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Dr. Kannalayam Gopalan Raveendran was born on 15th of July 1963 in a traditional family of ayurvedic Physicians. His father - Azhakath Gopala Poduval belonged to the Kuttengeri tradition, one of the limbs of the famous Ashtavaidya Tradition and who had special training in traditional paediatrics from Padinjare Kunnath Mana and traditional toxicology from Thripunithura Midukkan Thampuran. Due to the excellence in his medical practice, Azhakath Gopala Poduval was appointed as the Royal paediatrician of the Thripunithura Palace that belonged to the Kochi kingdom and was recognized by the Madhya Pradesh government and was awarded Fellowship by the National Academy of Ayurveda. Dr. Raveendran is the only Physician in the tradition now and reflects his paternal excellence at even a younger age, the credit of which is attributed by himself to his ardent spiritual practices.

Inspired by his father who was and is the role model in his career, Dr. Raveendran joined Ayurveda College, Coimbatore in the year 1981. The course was designed according to the ancient Gurukula pattern and was for 7 ½ years. He learned Sanskrit, science subjects like physics, chemistry. Botany and zoology, Ayurvedic texts like Charakasamhita, Susrutasamhita and Ashtangasamgraha, Yoga and Kalari from gurus who were trained traditionally and institutionally. He graduated in 1989 from Madras University as AYURVEDA ACHARYA (Bachelor of Ayurvedic Medicine and Surgery). Dr. Raveendran went back to his father for final initiation to independently practice what he had learned. He also had an informal training in western medicine under an expert – Dr. P K R Warier.

He joined The Arya Vaidya Pharmacy (Coimbatore) Limited (AVP) in 1989 and started his career with a short training in the hospital – Arya Vaidya Chikitsalayam and Research Institute (AVC&RI)– where he later became the Medical Director. Later he also became a Director of The Arya Vaidya Pharmacy (CBE) Ltd. He worked in different branches of AVP and contributed towards developing all of them into the leading outlets of the institution. In course of time, he became renowned for Ayurvedic management of rheumatism, metabolic disorders, renal, cardiac, cancer and infertility.

Dr. Raveendran succeeded Arya Vaidyan KS Varier as the Chief Physician of the AVC&RI in 1998 and served selflessly in the hospital from 1998 to 2018. With the Blessings of Lord Dhanvantari, who is the main deity of the temple located in the campus, before whom he offered his daily prayers before consulting his patients, the hospital developed into a nationally and internationally acclaimed centre for excellence in Ayurvedic treatment. The National Institutes of Health (NIH) U.S.A. funded through its National Center for Complementary and Alternative Medicine (NCCAM) to develop and consolidate long-term scientific collaborations between India and USA in the field of Ayurveda. The Ayurvedic Trust headed by Dr. Raveendran was identified as the proposed Ayurvedic Center for Collaborative Research to study Ayurveda in India. This highly competitive, prestigious grant was awarded based on the Ayurvedic Trust's experience with the seven year WHO-ICMR (world Health Organization

– Indian Council for Medical Research) study of Ayurvedic treatment for rheumatoid arthritis, its facilities, and its already strong clinical excellence. This was the first-ever grant that the National Institutes of Health has awarded to study traditional Ayurveda in India. The study conducted as part of the project was to compare classic Ayurveda, methotrexate, and their combination in rheumatoid arthritis, in a first-ever double-blind, randomized, double-dummy, pilot trial. In this study, all three treatments were approximately equivalent in efficacy and adverse events were numerically fewer in the Ayurveda-only group. This study demonstrated that double-blind, placebo-controlled, randomized studies are possible when testing individualized classic Ayurvedic versus allopathic treatment in ways acceptable to western standards and to Ayurvedic physicians (Paper attached) This study was promoted as a blueprint for testing the efficacy of similarly complex interventions as it showed that individualised treatments can be tested using an otherwise standard RCT design, and that blinding can be successful if more than one placebo preparation is required (paper attached). Currently Dr. Raveendran is heading the clinical team in associating with Central Council for Research in Ayurveda Sciences (CCRAS) to conduct Phase III multicentric clinical trial on rheumatoid arthritis, as a continuation of this.

Dr. Raveendran's clinical expertise was invited by Molecular Diagnostics, Counselling, Care and Research Centre (MDCRC) Coimbatore, a not-for-profit NGO working to provide multidisciplinary care to kids suffering from Duchenne Muscular Dystrophy (DMD) – a disease, the therapeutic approaches for which are still in the research phase. While there are guidelines to improve the quality of life in kids, the medications that are available for this condition does not suit all the patients and are having several adverse effects. Ayurveda approaches are given free of cost under Dr. Raveendran's supervision for the past 6 years totally free of cost with an objective to see the improvement in the quality of life, alleviation to the suffering and a probable enhancement of lifespan. The project is currently supported by Ministry of AYUSH, the children are closely monitored by MDCRC's multidisciplinary team, and the interim reports are highly encouraging.

He was also the Co-Investigator for the project titled Efficacy of Ayurveda as add-on Therapy in Type 2 DM conducted in association with University of Latvia.

The former President of India Shri K R Narayanan was under his treatment in 2001 – 2002 and was awarded a Letter of Appreciation for the medical assistance that he received. Dr. Raveendran's patients' list include heads of States and countries, bureaucrats, leading industrialists, and artists along with the most ordinary people from around the globe. Students across the globe have been coming in groups for training under him. He was conferred 'The Doctor Excellence' Award instituted by the K.G. Health Foundation, Coimbatore, creating a history of sorts as it was for the first time that an Ayurvedic Physician was being considered for his prestigious award which is given annually by a renowned western medical hospital. Dr. K.G. Raveendran has authored two books in Tamil under Anandha Vikatan Publications, had written numerous articles, made several scientific presentations and also featured in TV shows in Malayalam and Tamil Languages.

After taking an early retirement from The Arya Vaidya Pharmacy (Coimbatore) Limited, Dr. Raveendran is now settled in Ottappalam, Kerala. He heads Gopala Poduval Lakshmi Trust, a not-for-profit entity created in his parents' memory and with an aim to promote authentic and comprehensive Ayurveda through the actualization of its medical potential to the fullest and through science popularization programs. He runs the clinic in a rural setting serving the needy with quality and effective Ayurveda care.

Double-Blind, Randomized, Controlled, Pilot Study Comparing Classic Ayurvedic Medicine, Methotrexate, and Their Combination in Rheumatoid Arthritis

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Objective: To compare classic Ayurveda, methotrexate (MTX), and their combination in a double-blind, randomized, double-dummy, pilot trial in rheumatoid arthritis (RA) for 36 weeks.

Methods: Forty-three seropositive RA patients by American College of Rheumatology (ACR) criteria with disease duration of less than 7 years were assigned to the following treatment groups: MTX plus Ayurvedic placebo (n = 14), Ayurveda plus MTX placebo (n = 12), or Ayurveda plus MTX (n = 17). Outcomes included the Disease Activity Score (DAS28-CRP), ACR20/50/70, and Health Assessment Questionnaire – Disability Index. All measures were obtained every 12 weeks for 36 weeks. Analyses included descriptive statistics, analysis of variance, χ^2 , or Student *t* test. The unique features of this study included the development of placebos for each Ayurvedic pharmacological dosage form and individualization of Ayurvedic therapy.

Results: All groups were comparable at baseline in demographics and disease characteristics. There were no statistically significant differences among the 3 groups on the efficacy measures. ACR20 results were MTX 86%, Ayurveda 100%, and combination 82%, and DAS28-CRP response were MTX -2.4 , Ayurveda -1.7 , and combination -2.4 . Differences in adverse events among groups were also not statistically significant, although the MTX groups experienced more adverse event (MTX 174, Ayurveda 112, combination 176). No deaths occurred.

Conclusions: In this first-ever, double-blind, randomized, placebo-controlled pilot study comparing Ayurveda, MTX, and their combination, all 3 treatments were approximately equivalent in efficacy, within the limits of a pilot study. Adverse events were numerically fewer in the Ayurveda-only group. This study demonstrates that double-blind, placebo-controlled, randomized studies are possible when testing individualized classic Ayurvedic versus allopathic treatment in ways acceptable to western standards and to Ayurvedic physicians. It also justifies the need for larger studies.

Key Words: Ayurvedic, methotrexate, rheumatoid arthritis, controlled trial

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Rheumatoid arthritis (RA) is a chronic, immune-mediated, systemic disease that causes a great deal of pain and suffering.¹ Although there have been significant advances, treatment remains unsatisfactory for many patients.² At present, methotrexate (MTX), which is a basic DMARD therapy for RA, achieves a response in 40% to 60% of patients,³ representing a gratifying but not satisfactory outcome. Further, MTX is associated with distressing and potentially serious adverse effects. Consequently, as surveys indicate, 68% to 94% of RA patients use complementary and alternative medicine (CAM) therapies, including Ayurveda.⁴ As documented in the media, an increasing number of RA patients from the West make the journey to India to undergo complete classic Ayurvedic treatment.^{5,6}

The pathogenesis and treatment of rheumatic diseases described in ancient Ayurvedic texts from 1500 BC show remarkable similarities to modern descriptions of RA features.⁷ Ayurveda is a 3000-year-old medicine system, which has been recognized by the World Health Organization as a complete system of natural medicine, and is used by millions. It is a holistic, multifaceted system of treatment which includes complex herbal-mineral combinations, dietary and lifestyle modification, oil therapies, and detoxification routines. Herbal-mineral formulations, which form the core of classic Ayurvedic treatment, include thousands of formulas in a variety of dosage forms to treat more than 200 diseases.⁸

Placebo-controlled trials of classic Ayurveda are necessary to establish whether it is effective, and this trial method will provide the basis for a meaningful comparison with allopathic treatment. Although a literature search on PubMed⁹ yielded 61 clinical trials of Ayurvedic medicine, there are no randomized clinical trials (RCTs) of classic Ayurvedic treatment as a system of care¹⁰ or any that used placebos for the traditional Ayurvedic pharmacological dosage forms so as to allow individualization of therapy as required by this system of care.

There is 1 published study of complete classic Ayurveda. It is an unblinded 7-year World Health Organization-sponsored study of 240 RA patients.^{11,12} Although this was not an RCT, its results were positive enough to warrant exploration of classic Ayurvedic treatment of RA.

Well-controlled double-blind studies of classic Ayurveda have been difficult to conduct because of the lack of placebos for its traditional, individually varied, pharmacological dosage forms and its therapies. For the first time, in this study, 6 placebos, appearing identical to the traditional pharmacological dosage forms for classic Ayurvedic treatment of RA, were developed and dispensed, including powders, liquids, pills, jams, and oils.

The primary objective of this pilot study was to compare the efficacy of outpatient classic Ayurvedic treatment versus

conventional allopathic treatment using MTX, or their combination, for RA in a randomized placebo-controlled 36-week study. All Ayurvedic formulations were based on classic texts of Ayurveda.

PATIENTS AND METHODS

The Indian government and the ethical review boards of the University of Washington, the University of California in Los Angeles, and the Ayurvedic Trust approved the pilot study protocol. All patients provided voluntary, written, informed consent before enrollment in the study.

Patients

Patients were recruited in Coimbatore, India, through advertising in the local media. They were screened for eligibility at the Ayurvedic Trust by the designated allopathic physician (P.G.S.), who documented their RA diagnosis by American College of Rheumatology (ACR) criteria and evaluated their responses.

Eligible patients were older than 18 years; had a history of RA symptoms for less than 7 years; had RA by ACR criteria; were ACR functional RA class I, II, or III; had hemoglobin level more than 8 g/dL without evidence of active bleeding; and were positive for rheumatoid factor (RF) or anti-cyclic citrullinated protein at study entry. Acetaminophen and nonsteroidal anti-inflammatory drug within the approved dosage regimens were allowed. Patients were asked to keep their dosing regimens of these drugs stable or use them as little as possible if used intermittently.

Exclusion criteria included other connective tissue diseases, previous treatment with greater than 6 weekly doses of methotrexate at any dose, joint trauma within 1 year, complete classic Ayurvedic treatment within 1 year or over-the-counter Ayurvedic medicines within 1 month, enrollment in another clinical study within 3 months, intra-articular corticosteroid injections within 2 months, oral corticosteroids, disease-modifying drugs (e.g., hydroxychloroquine, sulfasalazine, azathioprine) within 1 month, leflunomide in the past 4 months, chronic infections or infections requiring antimicrobial therapy within 1 month, or biologic agents such as adalimumab, anakinra, etanercept, or infliximab within 3 months. Also excluded were those with poorly controlled diabetes or hypertension; with active or chronic hepatitis; with active, unresolved, or previous chronic liver disease (serum alanine aminotransferase and/or total bilirubin >2 times above the laboratory upper limit of normal); with cardiac failure (New York Heart Association classification stage III or IV); with history of cancer or lymphoproliferative disease in the past 5 years (exception: history of basal or squamous cell carcinoma, free of cancer for at least 1 year after carcinoma in situ); with active tuberculosis; with congenital or acquired immunodeficiency (including human immunodeficiency virus); with serum creatinine more than 1.5 times laboratory ULN; white blood cell count less than 3000/mL; platelet count less than 100,000/mL, requiring more than 4 g of acetaminophen or daily dose of nonsteroidal anti-inflammatory drug greater than that approved for the treatment of RA; and pregnant or lactating. Other exclusion criteria included compromised ability to absorb, metabolize, or excrete study medications; history of recent drug or alcohol abuse; life expectancy of less than 2 years for any reason; noncompliance; and any condition that would prevent them from giving voluntary, fully informed consent.

Study Design

Eligible RA patients were randomized in a 1:1:1 ratio as follows: group 1, MTX verum plus placebo Ayurveda; group

2, verum Ayurveda plus MTX placebo; and group 3, MTX verum plus verum Ayurveda. The treatment duration was set at 36 weeks because the Ayurvedic physicians felt that it might take that long for the outpatient Ayurvedic treatment's effects to become evident. Because clinical trials using disease-modifying antirheumatic drugs typically have study durations of 6 months, we report results for 24 weeks as well.

Patients were seen once every 2 weeks at the Ayurvedic Trust by both Ayurvedic and allopathic physicians. In keeping with the double-blind design of the study, neither the Ayurvedic physician nor the allopathic physician knew whether the patients were on verum MTX, or verum Ayurvedic therapies, or both.

Potential participants were screened in 2 phases. At the initial screening, all those who responded to recruitment efforts underwent preliminary screening for eligibility including RA disease and medication history, joint count, and physical examination but had no laboratory tests. Those who satisfied the initial screening criteria proceeded to the final screening, when blood and urine samples were collected and radiography was done as per the exclusion criteria.

MTX Dosing

The oral MTX dose was adjusted for milligrams per meter square and for the albumin level (which is lower in Indian patients), so that the equivalent starting dose of 10 mg/m² for North American patients was adjusted to 8 mg/m². This was then adjusted for the 2.5-mg tablets available for prescription. Thus, patients weighing 30 to 39 kg and height up to 137 cm started at 7.5 mg/wk, patients weighing 40 to 59 kg and height 138 cm and taller started at 10 mg/wk, and for those 50 to 70 kg and 138 cm or taller or 70 to 79 kg but up to 138 cm in height, the starting dose was 12.5 mg/wk. For those taller than 137 cm and weighing 70 kg or more, the starting doses were from 15 to 17.5 mg/wk. Doses were up-titrated to tolerance in 2.5-mg/wk increments every 8 weeks. The maximum dose was 25 mg/wk. The range of doses at 24 weeks was 2.5 to 22.5 mg/wk, with a mean of 18.5 mg/wk orally. The range of doses at 36 weeks was 5 to 25 mg/wk, with a mean of 20.3 mg/wk orally. A pharmaceutical firm (Stanpro Pharmaceuticals, Coimbatore, India) manufactured the MTX placebo, which was identical in appearance to the true MTX tablets.

Ayurvedic Treatment and Placebos

Before the start of the study, the Ayurvedic physician provided a list of all possible medicines that he might use in individualizing therapy over the course of the study. This list contained 148 separate multiherbal compounds. However, they were contained within 6 dosage forms of Ayurvedic pharmacological medicine (decoction, powder, pills, jam, herbal wine, and herb-infused oil). Each dosage form included 20+ multiherbal compounds. We therefore made and tested placebo formulations for these dosage forms. We found from blinded tests before the study began that we could use 1 placebo formulation for all the herbal compounds within a given dosage form because there was no appreciable difference in appearance, color, texture, taste or smell when the herbs were combined within that particular dosage form. Therefore, 1 placebo formulation for each of the 6 dosage forms was developed. The number of placebos was 6, with each placebo representing the 20+ herbal compounds of that particular dosage form.

Of the 148 multiherbal compounds in the original list, the Ayurvedic physician used 40 compounds during the course of the study when the treatment called for verum Ayurveda. The placebo formulations alone were used when placebo Ayurveda

was called for. These placebos were shown to effectively double-blind the trial; details of the success of blinding and related issues have been published.¹³

Because this was a study of classic Ayurvedic treatment, the Ayurvedic physician was free to prescribe any combination of medicines and therapies for all patients, based on his clinical judgment. Thus, the patients received individualized therapy as per true Ayurvedic precepts. Consequently, not all patients were expected to receive all the dosage forms (or corresponding placebos) but were dispensed verum or placebo for all their prescriptions, depending on their particular treatment group assignment. All medicines and placebos were well within US Food and Drugs Administration standards for heavy metals and microbiological contaminants and were cleared for use in the study by the University of Washington's institutional review board. Periodic quality control checks were done, and appropriate action was taken as needed to ensure the safety of the placebos and medicines.

Because this was a study of outpatient RA treatment, patients were not expected to undergo intensive Ayurvedic therapies that are part of classic Ayurvedic inpatient treatment of RA (e.g., enemas) requiring hospital stay. Nevertheless, we had prepared protocols for sham therapies in case the Ayurvedic physician wished to prescribe intensive therapies.

Blood and urine samples were obtained and tested at an accredited laboratory. Blood tests done at weeks 0, 6, 12, 18, 24, 30, and 36 included complete blood cell count, C-reactive protein (CRP), liver and renal function tests, electrolytes, and lipid profile. Our previous experience with erythrocyte sedimentation rate (ESR) in the United States showed that, when a sample was kept in the laboratory for more than 4 hours at room temperature before analysis, ESR increased (unpublished observations). Because prolonged waiting times for laboratory tests were common in India, we used CRP in the calculations of DAS28 and ACR20/50/70 instead of ESR.

Statistical Analysis

Because this was a pilot, exploratory study, the sample size of 43 patients was based on a convenience sample; analysis was exploratory and was limited by the small sample size.

Descriptive statistics were calculated for baseline demographics and disease assessments. The primary endpoint of the study was response at week 36, based on the Disease Activity Score (DAS28-CRP), which is a composite index using tender and swollen joint counts of 28 joints, the CRP, and a visual analog scale indicating the patient's global assessment of disease activity.¹⁴ Secondary endpoints included the following: the proportions of patients achieving a response according to the ACR20/50/70 criteria for clinical improvement¹⁵ at weeks 24 and 36; changes in the DAS28-CRP from baseline to weeks 24 and 36; changes in the individual components of the DAS28 and ACR criteria, including the Ayurvedic and allopathic physicians' global assessment of disease activity; and changes in the Health Assessment Questionnaire – Disability Index (HAQ-DI) to weeks 24 and 36. The HAQ-DI evaluates physical function in 8 domains on a 0 to 3 scale.¹⁶ Comparisons among groups utilized Analysis of variance with last abbreviation carried forward.

Safety Assessments

Patients were monitored for adverse events (AEs) during each visit for the entire duration of the study. Evaluation of drug and placebo safety and tolerability was based on detailed records of AEs, focusing on the types and frequencies of common and serious AEs that occurred. A serious AE was defined

as an AE that was fatal or life threatening; that required prolonged inpatient hospitalization; resulted in persistent or significant disability, congenital anomaly, birth defect, miscarriage or elective abortion; or that required medical/surgical intervention to prevent another serious outcome.

RESULTS

Disposition of Patients

Figure 1 summarizes the disposition of the patients in the study. Of the 249 patients who gave informed consent, 172 were eliminated at initial screening (see Fig. 1 for reasons). A further 11 patients were eliminated at the final screening (Fig. 1). Records for 3 individuals who were not recruited contained no reason for their exclusion.

Sixty-three patients were enrolled, of whom 20 were terminated or dropped out at various points during the study as noted in Figure 1. Forty-three patients completed 24 weeks. Three patients were terminated at 24 weeks because of neuropathy (MTX group), fractured femur (Ayurveda group), and pregnancy (Ayurveda group), and the remaining 40 patients completed the trial at 36 weeks. They had been randomized as follows: group 1, MTX verum plus Ayurvedic placebo (MTX group) n = 14; group 2, verum Ayurveda plus MTX placebo (Ayurveda group) n = 12; and group 3, verum Ayurveda plus MTX verum (combination group) n = 17.

Demographic and Baseline Characteristics

Patients in all 3 groups were comparable at baseline in demographic and disease characteristics (Table 1). The groups' mean ages ranged from 45 to 47.9 years, they had mean weights from 56.06 to 63.3 kg, and 83% to 88% of all patients were women. Mean disease duration was between 1.1 and 2.7 years, and mean CRP levels ranged from 27 to 42 mg/dL. Scores in

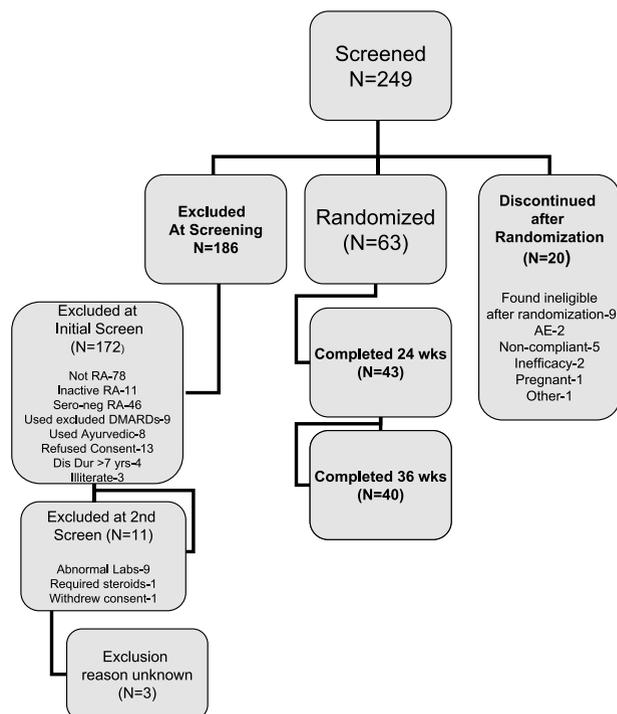


FIGURE 1. Disposition of patients during the study. Color online-only figure is available at <http://www.jclinrheum.com>.

TABLE 1. Patient Mean (SD) Demographics and Disease Characteristics at Baseline (N = 43)

	Group 1: MTX + Ayurvedic Placebo (n = 14)	Group 2: Ayurveda + MTX Placebo (n = 12)	Group 3: MTX + Ayurveda (n = 17)	P for Comparisons
Age, yr	47.3 (15.5)	47.2 (10.6)	47.1 (12.7)	0.999 ^a
Women, n (%)	12 (85.7)	10 (83.3)	15 (88.2)	0.931 ^b
Primary language, n (%)				
Malayalam	4 (28.6)	0 (0)	4 (23.5)	0.370 ^b
Tamil	10 (71.4)	11 (91.7)	11 (64.7)	
Kannada	0 (N/A)	0 (N/A)	1 (5.9)	
Telugu	0 (N/A)	1 (8.3)	1 (5.9)	
Weight	123.6 (33.4) lb 56.06 (15.1) kg	139.6 (33.6) lb 63.3 (15.2) kg	132.0 (28.8) lb 59.8 (13.06) kg	0.443 ^a
Disease duration (<1 yr = 0)	2.3 (2.2)	1.1 (0.7)	2.7 (2.4)	0.094 ^a
RF+, n (%)	11 (78.6)	11 (91.7)	12 (71)	0.388 ^b
Anti-CCP+ in RF- patients, n (%) ^{c,d,e}	3 (21.4)	1 (8.3)	5 (29.4)	0.388 ^b
Erosions, %	61.5	69.2	64.7	0.918 ^b
No. tender/painful joints (28-count)	18.3 (6.5)	16.4 (6.2)	18.3 (3.6)	0.593 ^a
No. swollen joints (28-count)	19.7 (5.8)	18.8 (5.4)	19.5 (4.5)	0.903 ^a
No. swollen joints (66-count)	31.3 (9.2)	31.5 (7.4)	31.7 (6.3)	0.984 ^a
No. tender/painful joints (66-count)	31.0 (10.1)	28.5 (10.0)	29.5 (8.2)	0.789 ^a
Patient's assessment of joint pain ^f	68.1 (16.1)	69.7 (15.5)	57.7 (21.36)	0.159 ^a
Patient's global assessment of disease activity ^f	72.3 (15.5)	68.5 (20.5)	60.0 (20.1)	0.214 ^a
Ayurvedic physician's global assessment of disease activity ^f	62.0 (6.4)	60.5 (7.5)	59.6 (10.7)	0.752 ^a
Allopathic physician's global assessment of disease activity ^f	71.9 (7.5)	74.2 (4.5)	72.3 (6.3)	0.633 ^a
CRP, mg/dL ^{c,d,g}	2.73 (3.79)	3.35 (3.26)	4.20 (5.86)	0.672 ^a
DAS28-CRP	6.5 (0.93)	6.5 (0.84)	6.5 (0.80)	0.997 ^a
HAQ-DI score	1.7 (0.60)	1.6 (0.49)	1.5 (5.9)	0.515 ^a
Creatinine, mg/dL (0.6–1.3) ^g	0.78 (0.13)	0.81 (0.12)	0.78 (0.15)	0.805 ^a
AST, U/L (15–37) ^g	18.9 (2.8)	21.1 (9.1)	18.6 (8.2)	0.638 ^a
ALT, U/L (30–65) ^g	28.3 (6.3)	35.4 (20.5)	30.3 (9.1)	0.355 ^g
Albumin, g/dL (3.4–5) ^g	3.6 (5.4)	3.4 (0.33)	3.5 (0.57)	0.472 ^a
Alkaline phosphatase, U/L (50–136) ^g	86.5 (42.2)	93.9 (34.8)	118.2 (99)	0.421 ^a
Platelet count, ×10 ³ /mL (150–400) ^g	311.1 (72.1)	391.0 (123.2)	354.1 (86.3)	0.108 ^a
WBC, ×10 ³ /mL (4–11) ^g	7.5 (2.1)	8.7 (3.3)	7.3 (1.7)	0.257 ^a
Hemoglobin, g/dL (11.5–15) ^g	11.8 (1.8)	11.1 (1.3)	11.2 (1.7)	0.474 ^a

This table represents the mean (SD), unless otherwise noted, of patient demographics and disease characteristics by treatment group at baseline.

^aOn the basis of one-way ANOVA.

^bOn the basis of Pearson χ^2 .

^cMax upper limit of normal = 1.0 mg/dL.

^dResults are imputed from a titer.

^ePatients who were RF-negative, but had 7 of 66 swollen joints, were tested for anti-CCP positivity.

^fUsing a 100-mm visual analog scale.

^gLaboratory reference range.

NA, not applicable.

DAS-CRP at baseline indicated high disease activity for all 3 groups (mean, 6.5). Sixty-one and one-half percent to 69.2% had erosions on radiographs of the hands and feet (determined by D.F.). Patients had active, seropositive disease. No statistically significant differences between groups were found among the baseline variables.

Efficacy Outcomes

Table 2 shows efficacy outcomes at weeks 24 and 36. A decrease of 1.2 or more in the DAS28-CRP score is indicative

of a good response to treatment. Patients in all 3 groups met this criterion at 24 and 36 weeks; there was no statistically significant difference between groups.

The MTX and the Ayurveda groups showed greater improvement ($P = NS$) in HAQ-DI scores than those receiving the MTX and Ayurveda combination. Patients in all 3 groups achieved a clinically meaningful reduction (>0.22) at weeks 24 and 36.

Figure 2 shows ACR20/50/70 responses. None of the tested differences between groups was statistically significant except

TABLE 2. Mean (SD) Treatment Outcomes at Weeks 24 and 36, by Group (N = 43)^a

Outcome Measure	Group 1: MTX + Ayurvedic Placebo (n = 14)		Group 2: Ayurveda + MTX Placebo (n = 12)		Group 3: MTX Plus Ayurveda (n = 17)		P Value by ANOVA		P Value for Paired Differences	
	0-24 wk	0-36 wk	0-24 wk	0-36 wk	0-24 wk	0-36 wk	0-24 wk	0-36 wk	0-24 wk	0-36 wk
DAS28-CRP (0-10 units)	-1.9 (1.5)	-2.4 (1.5)	-1.2 (1.1)	-1.7 (1.4)	-2.1 (1.4)	-2.4 (1.5)	0.222	0.379	0.000	0.000
Tender joint count (max = 28)	-10.5 (7.5)	-13.7 (7.0)	-9.1 (7.5)	-11.3 (8.2)	-11.8 (6.5)	-13.8 (5.2)	0.596	0.581	0.000	0.000
Swollen joint count (max = 28)	-9.1 (7.4)	-11.3 (7.7)	-5.3 (7.4)	-8.2 (8.8)	-10.9 (7.9)	-11.6 (7.4)	0.162	0.492	0.000	0.000
Patient pain assessment ^b	-31.6 (32.1)	-44.0 (25.4)	-27.5 (16.9)	-44.9 (14.4)	-13.7 (27.2)	-23.2 (27.9)	0.157	0.026	0.000	0.000
Patient's global assessment of disease activity ^b	-35.7 (29.5)	-43.8 (23.8)	-28.3 (18.6)	-45.2 (18.7)	-16.2 (28.8)	-25.4 (31.1)	0.133	0.073	0.000	0.000
Ayurvedic physician's global assessment of disease activity ^b	-16.6 (3.6)	-22.8 (8.6)	-15.7 (5.4)	-15.7 (7.4)	-13.1 (11.6)	-17.8 (13.9)	0.466	0.223	0.000	0.000
Allopathic physician's global assessment of disease activity ^b	-31.8 (20.7)	-45.1 (13.0)	-25.2 (16.9)	-44.6 (19.4)	-31.4 (17.7)	-46.3 (18.1)	0.596	0.959	0.000	0.000
CRP, mg/dL	-10.3 (34.1)	-12.9 (37.4)	-9.33 (37.8)	-2.8 (41.0)	-30.1 (58.8)	-26.2 (44.8)	0.383	0.327	0.015	0.020
HAQ-DI score	-0.64 (0.71)	-0.87 (0.72)	-0.67 (0.63)	-0.86 (0.58)	-0.60 (0.65)	-0.64 (0.55)	0.966	0.508	0.000	0.000

This table illustrates the mean and standard deviation of patient disease characteristics and quality of life outcomes at weeks 24 and 36 by treatment group. Statistical tests compare the changes between groups and the differences that occurred within patient groups over time.

^aIntent-to-treat population with last observation carried forward.

^bOn the basis of 100-mm visual analog scale.

for the ACR70 response at week 24 (MTX, 29%; Ayurveda, 0%; combination, 6%; $P = 0.049$). Because this represents one result among many comparisons, this result can be by chance alone.

All treatments were generally well tolerated in this study, with a similar incidence of AEs (Table 3). Nearly all AEs were mild or moderate in intensity. The most commonly occurring AEs in all 3 treatment groups were in the ear, nose, and throat category. There was a greater frequency of AEs in the MTX-containing than the Ayurveda regimens (MTX, 174; Ayurveda, 112; combination, 176; $P = NS$). Although numerical differences in specific AEs were frequently noted, they were not statistically significant. The largest differences were in stomatitis (MTX, 8; Ayurveda, 2; combination, 7), dyspepsia (MTX, 5; Ayurveda, 3; combination, 17), abdominal pain (MTX, 4; Ayurveda, 0; combination, 5), headache (MTX, 18; Ayurveda, 8; combination, 8), and nausea (MTX, 8; Ayurveda, 1; combination, 11).

Only 2 serious AEs occurred, requiring hospitalization: peripheral neuropathy (MTX group) and fractured femur due to a fall (Ayurveda group). Neither of these was considered to be related to the study treatments (Table 4). Each group developed 6 infections requiring oral antibiotics, and 1 pregnancy occurred (in the Ayurveda group). No deaths occurred.

DISCUSSION

Thus far, Ayurveda has not been studied as a system of care or in the context of a double-dummy, double-blind, randomized, placebo-controlled trial. This pilot study of allopathic treatment (using MTX) and classic Ayurvedic outpatient treatment of RA represents the first trial of its kind. Its unique features include the development of placebos for each of the several pharmacological dosage forms used in the Ayurvedic treatment of RA and the Ayurvedic physician having the freedom to individualize Ayurvedic therapy, as per true Ayurvedic precepts. The double-blind was successful.¹³

A systematic review of the literature on Ayurvedic medicine for RA identified only 7 studies that fit the criteria of RCTs.¹⁷ Only 3 of these studies were placebo-controlled RCTs.¹⁸⁻²⁰ None studied classic Ayurvedic treatment of RA or allowed individualization of therapy. In the only methodologically high-quality trial¹⁸ (based on a Jadad score²¹ of 5) from this group, except for a significant increase in hemoglobin and a decrease in RF ($P < 0.01$) in the experimental group, the active treatment was not significantly superior to placebo. The second study,¹⁹ which indicated potentially beneficial effects of an Ayurvedic preparation compared with placebo, was not reported completely. The third trial's incompletely reported results showed no difference between the active treatment and placebo.²⁰ In general, because there were methodological flaws, none of these RCTs was credible enough to allow any opinion.

An important feature of Ayurvedic pharmacological treatment is that it requires multiple and individually changing medications, dispensed in various dosage forms over time. The studies reviewed above used fixed combinations of the same formulations throughout and did not allow for the individualization of therapies. They are thus not tests of true classic Ayurveda. For example, in the trial by Chopra et al.,¹⁸ the individual herbs they used are part of the Ayurvedic pharmacopoeia, but the particular combination was used in an unvarying dose, and none were based on classic Ayurvedic texts nor was there any rationale provided for using this particular herbal combination and dosing for the treatment of RA. Further, the capsular form in which the active treatment and placebo were administered is not a traditional Ayurvedic dosage form. Findings from such studies may support the notion of herbs as

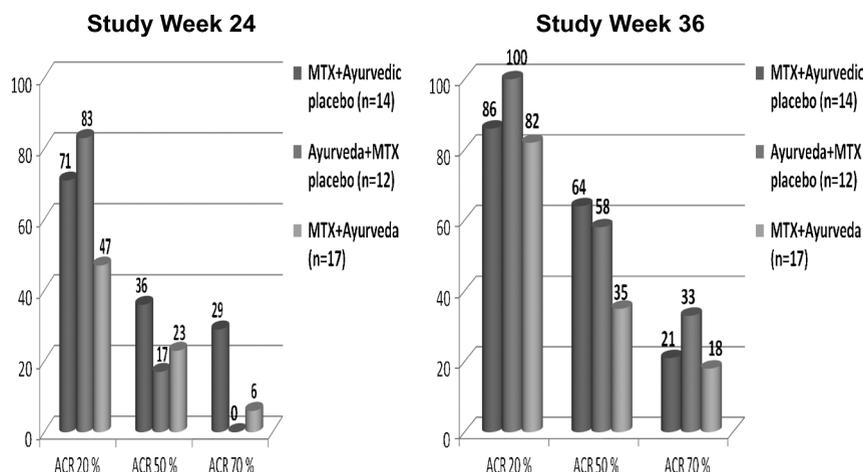


FIGURE 2. Percentage of ACR20/50/70 responses at weeks 24 and 36. Color online-only figure is available at <http://www.jclinrheum.com>.

medicines²¹ but are not to be considered as studies of classic Ayurveda. Therefore, the outcomes from such studies cannot be taken as proving, or disproving, the usefulness of Ayurveda per se.

Although our study was a pilot study, the findings indicate the possibility that there was no difference in efficacy among classic Ayurvedic treatment, MTX, and their combination in this 36-week trial. Except for ACR70 response at week 24, there were no statistically significant differences among the 3 groups in the disease activity measures such as DAS28-CRP, the ACR 20, ACR 50, and HAQ-DI. Even this result, among so many comparisons, could have occurred by chance alone. The combination group (verum MTX plus verum Ayurveda) patients did no better than either Ayurveda or MTX alone.

It is important to note that there were no statistically significant differences among the 3 groups. However, patients in the Ayurveda group showed the most improvement overall at 36 weeks (Table 2). This supports the general view that Ayurveda takes longer than allopathic medicine to show its effects.

Numerous AEs were reported during the course of the study, in keeping with the finding that 70% to 92% of patients in clinical trials report AEs.^{22–24} All patients received more attention than is usually available in clinical trials because they were queried about their symptoms once every 2 weeks by the 2 physicians and a study coordinator. Adverse events were distributed approximately equally among the 3 groups. Although statistically not significant, the 3 groups did show some differences, numerically. The Ayurveda group had the fewest number of AEs relative to the other 2 groups, and the combination group had the most. The small sample size limits the interpretation of these findings. One may speculate that the AEs associated with each of the single therapies (MTX and Ayurveda) may have been additive and therefore served to increase the number of such events in the combination group.

The principal limitation of this study was the small sample size, which, although adequate for a preliminary study of this kind, requires a larger trial to achieve adequate statistical power to definitively compare classic Ayurveda and allopathic

TABLE 3. Incidence of Clinically Important AEs by Group (N = 43)

AEs	Group 1: MTX + Ayurvedic Placebo (n = 14)	Group 2: Ayurveda + MTX Placebo (n = 12)	Group 3: MTX Plus Ayurveda (n = 17)
Pregnancy	0	1	0
Hospitalization	1 ^a	1 ^b	0
Infections not requiring hospitalization; treated with intravenous antibiotics	1	0	0
Infections not requiring hospitalization; treated with oral antibiotics	6	6	6
Tuberculosis or opportunistic infection	0	0	0
Died	0	0	0
Life-threatening event	0	0	0
Congenital anomaly or birth defect	0	0	0
Cancer	0	0	0

This table provides the count of clinically important AEs that occurred during the study by treatment group.

^aPeripheral neuropathy.

^bFractured femur due to accidental fall.

TABLE 4. Adverse Events by Body System and Treatment Group (n [%])

Body System – AE	Group 1: MTX + Ayurvedic Placebo (n = 14)	Group 2: Ayurveda + MTX Placebo (n = 12)	Group 3: MTX + Ayurveda (n = 17)	Total ^a
1. General				
Fatigue	5	5	8	18
2. Constitutional				
Fever ^b	7	2	7	16
3. ENT				
Stomatitis	8	2	7	17
Teeth	1	0	2	3
Cough	12	12	11	35
Cold	2	2	3	7
Eye	7	8	5	20
Other	6	10	8	24
Dysgeusia	2	5	6	13
4. Pulmonary				
Other	0	0	2	2
5. Cardiovascular				
Chest pain	1	3	5	9
Other	1	0	0	1
6. Gastrointestinal				
Abdominal pain	5	0	5	10
Gastrointestinal bleeding	1	0	0	1
Hemorrhoids	1	0	0	1
Dyspepsia	5	3	17	25
Nausea	8	1	11	20
Vomiting	6	3	6	15
Diarrhea	6	9	5	20
Constipation	6	1	4	11
Other	5	3	8	16
7. Genitourinary				
UTI	1	0	2	3
Menstrual abnormalities	8	5	3	16
Other	2	1	0	3
8. MSK				
Pain	11	10	12	33
Other	6	0	2	8
9. Neurological				
Headache	18	8	8	34
Vertigo	4	2	8	14
Other	9	5	4	18
10. Integument				
Rash	4	1	1	6
Hair loss	5	2	5	12
Pruritus	5	3	4	12
Other	1	6	1	8
11. Psychological				
Feeling hyperactive				
Other	2	0	2	4

TABLE 4. (Continued)

Body System – AE	Group 1: MTX + Ayurvedic Placebo (n = 14)	Group 2: Ayurveda + MTX Placebo (n = 12)	Group 3: MTX + Ayurveda (n = 17)	Total ^a
12. Hematologic				
Anemia	1	0	4	5
Other	2	0	0	2
Total ^a	174	112	176	462

This table presents the number of AEs experienced by patients in each treatment group. This represents the number of instances of an AE, not the number of patients with AE. The AEs are presented by body system and are totaled by specific type and treatment group.

^aP values by statistical test; Pearson $\chi^2 = 0.022$ (66% of cells had expected counts <5).

^bBy patient report except as noted otherwise.

MSK, musculoskeletal; UTI, urinary tract infection.

treatment of RA. The relatively equal degree of response among the 3 groups, however, is encouraging for further testing of Ayurveda. Another factor that may limit the generalizability of this study is that it was done in India, where people are familiar with and accept classic Ayurveda.

This study demonstrated that CAM can be compared with allopathic medicine in the context of a placebo-controlled, double-blind, randomized trial. Ayurvedic treatment was also recorded systematically and concurrently, allowing for possible future analyses. This study not only compared classic Ayurveda with allopathic medicine, but also a combination of the two, which has not been done before. This is significant because it addresses the concerns about possible interaction effects when combining herbal medicines with allopathic medicines.

The development of a method to allow placebo controls for changing and individualizing therapies is an important step in providing the basis for a meaningful comparison of not only classic Ayurveda but also other traditional medicine systems with allopathic treatment in ways acceptable to western standards. This approach also shows that double-blind, placebo-included, randomized controlled studies are possible when testing classic Ayurvedic versus allopathic medications. Larger trials are needed and are clearly possible.

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A blueprint for placebo-controlled double-blind studies of complex, individualised interventions

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Furst DE, Venkatraman MM, Krishna Swamy BG, McGann M, Booth-Laforce C, Ram Manohar P, Sarin R, Mahapatra A, Krishna Kumar PR.

Well controlled, double-blind, placebo-controlled trials of classical Ayurvedic treatment are possible in rheumatoid arthritis.

Ann Rheum Dis 2010; Epub ahead of print.

Aim

To test the feasibility of an innovative study design for evaluating complex treatments.

Design

Randomised, placebo-controlled trial with three parallel arms.

Participants

Forty-six adult patients with rheumatoid arthritis, as defined by American College of Rheumatology criteria.

Intervention

Participants were randomly assigned to one of three groups:

- 1 methotrexate plus placebo Ayurvedic treatment,
- 2 Ayurvedic treatment plus placebo methotrexate, or
- 3 methotrexate plus Ayurvedic treatment.

Patients assigned to Ayurvedic treatment received one of 148 formulations, presented in six different

forms: decoctions, powders, pills, wines, jams or oils. Patients assigned to placebo received one of six different types of placebos, which matched the various forms of Ayurvedic treatment.

Main outcome measure

The primary outcome was success of blinding.

Main result

The study design was successful in blinding participants to group assignment.

Authors' conclusion

'Using different formulations for placebos enables individualization of therapy and blinding of patients in RCTs where this approach is required.'

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Commentary

Much of alternative medicine is individualised, and the various therapeutic options practitioners may need to choose from do not come together as one 'item'. Ayurvedic herbal medicine is one such treatment. An Ayurvedic doctor would generally insist that, for optimal results, they must be able to prescribe herbal decoctions, powders, pills or oils tailored to the patient's needs, conditions and symptoms. This renders placebo controls and successful blinding a true obstacle.

The authors of this trial have demonstrated that the obstacle is surmountable. The results show that individu-

alised treatments can be tested using an otherwise standard RCT design, and that blinding can be successful if more than one placebo preparation is required. The study might therefore be used as a blueprint for testing the efficacy of similarly complex interventions.

E Ernst, Peninsula Medical School, University of Exeter, Exeter, UK

Conflict of interest None declared.



Authors' reply

We appreciate the generous comments of the reviewer, and agree that one important outcome of our pilot trial was to show that there is a way to do an RCT using the tenet that Ayurvedic physicians must be able to individualise therapy. This approach requires close co-operation between the pharmacist and physician so that the pharmacist knows what to change; pharmacists must also keep meticulous records of the changes as multiple placebos must be used.

The Ayurvedic medicines used in this study were presented in six traditional pharmacological forms (e.g.

jams, decoctions, pills); each consisting of several multi-herbal formulations. It was possible to formulate one placebo to represent each category, for a total of six placebos, thus simplifying the regimens needed and eliminating the need to develop placebos for each formulation and herb. We hope that this approach will provide the necessary evidence to support the use of such therapy in the overall care of patients with rheumatoid arthritis.

DE Furst, Los Angeles, California, USA

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- Shri. Subramaniyam: *Secretary, Andhra Pradesh*
- Shri Chaturvedi (Rtd):*I.A.S*
- Shri Chandrakumar.J:*Rtd Director of land reforms*
- Shri Ilango. P:*Joint secretary Govt of Tamilnadu.*
- Smt. Thilagavathi.G.:*Former DGP, Tamilnadu*
- Smt. Bala Naga Devi:*Inspector General of Police, Telangana*
- Smt. Vidya Kulkarni:*DIG, CB CID , Chennai*

BUSINESS PERSONALITIES

- Shri. Ratan Tata: *Chairman emeritus of Tata Sons*
- Shri. A.M Naik : *Chairman, L&T*
- Shri. Dilip Shanghvi: *Founder and Managing Director Sun Pharma*
- Sheikh Kanak Khimji: *Renowned Business Conglomerate, Sultanate of Oman*
- Sheikh Khalid Ali Alturki: *Renowned Business Conglomerate of Saudi Arabia*
- Shri Venu Srinivasan: *Chairman of Sundaram –Clayton Group*
- Smt Mallika Srinivasan: *Chairman And C E O TAFE*
- Shri. Ajay Lakhanpal: *Chairman, Novino Battery*
- Shri Pratap Reddy : *Chairman , Apollo Group*
- Shri B.K.Birla : *Chairman, Birla Group*
- Shri Mickey Jagtani : *Chairman, Land Mark Group*
- Dr.Ram Buxani : *President, ITL groups*
- Shri Irshad Mirza: *Chairman, Mirza International*
- Shri Ashok Gokul Jamdhade : *Businessman*
- Shri Kushgara Nayan Bajaj : *Vice Chairman, Bajaj Hindustan Ltd.*
- Shri Rahul Bhatia : *Managing Director, Indigo Airways.*
- Shri Mahendra Mehta: *Chief executive of Vedanta Resources, Uganda*

VICE CHANCELLORS

- Sri Kulandaiswamy : *Former, Vice chancellor Anna University*
- Sri. Marimuthu : *Former, Vice Chancellor Bharathiar University Coimbatore*
- Dr.Swaminathan : *Former, Vice Chancellor Bharathiar University Coimbatore*
- Sri Karnik S D: *Former Vice Chancellor, University of Mumbai*

CLASSICAL MUSICIANS

- Shri. K.J.Yesudas: *Renowned classical vocalist and Playback singer*
- Shri Lalgudi Jayaraman: *Acclaimed Violinist*
- Mr. Anand Vaidyanatha : *Voice Trainer – Tamil Music industry*
- Ms, Padma Subramaniam: *Revered Danseuse and Exponent of Bharatnatyam*
- Shri T.V. Gopalakrishnan: *Renowned Mridangam and Vocal maestro*
- Shri Sengottai Hariharan : *Renowned classical Singer*
- Pandit Jasraj : *Indian classical. Hindustani Vocalist*
- Ustad Amjad Ali khan: *Acclaimed sarod Maestro, India*
- Smt Malavika Sarukkai: *Renowned classical Dancer*
- Smt Kala Ramanath : *Violinist*
- Shri.O.S.Arun : *Classical Singer*
- Shri Karunamoorthy : *Percussionist*

SPORTS PERSONALITIES

- Shri. Ravi Shashtri : *Cricketer- India*
- Shri. V.V.S..Lakshman : *Cricketer- India*
- Shri. Sreesanth : *Cricketer- India*

- Shri. Narain Karthikeyan: *Formula one Racer*

RENOWNED PLAY BACK SINGER

- Ms. Latha Mangeshkar: *Bharat Ratna Recipient and living musical legend of India*
- Smt. Asha Bhosle : *Acclaimed play back singer of India*
- Smt. K.S. Chitra : *Play back singer Indian film industry*
- Shri. Sujatha: *Renowned Playback, Singer*
- Shri. P. Jayachandran: *Acclaimed playback singer, Malayalam*
- Shri. G. Venuopal : *Play back singer, Malayalam, film industry*
- Smt. Rimi Tomy : *Play back singer Malayalam film industry*
- Shri Malaysia Vasudevan (late) : *Veteran play back singer, South Indian film industry*
- Shri. Abhijeeth : *Renowned playback singer, Hindi Film industry*
- Shri Sarath : *Music director Malayalam*
- Shri Hariharan : *Renowned Playback, Singer*
- Shri Madhu Balakrishnan : *Renowned Playback, Singer*

RENOWNED FILM PERSONALITIES

- Shri Rajini Kanth : *Renowned Cine Actor*
- Shri. Mohanlal: *Actor Malayalam*
- Shri Jayaram: *Actor Malayalam*
- Smt Kavya Madhavan: *Actress, Malayalam*
- Smt Manju Varrier: *Actress, Malayalam*
- Ms. Samvrutha Sunil: *Actress, Malayalam*
- Ms Anushka Shetty: *Renowned Cine Actress*
- Ms Namitha Pramod: *Actress, Malayalam*
- Smt. Helen Khan: *Actress, Hindi*
- Smt. Asha Parekh: *Actress, Hindi*
- Smt. Juhi Chawla: *Actress Hindi*
- Smt. Nanditha Das: *Actress Hindi*
- Shri Vikram : *Actor, Tamil*
- Shri Jeyam Ravi: *Actor Tamil*
- Shri Aravind Swamy: *Actor, Tamil*
- Shri .Vivek: *Actor Tamil Cinema*
- Shri. Innocent: *Actor Malayalam*
- Shri Mohan Babu: *Actor, Telugu*
- Smt Radha : *Actress, Malayalam. Tamil*
- Smt Mukesh : *Actor, Malayalam*
- Shri Bharathiraja: *Cine Director*
- Shri Balu Mahendra : *Cine Director*
- Shri Chandrasekar : *Cine Director*
- Shri Linga Swamy : *Cine Director*
- Shri Renjith: *Cine Director*