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A novel bioavailable hydrogenated curcuminoids formulation (CuroWhite™) improves symptoms and diagnostic indicators in rheumatoid arthritis patients - A randomized, double blind and placebo controlled study

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ABSTRACT

Rheumatoid arthritis (RA) is an inflammatory disease that cause chronic pain, disability and joint destruction. The present placebo controlled randomized study aimed to evaluate the efficacy of a novel hydrogenated curcuminoid formulation-CuroWhite™, in rheumatoid arthritis (RA) patients. Twenty four RA patients were randomized in 1:1:1 ratio to receive 250 mg, 500 mg CuroWhite or placebo as one capsule a day, over a period of three months. Improvement in the ACR response, changes in disease activity assessed using the DAS 28 score, change in physical function assessed on change in ESR, CRP, RF values were evaluated before and after the study. Results suggested that patients who received CuroWhite both low and high doses reported statistically significant changes in their clinical symptoms towards end of the study when compared with placebo. There were significant changes in DAS28 (50−64%) VAS (63−72%) ESR (88−89%), CRP (31−45%) RF (80−84%) values and ACR response for CuroWhite groups in comparison with placebo. Thus, CuroWhite acts as the analgesic and anti-inflammatory product for management of RA by the reduction of the inflammatory action which was confirmed by improvement in ESR, CRP, VAS, RF, DAS-28 and ACR responses. CuroWhite was significantly effective against RA with highly safe without serious side effects and well tolerated.

1. Introduction

Rheumatoid arthritis (RA) is a disease by inflammation of unknown etiology that is known to cause chronic pain, disability, and joint destruction.[1,2] RA is marked by synovial hyperplasia with local invasion of bone and cartilage leading to joint destruction.[3] The inflammatory process, primarily in the synovial tissue, is characterized by the involvement of proinflammatory cytokines, such as interleukin (IL)-1 and tumor necrosis factor-α (TNF-α), has been found to play a key role in promoting the diseased state.[4]

There are lot of drugs available in market for treatment of rheumatoid arthritis and long term use of these drugs include analgesics, steroids, which have potential side effects such as gastrointestinal tract disturbances, liver injury, low blood cell count, hear failure, hair loss and immunodeficiency.[5,6] Even though the recent advances in this field, the pathogenesis of rheumatoid arthritis has not been fully revealed yet, and this cannot be cured completely. Hence, there is a need for inexpensive, high tolerance newer drugs, which can offer effective treatment without side effects. Thus, natural phytonutrients could serve as a better alternative strategy for the effective management of the symptoms of rheumatoid arthritis. In particular, natural compounds from plants,

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such as flavonoids, terpenes, catechins, alkaloids, anthocyanins and anthoxanthins, all of which are known to draw out antioxidant effects, can modulate the expression of pro-inflammatory signals and exhibit potential against arthritis.[7–12]

Among these phytonutrients, curcuminoids, which are obtained from the rhizomes of turmeric (*Curcuma longa*) have many biological and pharmacological properties such as antioxidant, anti-inflammatory, chemo preventive, cardiovascular, various neurological, metabolic, hematological and Alzheimer's diseases *in vitro* and *in vivo*.[13–27] It also has therapeutic effects against arthritis[28,29] and studies showed that the curcuminoids interact with numerous molecular targets involved in inflammation, including TNF *in vitro* and *in vivo*.[30,31] Hence curcumin and its formulations can be a promising therapeutic agent in rheumatoid arthritis,[32–35] but it has limited pharmaceutical application due to poor bioavailability.[36–38] Although various biological and pharmacological activities of curcumin have been reported, its therapeutic potential within the field of RA is limited.

Curcumin can be hydrogenated to Tetrahydrocurcumin, (THC), Hexahydrocurcumin (HHC) and Octahydrocurcumin (OHC) or Hexahydrocurcuminol[39–41] by catalyst. The obtained product have more bio-availability than the parent curcuminoids when encapsulated with β-cyclodextrin.[41] These are the major metabolites of curcumin[42,43] and they inhibited various Lipopolysaccharide (LPS) induced responses *in vitro*, including excess NO production, increased iNOS and COX-2 protein expression as well as LPS-induced degradation of IκB-α and overexpression of nuclear p65.[44]

THC showed good anti-oxidative property and greater inhibitory effect than curcumin on the lipid peroxidation of erythrocyte membrane *in vitro* and *in vivo*.[45,46] It may also exhibit the same physiological and pharmacological properties as curcumin *in vivo* by its β-diketone moiety and phenolic hydroxy groups. The antioxidant activity of the THC is due to the β-diketone moiety by cleavage of the C-C bond at the active methylene carbon between two carbonyls in the β-diketone moiety.[45] THC induced antioxidant enzymes such as glutathione peroxidase, glutathione S-transferase and NADPH: quinone reductase, hence THC can be a promising chemo-preventive agent *in vivo*.[46] Both curcumin and THC were cytotoxic to MCF-7 cells in a dose dependent manner.[47] THC inhibits the efflux function of P-gp, MXR and MRP1 and it is able to extend the MDR reversing activity of curcuminoids *in vivo*.[48]

Similarly, one study showed that the DPPH radical-scavenging activity of HHC is higher than that of 6-shogaol and 6-dehydroshogaol[49] and cytotoxicity of HHC to colorectal cancer cells SW480 is significant.[50] Treatment of human platelet-rich plasma with HHC resulted in an inhibitory effect on platelet aggregation, suggests that it can be used as an anti-atherosclerogenic agent in humans.[51]

From all these examples it is clear that the metabolites of curcuminoids can be played a marked role to reduce the inflammatory diseases. Even though, apart from the pharmacological properties there is no particular scientific evidence of the effectiveness of these metabolites of curcumin towards RA. Hence Aurea Biolabs developed a unique formulation of the hydrogenated curcuminoids encapsulated with β-cyclodextrin branded as CuroWhite™ and by this method the hydrogenated molecules can be entrapped in cyclodextrin lipohilic cage, consequently, the cyclodextrin matrix have more bio-availability, solubility and stability.[41] CuroWhite contains THC (18–22%), HHC (3–6%) and OHC (0.5–2%) and β-cyclodextrin (75%) as its chemical constituents. Herein we first report, to the best of our knowledge, a study of a randomized, double blind, placebo controlled and parallel group study to evaluate the comparative efficacy of CuroWhite in active rheumatoid arthritis patients.

2. Materials and methods

2.1. Study design

A double blind and randomized pilot study conducted to evaluate the effectiveness of oral administration of hydrogenated bioavailable curcumin formulation CuroWhite with placebo in patients with active rheumatoid arthritis. Twenty four patients were randomly divided into three equal groups to receive either low dose (250 mg, 4 male and 4 female), high dose (500 mg, 5 male and 3 female) of CuroWhite or placebo (3 male and 5 female). The study was over a period of 3 months, as one capsule a day, 30 min after the meal.

The CuroWhite™ was supplied by Aurea Biolabs (P) Ltd, Cochin, Kerala, India and prepared according to the procedure described Sreeraj et al.[41] The purity of the hydrogenated curcuminoids in CuroWhite was determined by HPLC[41] and which contains 20.8% of THC, 3.7% of HHC and 0.83% of OHC. This study was performed at Dhanwantri Ayurvedic College Hospital and Research Centre, Siddapur, Karnataka, India.

The medical history including associated medications and demographic data of patients were collected before the study. Vital signs (blood pressure, pulse rate and respiratory rate) were measured and laboratory parameters including haematology, blood parameters, serology, biomarkers such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and rheumatoid factor (RF) were performed. Pregnancy test in women and duration of morning stiffness, tender and swollen joint count assessment were assessed. The flow chart of the patients' allocation is described in Fig. 1.

2.2. Inclusion and exclusion criteria of patients

Twenty-four patients with active RA were enrolled in this clinical trial having 18–65 year of age, either male or female and all were diagnosed to have RA according to the revised 1987 American College of Rheumatology (ACR) criteria (with RA functional class or II). Total number of the Swollen Joint Count (SJC) and Tender Joint Count (TJC) should be greater than 8 at screening and baseline. The patients had either CRP >0.6 mg/dL or ESR >28 mm/h and Secondary Sjogren's syndrome or limited cutaneous vasculitis was permitted.

The exclusion criteria included patients with any of the following conditions like treatment with disease-modifying anti-rheumatic drugs (DMARD), non-steroidal anti-inflammatory drug (NSAID), patients with any surgical procedure, including bone or joint surgery or synovectomy within 12 weeks prior to screening, significant systemic involvement of secondary RA (including diseases such as vasculitis, pulmonary fibrosis or Felty's syndrome), inflammatory joint disease other than RA (e.g. gout, psoriatic arthritis, seronegative spondyloarthropathy and Lyme disease) and other systemic autoimmune disorder (e.g. systemic lupus erythematosus, inflammatory bowel disease, scleroderma, inflammatory myopathy, overlap diseases). Pregnant women and patients who used any anti-inflammatory, anti-rheumatoid, analgesics, steroids or other drugs that would interfere with the study were not permitted for 4 weeks in the case of intraarticular drugs and 2 weeks in the case of oral drugs before study enrolment and during the study period.

2.3. Statistical analysis

The data analysis was performed using SAS statistical software and all the values expressed as the mean ± standard deviation (SD). 'P' value ≤ 0.0001 was considered as a significant value and paired *t*-test used to measure the change from the baseline. All various

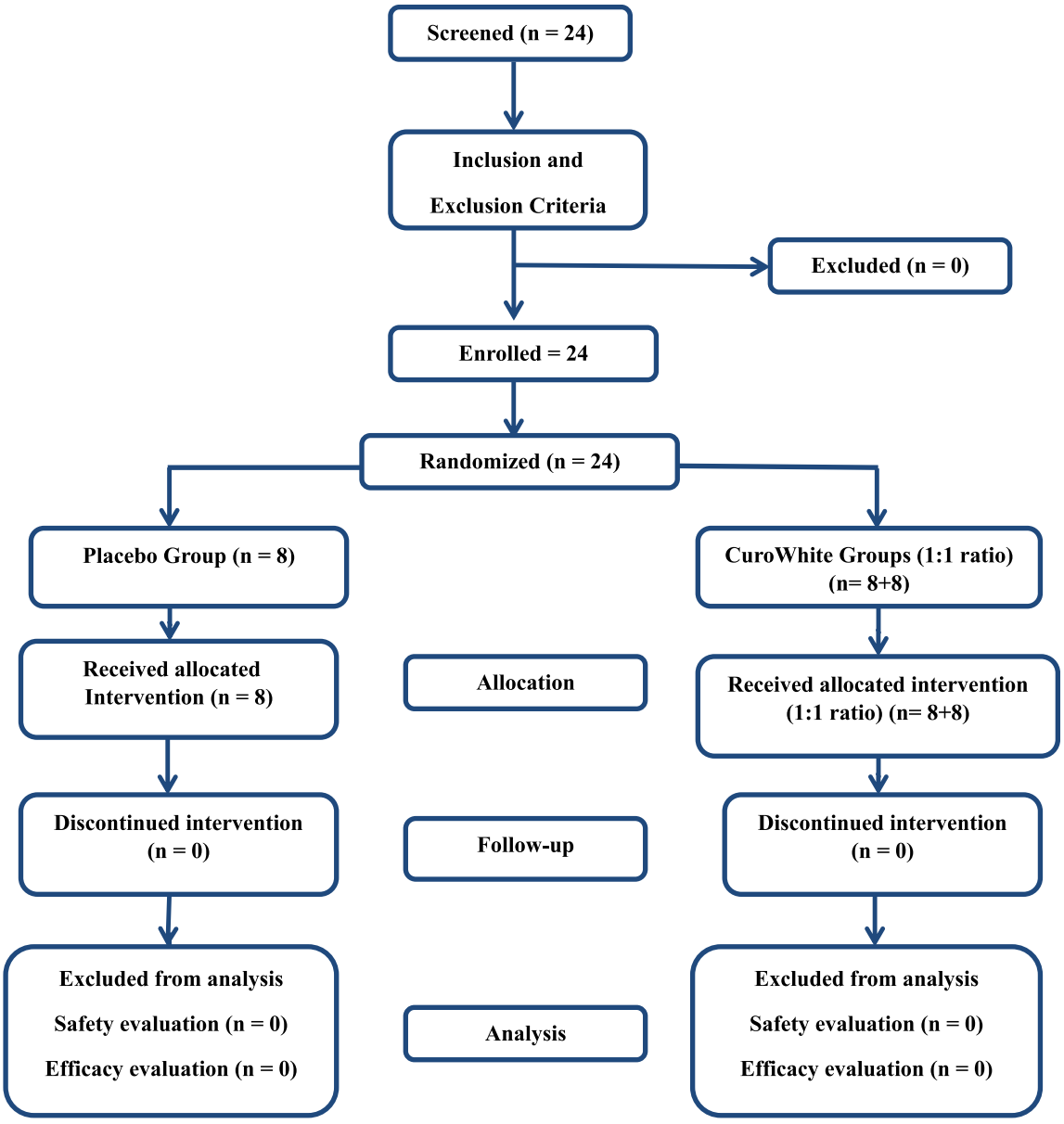

Fig. 1. Patient flow chart.

parameters were analyzed using ANOVA model to observe the changes after the follow up visits scheduled, followed by appropriate post-hoc test.

2.4. Ethical considerations

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. All the patients were informed of the details of the study prior to the signing of a consent form. 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). All the patients gave written informed consent before participating in the study.

3. Results

The twenty-four patients who were enrolled into the study were randomized into three groups (8 in CuroWhite low dose, 8 in high dose and 8 in placebo) and all RA patients had an active disease. None of the enrolled subjects had abnormal medical history. No abnormality in physical findings was observed on the screening visit or during the study visits.

3.1. Efficacy assessment of DAS28 and VAS against RA

The results of efficacy assessment of DAS28 and VAS against RA were summarized in Tables 1 and 2. Among the three treatment groups, DAS and VAS scores for pain were comparable at baseline, but the CuroWhite groups showed the higher reduction in both DAS and VAS score on day 90 (Tables 1 and 2) and it showed a significant improvement ($P \leq 0.0001$). The percentage of change of CuroWhite groups registered higher values as 50.80% (250 mg

Table 1
Treatment efficacy results of disease activity score-28 (DAS-28).

Treatment group	Baseline	End of treatment	% Change	95% confidence interval	*P* value
CuroWhite 250 mg	4.39 ± 0.16	2.16 ± 0.62	50.80	−1.72 to −2.72	<0.0001
CuroWhite 500 mg	4.42 ± 0.61	1.59 ± 0.37	64.02	−2.45 to −3.19	<0.0001
Placebo	3.57 ± 0.52	3.53 ± 0.49	1.12	−0.1327 to 0.0552	0.3621

Table 2
Treatment efficacy results of visual analog scale (VAS).

Treatment group	Baseline	End of treatment	% Change	95% confidence interval	*P* value
CuroWhite 250 mg	7.20 ± 0.96	2.62 ± 0.87	63.61	−4.105 to −5.045	≤0.0001
CuroWhite 500 mg	7.18 ± 1.03	2.0 ± 0.0	72.14	−4.3239 to −6.0511	≤0.0001
Placebo	6.72 ± 0.83	6.82 ± 0.76	−1.49	−0.3192 to 0.5192	0.5903

dose) and 64.02% (500 mg dose) for DAS28. The same trend observed for VAS and the values are 63.61% and 72.14% for low and high doses respectively. In the case of placebo group, there are no significant changes registered.

3.2. Efficacy assessment of ESR values against RA

The ESR values of patients showed significant decrease in the treatment group than that of placebo (Table 3). The mean ESR values of the CuroWhite group decreased from 179.12 to 20.75 mm/h at the end of treatment for low dose and 189.37 to 20.50 mm/h for high dose. The ESR values of placebo were found to be 183.75 mm/h on the screening day and 130.75 mm/h at the end of the treatment. The changes in ESR values were highly significant ($P \leq 0.0001$) in both the CuroWhite treatment groups. In the percentage of changes, higher ESR value was found in CuroWhite groups, i.e., (88.42%) and (89.17%) for low and high doses respectively. In placebo study group, the very minimum percentage of change in ESR value (28.84%) was registered.

3.3. Efficacy assessment of C-reactive protein (CRP) values against RA

The mean CRP values of treatment groups were given in Table 4 and the values of CuroWhite treatment group were indicating a considerable reduction compared to placebo treatment group ($P \leq 0.0514$). The mean CRP value of CuroWhite group was 0.97 at the baseline and 0.66 at the end of treatment for the low dose CuroWhite, while values are 1.14 and 0.62 for the high dose. The percentage of changes CRP values were significantly increased in CuroWhite groups, 31.96% for low dose and 45.61% for high dose, than the placebo study group (−6.06%).

3.4. Efficacy assessment of rheumatoid factor against RA

The RF values of CuroWhite treatment groups was showing considerable reduction when compared to placebo treatment group (Table 5). The RF values decreased from 120.55 to 23.43 IU/mL and 137.12 to 21.15 IU/mL in CuroWhite low dose and high dose treatment groups respectively. The RF values in placebo showed an uneven trend where the values are 68.47 IU/mL in the baseline and 75.60 at IU/mL the end of the treatment. The percentage of changes in CuroWhite study group registered higher RF value (80.56% for low dose and 84.58% for high dose) than the placebo study group (−10.41%).

3.5. Efficacy assessment of ACR20 against RA

The data of the American college of Rheumatology responses such as ACR20, total swollen joints and total tender joint were given in Fig. 2. ACR improvement criteria were analyzed for each group. The number of tender joints, number of swollen joints, patient's assessment of pain, patient's and physician's global assessments of disease activity, and patient's assessment of physical function improved significantly in the CuroWhite treatment group. The mean values of ACR for the CuroWhite treatment group were 20.25 at baseline and it has increased to 65.25 at the end of treatment in low dose and the same trend observed as the values increased from 18.75 to 75.38 in high dose. The improvement rates of ACR were statistically significant ($P \leq 0.0001$) in patients treated with the both CuroWhite groups, compared with those treated with placebo. Among the three treatment groups, the study of total swollen joints and total tender joint showed higher percentage of improvement changes at the CuroWhite low dose group (from 14.12 to 2.62) and high dose group (from 19.25 to 2.5). CuroWhite treatment group showed significant improvement ($P \leq 0.0001$) in total swollen joint and total tender joint studies, but there was no any significant improvement in the case of placebo treatment group.

4. Discussion

Recently, *in vitro* and *in vivo* studies indicated that hydrogenated curcumin such as THC, HHC and OHC exhibit antioxidant,[52] anti-tumor,[53] anti-diabetic,[54,55] anti-hepatotoxicity[56] and anti-inflammatory properties.[57] On this basis, these molecules can be potential therapeutic agents for the prevention and/or treatment of various malignant diseases such as arthritis, Alzheimer's disease, allergies, and other inflammatory illnesses. They are more active than curcumin in suppressing NFκB activation,[58,59] protecting from

Table 3
Treatment efficacy results of erythrocyte sedimentation rate (ESR) in mm/hour.

Treatment group	Baseline	End of treatment	% Change	95% confidence interval	*P* value
CuroWhite 250 mg	179.12 ± 13.85	20.75 ± 5.65	88.42	−147.1 to −169.6	≤0.0001
CuroWhite 500 mg	189.37 ± 8.01	20.50 ± 4.98	89.17	−160.9 to −176.8	≤0.0001
Placebo	183.75 ± 11.97	130.75 ± 19.57	28.84	−30.84 to −75.16	≤0.0008

Table 4
Treatment efficacy results of C-reactive protein (CRP) in mg/dL.

Treatment group	Baseline	End of treatment	% Change	95% confidence interval	*P* value
CuroWhite 250 mg	0.97 ± 0.17	0.66 ± 0.10	31.96	−0.17 to −0.45	≤0.0013
CuroWhite 500 mg	1.14 ± 0.22	0.62 ± 0.06	45.61	−0.34 to −0.69	≤0.0002
Placebo	0.99 ± 0.16	1.05 ± 0.13	−6.06	0.1255 to −0.0005	≤0.0514

Table 5
Treatment efficacy results of rheumatoid factor (RF) in IU/mL.

Treatment group	Baseline	End of treatment	% Change	95% confidence interval	*P* value
CuroWhite 250 mg	120.55 ± 40.69	23.43 ± 3.43	80.56	−64.76 to −129.5	0.0002
CuroWhite 500 mg	137.12 ± 27.83	21.15 ± 2.69	84.58	−91.62 to −140.3	<0.0001
Placebo	68.47 ± 16.99	75.60 ± 17.73	−10.41	3.67 to 10.58	0.0018

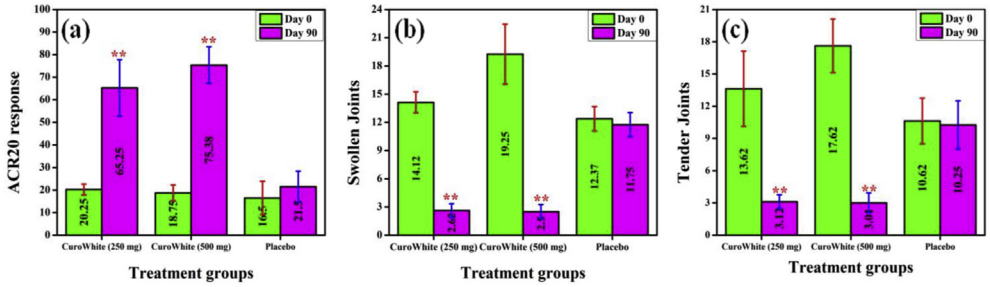

Fig. 2. Data of American College of Rheumatology (ACR) responses: (a) ACR responses, (b) swollen joints and (c) tender joints.

hepatotoxicity[56] and preventing brain lipid preoxidation in diabetic rats.[60] Most chronic diseases are mediated through dysregulated inflammation, THC, HHC and OHC have potential use in the prevention of these diseases.[57] Our research group developed CuroWhite-a hydrogenated bioavailable curcumin to overcome the shortcoming of curcumin such as low aqueous solubility, poor bioavailability, poor membrane permeability inadequate tissue absorption etc. by using a proprietary preparation of curcumin, CuroWhite has 7 fold enhanced bioavailability than 95% curcuminoids.[41]

The results of the present randomized, double blind placebo controlled study clearly favor the efficacy of CuroWhite in alleviating the symptoms of RA, as reflected by marked improvements in all assessed efficacy measures such as ACR 20, DAS 28, VAS, ESR, CRP and RF. Best of our knowledge, this is the first study using hydrogenated curcuminoids for treatment of RA and it has received considerable interest as a potential anti-inflammatory and therapeutic agent for the prevention and/or treatment of various diseases, allergies and other inflammatory illnesses. THC is more potent than curcumin for modulation of blood glucose, plasma insulin and erythrocyte TBARS in diabetic rats[59,60] and hydrogenated derivatives of curcumin exhibited stronger DPPH scavenging activity compared to parent curcumin and a reference antioxidant, trolox. Hence, hydrogenation at conjugated double bonds of the central carbon chain and carbonyl groups of curcumin to THC, HHC and OHC remarkably enhance antioxidant activity.[61]

In this study, all the enrolled subjects completed 90 days of treatment. Of these patients, 16 in the CuroWhite group (8 in low dose and 8 in high dose) experienced disease improvement, fulfilling the ACR improvement criteria. In contrast, none of the patients in the placebo group attained these criteria. The differences between the CuroWhite and placebo groups were statistically significant. CuroWhite high dose group showed higher improvement in DAS-28, VAS scores and CRP, ACR responses than the low dose. But in ESR and RF there were no significant difference between the low dose and high dose. Similar results were obtained when the individual components of the ACR improvement criteria were analyzed for each group, the number of tender and swollen joints, patient's assessment of pain and physical function and global assessments of disease activity improved significantly in the CuroWhite treatment groups. But in the placebo group, decreases were occasionally seen in the number of tender and swollen joints, and physician's global assessment. In contrast, patient's assessment of pain and global assessment of disease activity were significantly increased compared with baseline in the placebo group. Decreases in the ESR and CRP levels were observed in the CuroWhite group and statistically significant compared with baseline. From all these results it is evident that the metabolites of curcumin can be play a marked degree of reduction in RA inflammatory diseases as the curcuminoids.

Between groups comparisons of the differences between the values at baseline and at each visit for the individual variables of the ACR improvement criteria were performed. Significant decreases in all variables were observed in both the CuroWhite groups compared with the placebo group. Along with the variables included in the ACR improvement criteria, morning stiffness and RF titers were also evaluated. As with the other clinical parameters, morning stiffness significantly decreased during the CuroWhite administration. Significant decreases in RF titers were observed after 90 days in the high dose group. In contrast, RF titers in the placebo group fluctuated and increased significantly in the 90 days follow-up compared with baseline.

Results from the present study indicate that the difference in ACR improvement rates was statistically significant in patients treated with the CuroWhite groups compared with those treated with placebo. These efficacy parameter values were found to be statistically significant ($P \leq 0.0001$) in both the groups when compared between baseline and end of treatment of CuroWhite groups patients. The change in the efficacy assessments was significant ($P \leq 0.0001$) between the three treatment groups when

their respective values were analyzed. The values of CRP, ESR, RA factor values decreased statistically ($P \leq 0.0001$) for CuroWhite receiving group patients but not for the placebo group. The product CuroWhite started showing its effect from the first month itself and reached significant during the end of the study. The findings of this study are significant, as these demonstrate that CuroWhite was not only safe[62,63] and effective, but was surprisingly more effective in alleviating pain. Best of our knowledge there is no studies reported using white curcumin including THC, HHC and OHC for the treatment of RA, but there are several reported studies on the molecular targets of curcumin that contributes to the chronic pain. Curcumin has the potential to alleviate chronic pains in different models,[64] including neuropathic pain.[65,66] The data from the study reveals that of hydrogenated curcuminoids have the potentials to reduce the symptoms of active RA, and this efficacy was better than that provided by placebo, and was not associated with any adverse events. Our observations that CuroWhite was able to alleviate symptoms of rheumatoid arthritis are quite encouraging and these results provide a suitable platform for investigating the potential of hydrogenated curcuminoids in other chronic diseases arising in the setting of days regulated chronic inflammation. Hence this study shows that both 250 mg and 500 mg doses of CuroWhite can provide significant improvement in treatment efficacy in active RA. Active rheumatoid arthritis patients, who received CuroWhite for a period of 90 days, reported statistically significant change/decrease in their clinical symptoms towards the end of the study. Moreover CuroWhite administration was to be safe and did not show any adverse effects in patients with active RA.

5. Conclusion

To conclude, CuroWhite – the high bioavailable form of hydrogenated curcumin has been used to reduce the inflammatory actions of RA, and the results are clearly indicated that the oral administration of CuroWhite registered superior percentage of improvement in patients with RA in both high and low doses than the placebo. Moreover, this is the first study using hydrogenated curcumin with superior and highly safe treatment for patients with RA. This study provides a clear evident of principle for the superiority of CuroWhite strongly favors the safe and effective application for the management of RA.

Disclosure of interest

Four of the authors (JJ, AA, JR and SG) are employees of Aurea Bio Labs Ltd., a subsidiary research center of Plant Lipids Ltd. CD and ABK have no conflicts of interest concerning this article.

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