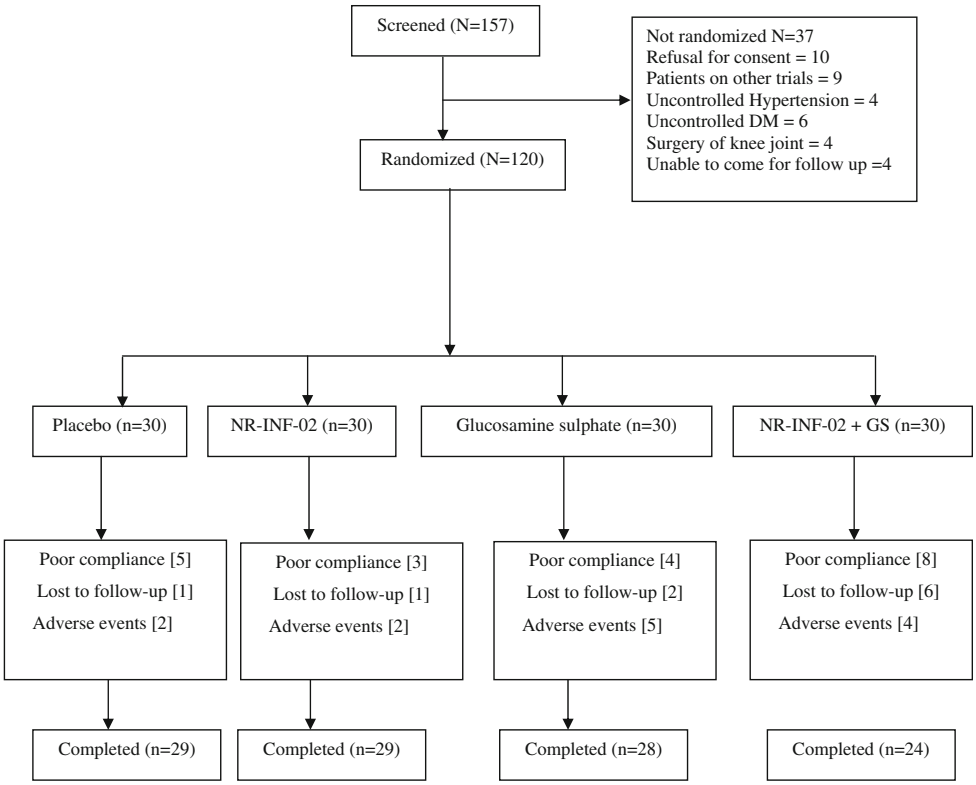

Fig. 1 Patient disposition for the study

Table 2 Baseline demographic, anthropometric, and clinical characteristics among the four study groups

General baseline characteristics	Treatment groups*				
	Placebo	NR-INF-02	Glucosamine sulphate (GS)	NR-INF-02 +GS	*P* value (One way ANOVA/Chi square)
Gender					
Male	13	13	5	6	
Female	17	17	25	24	0.03** Significant
Age (year)	56.77 ± 9.98	56.63 ± 10.58	56.80 ± 7.99	58.17 ± 9.30	0.91 Not significant
Weight (kg)	67.13 ± 9.54	65.53 ± 12.59	66.27 ± 9.34	67.00 ± 12.73	0.91 Not significant
Height (cm)	155.13 ± 8.31	155.67 ± 8.08	154.27 ± 7.43	155.13 ± 6.32	0.94 Not significant
Body mass index [BMI]	27.97 ± 4.21	27.01 ± 4.60	27.80 ± 3.08	27.89 ± 5.20	0.81 Not significant
Grade of OA					
Mild	1	2	2	2	0.72 Not significant
Moderate	22	23	18	22	
Severe	7	5	10	6	
Diabetes (yes/no)	5/25	7/23	4/26	4/26	0.69 Not significant
Hypertension (yes/no)	9/21	7/23	9/21	8/22	0.92 Not significant
Local NSAID's application (yes/no)	11/19	4/26	4/26	7/23	0.90 Not significant
Oral NSAID's intake (yes/no)	6/24	2/28	0/30	7/23	0.019**Significant
Baseline VAS	61.50 ± 13.71	66.50 ± 21.06	60.97 ± 16.80	65.83 ± 15.48	0.466 Not significant
Baseline WOMAC	57.23 ± 9.63	54.97 ± 9.85	58.30 ± 12.73	60.73 ± 11.47	0.240 Not significant
Baseline CGIC	05.77 ± 0.85	05.13 ± 1.16	05.67 ± 1.093	05.33 ± 1.32	0.110 Not significant

* All values are mean ± SD except for Gender, Diabetes, Hypertension, Local and Oral NSIAD's application

** $p < 0.05$

Table 3 Effect of treatment on VAS, WOMAC, and CGIC over 21st day and 42nd day follow-up

Variables + GS	Placebo ($n = 29$)	NR-INF-02 ($n = 29$)	Glucosamine ($n = 24$)	NR-INF-02 + GS ($n = 28$)
VAS[#]				
Baseline	61.50 ± 13.71	66.50 ± 21.06	60.97 ± 16.80	65.83 ± 15.48
21st day[1]	53.83 ± 15.84	38.83 ± 21.36[a,c]	41.33 ± 17.66[a,c]	49.48 ± 24.14
42nd day[2]	46.03 ± 20.84	19.48 ± 17.84[a,c]	29.29 ± 20.58[a,c]	36.33 ± 28.99
WOMAC[#]				
Baseline	57.23 ± 9.63	54.97 ± 9.85	58.30 ± 12.73	60.73 ± 11.47
21st day[1]	52.23 ± 9.63	36.67 ± 16.08[a,c]	44.17 ± 15.77	47.31 ± 19.16
42nd day[2]	47.90 ± 12.59	27.14 ± 16.13[a,c]	34.92 ± 19.48	36.21 ± 24.74
CGIC[#]				
Baseline	5.77 ± 0.85	5.13 ± 1.16	5.67 ± 1.09	5.33 ± 1.32
21st day[1]	5.53 ± 0.97	3.73 ± 1.92[a,b]	4.57 ± 1.40	4.41 ± 1.82[a,b]
42nd day[2]	4.72 ± 1.27	2.21 ± 1.80[a,b]	3.32 ± 1.78	3.37 ± 2.41[a,b]

[#] Significant interaction effect between time and treatment ($p < 0.01$)

[1] Significantly different from baseline to first follow-up ($p < 0.01$)

[2] Significantly different from baseline to second follow-up ($p < 0.01$)

[a] Significantly different from Placebo ($p < 0.05$); [b] Significantly different from GS ($p < 0.05$); [c] Significantly different from NR-INF-02 + GS ($p < 0.05$)

Table 4 Findings of parameters following clinical assessment among various treatment groups expressed as number (n) of patients and percentages (%)

Parameters of clinical examination	Placebo	NR-INF-02	Glucosamine sulphate (GS)	NR-INF-02 + GS
Presence of joint tenderness				
Baseline (n)	30 (100)	29 (100)	29 (100)	27 (100)
21st day	25 (83.3)	13 (44.8)	16 (55.1)	17 (62.9)
42nd day	20 (66.7)	4 (13.7)	8 (27.5)	10 (37.0)
Number and % reduction	10 (16.7)	25 (86.2)**	21 (72.4)	17 (62.9)
Presence of joint crepitation				
Baseline (n)	30 (100)	27 (100)	29 (100)	29 (100)
21st day	29 (96.7)	22 (81.4)	28 (96.5)	27 (93.1)
42nd day	28 (93.3)	17 (62.9)	26 (89.6)	18 (62.8)
Number and % reduction	2 (6.7)	10 (37)**	3 (10.3)	11 (37.9)**
Joint effusion				
Baseline (n)	11 (100)	13 (100)	13 (100)	13 (100)
21st day	8 (72.7)	2 (15.3)	3 (23.3)	1 (7.6)
42nd day	8 (72.7)	0 (0)	3 (23.3)	1 (7.6)
Number and % reduction	3 (27.2)	13 (100)**	10 (76.9)**	12 (92.3)**
Terminal limitation of joint movement				
Baseline (n)	7 (100)	6 (100)	6 (100)	6 (100)
21st day	6 (85.7)	2 (33.3)	0 (100)	3 (50)
42nd day	8 (114)	1 (16.6)	0 (100)	3 (50)
Number and % reduction	−1 (14.2)	5 (83.3)**	6 (100)**	3 (50)**

** Indicates $p < 0.01$

The use of acetaminophen (paracetamol) tablets in a dose range of 2,000 to 4,000 mg/day as rescue medication was reported as a secondary outcome measure which was significantly lesser in the NR-INF-02 group compared to other groups ($p < 0.01$) (Table 5). The assessment on patients' acceptability of the study medications from those available showed significantly [$p < 0.05$] higher rating for NR-INF-02 followed by GS, combination of NR-INF-02 with GS and placebo (93.1, 83.3, 67.9, and 60 %), respectively (data not shown).

Table 5 Extent of use of acetaminophen as rescue medication by patients in various treatment groups

[a] Significantly different from placebo ($p < 0.01$)

Variables	Placebo ($n = 30$)	NR-INF-02[a] ($n = 30$)	Glucosamine sulphate (GS) ($n = 30$)	NR-INF-02 + GS ($n = 30$)
Rescue medications				
Yes	25 (83.3 %)	13 (43.3 %)	22 (73.3 %)	18 (60.0 %)
No	5 (16.7 %)	17 (56.7 %)	8 (26.7 %)	12 (40.0 %)

Table 6 Pattern and extent of Adverse events (AEs) reported in various treatment groups

Pattern of AEs	Placebo ($n = 30$)	NR-INF-02 ($n = 30$)	GS ($n = 30$)	NR-INF-02 + GS ($n = 30$)
Generalized body pain	1	–	1	–
Cough	1	–	–	1
Dyspepsia	–	2	1	1
Fever	–	–	1	1
Sore throat	–	–	2	0
Pedal edema	–	–	–	1
Total AEs—13 (10.8 %)	2 (6.6 %)	2 (6.6 %)	5 (16.6 %)	4 (13.3 %)

A total of thirteen [10.8 %] adverse events (AEs) were observed across four treatment groups. The patients treated with NR-INF-02 exhibited least number of AEs during the intervention period. The AEs in all the study groups were mild and did not warrant the withdrawal of any study medications (Table 6).

Discussion

Osteoarthritis is one of the most common types of arthritis among elderly population with a significant impact on quality of life. To the best of our knowledge, this would be the first clinical study using curcuminoids-free *Curcuma longa* Linn. as a single ingredient in the treatment of knee OA. Hence, in the present study, safety and efficacy of NR-INF-02 was investigated and compared with placebo, GS alone and combination of NR-INF-02 with GS. The results showed a significant reduction in pain as the primary efficacy outcome measure following administration of NR-INF-02 over a period of 42 days using standard validated scales viz. VAS, WOMAC, and CGIC. In addition, a reduced intake of rescue medications was observed in this group which is further supportive of efficacy profile of NR-INF-02.

The mechanisms of actions of *Curcuma longa* Linn. implicated in improving symptoms and signs of OA have been explored extensively in the past which primarily include anti-inflammatory and anti-oxidant properties. In addition, the various biochemical parameters that influence pharmacological activity have been proposed which include phospholipase, lipoxygenase, cycloxygenase 2, leukotrienes, thromboxane, prostaglandins, nitric oxide, and many other are reported to be involved in its beneficial effects (Chainani-Wu 2003; Badreldin et al. 2006).

The VAS scores are reported to indicate severity of subjective symptomatic pain in patients with chronic conditions like OA, whereas WOMAC is mainly for functional assessment of pain. In the present study, NR-INF-02 treatment significantly reduced both VAS and WOMAC scores in comparison with placebo thus supporting its dual beneficial effects among OA patients in terms of symptomatic and functional improvement along with pain relief thereby contributing to overall efficacy. It is interesting to note that the onset of beneficial effect of NR-INF-02, an herbal product was observed within 1 month. While it is difficult to justify the same, it may be attributed to the physicochemical properties of improved extract of polysaccharides contributing to enhanced potency and therefore pharmacological activity of this investigational product.

The use of functional scale WOMAC is an established validated scale for the evaluation of pain as a manifestation of OA. A number of national and international studies have been conducted using the same (Clegg et al. 2006; Bellamy 1989). However, in the present study the source WOMAC modified for Indian use (CRD Pune version) validated in the previous studies was used for convenience (Chopra et al. 2004). A differential response as a significant decrease in algofunctional parameters was observed in patients treated with NR-INF-02 compared to placebo and its combination with GS. The failure to observe similar response in patients treated with GS alone may be attributed to its lack of optimal anti-inflammatory effects within 42 days of treatment as against 6-month treatment in the previous study (Clegg et al. 2006). Further, a recent meta-analysis on glucosamine and chondroitin supplements has

reported that the joint health ingredients do not reduce joint pain or have a significant impact on narrowing of joint space (Wandel et al. 2010) indicating lack of their efficacy on structural changes. In addition, it may be important to note that the unfavorable pharmacokinetic characteristic profile of regular GS formulation involving negligible concentration attainable in the joint cartilage may be contributing to observed ineffectiveness in OA (Kulkarni 2012). Surprisingly, the combination of GS and NR-INF-02 was not superior to effects of NR-INF-02 alone as would be anticipated except in improving a few of the clinical outcome parameters such as joint crepitation and effusion in a limited number of patients.

A third scale—Clinician Global Impression of Change [CGIC] adopted based on clinical examination of affected joint/joints by an orthopedic consultant showed significant improvement in patients treated with NR-INF-02. This effect may be considered as an additional parameter supporting its therapeutic efficacy. As clinical examination plays a crucial role in evaluation of symptoms the observed decrease in the joint tenderness and effusion in the present study following treatment with NR-INF-02 may be attributed to its possible anti-inflammatory effect.

It is a well established fact that radiological features correlate poorly with pain relief in OA (Sharma 2003) and hence it was felt reasonable to do X-ray examination only for diagnostic purposes at the time of enrollment. Studies with long-term GS administration have revealed recognizable radiological improvement due to its modulatory effects on structural changes in OA. Hence, it may be prudent to examine the influence of NR-INF-02 on structural changes in OA through radiological examination only following its long-term administration. A significant reduction in pain along with reduced intake of acetaminophen [NSAID] permitted as rescue medication in patients treated with NR-INF-02 implies its efficacy in relieving pain and hence may benefit patients by minimizing treatment costs as well as reduced risk of ADRs associated with regular NSAID consumption in the elderly.

Different classes of immunomodulatory polysaccharides are known to be present in herbal products which include glucans and mannans and are found to possess anti-inflammatory activity in vivo after oral administration. These polysaccharides have been demonstrated to have good bioavailability after oral administration (Ramberg et al. 2010; Trnovec and Hrmová 1993). In addition, *Curcuma longa* Linn. is reported to contain bioactive polysaccharides, ukonans, as shown in various in vitro models (Gonda et al. 1993). Hence, it is hypothesized that these polysaccharides may be a contributory factor for the observed efficacy despite short-term treatment with NR-INF-02. Further, the efficacy outcome measures of our study are similar to those seen in earlier study with RA-11 (ARTREX, MENDAR), a standardized polyherbal *ayurvedic* formulation containing *Curcuma longa* Linn. as one of its components. This study design was a double blind, randomized, placebo-controlled trial for 32 weeks and the inclusion and exclusion criteria were similar to the present study. The results of this study showed a significant improvement in scores in the RA-11 treated group (Chopra et al. 2004). Another study by Kulkarni et al. (1991) has also evaluated the clinical efficacy of a herbo-mineral formulation containing roots of *Withania somnifera*, the stem of *Boswellia serrata*, rhizomes of *Curcuma longa*, and a zinc complex (Articulin-F), which was a randomized, double-blind, placebo-controlled, cross-over study in patients with OA for 12 weeks. The primary efficacy parameters were assessed based on severity of pain, morning stiffness, Ritchie articular index joint score, disability score, and grip strength. This study showed a significant decrease in the severity of pain ($p < 0.001$) and disability score ($p < 0.05$) with no improvement in radiological assessment in either groups. Hence, in the present study trial patients were subjected for X-ray examination only as inclusion criteria and not for post-treatment evaluation. It is important to note that the above studies did not involve clinical examination of the affected joint/joints by the orthopedic expert. In addition, in both these studies *Curcuma longa* Linn. was used in combination with other herbs/mineral components as against NR-INF-02 which contained polysaccharide extract as a single ingredient which produced significant effect within 21 days of its oral administration.

The present study has many strengths: (1) the trial product had a single ingredient (2) the study design was a parallel group, placebo-controlled evaluation (3) validated tools such as VAS and WOMAC were used for assessment of efficacy along with CGIC (4) efficacy outcome also included patients' overall acceptability of the trial formulation (5) study analysis was adjusted for the covariables such as age, gender, and BMI which removed the confounding variables. A few limitations to the present study include—(1) a small sample size (2) the study design was a single blind, due to differences in doses and formulations (3) short treatment duration not sufficient enough to assess safety and efficacy in long-term pain management (4) lastly even though validated scales were used to assess the OA pain these were subjective. It would have been appropriate to document the improvement and future course of OA in terms of preventing progression of structural damage seen as pathological sequel of OA to confirm the reliable efficacy outcome. The same was not possible due to shorter duration of treatment which was inadequate to reflect on these parameters. Hence, there is a need to confirm the above results in a larger number of patients with longer duration of treatment. However, the clinical and subjective

correlation of the achieved pain reduction is valid and the study provides supportive evidence for the basic proof of concept data on efficacy of NR-INF-02 for symptomatic management of painful knee OA.

Conclusions

The present study evaluated the efficacy and safety of NR-INF-02, GS and combination of two in the treatment of painful knee OA, in a placebo-controlled trial. This study effectively demonstrated acceptable efficacy and tolerability profile of NR-INF-02 in a small group of subjects indicating its utility as one of the treatment options in symptomatic management of pain among patients with uncomplicated knee OA.

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