

A Novel Highly Bioavailable Curcumin Formulation Improves Symptoms and Diagnostic Indicators in Rheumatoid Arthritis Patients: A Randomized, Double-Blind, Placebo-Controlled, Two-Dose, Three-Arm, and Parallel-Group Study

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ABSTRACT Rheumatoid arthritis (RA) is an autoimmune, chronic systemic inflammatory disorder. The long-term use of currently available drugs for the treatment of RA has many potential side effects. Natural phytonutrients may serve as alternative strategies for the safe and effective treatment of RA, and curcuminoids have been used in Ayurvedic medicine for the treatment of inflammatory conditions for centuries. In this study, a novel, highly bioavailable form of curcumin in a completely natural turmeric matrix was evaluated for its ability to improve the clinical symptoms of RA. A randomized, double-blind, placebo-controlled, three-arm, parallel-group study was conducted to evaluate the comparative efficacy of two different doses of curcumin with that of a placebo in active RA patients. Twelve patients in each group received placebo, 250 or 500 mg of the curcumin product twice daily for 90 days. The responses of the patients were assessed using the American College of Rheumatology (ACR) response, visual analog scale (VAS), C-reactive protein (CRP), Disease Activity Score 28 (DAS28), erythrocyte sedimentation rate (ESR), and rheumatoid factor (RF) values. RA patients who received the curcumin product at both low and high doses reported statistically significant changes in their clinical symptoms at the end of the study. These observations were confirmed by significant changes in ESR, CPR, and RF values in patients receiving the study product compared to baseline and placebo. The results indicate that this novel curcumin in a turmeric matrix acts as an analgesic and anti-inflammatory agent for the management of RA at a dose as low as 250 mg twice daily as evidenced by significant improvement in the ESR, CRP, VAS, RF, DAS28, and ACR responses compared to placebo. Both doses of the study product were well tolerated and without side effects.

KEYWORDS: • C-reactive protein • curcumin • curcuminoids • rheumatoid arthritis • rheumatoid factor • visual analog scale

INTRODUCTION

RHEUMATOID ARTHRITIS (RA) is an autoimmune disease and chronic systemic inflammatory disorder with joint destruction, which leads to significant pain and disability.^{1,2} The inflammatory process, primarily in the synovial tissue, is characterized by the accumulation of inflammatory cells, macrophages, inflammatory cytokines, including tumor necrosis factor- α (TNF)- α and anti-interleukin IL-1 β and IL-6, and synovial fibroblasts. The inflamed synovium may invade cartilage and bone, leading to bone erosion and cartilage damage.^{3,4} IL-1 β and TNF- α are believed to be the key proinflammatory cytokines mediating cartilage degradation in patients with RA.^{5,6}

The prevalence of RA has been estimated to be around 40/100,000 of the population worldwide,⁷ with women being affected 2:1 to 3:1 times more than men. In general, the lifetime risk of RA in adults is about 3.6% (1 in 28) for women and 1.7% (1 in 59) for men.^{7–9} In the United States, RA and osteoarthritis (OA) affect more than 40 million people, with huge healthcare costs and an urgent need for more effective therapeutic treatments. The prevalence of RA in India is similar to Western countries.²

Treatments targeting cytokines such as anti-TNF- α antibodies, soluble TNF receptor, IL-6 receptor antibody, and IL-1 receptor antagonists are currently used as therapeutic approaches for the management of RA. In addition, anti-inflammatory agents and disease-modifying antirheumatic drugs (DMARDs) such as methotrexate are used. Other currently available drugs used long term for the treatment of RA include analgesics, steroids, nonsteroidal anti-inflammatory drugs (NSAIDs), and immunosuppressive agents, all of which

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have many potential side effects, including gastrointestinal tract disturbances, liver injury, low blood cell count, heart failure, hair loss, and immunodeficiency.^{10,11} Hence, there is a need for newer therapeutic approaches that can offer effective management without side effects and with high tolerance at relatively low cost.¹²

Curcuminoids are compounds extracted from the spice turmeric, which is obtained from the rhizomes of *Curcuma longa*, a member of the family Zingiberaceae, and have been used in Ayurvedic medicine as a treatment for inflammatory conditions for centuries.^{13,14} The three major curcuminoids isolated from *C. longa* are curcumin, demethoxycurcumin, and bisdemethoxycurcumin, with curcumin being the primary component. Numerous studies have demonstrated the antioxidant, antimicrobial, anti-inflammatory, anticarcinogenic, and proapoptotic properties of curcumin.^{12–15} Curcumin has also been shown to exhibit therapeutic effects against arthritis¹⁶ and various neurological,¹⁷ pulmonary,¹⁸ hematological,¹⁹ and cardiovascular ailments.²⁰

Curcuminoids exhibit pleiotropic actions, interacting with numerous molecular targets involved in inflammation, including TNF- α , IL-1 β , IL-6, IL-8, nuclear factor- κ B (NF- κ B), and cyclooxygenase-2 (COX-2).^{21,22} Cell culture and animal studies indicate that curcumin has potential as a therapeutic agent in RA.^{23,24} A meta-analysis of eight randomized clinical trials concluded that doses of about 1000 mg of curcumin per day were effective in treating RA, although the authors noted that additional studies were required to confirm the efficacy of curcumin.²⁵

Although curcumin has exhibited much therapeutic promise, its use has been limited due to its inherently poor intestinal absorption, rapid metabolism, and limited systemic bioavailability.^{26,27} To increase the water solubility, stability, bioavailability, and potential applications of curcumin/curcuminoids, various strategies have been proposed and investigated, including nanoparticles, liposomes, solid dispersions, solid lipid nanoparticles, microemulsions, and complexation with phospholipids and cyclodextrins.^{27–32} While each of these novel delivery strategies offers promise, there are still limitations to their potential use. Most of these technologies are not able to accommodate high loading of curcumin/curcuminoids, thus limiting the bioactivity of the finished products, and some of the delivery systems are not readily suitable for food, drug, and related applications due to various inherent issues.²⁷

The association of curcuminoids with the natural turmeric matrix may be an excellent strategy to overcome these limitations and improve their efficacy against RA as well as other inflammatory conditions. A novel highly bioavailable curcumin/curcuminoid product has been developed based on the recreation of a completely natural turmeric matrix with 95% active curcuminoids ($\sim 50\%$ w/w in the finished product). The turmeric matrix is recreated by extracting three different entities: curcuminoid, turmeric essential oil, and water soluble fractions of turmeric. The detailed turmeric components present in the curcumin/curcuminoids in a turmeric matrix product are given in Table 1.

Curcuminoids with 95% purity are extracted from dried turmeric rhizomes, using the food grade solvent ethanol and

TABLE 1. COMPOSITION OF CURCUMINOID TURMERIC MATRIX FORMULATION

Fraction	Chemical constituent	Composition (%)
1.	Total curcuminoids	50.0
	Curcumin	41.2
	Demethoxycurcumin	7.3
	Bisdemethoxycurcumin	1.5
2.	Essential oil	3.0
3.	Protein	2.0
	Total carbohydrate	40.0
	Dietary fiber	5.0

the resulting oleoresin is crystallized to obtain curcuminoid powder. Turmeric essential oil is separated by steam distillation ($\sim 3\%$). The powdered turmeric is extracted with water to obtain the carbohydrates ($\sim 40\%$), dietary fiber ($\sim 5\%$), and turmerin protein ($\sim 2\%$), which can efficiently cross over the lipid bilayer. These three components are combined with the curcuminoids by a unique patent-pending process of polar-nonpolar-sandwich technology through which curcumin/curcuminoids are protected inside the resulting matrix.

The bioactive molecules present in this novel product other than curcuminoids play an important role in the bioavailability of curcumin/curcuminoids. The presence of bisabolanes and sesquiterpenes in the turmeric essential oils in the product provide the nonpolar component, while the water soluble proteins and the carbohydrates provide the polar components of the sandwiched matrix. The matrix provides advantages such as enhanced physical stability, protection of the curcuminoids from degradation in the body, controlled curcuminoid release, biocompatibility, and laboratory to industrial scalability.

With respect to the pharmacokinetics of the study product in humans, a pilot, randomized, open-label, cross-over, single-dose bioequivalence study was conducted involving 500 mg of the turmeric matrix formulation, 500 mg of unformulated 95% curcumin, or placebo.³³ Twelve human healthy male adults of body mass index (BMI) 18.5–30.0 kg/m² between the ages of 18–45 were included in the study. Analyses of curcuminoids were carried out by ultraperformance liquid chromatography, which had been validated using curcumin standards, and contents of curcuminoids in the plasma samples were quantified. The bioavailability as measured by the maximum plasma concentration (C_{max}) and area under the curve showed that the novel curcumin matrix formulation was ~ 10 -fold more bioavailable than the unformulated 95% curcumin.³³

Other research has demonstrated the efficacy of this study product as an antioxidant,³⁴ antineoplastic,³⁵ elastase inhibitor,³⁶ and antiaging product.³⁷ The present investigation evaluated the efficacy of this novel curcumin product with that of a placebo in active RA patients.

MATERIALS AND METHODS

Study design

The present study was a randomized, double-blind, three-arm pilot designed to determine the efficacy and safety of oral

administration of two different doses of the novel highly bioavailable curcumin in a turmeric matrix formulation with placebo in patients with active RA. The curcumin study product (Acumin™) was supplied by Aurea Biolabs (P) Ltd., Cochin, Kerala, India. Thirty-six patients were randomized in a 1:1:1 ratio to receive 250 mg of the study product as the low-dose curcumin, 500 mg as the high-dose curcumin, and placebo (500 mg of food grade starch) over a period of 3 months as one capsule twice daily 30 min after meals. Dose setting of the study product was based on the bioavailability of the product compared to the 95% curcumin.³³ The study was conducted at Dhanwantri Ayurvedic College Hospital and Research Centre, Siddapur, Karnataka, India.

Randomization of the subjects who met the inclusion criteria resulted in four females and eight males in the low-dose group, four females and eight males in the high-dose group, and seven females and five males in the placebo group (Table 2). The mean ages were 36.7 years in the low-dose group, 38.3 years in the high-dose group, and 39.6 years in the placebo group.

Demographic data of the subjects with characteristics, medical history, and prior and concomitant medications were collected. Body weights and heights were measured, and physical examinations were performed (Table 2). Vital signs, including blood pressure and heart rates, were determined. There were no significant differences in baseline characteristics, including BMI and biochemical parameters such as cholesterol, random blood sugar, creatine, sodium, potassium, urea, total bilirubin, total protein, albumin, and alkaline phosphatase (Tables 2 and 3).

Laboratory parameters as biomarkers of RA included erythrocyte sedimentation rates (ESR), C-reactive protein (CRP), and rheumatoid factor (RF). Pregnancy tests were performed in women. A joint assessment was performed for a tender joint count (TJC), swollen joint count (SJC), and duration of morning stiffness.

Inclusion and exclusion criteria of patients

Eligible subjects were either male or female with diagnosed RA according to the revised 2010 American College of Rheumatology (ACR) criteria (with RA functional class of II), a Disease Activity Score (DAS) greater than 5.1, and the sum of the SJC and TJC greater than eight at screening and baseline. At the screening, the patients had either CRP >0.6 mg/dL or ESR >28 mm/h. Secondary Sjögren's syndrome or limited cutaneous vasculitis was permitted.

The exclusion criteria included patients with any of the several conditions requiring treatment with DMARDs, NSAIDs, RA with significant secondary involvement of any systemic organ (including but not limited to vasculitis, pulmonary fibrosis, or Felty's syndrome), inflammatory joint disease other than RA (*e.g.*, gout, reactive arthritis, psoriatic arthritis, seronegative spondyloarthritis), and Lyme disease), or other systemic autoimmune disorders (*e.g.*, systemic lupus erythematosus, inflammatory bowel disease, scleroderma, inflammatory myopathy, mixed connective tissue disease, or any overlap syndrome), and patients with any surgical

TABLE 2. DEMOGRAPHICS, BASELINE, AND END OF TREATMENT CHARACTERISTICS OF STUDY SUBJECTS OF TWICE-DAILY LOW (250 MG)- AND HIGH (500 MG)-DOSE TURMERIC MATRIX PRODUCT

Parameter/ statistics	Low-dose turmeric matrix formula	High-dose turmeric matrix formula	Placebo	Total
Age (years)				
N	12	12	12	36
Mean ± SD	36.7 ± 10.7	38.3 ± 5.8	39.6 ± 8.8	38.2 ± 8.5
Median	34.5	38.5	40.0	36.5
Minimum, maximum	22.0, 55.0	30.0, 51.0	24.0, 55.0	22.0, 55.0
Sex, N (%)				
Female	4 (33.3)	4 (33.3)	7 (58.3)	15 (41.7)
Male	8 (66.7)	8 (66.7)	5 (41.7)	21 (58.3)
Height at baseline (cm)				
N	12	12	12	36
Mean ± SD	170.8 ± 9.50	170.3 ± 8.20	165.7 ± 9.76	168.9 ± 9.21
Median	170.0	174.0	165.5	169.0
Minimum, maximum	155.0, 187.0	158.0, 182.0	152.0, 184.0	152.0, 187.0
Weight at baseline (kg)				
N	12	12	12	36
Mean ± SD	69.2 ± 12.2	68.7 ± 7.6	60.8 ± 9.0	66.2 ± 10.3
Median	73.0	70.0	59.0	68.0
Minimum, maximum	50.0, 84.0	56.0, 78.0	48.0, 78.0	48.0, 84.0
BMI at baseline				
N	12	12	12	36
Mean ± SD	23.6 ± 2.6	23.7 ± 1.8	22.1 ± 2.2	23.1 ± 2.3
Median	23.4	23.1	22.0	23.1
Minimum, maximum	18.0, 27.0	21.3, 27.5	18.3, 25.9	18.0, 27.5
Weight after treatment (kg)				
N	12	12	12	36
Mean ± SD	68.7 ± 11.2	67.4 ± 7.4	59.5 ± 8.3	65.2 ± 9.8
Median	72.0	69.0	57.0	66.0
Minimum, maximum	51.0, 83.0	55.0, 77.0	46.5, 75.0	46.5, 83.0
BMI after treatment				
N	12	12	12	36
Mean ± SD	23.4 ± 2.3	23.2 ± 1.6	21.7 ± 2.3	22.8 ± 2.2
Median	23.3	22.6	22.3	22.6
Minimum, maximum	18.7, 26.9	21.3, 26.4	17.4, 25.9	17.4, 26.9

BMI, body mass index; SD, standard deviations.

procedure, including bone/joint surgery/synovectomy (including joint fusion or replacement) within 12 weeks before baseline or planned within 24 weeks of randomization. Patients who used any anti-inflammatory, antirheumatoid, analgesic, steroid, or other drugs that in the opinion of the investigators would interfere with the study were not permitted for 4 weeks in the case of parenteral or intra-articular drugs and 2 weeks in the case of oral drugs before study enrollment and during the study period.

Efficacy and safety evaluation

The primary endpoints involved the evaluation of the comparative efficacy tests of 250 and 500 mg of the study

TABLE 3. SUMMARY OF MEAN CHANGES IN BIOCHEMICAL PARAMETERS FROM BASELINE TO END OF TREATMENT

Parameters	Low-dose turmeric matrix formula			High-dose turmeric matrix formula			Placebo		
	Baseline	End of treatment	% Change	Baseline	End of treatment	% Change	Baseline	End of treatment	% Change
Cholesterol (mg/dL)	176.6±23.0	174.0±21.5	1.46	181.4±22.0	171.3±18.1	5.63	170.6±14.3	171.6±14.2	-0.58
RBS (mg/dL)	118.5±14.7	122.0±11.0	-2.95	114.2±14.0	108.7±8.8	4.87	108.8±16.1	106.3±11.4	2.29
Creatine (mg/dL)	0.93±0.22	0.78±0.15	15.67	1.00±0.26	0.88±0.18	12	0.86±0.19	0.89±0.18	-3.48
Sodium (mmol/L)	137.9±5.2	137.0±4.9	0.65	139.8±3.9	139.1±3.9	0.52	137.4±4.2	137.2±4.2	0.14
Potassium (meq/L)	3.87±0.45	3.90±0.34	-0.77	4.05±0.58	4.01±0.57	0.98	3.73±0.29	3.71±0.27	0.53
Urea (mg/dL)	13.92±4.16	12.25±3.06	11.99	16.86±3.97	15.58±3.47	7.67	16.14±2.92	15.72±2.46	2.72
Total bilirubin (mg/dL)	1.15±0.43	1.10±0.29	4.34	1.10±0.33	0.98±0.22	10.90	0.87±0.23	0.89±0.21	-2.29
Total protein (g/dL)	6.86±0.82	6.85±0.83	0.14	7.31±0.80	7.13±0.79	2.46	6.56±0.63	6.16±0.623	6.09
Albumin (g/L)	39.2±4.7	39.4±3.4	-0.58	45.4±7.8	45.1±7.8	0.59	38.8±3.8	38.1±3.8	1.90
Alkaline phosphatase (μU)	63.7±27.1	63.1±27.2	0.94	76.7±23.4	74.6±17.4	2.71	71.8±18.8	72.0±16.9	-0.20

RBS, random blood sugar.

product twice daily with that of a placebo. The secondary efficacy endpoints included the assessment of the safety and tolerability of the active products and assessment of the changes in various biomarkers during the study period among all the study group subjects. Efficacy assessments included ACR response, visual analog scale (VAS), CRP, DAS28, ESR, and RF values. The baseline values of these parameters were compared to that of the end of treatment visit by appropriate statistical tools. Laboratory data were summarized by presenting summary statistics of raw data and change from baseline values (means, standard deviations [SD]) as well as tables showing the percentage change from baseline to end of treatment in laboratory values.

Statistical analysis

Statistical analysis was performed using SAS statistical package, expressed as the mean ± SD and a “*P*” value ≤.001 was considered as a significant difference. The paired *t*-test and Mann–Whitney test were used to measure the change from the baseline. Paired *t*-test was used to measure the change from the baseline, while the Mann–Whitney U test was used to compare mean differences between the two treatment groups. The correlation coefficients were computed and significance of the differences was defined as *P* < .01.

Ethical conduct

This research was carried out in accordance with the principles of Declaration of Helsinki (Ethical Principles for

Medical Research Involving Human Subjects, revised by the WMA General Assembly, Seoul, October 2008), “ICH GCP,” National Regulations (ICMR Guidelines), EMEA 2001, Indian GCP, and Schedule Y of Indian Drugs and Cosmetics Act. The study protocol was reviewed and approved by Institutional Ethics Committee from Dhanwantri Ayurvedic College Hospital and Research Centre, Siddapur, Karnataka (Reference No. DAC/Research/2016-04 dated January 29, 2016). No clinically significant abnormal laboratory values were identified and no statistically significant changes in the vital signs were observed from the baseline to final visits. All subjects were given detailed information about the study and willingly provided written and signed informed consent.

RESULTS

No abnormalities in physical findings were observed on the screening visit or during the study visits, no statistically significant changes in vital signs were observed between baseline and end of visit or between the treatment groups (Tables 2 and 3). There were no serious adverse events reported or observed in this study.

Efficacy assessment of DAS28 and VAS against RA

The results of efficacy assessment of DAS28 and VAS against RA are summarized in Tables 4 and 5, respectively. Among the three treatment groups, DAS and VAS scores for pain were comparable at baseline. Both treatment groups

TABLE 4. RESULTS OF DISEASE ACTIVITY SCORE-28 FROM BASELINE TO END OF TREATMENT FOR TWICE-DAILY LOW (250 MG)- AND HIGH (500 MG)-DOSE TURMERIC MATRIX FORMULATION

Treatment group	Baseline (N=12)	End of treatment (N=12)	% Change	95% confidence interval	<i>P</i> ^a
Low-dose turmeric matrix formula	4.51±0.64	2.14±0.16	52.55	0.0877–0.3628	≤.001*
High-dose turmeric matrix formula	5.29±0.54	1.80±0.36	65.97	0.2033–0.3078	≤.001*
Placebo	3.53±0.47	3.53±0.47	—	—	.462

^aPaired *t*-test and Mann–Whitney test used throughout for comparisons.

*Statistically significant at *P* < .01 level.

TABLE 5. RESULTS OF VISUAL ANALOG SCALE FROM BASELINE TO END OF TREATMENT FOR TWICE-DAILY LOW (250 MG)- AND HIGH (500 MG)-DOSE TURMERIC MATRIX FORMULATION

Treatment group	Baseline (N=12)	End of treatment (N=12)	% Change	95% confidence interval	P ^a
Low-dose turmeric matrix formula	7.01±0.86	2.63±0.74	62.48	0.4201–0.4858	≤.001*
High-dose turmeric matrix formula	7.99±0.71	2.21±0.45	72.34	0.2547–0.4019	≤.001*
Placebo	6.61±0.73	6.84±0.63	3.48	0.3541–0.4140	.954

^aPaired *t*-test and Mann–Whitney test used throughout for comparisons.

*Statistically significant at *P*<.01 level.

showed a significant improvement in DAS28 and VAS scores at the end of the 90-day study based on the paired *t*-test and Mann–Whitney test (*P*≤.001). In addition, the correlation coefficients also indicated the occurrence of significant improvement for both dosage treatment groups (*P*<.01) (Tables 4 and 5), with the high-dose curcumin group showing modestly greater reductions in both DAS and VAS scores from baseline (Tables 4 and 5). The percentage changes from baseline for the high-dose curcumin group resulted in decreases of ~66% and 72% for DAS28 and VAS, respectively, while the low-dose group had decreases of ~53% and 62%, respectively (Tables 4 and 5). There were no significant changes in the placebo group.

Efficacy assessment of ESR values against RA

The ESR values of the patients showed significant decreases in both treatment groups between baseline and end of study (Table 6). Both active treatment groups resulted in decreases in ESR values of ~88%. In the placebo study group, a nonsignificant decrease in the ESR value of about 29% was observed. The changes in ESR values were similar and highly significant (*P*≤.001) for both treatment groups using paired *t*-test and Mann–Whitney test. Correlation coefficients also indicated the occurrence of significant improvements in ESR values for both curcumin groups (*P*<.01) (Table 6).

Efficacy assessment of CRP values against RA

The mean CRP values of the two active treatment groups and the placebo group are given in Table 7. A dose-dependent response was observed with respect to reductions in CRP values at the end of the study. Both the decreases were significant (*P*≤.001) compared to the placebo group based on the paired *t*-test and Mann–Whitney test. The percentage decreases were highly significant (*P*<.01) by

using correlation coefficients (Table 7). CRP values for the low-dose and high-dose curcumin groups were ~30% and 51%, respectively, between baseline and end of study. A small nonsignificant decrease was observed for the placebo study group between baseline and end of study.

Efficacy assessment of RF against RA

The RF values of both curcumin treatment groups showed significant (*P*≤.001) reductions at the end of the 90-day treatment period compared to baseline (Table 8). Although a slightly greater decrease was shown with the higher dose of the study product, the difference between the two doses was not significant. The percent decreases with the low and high dose of curcumin were ~80% and 84%, respectively. The percentage change in the placebo group between baseline and end of study was ~13%, which was not statistically significant.

Efficacy assessment of ACR20 against RA

The data for the ACR improvement criteria that were analyzed for each group included the number of tender joints and number of swollen joints, while the ACR20 assessment also included the patient's assessment of pain, patient's and physician's global assessments of disease activity, and patient's assessment of physical function. The results are provided in Table 9. The mean values of ACR20 for the low-dose curcumin group were ~19 at baseline and increased to 65 at the end of treatment, while for the high-dose curcumin group the ACR20 was 16 at baseline and increased to 68 at the end of treatment. Both treatment groups showed significant improvements in ACR20 scores as well as total swollen joints and total tender joints based on paired *t*-test and Mann–Whitney test (*P*≤.001), and on correlation coefficient analysis (*P*<.01). There was no significant improvement in the placebo group. The differences

TABLE 6. EFFICACY RESULTS FOR ERYTHROCYTE SEDIMENTATION RATE FROM BASELINE TO END OF TREATMENT FOR TWICE-DAILY LOW (250 MG)- AND HIGH (500 MG)-DOSE TURMERIC MATRIX FORMULATION

Treatment group	Baseline (N=12)	End of treatment (N=12)	% Change	95% confidence interval	P ^a
Low-dose turmeric matrix formula	175.9±12.9	21.0±4.8	88.1	2.7081–7.2876	≤.001*
High-dose turmeric matrix formula	181.7±4.8	21.2±2.9	88.6	1.6333–15.2494	≤.001*
Placebo	180.2±12.4	126.9±17.3	29.6	6.9999–9.7685	.863

^aPaired *t*-test and Mann–Whitney test used throughout for comparisons.

*Statistically significant at *P*<.01 level.

TABLE 7. TREATMENT EFFICACY RESULTS FOR C-REACTIVE PROTEIN RELATIVE TO BASELINE FOR TWICE-DAILY LOW (250 MG)- AND HIGH (500 MG)-DOSE TURMERIC MATRIX FORMULATION

Treatment group	Baseline (N=12)	End of treatment (N=12)	% Change	95% confidence interval	P ^a
Low-dose turmeric matrix formula	0.97 ± 0.15	0.68 ± 0.10	29.9	0.0578–0.0847	≤.001*
High-dose turmeric matrix formula	1.21 ± 0.18	0.59 ± 0.08	51.2	0.0441–0.1030	≤.001*
Placebo	0.97 ± 0.15	1.08 ± 0.15	11.3	0.0867–0.0882	.891

^aPaired *t*-test and Mann–Whitney test used throughout for comparisons.

*Statistically significant at *P* < .01 level.

between the two treatment groups were not statistically significant. The percent improvements in the ACR20 responses by the patients receiving low- and high-dose curcumin were ~70% and 76%, respectively. No change was observed in the placebo group with respect to ACR20 scores (Table 9).

With respect to swollen joints and total tender joints, the high-dose treatment group exhibited decreases of ~85% and 88%, respectively, while the low-dose treatment group exhibited slightly lower decreases of ~80% and 78%, respectively, between baseline and end of study treatment (Table 9). The improvements in total swollen joints and total tender joints after treatment with both low- and high-dose curcumin study product were statistically significant (*P* < .01), which was confirmed by using correlation coefficient analysis. Again, the differences between the low- and high-dose treatment groups were not statistically significant. No significant changes occurred in the placebo group with respect to total swollen joints and total tender joints from baseline to end of the study (Table 9).

DISCUSSION

In vitro and *in vivo* studies indicate that curcumin exhibits antioxidant, antineoplastic, antiviral, antiarthritic, antiamyloid, and anti-inflammatory properties. Accordingly, it has received much interest as a potential therapeutic agent for the prevention and/or treatment of various malignant diseases, allergies, arthritis, Alzheimer's disease, and other inflammatory illnesses. Because most chronic diseases are mediated through dysregulated inflammation,^{38–40} curcumin has potential use in the treatment of numerous diseases. However, its use in an unmodified form is limited due to its poor bioavailability,²⁷ and enhancing the bioavailability of curcumin greatly increases its potential usefulness for the prevention and treatment of human diseases.⁴¹

Curcumin in a natural turmeric matrix has approximately a 10-fold enhanced bioavailability compared to unformulated 95% curcumin,^{34–37} and was developed to overcome shortcomings such as low aqueous solubility, poor bioavailability, poor membrane permeability, and inadequate tissue absorption.

The results of the current investigation indicate that the study product can provide significant improvement in relieving the symptoms associated with active RA. Active RA patients, who received the study product at both 250 and 500 mg twice daily for a period of 90 days, reported statistically significant changes/decreases in their clinical symptoms. This was evident from changes in the ACR responses, and DAS28 and VAS questionnaires administered by the physician/designee. Furthermore, these results were confirmed by significant changes in CRP, ESR, and RA factor values.

All enrolled subjects completed 90 days of treatment. Patients in both the low- and high-dose groups experienced significant disease improvement and fulfilled the ACR improvement criteria (Tables 4, 5, and 9). In contrast, none of the patients in the placebo group attained these criteria. Similar results were obtained when the individual components of the ACR improvement criteria were analyzed for each treatment group, which included the number of tender joints, number of swollen joints, patient's assessment of pain, patient's as well as physician's global assessments of disease activity, and patient's assessment of physical function. Along with the variables included in the ACR improvement criteria, morning stiffness was also evaluated and decreased significantly during curcumin administration.

Significant decreases (*P* ≤ .001) were observed in the ESR (Table 6), CRP (Table 7), and RF (Table 8) levels in both the low- and high-dose treatment groups compared to baseline. The CRP decreases were dose dependent, while similar results were observed for the two doses with respect to ESR

TABLE 8. TREATMENT EFFICACY RESULTS FOR RHEUMATOID FACTOR RELATIVE TO BASELINE IN IU/ML FOR TWICE-DAILY LOW (250 MG)- AND HIGH (500 MG)-DOSE TURMERIC MATRIX FORMULATION

Treatment group	Baseline (N=12)	End of treatment (N=12)	% Change	95% confidence interval	P ^a
Low-dose turmeric matrix formula	123.3 ± 36.9	24.4 ± 5.7	80.2	3.2159–20.8992	≤.001*
High-dose turmeric matrix formula	150.6 ± 41.7	23.8 ± 6.0	84.2	3.3821–23.6062	≤.001*
Placebo	64.4 ± 22.0	72.8 ± 24.5	13.1	12.4474–13.8794	.912

^aPaired *t*-test and Mann–Whitney test used throughout for comparisons.

*Statistically significant at *P* < .01 level.

TABLE 9. AMERICAN COLLEGE OF RHEUMATOLOGY RESPONSES FROM BASELINE TO END OF TREATMENT FOR TWICE-DAILY LOW (250 MG)- AND HIGH (500 MG)-DOSE TURMERIC MATRIX FORMULATION

Parameters	Low-dose turmeric matrix formula				High-dose turmeric matrix formula				Placebo				
	Baseline (N = 12)	End of treatment (N = 12)	% Change	95% confidence interval	Baseline (N = 12)	End of treatment (N = 12)	% Change	95% confidence interval	Baseline (N = 12)	End of treatment (N = 12)	% Change	95% confidence interval	P ^a
ACR20	19.33±2.81	65.17±10.67	70.3	1.5881–6.0354 ≤.001*	16.50±3.78	67.83±8.60	75.7	2.1375–4.8661 ≤.001*	14.75±6.58	14.75±6.58	—	—	≤.001*
Total swollen joints	14.42±1.68	2.83±0.83	80.4	0.4724–0.9485 ≤.001*	17.00±1.35	2.58±0.67	84.8	0.3783–0.7629 ≤.001*	11.08±2.23	10.67±1.97	3.7	0.0281–0.0621	≤.096
Total tender joints	13.33±3.17	2.92±0.67	78.1	0.3783–1.7946 ≤.0*01	16.67±1.92	2.00±0.74	88.0	0.4179–1.0879 ≤.001*	9.50±3.23	9.92±1.93	4.4	0.0473–0.1087	.614

^aPaired *t*-test and Mann–Whitney test used throughout for comparisons.

*Statistically significant at *P* < .01 level.

ACR, American College of Rheumatology.

and RF values. The study product started showing beneficial effects from the first month of treatment (data not shown) and was highly significant at the end of the study.

The results of this study indicate that the novel curcumin in a turmeric matrix product was safe and effective, acting as an analgesic and anti-inflammatory, and was efficient in pain management associated with RA. There are several reported studies on the molecular targets of curcumin, contributing to chronic pain. Curcumin has been shown to alleviate chronic pain in several different models,^{42,43} including neuropathic pain.^{44,45} The data from the current study show that curcumin has the potential to produce positive responses in patients with active RA relative to the placebo group, and was not associated with any adverse events. These results provide a suitable platform for investigating the potential of curcumin to relieve symptoms in other chronic diseases associated with inflammation and pain.

No adverse effects were observed or reported by the study subjects within any group. Turmeric and curcumin have been shown to be in numerous clinical studies and systematic reviews.^{45–47} No toxicological effects have been reported in conjunction with long-term use of curcumin.⁴⁵ The only adverse effects reported with curcumin include mild nausea and diarrhea at very high (8–12 g) doses⁴⁷; doses greatly exceeding those used in the current study.

The potential therapeutic efficacy of curcumin against cardiovascular, neurodegenerative, pulmonary, metabolic, autoimmune, and neoplastic diseases was well summarized.⁴⁵ Since this review, numerous additional studies have been conducted with curcumin in conjunction with various inflammatory diseases. Daily *et al.*²⁵ conducted a literature search regarding curcumin and arthritis and OA, and identified 29 studies. Of these, eight studies met their criteria for inclusion in their meta-analysis, which supports the efficacy of curcumin in the treatment of arthritis. Two of these studies used curcumin powder, two studies used ethanolic extracts of turmeric with powdering of the product, one study used turmeric with polysaccharides, one study used a curcuminoid mixture with phosphatidylcholine and microcrystalline cellulose, one study used curcuminoids with pepper oil extract, and one study used a water dispersible curcumin powder. Thus, most studies used some method for enhancing bioavailability.

Douglass and Clouatre²⁷ examined the bioavailability of six different curcumin formulations relative to unformulated 95% curcuminoid powder of uncontrolled particle size. Relative mass efficacy was used to normalize results since the percentage of curcuminoids in the various formulations varied markedly. They concluded that a hydrophilic carrier dispersed curcuminoid formula exhibited greatest bioavailability. This product contained curcuminoids dispersed on a water soluble carrier composed of polyvinyl pyrrolidone and cellulose derivatives with a small amount of lipid.

The novel turmeric matrix system used to deliver curcuminoids in the current study is composed of curcuminoids (~50%), carbohydrates (~40%), fiber, protein, and essential oil (Table 1). This unique product may be expected to have properties similar to the hydrophilic carrier dispersed curcuminoid product because of the nature of the composition.²⁷

However, the turmeric matrix system offers the unique advantage of being all natural, consisting of reconstituted turmeric components in a specifically defined ratio. As previously noted, this product has greatly enhanced bioavailability compared to 95% curcumin powder.^{34–37}

In summary, the results of this study indicate that treatment of RA with the novel bioavailable curcuminoids in a turmeric matrix significantly improved symptoms and biomarkers. This is the first clinical investigation using curcumin in a completely natural turmeric matrix that contains no excipients or other additives. The trial was a 90-day randomized, double-blind, placebo-controlled, three-arm, parallel-group, clinical trial. Active RA patients who received both high (500 mg) and low (250 mg) doses of the study product twice daily reported statistically significant changes in their clinical symptoms. The curcumin product demonstrated significant analgesic and anti-inflammatory properties by improving ESR, CRP, VAS, RF, DAS28, and ACR responses relative to baseline. Based on some indicators, the high dose was slightly more effective. No adverse events were observed or reported by the subjects receiving either dose of curcumin over the 90 days of the study.

This study supports the results of other studies indicating that curcumin is effective in relieving the symptoms of rheumatoid arthritis. Although the number of subjects in each group was adequate for statistical purposes, larger numbers of subjects in each group would have been desirable. Additional studies are needed to compare the efficacy of this product with other curcumin products as well as anti-inflammatory drugs, and to assess the efficacy in other inflammatory diseases. In addition, it may be desirable to use other endpoints as the effects on inflammatory cytokines and synovial fibroblasts as well as imaging results to assess the effectiveness of this unique, highly bioavailable curcumin product.

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AUTHOR DISCLOSURE STATEMENT

Four of the authors (A.A., K.V., J.J., and S.G.) are employees of Aurea BioLabs Ltd., a research subsidiary of Plant Lipids Ltd. All other authors have no conflicts to report.

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