A 32-Week Randomized, Placebo-Controlled Clinical Evaluation of RA-11, an Ayurvedic Drug, on Osteoarthritis of the Knees

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Background: The ancient Indian (Asian) Ayurvedic medicinal system uses herbomineral drugs to treat arthritis. Despite centuries of use, very few have been tested by drug trials. RA-11 (ARTREX, MENDAR), a standardized multiplant Ayurvedic drug (*Withania somnifera, Boswellia serrata, Zingiber officinale,* and *Curcuma longa*) is currently used to treat arthritis.

Objective: The objective of this study was to evaluate the efficacy and safety of RA-11 in patients with symptomatic osteoarthritis (OA) of the knees.

Methods: A total of 358 patients with chronic knee pain were screened free-of-cost in "arthritis camps" in an Indian metropolis. Ninety patients with primary OA of the knees (ACR classification; *Arthritis Rheum* 1986;29:1039–1049) were found eligible (postanalgesic washout pain visual analog score [VAS] ≥40 mm in either or both knees on body weight-bearing activities) to enroll into a randomized, double-blind, placebo-controlled, parallel efficacy, single-center, 32-week drug trial (80% power to detect 25% difference, $P = 0.05$, 2-sided). Concurrent analgesics/nonsteroidal antiinflammatory drugs and steroids in any form were not allowed. Lifestyle and/or dietary restrictions, as per routine Ayurveda practices, were not imposed. Pain VAS (maximum pain in each knee recorded by the patient during the preceding 48 hours) and modified WOMAC (Western Ontario McMaster University OA Index, Likert scale, version 3.0) were the primary efficacy variables. The WOMAC section on "physical function difficulty" was modified for Indian use and validated before the trial. Routine laboratory testing was primarily done to monitor drug safety. At baseline, the groups (active = 45, placebo = 45) were well matched for several measures (mean pain VAS: active = 6.17; placebo = 6.5).

Results: 1) Efficacy: Compared with placebo, the mean reduction in pain VAS at week 16 (active = 2.7, placebo = 1.3) and week 32 (active = 2.8, placebo = 1.8) in the active group was significantly ($P < 0.05$, analysis of variance [ANOVA]) better. Similarly, the improvement in the WOMAC scores at week 16 and week 32 were also significantly superior ($P < 0.01$, ANOVA) in the active group. 2) Safety: Both the groups reported mild adverse events (AE) without any significant difference. 3) Withdrawals: Twenty-eight patients were discontinued. None reported drug-related toxicity. The majority failed follow up/compliance. No differences were observed between the groups.

Conclusion: This controlled drug trial demonstrates the potential efficacy and safety of RA- 11 in the symptomatic treatment of OA knees over 32 weeks of therapy.

Key Words: Ayurvedic medicine, herbal medicine, osteoarthritis, clinical drug trial, WOMAC

(*J Clin Rheumatol* 2004;10: 236–245)

Ayurvedic medicine has been popularly practiced in India since pre-Biblical times. The ancient Ayurvedic texts describe various forms of arthritis. It is difficult, if not impossible, to translate the Ayurvedic nomenclature into modern medicine terminology. However, Ayurvedic texts do make some distinction between diseases that are quite akin to the modern-day description of rheumatoid arthritis (RA) and osteoarthritis (OA). There is a unifying hypothesis that links gut with several forms of arthritis, and thus gut is the chief target for all antiarthritis therapies. No two individuals are alike. Ayurveda adopts a highly individualized holistic approach. Besides drugs and mind-boggling complex therapeutic interventions and maneuvers, Ayurveda advocates a number of lifestyle and dietary norms that would be tedious and frustrating to follow, at least in the modern context. The author (AC) has recently reviewed this subject, with special reference to rheumatology,[2–4] for readers of modern medicine literature.

The clinical efficacy and safety of the large number of current Ayurvedic formulations has not been evaluated in

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This study was funded and supported by BIO-VED Pharmaceuticals, Inc., USA and BIO-VED Pharmaceuticals, Pvt. Ltd., Pune, India. Deepa Chitre, MD, is the CEO and Medical Director of BIO-VED Pharmaceuticals, Inc., USA.

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ISSN: 1076-1608/04/1005-0236
DOI: 10.1097/01.rhu.0000138087.47382.6d

controlled clinical drug trials.[5] However, there is a strong community belief that Ayurvedic medicines are safe compared with modern medicines. Of late, there have been several publications supporting the purported antiinflammatory and biologic effects of some of the popularly used antiarthritic medicinal plants in Ayurveda.[6–9] Several of the modern studies demonstrate biologic effects that suggest immunomodulation and immune stimulation. Such an immunologic basis has been conceptually captured by the *Rasayana* (a Sanskrit word that basically means "strengthening and rejuvenation") branch of Ayurvedic science.[4,6] The Ayurvedic pharmacopeias[10] contain lucid descriptions of the *Rasayanic* properties of medicinal herbs and minerals, several of which are used to treat arthritis.

In an earlier randomized, placebo-controlled, parallel efficacy clinical drug trial[11] in patients of RA, the authors demonstrated that RA-1 had modest efficacy and an excellent safety profile. RA-1 was a standardized multiplant Ayurvedic formulation. The current RA-11 (trade name ARTREX, MENDAR) formulation, which is being evaluated for efficacy in patients with OA knees, is a further development of RA-1 in terms of greater potency, purity, and standardization. Interestingly, Ayurvedic physicians have often treated seemingly different diseases from modern medicine's viewpoint, with similar plant–mineral-based formulations. RA and OA are one such example. The RA-11 formulation, although derived from the Ayurvedic pharmacopoeia, has been standardized and manufactured using modern means and standards (see Appendix A). RA-11 contains purified plant extracts of *Withania somnifera, Boswellia serrata, Zingiber officinale,* and *Curcuma longa.* The Ayurvedic physicians have been using these medicinal plants to treat arthritis for several centuries. Some of their analgesic and antiinflammatory properties have been recently evaluated and reported.[12–21]

The efficacy and safety of the orally administered RA-11 active preparation was compared with that of a placebo in the treatment of patients with symptomatic primary OA of the knees.

MATERIALS AND METHODS

This was a randomized, double-blind, parallel efficacy, placebo-controlled, outpatient-based, single-center drug trial study. There were 2 phases of this study: screening/washout followed by a randomized, double-blind phase.

The trial was conducted at the Center for Rheumatic Diseases (CRD) situated in the metropolis city of Pune (Western State of Maharashtara), India. CRD is a referral clinical outpatient and research center recognized by the Government of India as a "scientific and industrial research organization" and University of Pune for doctorate and postdoctorate research. The monthly attendance ranges from 1200 to 1400 patients.

Screen/Washout

Arthritis camps were conducted in CRD and a nearby large medical diagnostic center to screen adult patients with "chronic knee pain" over a 6-week period by the chief investigator (AC). These camps were advertised in the local newspapers and were free-of-cost to the patient. The detail methodology of these camps has been described.[11] A total of 358 patients (OA = 246 [predominantly knees = 135; spine and knees = 76; primary generalized = 35], rheumatoid arthritis [RA] = 14, undifferentiated inflammatory arthritis = 8, soft tissue rheumatism = 9, ill-defined symptoms, probably related to occupation = 39, trauma = 8, gout = 1, miscellaneous [including juvenile-onset arthritis, hypermobility, systemic diseases, neurogenic, and so on] = 33) attended these camps. The first 90 patients who satisfied the inclusion criteria, and who were willing to participate in the study, signed the informed consent before enrollment. Patients of symptomatic primary OA knees, who were on a stable dosage of a nonsteroidal antiinflammatory drug (NSAID), were asked to indicate the maximum pain experienced in the knees within the last 48 hours on a pain visual analog scale (VAS), especially during body weight-bearing activities (like walking, standing) and considered eligible if the pain VAS was ≥40 mm. Subjects were not to be in wheelchair or bedbound. Detailed medical history, general physical examination, and rheumatologic evaluation were recorded at the screen by the designated rheumatologist and chief investigator (AC) of the trial. Laboratory tests, and radiography if indicated, were carried out as per protocol. Subsequently, all patients were examined by AC at every visit during the trial.

After signing the informed consent form (visit 1), patients were begun on an NSAID/analgesic washout period. The washout period was guided by prior NSAID use but kept to a minimum of 3 days. If the pain experienced by the patient during the washout period became intolerable, he or she could report for enrollment. Before enrollment, the patients were again asked to record their maximum pain within the preceding 48 hours during weight-bearing activities on a VAS. If the pain recorded was ≥40 mm in either or both knees, the patient was enrolled into the randomized phase to receive the study medication. The qualified knee(s) were then recorded as the index joint and were not to be changed thereafter during the trial.

Patients were encouraged to carry on their daily activities. They were also asked to continue any kind of exercises that they had been doing before enrollment.

Randomized Double-Blind Phase

This phase lasted for 32 weeks.

Randomization Code

Patients were assigned to the active or placebo group as per a predetermined computer-generated randomization

schedule for 90 patients on 1:1 basis. A sealed copy of the randomization code was kept with the sponsor and the chief investigator (AC) but was not revealed to the subjects or the clinical staff until completion of the study. In case of an emergency situation/severe adverse event suspected to be related to the investigational drug, the chief investigator was to provide the code to the concerned physician (not connected with the trial).

Evaluation End Points

After enrollment (week 0, visit 2), study visits were made by the patients on week 2 (visit 3), week 4 (visit 4), week 8 (visit 5), and 4 weekly thereafter till week 32 (visit 11).

Inclusion Criteria

Inclusion criteria consisted of: 1) age ≥35 years, 2) subjects with symptomatic osteoarthritis of the knee, classified as per the ACR[22] clinical plus radiologic criteria, 3) subjects with pain VAS ≥40 mm on weight-bearing activities, 4) stable dose of a NSAID for at least 1 month before enrollment, and 5) females of child-bearing potential only if practicing contraception for at least 1 month before and during the study; a negative urine pregnancy test within 1 week of study entry was mandatory.

Exclusion Criteria

Exclusion criteria consisted of: 1) rheumatoid arthritis, active gout, recent joint trauma (target joint), or joint infection; 2) patients with known hypersensitivity to RA-11 or any of its components; 3) patients who have received intraarticular corticosteroid injections in the knee joint within the previous 3 months; 4) a history of narcotic or alcohol abuse; 5) any serious and/or uncontrolled medical disease such as active peptic ulcer disease, coronary artery disease, or severe diabetes mellitus; 6) significantly abnormal renal and hepatic function; 7) pregnant or lactating women; and 8) any other condition considered unfit for enrollment by the investigator.

Clinical Evaluation

At each study visit, the knees were evaluated for soft tissue swelling/synovitis (graded: 0 = none, 1 = mild, 2 = moderate, 3 = severe). The patient and physician made an independent global assessment of the knee condition (graded: 0 = asymptomatic, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe). Patients completed the VAS and WOMAC (Western Ontario and McMaster University Osteoarthritis Index)[23] at all study visits.

Detailed general physical examination was carried out at entry, week 16, week 32, and on withdrawal.

Medications

Patients took 2 capsules of study medication (RA-11 or matching placebo) twice a day after meals, and this dosage remained constant during the double-blind phase. No concurrent analgesics/NSAIDs in any form, oral, injectable or topical, were permitted. Similarly, no form of steroid medication, including intraarticular, was allowed. Patients were not given any advice on lifestyle modification and diet. Patients were to continue a stable-and-fixed dose of medication for other systemic illnesses.

Adverse Events

Adverse events (AEs) were recorded at each study visit. However, a checklist containing commonly encountered symptoms, which could be the result of side effects, was served by the trial nurse to the patients. The following AE categories considered important by our Ayurvedic colleagues and also considered frequent in our community were inquired in the checklist: anorexia, nausea, abdominal pain, pruritus, stomatitis, insomnia; all other symptoms and signs considered as AEs could be added to this list.

Compliance

Study personnel conducted regular home visits to ensure compliance as per the protocol with special reference to medications and follow-up visits. A diary was provided to the patients to record their daily study and nonstudy medications, and any adverse health event. The trial coordinator (MS) checked the diary and further ensured compliance.

Withdrawal

If the patient's pain became intolerable and necessitated pain medications, he or she was withdrawn from the study. Every attempt was made to contact patients who withdrew themselves (without notifying) or failed to follow up to determine the reasons for withdrawal.

Laboratory Tests

Laboratory testing was carried out at entry, week 16, week 32, and on withdrawal. The following tests were done at entry and at completion of the study and/or at withdrawal: 1) hematology—erythrocyte sedimentation rate (Westergren, mm per hour), hemoglobin, hematocrit, red cell count, leukocyte count with differential and platelet count; 2) biochemistry—fasting blood sugar (65–110 mg/dL), serum bilirubin (0.1–1.0 mg/dL), SGPT/alanine amino transferase (male 0–40 IU/L; female 0–31 IU/L), SGOT/aspartate amino transferase (male 0–37 IU/L; female 0–31 IU/L), serum cholesterol (elevated if above 200 mg/d), blood urea nitrogen (8–23 mg/dL), serum calcium (8.8–10.6 mg/dL), serum creatinine (male 0.9–1.5 mg/dL; female 0.8–1.2 mg/dL), serum uric acid (male 3.4–7.0 mg/dL; female 2.4–5.7 mg/dL),; serum alkaline phosphatase (29–132 IU/L); 3) urinalysis—specific gravity, pH, protein, glucose, and microscopic examination of sediment; 4) urine pregnancy test in appropriate female subjects; and 5) 24-hour urine for free cortisol (30–150 μg) and creatinine (male 1–2 g; female 0.8–1.8 g). Normal laboratory values and their unit of measurement are indicated in parentheses.

The 24-hour urinary analysis for cortisol and creatinine was performed in the first 20 patients from each of the groups. This test was repeated in the same cohort at week 4 and week 16.

Efficacy Evaluation

Both pain VAS[24,25] and WOMAC Index were identified as primary efficacy variables. 1) Pain VAS[25]: The patient was asked to indicate the maximum pain experienced in the preceding 48 hours by putting a short vertical mark on a 10-cm horizontal linear scale, anchored at 0 and 100 mm (0 indicating nil pain) and graded at 10-mm intervals. A separate scale was used for each knee. 2) WOMAC Index (version Likert 3.0): This functional assessment instrument, containing 24 questions (Q) was used to grade the pain (Q1–5), stiffness (Q6–7), and physical function difficulty (Q8–24) pertaining to the knee joint. The patient's answer was graded on a qualitative scale (0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = extreme). The maximum score could be 96 (pain = 20, stiffness = 8, difficulty = 68). The source WOMAC was modified for Indian (Asian) use and validated primarily through a consensual approach and pilot testing in the community and patients before this trial by the author (AC). The details of this validation exercise and the format of the modified WOMAC are as per Appendix B. WOMAC was administered by interview/self-reported in the regional language of the patient. The Indian (Asian) WOMAC Index (CRD Pune version) is currently available in English, Hindi, Marathi, Gujrathi, and Telgu languages.

Other assessment measures included walk time (time to walk, unaided, a marked distance of 50 ft on a flat ground), physician and patient global assessment of disease (graded as asymptomatic, mild, moderate, severe, and very severe), early-morning stiffness (minutes), and knee swelling (graded as 0 = none, 1 = detectable synovial thickening without loss of bony contours, 2 = synovial thickening and swelling with loss of bony contours, 3 = bulging synovial proliferation with cystic characteristics).

Efficacy Failures

Patients withdrawn from the randomized phase as a result of intolerable pain by the investigator were considered to be efficacy failure.

Patients whose pain VAS was found to have increased by 30 mm or more over and above the baseline at evaluation end points were considered as "poor efficacy." Poor efficacy could be recorded on more than one end point in any single patient. Each "poor efficacy" was counted as a separate episode/event.

Statistical Analysis Plan and Methods

Efficacy Analysis

An intent-to-treat analysis, with last observation carried forward, was performed. When both the knees were identified at baseline as index knees, their combined pain VAS were averaged at every visit to obtain the "index knee score." The main objective was to evaluate the difference in pain VAS and WOMAC Index between the groups (active versus placebo) and not within the groups. However, a within-group analysis was done to determine the onset of action of RA-11. The mean differences in the efficacy measures from baseline to week 16 and week 32 in the 2 treatment groups were computed and compared using ANOVA, with baseline value as a covariate.

Safety Analysis

Safety assessments were based on results of the physical examinations (including vital signs), clinical laboratory tests, and AEs. AEs between the groups were compared by χ^2/Fisher exact test. Laboratory measurements were compared with baseline using an analysis of covariance. The frequency of AEs, defined as a laboratory value becoming twice the upper or lower limit of normal, was compared using Fisher exact test.

Sample Size Determination

The sample size was determined by the following specifications. 1) There would be an 80% power for detecting a difference between the treatment groups in the percentage of patients who have a value of 1 for the primary efficacy variable VAS, ie, who achieve pain relief on RA-11 alone. 2) An improvement on pain VAS to be detected would be at least 30% for the placebo group and 55% for the RA-11 group. 3) The test of the null hypothesis will be conducted at a 2-sided 5% significance level. Under these assumptions, the required sample size was 30 subjects per group. However, considering several factors, including expecting a higher dropout rate and lack of sufficient data from published OA drug trials using Ayurvedic medicines, the latter was considered to be too conservative. It was then decided to enroll 45 patients into each group.

RESULTS

Ninety patients, 45 assigned to each of the treatment groups, were enrolled. 78 patients and 62 patients completed 16 and 32 weeks of the randomization phase, respectively.

Baseline Variables

The active (mean age 59 years, range 35–75; 35 females) and the placebo (mean age 55 years, range 42–78; 32 females) groups were well balanced in several of the demographic and other measures (Table 1) except for the somewhat higher mean body weight in the placebo group. In the active group, the index knee was left knee, right knee, and both knees in 9 (20%), 5 (11.1%), and 31 (68.9%) patients, respectively. In the placebo group, the index knee was left

TABLE 1. Baseline Measures, Including Primary Efficacy (Mean and Standard Error)

Variable	Treatment		*P*
	Active	Placebo	
Body weight (kg)	56.3 ± 1.80	63.3 ± 1.48	0.003
Early-morning stiffness (min)	7.98 ± 1.49	12.5 ± 2.21	0.091
Knee swelling	0.01 ± 0.01	0.02 ± 0.02	0.656
Visual analog scale for pain (cm)	6.17 ± 0.13	6.50 ± 0.16	0.113
Left knee: visual analog scale	5.48 ± 0.37	5.49 ± 0.35	0.983
Right knee: visual analog scale	5.48 ± 0.25	5.92 ± 0.32	0.276
Time to walk 50 feet (sec)	15.9 ± 0.55	16.6 ± 0.68	0.438
WOMAC: combined	46.8 ± 2.16	51.0 ± 2.07	0.168
WOMAC: difficulty	34.7 ± 1.60	37.9 ± 1.46	0.138
WOMAC: pain	9.51 ± 0.49	10.6 ± 0.54	0.141
WOMAC: stiffness	2.60 ± 0.26	2.42 ± 0.25	0.627

Note: pain visual analog scale scores pertain to index knee/knees (see text).

knee, right knee, and both knees in 8 (17.8%), 8 (17.8%), and 29 (64.4%) patients, respectively.

Analysis of Efficacy

Table 2 shows the mean change of several efficacy variables from baseline to week 16 and week 32. On comparison, the reduction in the pain VAS and the modified WOMAC Index scores (combined, pain, stiffness, and physical function difficulty) in the active group were significantly better than in the placebo group.

Both the treatment groups showed a rapid decline in the mean value of pain VAS and WOMAC Index in the initial 12 to 16 weeks followed by a more plateau-like effect (Fig. 1). The separation of the graph lines was distinct by 2 to 4 weeks of therapy.

A total of 32 "poor efficacy" (active = 10, placebo = 22) episodes were recorded. Three patients (active = 1, placebo = 2) were withdrawn from the study because of "efficacy failure."

Analysis of Safety:

Laboratory Variables

Table 3 shows that there was no significant difference in the mean change in laboratory values from baseline to week 16 and week 32 in treatment groups with regard to several routine biochemical–metabolic measures, including hepatic functions.

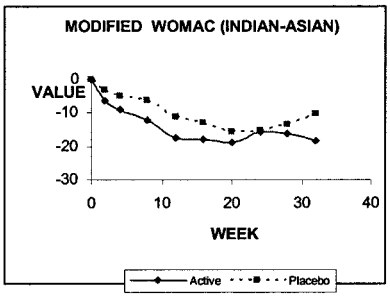
Patient Withdrawals

Twenty-eight patients (active = 14, placebo = 14) were withdrawn from the study. None were the result of drug toxicity. We withdrew 3 patients as a result of efficacy

TABLE 2. Mean Change in Efficacy Measures at Week 16 and Week 32 From Randomization Baseline (Mean and Standard Error)

Variable e	Week 16 Treatment			Week 32 Treatment		
	Active	Placebo	*P**	Active	Placebo	*P**
Visual analog scale for pain (VAS)	−2.68 ± 0.29	−1.30 ± 0.31	0.000	−2.83 ± 0.38	−1.80 ± 0.36	0.034
WOMAC: combined	−18.2 ± 1.99	−13.7 ± 2.51	0.040	−18.5 ± 2.83	−10.0 ± 3.06	0.014
WOMAC: difficulty	−12.8 ± 1.50	−9.21 ± 1.85	0.028	−12.7 ± 2.11	−6.90 ± 2.36	0.027
WOMAC: pain	−3.80 ± 0.52	−3.26 ± 0.66	0.153	−4.39 ± 0.69	−2.29 ± 0.70	0.005
WOMAC: stiffness	−1.57 ± 0.28	−1.19 ± 0.24	0.235	−1.42 ± 0.38	−0.81 ± 0.29	0.140
Time to walk 50 feet (sec)	−1.80 ± 0.67	−2.27 ± 0.82	0.760	−1.37 ± 0.69	−1.77 ± 0.62	0.917

*Analysis of variance.



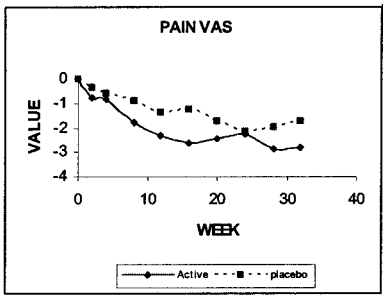


FIGURE 1. The mean change in modified WOMAC and pain visual analog scale at efficacy week endpoints by treatment groups.

failure. Two female patients (aged 65 and 66) from the active group died as a result of myocardial infarction and cerebral hemorrhage, respectively. Both the latter patients were known cases of hypertension, ischemic heart disease, and diabetes mellitus. Twelve patients (active = 3, placebo = 9) withdrew by week 16.

The remaining 23 patients were dropped from the study because they failed to fulfill the protocol requirement of follow up and/or compliance. The majority of the latter patients did not notify any specific reason.

Subsequently, we were able to contact several of these patients who had withdrawn themselves from the study and determine the likely cause. At least 4 patients from the active group expressed dissatisfaction with the therapeutic response. Another 4 patients in the active group stopped medication after 16 to 24 weeks because of significant pain relief and overall improved knee function. At least 2 to 3 patients from each group apparently stopped study medication because of concurrent medical illnesses (mostly related to respiratory and gut).

Adverse Events/Side Effects

Adverse events data were recorded for 83 patients during the randomization phase. None of the AEs reported continued beyond 2 visits in the follow up during the randomization phase. None of the patients during the entire study ever required any kind of intervention, including hospitalization. None of the AEs ever lasted for more than a week. The side effects, if requiring medication, were treated symptomatically. Overall, these side effects were mild. Table 4 summarizes the AEs recorded during the randomization phase, and it can be concluded that there were no statistically significant or clinically meaningful differences between the active (RA-11) and the placebo groups.

Miscellaneous

It was also demonstrated (Table 3) that there was no significant difference in the 24-hour urinary cortisol excretion between the 2 groups both at baseline (active = 58.7 ± 7.21, placebo = 61 ± 6.41) and at week 16 (active = 1.25 ± 9.91, placebo = 5.84 ± 8.54).

DISCUSSION

It is difficult to assess objectively meaningful therapeutic responses in chronic noninflammatory musculoskeletal diseases such as osteoarthritis. Currently, the instruments for

TABLE 3. Change in Laboratory Values From Baseline to Week 16 and Week 32

	Week 16 Treatment			Week 32 Treatment		
Variable	**Active**	**Placebo**	***P***	**Active**	**Placebo**	***P***
Erythrocyte sedimentation rate	−7.6 ± 2.42	−1.7 ± 2.26	0.081	5.10 ± 3.18	7.97 ± 2.58	0.487
Hemoglobin	0.27 ± 0.19	0.23 ± 0.13	0.852	0.84 ± 0.36	0.16 ± 0.30	0.153
Serum albumin	0.01 ± 0.11	−0.02 ± 0.05	0.844	0.41 ± 0.15	0.44 ± 0.12	0.902
Serum globulin	−0.02 ± 0.07	0.04 ± 0.09	0.849	0.17 ± 0.16	0.08 ± 0.20	0.715
AST IU/L	−2.5 ± 1.13	−2.3 ± 1.11	0.905	−0.07 ± 2.54	1.80 ± 1.84	0.554
ALT IU/L	−3.5 ± 1.29	−6.3 ± 1.75	0.204	−9.0 ± 1.93	−7.3 ± 1.48	0.487
Serum alkaline phosphatase	−6.4 ± 2.86	0.32 ± 3.42	0.132	−36 ± 3.89	−39 ± 3.59	0.621
Serum uric acid	0.06 ± 0.13	0.38 ± 0.17	0.134	1.43 ± 0.29	1.04 ± 0.26	0.317
Serum calcium	0.05 ± 0.19	0.01 ± 0.13	0.877	−2.2 ± 0.33	−3.0 ± 0.35	0.136
24-hour urine cortisol	1.25 ± 9.91	5.84 ± 8.54	0.728			
24-hour urine creatinine	0.06 ± 0.04	0.15 ± 0.08	0.348			

TABLE 4. Adverse Event Rates

Adverse Event Type	Active (n = 45)	Placebo (n = 45)	P*
Anorexia	9 (10.8%)	7 (8.4%)	1
Nausea	10 (12.0%)	8 (9.6%)	1
Abdominal pain	9 (10.8%)	10 (12.0%)	0.6097
Skin rash	11 (13.3%)	6 (7.2%)	0.4144
Stomatitis	6 (7.2%)	8 (9.6%)	0.5585
Insomnia	7 (8.4%)	8 (9.6%)	0.7759
Others	3 (7.2%)	9 (10.8%)	0.392
Any adverse event	23 (27.7%)	22 (26.5%)	0.8259

*Fisher χ^2 test.

subjective measurement of pain (VAS) and functional assessment (eg, WOMAC Index) seem to be the most acceptable and validated. However, application of such measures in countries with a vast degree of sociocultural diversity such as India requires certain modifications, adaptation, and further validation.[26] The physical "difficulty" section of the WOMAC was modified for use in the Indian (Asian) community and later validated by the author (AC) in a pilot study (unpublished) of patients with OA before this trial study (see Appendix B). In passing, it could be worth highlighting that some of the newly introduced questions in the physical "difficulty" subsection of the Indian version are much more physically demanding (eg, sitting cross-legged/squatting on the floor). This would then make the therapeutic targets even more difficult. It could be argued that the Indian population is culturally adapted to these difficult "knee floor positions," but the adaptation fails to provide solace when those very knees begin to suffer from painful OA. In all probability, the attempts of the patient with failing arthritic knees, to tolerate pain and persistently continue to use these floor positions for daily activities, accelerates the disease progression. However, the culturally conditioned Indian mind will not accept anything less than that of the "lost dexterity" (the floor knee positions) from a promising OA therapy. It is in the latter context that the result of the current clinical drug trial of RA-11 carried out in India assumes critical significance.

Our methodology in certain aspects might not conform to the popular methods in the literature. When both knees qualified for index knee at baseline, we preferred "averaging the pain VAS of both the knees" to the pain VAS of a single knee chosen randomly. We believe that by averaging, we have also considered situations in which the nonindex knee worsened or had a higher follow-up score. As stated here, both the knees qualified in majority of the patients. Although our "averaging technique" lessens the variability in pain VAS scores, it is likely to find favor with the usual OA clinical profile in which both knees are often affected and the pain is so variable and unpredictable. We did not find any data on pain VAS and WOMAC in the published peer-reviewed literature on Indian (Asian) patients with OA. Thus, we chose both pain VAS and WOMAC as primary efficacy variables in the current drug trial, although any one of them would have sufficed.

OA is a widely prevalent cause of significant morbidity during the age period when "mobility" is a critical determinant of quality of life. The current therapeutic options[27,28] are grossly limited and at best can only provide symptomatic relief. Long-term use of analgesics and NSAIDs is fraught with the dangers of drug-related toxicity, gastrointestinal in particular. The apathy of the medical profession toward such degenerative diseases only drives the patient to consume painkillers without supervision or to experiment with unproven therapies. Also, in some cases, irrespective of the health care (including ideal body weight and regular appropriate exercise therapy), OA knees progress relentlessly and is then believed to be a function of increasing age and deranged knee mechanics. Against the latter perspective, the results of the current study on the efficacy and safety of RA-11, a plant-derived Ayurvedic formulation, are very encouraging.

Of note is the fact that during the entire 32-week randomized period in the current study, absolutely no pain or escape medication was permitted. The results of the current trial thus assume much more significance.

Kulkarni et al. demonstrated the efficacy of a similar medication[29] in a limited study on OA. Interestingly, an earlier formulation of RA-11 was shown to be modestly effective with excellent safety profile in patients of active RA in a controlled drug trial.[11] However, the results of RA-11 in patients with OA knees in the current study are more conclusive. Although planned as a pilot study, the protocol of the current drug trial was designed to address the overwhelming concerns of a randomized, double-blind, controlled Phase II study. The statistical design of the study ensured a proper sample size and an analysis of primary efficacy variables.

The authors had reported an unexpected high placebo response in the Indian community in a previous study[11] in which the dose (of RA-1) was half of the dose used (of RA-11) in the current study. Although a number of plausible reasons were speculated, it was difficult to precisely explain this phenomenon. Of course, it made the interpretation of efficacy results difficult. Such a strong placebo response also complicates future trial design. The 32-week duration of the current trial was considered sufficient by the investigators and Ayurvedic colleagues to overcome the earlier experienced placebo response.[11] Throughout the current trial period, patients were nurtured and at each visit constantly under the direct observation of a single investigator (AC); this could have contributed sufficiently to the robust placebo response. In Figure 1, there was obvious persistent separation between

the active and the placebo group over most of the study time period. By 32 weeks, one would have expected a higher degree of regression to the mean in case of placebo. Maybe a longer period of study observation was required to sufficiently calm down the placebo response.

Both the treatment groups in the current trial suffered from significant symptomatic OA knees (mean pain VAS >6, and in >60% patients both knees qualified) at baseline. Although the groups matched well at baseline, the mean body weight in the placebo group (Table 1) was greater. The relationship of the body weight with OA knees has been reported in several studies.[30] Although the latter is of concern, its influence on the outcome to a large extent appears to have been offset by the matching overall baseline profile of patients in the 2 groups and the subsequent efficacy results.

The improvement in pain VAS and WOMAC (total and individual components) Index in the active group was significantly superior ($P < 0.05$) to that seen in the placebo group. The individual components of pain, stiffness, and physical function difficulty were appropriately addressed by an elaborate questionnaire contained in the modified WOMAC version used in this trial. RA-11 has significantly improved each of these components in the active group. These results are further consolidated by demonstration of an excellent safety profile, both clinical and laboratory. In passing, it could be of interest that an impressive change (Table 3) was found for erythrocyte sedimentation rate (at week 16) and hemoglobin (at week 32) in the active group. The observation in respect of hemoglobin assumes more significance, especially in our undernourished community, because we reported a similar result in the earlier trial of RA-1.[11] The urinary cortisol levels did not differ between the treatment groups, thereby providing some evidence to suggest that the formulation does not contain commonly known natural steroid molecules.

There are limitations of this study. This was a relatively short 32-week Phase II study with a sample size of only 90 patients carried out in a single medical center. We are unable to explain the precise reasons for the strong placebo response in our community. Also, the modified Indian (Asian) version of WOMAC used by us in the current trial would need to be evaluated in similar trials. However, the latter is a useful contribution to rheumatology practice in the Indian subcontinent and other Asian communities with lifestyles similar to ours.

In conclusion, this controlled drug trial demonstrates the potential efficacy and safety of RA-11 in the symptomatic treatment of OA knees over 32 weeks of therapy. It is tempting to speculate on its chondroprotective role. In view of this trial report and relevant documented Ayurvedic knowledge, RA-11 should be further tested for long-term clinical use and mechanism of action.

ACKNOWLEDGMENTS

Numerous experts from diverse fields (including plant chemistry and Ayurveda) have significantly provided their expertise to this study. The protocol was codeveloped with Dr. Richard Polisson, and his invaluable assistance is gratefully acknowledged. Numerous other colleagues have provided invaluable assistance both for the trial and this manuscript: Dr. J. Patil (Ayurvedic Physician, CRD, Pune, India), Mr. S. Karnataki (Pune, India), Ms. Manjit Saluja (Coordinator, CRD, Pune, India), Ms. Anuradha V. (in charge of the laboratory, CRD, Pune, India), and Dr. Anagha Kortikar (BIO-VED, USA).

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APPENDIX A

Manufacturing and Standardization of RA-11 (Trade Name: ARTREX)

The formulation of RA-11 is highly reproducible from batch to batch using International and USP standards. The USP currently has very few monographs for plant extracts even though they are steadily increasing in number. The most quoted references for plant extracts' standards are in the British Pharmacopoeia and the German Commission E references.[31] The US Food and Drug Administration (FDA) has recently (March 2003) published for comment (before being enacted) a set of rules covering GMP for natural plant extract products. The manufacturing practices for RA-11 (including the materials for this study) already adhered to all of the proposed rules as published by the US FDA. NMR, HPLC/HPTLC, UV spectrophotometer, and NMR spectroscopy are used for standardization and confirmation.

A *Certificate of Analysis* is attached with each batch. An independent laboratory takes random samples from each batch and performs the following analytical tests:

Potency

For each extract and for the blend together, performed by using HPLC (high-performance liquid chromatography) to measure the amount of marker compound present for each plant extract, in comparison to the labeled formula. Each batch of medicinal plant extract is analyzed qualitatively and quantitatively for known markers of individual plants as follows: *Withania somnifera*—Withanolides; *Boswellia serrata*—Boswellins, *Curcuma longa*—Curcuminoids, *Zingiber officinale*—Gingerol. HPLC and similar measurements (HPTLC and gas chromatography) are worldwide-accepted methods to assure potency in natural products.

Toxicity

There are 3 separate tests done for each batch as follows:

1. Microbial testing to assure the absence of *Escherichia coli* and *Salmonella*.
2. Testing to measure any pesticide residue using European (EU) standards, there being no U.S. standards at present.
3. Testing to measure any residue of heavy metals (lead, mercury, and so on) using USP standards.

APPENDIX B

Modification and Validation of WOMAC for Indian Asian Use

The source WOMAC (Western Ontario and McMaster University Osteoarthritis Index)[23] was modified for Indian (Asian) use and validated through several steps by consensus.

Steps

1) Step 1—Translation into the regional language (Marathi) and back translation (English) by 1 independent college-level language teacher; the translations, more idiomatic than literal, were repeatedly assessed by a group (group A) of 3 investigators (AC, JP, MS) and 2 paramedics/nurses (not connected with the trial). For ease of comprehension and translation, the words "severe" and "degree" in the questions from the original WOMAC were substituted in the modified version by "much," eg, "how severe is your stiffness" now read as "how much is your stiffness," and "degree of difficulty" now read "how much is your difficulty." 2) Step 2—Asking a group (group B) of 10 patients and 10 healthy people from different socioeconomic strata and religious communities to state the various body positions and physical activities (in particular concerning ADLs) that they thought were relevant to the knee function. 3) Step 3—Substituting the inappropriate questions of the source version by the questions based on "activities relevant to the Indian community" provided by group B. The "new" questions included were finally structured and agreed by a judgmental–consensus approach undertaken by group A. The group agreed that the now modified version appeared to capture (face and

content validity) the various difficulties that the Indian patients might encounter because of their knee ailment. Although 5 questions pertaining to sitting cross-legged and arising, kneeling and arising, and squatting positions were included, the 3 questions on putting on/off socks/stockings and getting in/out of bath were excluded. The question on travel by car also included travel by bus and auto rickshaw. The question on toilet use included the Indian model (at ground level). Finally, compared with the original version, there were now 2 additional questions in the "difficulty" section. *The sections on "pain" and "stiffness" contained in the original WOMAC remained unchanged.* 4) Step 4—The modified WOMAC (Indian–Asian) was called the CRD-Pune version. It was pilot-tested for easy comprehension and use in 20 patients with OA knees by 2 paramedics (1 nurse) not connected with the trial team. Both language versions (English and Marathi) were available to the patient. Few patients stated that while performing house chores or spending leisure time, they customarily sat on the floor with both legs folded–uncrossed and positioned either in front or on any one side and/or sat on the floor with legs extended, not necessarily the result of the knee ailment. Although patients were encouraged to self-report, they invariably asked the interviewer to jot down their answer (even when they were literate). The patients also marked a pain VAS and scored an Indian version of the modified Health Assessment Questionnaire (HAQ).[11,32] Crude correlations (construct validity) between the scores of pain VAS, HAQ, walk time, and modified WOMAC (total and components) were computed by the statistician and none were found to exceed fair–moderate level of agreement. 5) Step 5—Subsequently, in the final evaluation, group A decided that the modified WOMAC (Indian–Asian) CRD-Pune version used in step 4 did not require any further change and was accepted for use in the RA-11 drug trial (Fig. 2). It was also decided that a single paramedic in the trial team (MS) will explain the content and use of the modified WOMAC CRD-Pune version to the patient before administrating the instrument by interview in the regional language.

STUDY JOINTS: ☐ RT KNEE ☐ LT KNEE ☐ BOTH

Please tick (√) in the appropriate column

	NONE	MILD	MODERATE	SEVERE	EXTREME	SCORE
HOW MUCH PAIN DO YOU HAVE?						
1.In walking on flat surface	☐	☐	☐	☐	☐	
2. Going up or down stairs	☐	☐	☐	☐	☐	
3. At night while in bed	☐	☐	☐	☐	☐	
4. Sitting or lying	☐	☐	☐	☐	☐	
5. Standing upright	☐	☐	☐	☐	☐	
HOW MUCH IS YOUR STIFFNESS ?						
6. After first wakening in the morning	☐	☐	☐	☐	☐	
7. After sitting, lying or resting later in the day	☐	☐	☐	☐	☐	
HOW MUCH DIFFICULTY DO YOU HAVE?						
8. Descending stairs	☐	☐	☐	☐	☐	
9. Ascending stairs	☐	☐	☐	☐	☐	
10. Standing up from a chair	☐	☐	☐	☐	☐	
11. While standing	☐	☐	☐	☐	☐	
12. Bending to floor (to pick up objects)	☐	☐	☐	☐	☐	
13. Walking on flat ground	☐	☐	☐	☐	☐	
14.Getting in and out of Autorickshaw/Bus	☐	☐	☐	☐	☐	
15. Going shopping	☐	☐	☐	☐	☐	
16. On rising from bed	☐	☐	☐	☐	☐	
17. While lying on bed	☐	☐	☐	☐	☐	
18. While sitting on chair	☐	☐	☐	☐	☐	
19. Going on/off toilet –Indian/Western	☐	☐	☐	☐	☐	
20. Doing heavy domestic duties (moving heavy boxes, scrubbing floor, lifting shopping	☐	☐	☐	☐	☐	
21. Doing light domestic duties (cleaning room/table/cooking/dusting)	☐	☐	☐	☐	☐	
22. While sitting cross legged on floor	☐	☐	☐	☐	☐	
23. Rising from cross legged position	☐	☐	☐	☐	☐	
24. While squatting on floor	☐	☐	☐	☐	☐	
					TOTAL	
REMARKS :						

FIGURE 2. Indian (Asian) WOMAC Index (CRD Pune version).