

Effectiveness of Iontophoretic Application of Curcumin Extracts among Patients Suffering from Rheumatoid Arthritis

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Miraj *et al.*: Effectiveness of Iontophoretic Application of Curcumin Extracts in Rheumatoid Arthritis

Curcumin has a powerful anti-inflammatory impact, despite its limited absorption when given orally. Earlier research has proved the efficacy of the curcumin extracts in the rat model and therefore the present study is an attempt to evaluate the effects of lyophilized curcumin extracts delivered through iontophoresis among patients suffering from rheumatoid arthritis. Lyophilized curcumin extracts having 29.79 % curcumin as its active ingredient was prepared using standardized method and it was applied to the inflamed hands of the rheumatoid arthritis patients, satisfying the inclusion criteria. Another group of patients were treated with oral curcumin. The prospective study was done among 20 patients at LifeLine Rehab Center who were diagnosed during January 2022 to August 2022. The experimental group use iontophoretically treated curcumin which showed significant improvement as compared to their matched controls. Iontophoretic application of lyophilized curcumin extracts has been found to provide a greater anti-arthritis impact due to improved curcumin penetration and bioavailability. Future studies can be conducted to examine the effects of different curcumin applications in arthritic conditions and examining their action pathways.

Key words: Iontophoresis, lyophilized curcumin, non-steroidal anti-inflammatory drugs, rheumatoid arthritis

Rheumatoid arthritis is a chronic inflammatory systemic condition marked by inflammation of small joints including episodes of extreme pain, stiffness, swelling and ultimately destruction of bone and cartilage^[1,2]. The illness includes involvement of other biological systems including eyes, lungs, heart, blood arteries, etc. This disease mainly affects females between age groups of 35-50 y, with male:female incidence ratio of 1:3. The disease affects upto 1 % of the global population afflicting about 2 million patients in United States (US) alone^[3,4]. Due to the incurability of the condition, the focus of treatment is predominantly palliative and therefore complementary and alternative medicine

treatments have generated wide interest globally and have been tried with varying degrees of success around the world^[5].

Under the modern traditional treatment, allopathic medicines forms the mainstay of treatment providing symptomatic reliefs to the patients using different drugs including Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) as well as Disease Modifying Anti-Rheumatic Drugs (DMARDs) etc.^[6]. Nonetheless, they have serious negative consequences on quality of life. Patients experience a wide variety of unpleasant side effects, such as hyperacidity, swelling, stomach ulcer, gastrointestinal bleeding, perforation, loss of appetite, etc.^[7,8].

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In recent years, there has been a surge of interest in the use of botanicals for the treatment of a variety of debilitating conditions^[8,9]. Among many, curcumin is one such compound that has been used in cooking for centuries for enhancing flavours^[9]. Literature review states its usage in a wide range of clinical conditions ranging from cancer to inflammatory diseases to gastrointestinal problems, etc. Moreover, curcumin has shown substantial anti-inflammatory, antioxidant, chemo preventive and chemotherapeutic action in cultured cells and animal models^[10-12].

Curcumin has shown promising results in the treatment and cure of rheumatoid arthritis and other joint inflammatory disorders, however one of its major limitation is its bioavailability, which has been found to be decreased significantly, especially when they are taken orally^[2,3,12]. Iontophoresis, a popular form of drug delivery is used in physical therapy for over more than 100 y. This non-invasive technique works on the electromagnetic principle where direct electrical current is used to drive ionic (charged) drugs into the body^[13-15]. The iontophoretic technique has been effectively used in physiotherapy practice to treat a range of clinical conditions ranging from musculoskeletal inflammatory conditions as seen in bursitis and tendonitis to hyperhidrosis to manage the scar tissue in cases of burns etc.^[15].

Our past research has shown promising results where lyophilized extract of *Curcuma longa* (*C. longa*) using its active component curcumin was used effectively in the arthritic rat models^[16]. Therefore, this study aimed to test the effects of lyophilized curcumin extracts on a subset of patients suffering from rheumatoid arthritis using iontophoresis.

MATERIALS AND METHODS

The study comprised of three parts. In the first part, the lyophilized curcumin extract having 29.79 % curcumin as its active ingredient was prepared as per the standard protocol^[15]. The second part comprised of selecting the subjects for the study. From January 2022 till August 2022, 30 female patients aged ≥ 18 y, diagnosed with rheumatoid arthritis (American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) 2010 criteria) by an orthopedic surgeon using radiographic and laboratory examinations were randomly recruited from LifeLine Rehab Center, Greater Noida. Sample size was determined based on previous study conducted on women with rheumatoid arthritis using statistics on

Activities of Daily Living (ADL) questionnaire^[17,18].

The other inclusion factors include atleast one painful wrist, Metacarpophalangeal (MCP), or Proximal Interphalangeal (PIP) joint; stable medication for 3 mo before participation and self-reported impaired ability to execute ADLs requiring the use of the hands. The exclusion criteria included patients having osteoarthritis of the hand, past history of fracture, hand surgery within 6 mo, prednisolone therapy, neuropathic condition, postoperative limb thrombosis or any contraindication or precaution for the use of iontophoresis^[17,18]. Written informed consent was taken from all participants as well as ethical approval was sought from the Institutional Review Board (IRB) Committee at Athar Institute of Health and Management Studies (AIHMS), New Delhi (Letter No: AIHMS/41/VIII/2022).

The third part of the study comprise the iontophoretic delivery of lyophilized curcumin extracts as per the standard procedure as reported earlier^[15,16]. The iontophoretic drug delivery system (Model No. 4201, HMS Corp., Tamil Nadu) has 4 major parts namely, the power source with batteries, the control circuitry termed as an electrical stimulator, the electrodes and the gauze pieces.

30 female patients who participated in the study were allocated into two groups, experimental iontophoretic lyophilized curcumin group (n=15) and other group being the placebo iontophoresis (n=15).

The lyophilized dose of *C. longa* for iontophoretic administration was delivered to the patients after taking informed consent from the acceptable participants as per the standard protocol which was also reported earlier by numerous authors^[16-20]. The patient was explained about the procedure and advised to lie in a position where they feel most at ease. However, before administration for the treatment of patients, it was ensured that no skin irritation or erythema was reported after the iontophoresis patches were removed from any of the 30 patients who participated in the study. Although they were instructed to do so when signing the agreement, none of the subjects had any adverse effects from the iontophoresis treatment after the experiments.

Patient's skin's resistance was lowered by exposing the area to be treated and cleaning it thoroughly beforehand to eliminate dust, oil or sweat. The lyophilized curcumin extract is delivered through the skin by placing an electrode patch containing the

medication on the skin, which acts as the working electrode and then placing another electrode elsewhere to complete the electrical circuit and applying a modest current of 1 mA/cm². Following the foregoing steps, 50 mg/ml of *C. longa* diluted in 0.2 % Dimethyl Sulfoxide (DMSO) was used to moisten using a cotton swab. After applying adhesive tape to the inflamed digits, the *C. longa* soaked gauze was securely positioned under the cathode electrode. Iontophoresis with direct current of 1 mA amplitude was applied to the arthritis patient for 10 min every day for 5 d. The various outcome measures used to evaluate the results were Visual Analog Scale (VAS) score, grip strength, self-reported ADL ability (ADL-questionnaire) as well as self-reported disability (Stanford Health Assessment Questionnaire (HAQ)-Disability Index (DI))^[21-23].

Statistical analysis:

The results of the two treatment groups i.e. experimental group delivering lyophilized curcumin extracts using iontophoresis was compared with the placebo iontophoretic group. The groups were tested for homogeneity using Levene's test followed by Mann Whitney U test. Statistical significance was measured using p-value of 0.05 or lower, was used. Data was analysed using IBM Statistical Package for the Social Sciences (SPSS) version 22.0 software.

RESULTS AND DISCUSSION

The current study was conducted on 30 female patients suffering from rheumatoid arthritis. The baseline data was given in Table 1.

The lyophilized *C. longa* extract tested positive for the active component curcumin has a Retention factor (R_f) value of 0.49 when analyzed by High-Performance Thin-Layer Chromatography (HPTLC). The specificity, precision, accuracy and linearity of the method for quantitative analysis of curcumin were all verified by comparing the results of the approach to both standards and samples as well as its specificity was confirmed. Comparison of the R_f value and the spot spectra to the standard and the achieved linearity is shown in fig. 1. This validated the presence of *C. longa* in the sample. It was determined that the average percentage of recovery is between 131.14 and 124.59±1.35. The concentration range examined (1-4 ng/spot) was linear ($r=0.97861±2.15$) (fig. 1A and fig. 1B).

Comparing the results of the two groups i.e. experimental lyophilized iontophoretic curcumin vs.

placebo iontophoretic group, it was observed that significant changes were observed in VAS and grip strength in the experimental group as compared to their matched controls (* $p<0.05$). With reference to pain scores, the dominant hand showed a significant reduction of 2.8 points with reference to iontophoretic application of curcumin in the inflamed hand as compared to the control group where pain reduced to just 0.7 points. Similarly in non-dominant hand too, significant reduction in VAS scores were observed in comparison to the control group (* $p=0.022$) as shown in fig. 2.

Likewise, on comparing the experimental iontophoretically applied curcumin group with the placebo group, it was observed that grip strength was significantly improved in both the dominant and the non-dominant hand (* $p=0.027$, * 0.031) respectively in the experimental group as compared to their matched controls (fig. 3). However, no changes were observed in the ADL as well as HAQ-DI questionnaire over the 7 d treatment period (Table 2).

The results of this study support the hypothesis that patients suffering from rheumatoid arthritis having rheumatoid arthritis-related hand impairments are more likely to be benefitted by iontophoretic application of lyophilized curcumin as compared to hand-exercise treatment alone.

Curcumin, the active element in *C. longa*, was found to have a higher amount, i.e. around 29.79 %, in the dried rhizomes extracts than in the fresh ones (fig. 1A and fig. 1B). Previous investigations utilizing spectrometric-based estimation showed conflicting findings with reference to *C. longa* detection and quantification were carried out at a wavelength of 366 nm^[24,25]. Even at concentrations as low as 1.96 %, curcumin was proven to be present in dried rhizomes extracts of *C. longa* using HPTLC, which was one of the earliest published methods^[16]. Studies by earlier researchers, found that curcumin concentration in the dried rhizome extracts of various *C. longa* species grown in Thailand was in the upper range of 46.45 % to 67.31 %^[25].

With reference to the various outcome measures including VAS and grip strength, they were used to assess the effectiveness of lyophilized curcumin administered through iontophoresis to the various patients under study. It was observed that significant reduction in VAS scores and grip strength were observed in both dominant and non-dominant hands as compared to their match controls (fig. 2 and fig.

3). Literature reviews shows that patients suffering from rheumatoid arthritis have inflamed digits which are one of the most common symptoms and therefore act as key obstacle in the performance of ADL activities especially related to hands and feet's. Study by Ramey *et al.*^[22] emphasized that reduction of pain acts a key motivator among rheumatoid arthritis patient for the improvement of strength and ability to perform ADL effectively.

Using the Laitinen questionnaire, we quantified

the frequency and severity of pain, as well as the usage of pain relievers and the impact they had on the participant's ability to engage in regular physical activities. Each indicator was given a score between 0 and 4, with 0 indicating no problem and 4 indicating the most severe problem. In our study, the iontophoretic group showed significant reduction in intensity of pain by an average of 3 (median=-3) as compared to the placebo where pain intensity reduced by an average of 0.5 (median=-0.5) (*p=0.031) as shown in Table 3.

TABLE 1: BASELINE CHARACTERISTICS OF THE SUBJECTS

	Experimental group	Control group	p-value
Age	41±10.3	43±11.5	0.73
Weight (kg)	59±11.4	60.5±12.4	0.82
Height (cm)	157±1.6	155±2.3	0.41
Disease duration	6.2±7.4	8.4±5.9	0.44

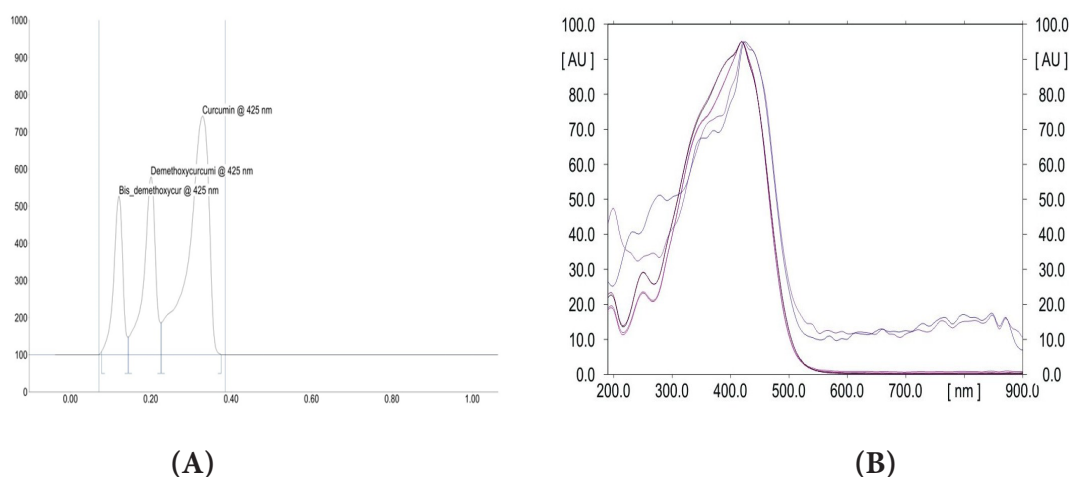


Fig. 1: Absorption spectra of conventional *C. longa* and the extract of *C. longa* taken on a (A) CAMAG Thin Layer Chromatography (TLC) scanner III, as well as on (B) HPTLC chromatogram of curcumin prepared from the *C. longa* extract respectively

Experimental Group

Day 1 7.1

Day 7 4.3

Control Group

Day 1 6.9

Day 7 6.2

Experimental Group

Day 1 6.7

Day 7 3.9

Control Group

Day 1 7

Day 7 6.6

Fig. 2: VAS scores of experimental group in both (■) Dominant hand and (■) Non-dominant hand as compared to their matched control over a 7 d treatment period

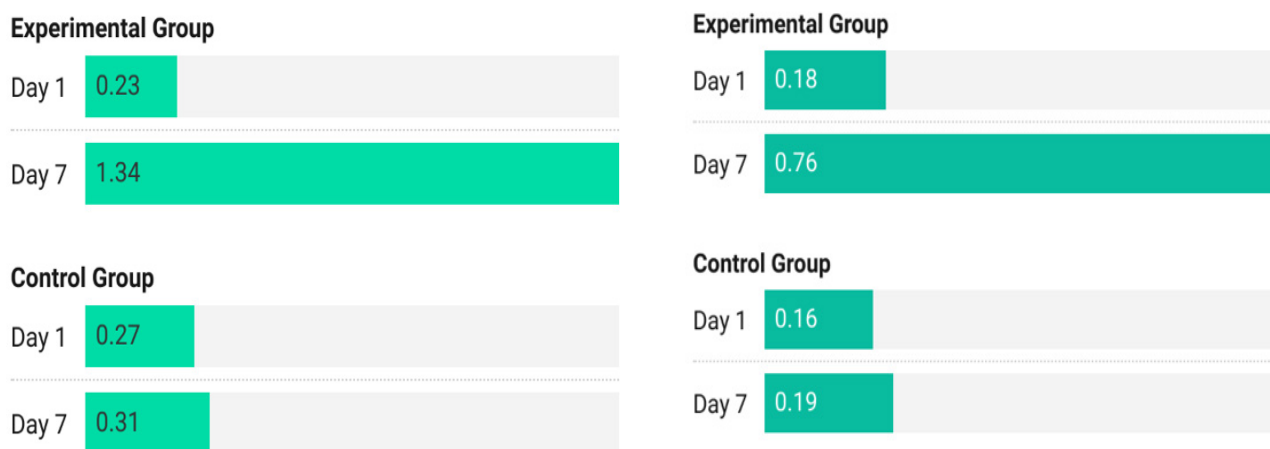


Fig. 3: Grip strength of experimental group in both (■) Dominant hand and (■) Non-dominant hand as compared to their matched control over a 7 d treatment period

TABLE 2: CHANGES IN THE DIFFERENT OUTCOME MEASURES OVER THE TREATMENT PERIOD AMONG THE TWO GROUPS

	Experimental group		Control group		p-value
	d 1	d 7	d 1	d 7	
VAS					
Dominant hand	7.1±2.2	4.3±0.6	6.9±1.9	6.2±1.5	0.031*
Non-dominant hand	6.7±1.8	3.9±1.1	7±1.3	6.6±1.4	0.022*
Grip strength					
Dominant hand	0.23±1.3	1.34±1.5	0.27±0.9	0.31±0.8	0.027*
Non-dominant hand	0.18±1.1	0.76±1.1	0.16±1.2	0.19±0.9	0.031*
ADL-questionnaire	0.08±0.19	0.08±0.20	0.09±0.19	0.09±0.17	0.88
HAQ-DI	0.01±0.19	-0.09±0.11	0.01±0.12	0.01±0.11	0.76

Note: *p<0.05

TABLE 3: LAITINEN SCALE SCORES AMONG THE 2 GROUPS UNDER STUDY

Intensity of pain	n=30	Percentage (%)	Experimental group (n=15)	Percentage (%)	Control group (n=15)	Percentage (%)
No improvement (0 %)	12	40 %	0	0 %	12	80 %
Unsatisfactory improvement (1 %-24 %)	3	10 %	0	0 %	3	20 %
Satisfactory improvement (25 %-49 %)	3	10 %	3	20 %	0	0 %
Good improvement (50 %-74 %)	5	16 %	5	33 %	0	0 %
Very good improvement (75 %-100 %)	7	24 %	7	47 %	0	0 %
Frequency of pain	n=30	Percentage (%)	Experimental group (n=15)	Percentage (%)	Control group (n=15)	Percentage (%)
No improvement (0 %)	11	36 %	0	0 %	11	73 %
Unsatisfactory improvement (1 %-24 %)	3	10 %	0	0 %	3	10 %
Satisfactory improvement (25 %-49 %)	5	16 %	4	26 %	1	7 %

Good improvement (50 %-74 %)	5	16 %	5	33 %	0	0 %
Very good improvement (75 %-100 %)	6	22 %	6	41 %	0	0 %
Use of pain killers	n=30	Percentage (%)	Experimental group (n=15)	Percentage (%)	Control group (n=15)	Percentage (%)
No improvement (0 %)	9	30 %	0	0 %	9	60 %
Unsatisfactory improvement (1 %-24 %)	7	23 %	1	6 %	6	40 %
Satisfactory improvement (25 %-49 %)	3	10 %	3	20 %	0	0 %
Good improvement (50 %-74 %)	6	20 %	6	40 %	0	0 %
Very good improvement (75 %-100 %)	5	17 %	5	34 %	0	0 %
Restriction of physical activity						
No improvement (0 %)	12	40 %	0	0 %	12	80 %
Unsatisfactory improvement (1 %-24 %)	3	10 %	0	0 %	3	20 %
Satisfactory improvement (25 %-49 %)	7	24 %	7	24 %	0	0 %
Good improvement (50 %-74 %)	4	13 %	4	13 %	0	0 %
Very good improvement (75 %-100 %)	4	13 %	4	13 %	0	0 %

Therefore the improvements observed with decrease in VAS scores and partial increase in grip strength might have translated into improved ADL activity, however, the change was not statistically significant (Table 2). This suggests that even though the iontophoretic application may help in reducing swelling in digits but may not translate into improved ADL ability within such short period of time. There are no much studies to supplement the findings. However, a study was found where authors have used nano application of curcumin and have been found effective^[20].

According to the research, direct current increases blood flow and decreases neuromuscular excitability. Iontophoresis, moreover, delivers therapeutic ions to the affected areas. The treatment's non-invasive nature is its primary benefit and the fact that a low concentration of the preparation is sufficient to achieve the intended effect is definitely a plus. The fact that the drug can be administered directly onto the affected area, skipping the first past metabolism and therefore reducing the risk of adverse reactions, especially with the use of NSAID's and DMARD's is of great importance and value especially as the nature of treatment in the condition is primarily palliative.

The results of the findings have significant implications for our understanding especially with reference to the pathophysiology and pharmacological regulation of inflammatory processes. Earlier a number of animal studies have proven the efficacy of different herbal compounds in the treatment of inflammatory arthritis. However, this study is probably one of its types to evaluate the effects of lyophilized curcumin extracts using iontophoresis among the human subjects. The present study supports the trend towards using herbal remedies for the treatment of arthritis, which has recently gained popularity in many Western industrialized countries due to the huge adverse effects of NSAIDs. Secondly, many rheumatoid arthritis symptoms, such as hand inflammation and swelling in the joints of the fingers and toes, manifest locally, where treatment was given systemically by the use of oral anti-inflammatory medications, which is of poor value^[1,5,7]. Consequently, there is significant justification for the investigation given for the backdrop of transdermal distribution by iontophoresis. Future studies should be done to evaluate the pharmacological pathways by which curcumin helps in relieving the symptoms in various rheumatoid arthritis patients. In addition

to this, further studies with larger sample size are recommended to understand the clinical implications of iontophoretic application in different disease conditions including arthritis.

As existing treatments are primarily palliative in nature, the study's findings are significant, because they may provide a novel starting point for the scientific explanation of the rising popularity of botanicals in the treatment of this particular class of ailments. In such circumstances, especially where oral administration of NSAID's and DMARD's is not a viable option due to their undesirable side effects or other physiological factors and transdermal iontophoretic delivery proved to be of great assistance. This study will also help to pave a path to enhance the scope of physical therapy services by highlighting the use of iontophoresis using different herbal medications in the treatment of not only arthritis but also other chronic diseases, such as diabetes, hypertension and cancer, for which prolonged treatment is currently inadequate. However, future research might be designed and carried out using more scientific models, where the plant molecules could be monitored and quantified for making bioavailability quantifiable, bringing more reliable proof to the use of such plant supplements in the treatment of various diseases and its application in human beings.

Acknowledgements:

The authors are grateful to Deanship of Scientific Research, Majmaah University for funding through Deanship of Scientific Research vide Project No.: RGP-2019-35. The authors are also thankful to AlMareefa University for providing support to do this research.

Conflict of interests:

The authors declared no conflict of interest.

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This article was originally published in a special issue, "Role of Biomedicine in Pharmaceutical Sciences" Indian J Pharm Sci 2023;85(2) Spl Issue "80-87"