

Topical Effects of *Capsicum frutescens* on Hand Pain in Patients with Rheumatoid Arthritis: A Case Report

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Abstract

Background: Rheumatoid Arthritis (RA) is a crippling autoimmune disease that predominantly affects individuals in the prime of their lives.

Patients and physicians dissatisfied with the currently therapeutic strategies, are integrating the complementary and alternative medicines in the control of the disease.

Given that topical treatment with *Capsicum frutescens* may be a new target in the control of the clinical manifestations of RA, it is our objective to evaluate the effectiveness of its application in pain, strength and health functional status.

Methods/Design: A group of four patients with clinical features of a specific Traditional Chinese Medicine syndrome and RA at remission stage applied a *Capsicum frutescens* prepared. We assessed the effects of the topical application in the pain, strength and the functional status.

Results: The patients' hand strength increased, with a favorable repercussion on functional capacity. Additionally, instances of self-reported pain improved.

Discussion: The findings of this study suggest that *Capsicum frutescens* may have favorable effects in pain relief, strength and functional status. This justifies the use of *Capsicum frutescens* in future controlled placebo studies.

Keywords: Rheumatoid arthritis; Turning Point Syndrome; Chinese herbs; *Capsicum frutescens*

Introduction

Rheumatoid Arthritis (RA) is a chronic inflammatory autoimmune disease that affects approximately 1% of the adult population. Although there is no cure, patients may reach a state of remission, which has become an achievable goal with optimal early treatment [1].

Over 90% of patients with RA have involvement of the wrist and small joints of the hand, including the knuckles and the middle joints of the fingers involving destructive polyarthritis of the synovium. Pain, lack of mobility, and fatigue diminish an RA patient's quality of life and contribute to limitations in the daily life of up to 30% of patients [2-4]. The pharmacological strategies currently offered to patients with RA are associated with various undesirable side effects, toxicity and limited efficacy [5]. The long-term effects of these therapies are still unknown and the medications do not suppress the progression of the disease [6,7]. Systematic approaches provide novel insights to medical studies. The topical application of *Capsicum frutescens* has been studied [8-12] raising the hypothesis that its application can constitute a new target in the relief of the pain and increase of the force and, hopefully, help to reduce the impact of RA disease on patient function and health-related quality of life.

C. frutescens is recognized for its properties in increasing blood microcirculation and its anti-inflammatory potential [13]. Phenolic and flavonoid compounds present in chili have been reported to exhibit anti-inflammatory activity as well as pain-reducing properties in patients with RA. It can also be absorbed topically and has a semi-life of about 24 h [14-16].

In addition to being a source of vitamin C, Peppers contain phenolic compounds, flavonoids and carotenoids [8]. Phenolic and flavonoid compounds present in peppers, are ubiquitous phytochemicals found in plants with a wide group of purposes, including warming effect, antioxidative and antimicrobial activity, antibiotic synergism, bacterial virulence removal, anti-inflammatory and analgesic properties [8,13,14,16].

Once absorbed, they influence several biological functions, including protein synthesis, angiogenesis, cell proliferation and differentiation, showing anticancer effects, act against high cholesterol levels and obesity and are used to treat various diseases that show a high worldwide prevalence, such as cancer, RA, asthma, diabetes, cardiovascular and neurodegenerative diseases, including atherosclerosis, Alzheimer's disease, and other age-related degenerative disorders [8,9]. Capsaicin and its analogs, known for their efficacy in topical absorption, have been used in creams and transdermal systems to treat chronic pain syndromes such as post-herpetic neuralgia, musculoskeletal pain, diabetic neuropathy, osteoarthritis, and RA [15-18]. It is a viable alternative for pain relief in patients who do not respond to other treatments [19]. Adverse effects (burning, stinging and erythema) are usually limited to the site of application, although respiratory irritations from inhalation of cream and occasional systemic effects have been reported [20]. We intend to assess the effects of the application of *C. frutescens* prepared in RA remission patients (according EULAR criteria's), with pain and lack of strength of the hands. The sample selected included RA patients with one specific stage defined as *Turning Point Syndrome*, which is explained in detail by the *Shang Han Lun* theory called Algor Leadsen Theory (ALT) by the Heidelberg Model (HM) of TCM in our previous paper [21].

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Although RA is classified as a single disease in Western medicine, in classical Chinese medicine it is believed to be the result of an invasion of the external pathogens (wind, cold, heat and damp), reactive heat with yin affection, *qi* and *xue* deficiency with stasis and phlegm, as well as of the deficiency patterns (liver and kidney yin or yang deficiency) [21]. The ALT is viewed as a technical regulative model including a cybernetic sine wave which explains that cold (designated by algor on the HM) passes the skin (*biao*) to reach the inner tissues of the body, causing neurological and immunological phenomena on its way, while overcoming the six defense levels. RA manifestations can be characterized in different syndromes according this mathematical regulative model as a deviation from the regulated state [21].

The *Turning Point syndrome*, explained by ALT, shows external symptoms of the conduits as a result of the agent algor/cold remaining in certain external conduits. The agent cold/algor fights against the remaining levels of *qi* and *xue*, which prevent the cold/algor from proceeding to the internal layers. Because the agent sometimes proceeds to the inside of the body (inner) and sometimes is repelled again, the symptoms of cold and heat as well as the autonomic signs alternate continuously. The characteristic feature of this syndrome is therefore an inconsistency, or contrariness, of the symptoms: cold and heat sensations, external and internal symptoms according to the affected *zang fu* (defined as orbs by the HM) in the respective layers [21]. The cold attack in RA patients can be described as a stiffness pain in the joints or muscles, which limits the comfortable range of motion. The pain is relieved with warm application, but increases with cold environment or cold application [22]. Our objective was to evaluate if and how the topical application of *C. frutescens* would relieve the pain and increase the strength of the patient's hand with RA. After one week without use the prepared, we assessed if the effect of the prepared endures in time.

Materials and Methods

Research criteria

The patients were included if they: had previously signed an informed consent; presented with remission RA fulfilling the American College of Rheumatology criteria; had impairment of hand strength with or without pain in the hands during the grip test; had chronic pain: either persistent or intermittent over a minimum period of three months prior to recruitment; had current pain greater than 30/100 mm on a VAS within the last 24 h despite medication and stable dose treatment for at least 3 weeks and the TCM diagnose of Turning Point Syndrome, determined by a well-trained doctor.

Patients were excluded from this study if they: were under the age of 18 years; report feeling of burning in the hands; wounds, burns, cuts, infections or irritated skin hands; allergy to capsaicin or other ingredients of the cream; had severe chronic or uncontrolled co-morbid diseases; or expressed interest in this study with the sole purpose of earning money.

Capsicum frutescens prepared

We used 1 Kg of mature chili fruits harvested from 10 plants. The milling process of the Capsicum peppers was carried out in a blender and by cold organic solvent, methanol was employed to extract of the oleoresin from Capsicum peppers. The solid: liquid maceration was given in a ratio of 1: 4 m/v (Capsicum pepper: organic solvent), packed in glass vials with a capacity of 1000 ml and closed with a lid of the same material. The mixture was then placed under a light for 48 h (the

temperature fixed at $25^{\circ}\text{C} \pm 1^{\circ}\text{C}$), after which it was sieved through filter paper. The extract was subjected to the rotavaporation process to recover the solvent by: heating it in a bath at 40°C , rotating the flask at 180 rpm (rotations per minute), vacuum pressure at -300 mmHg, and placed under a light. The process was repeated until the solvent was completely evaporated.

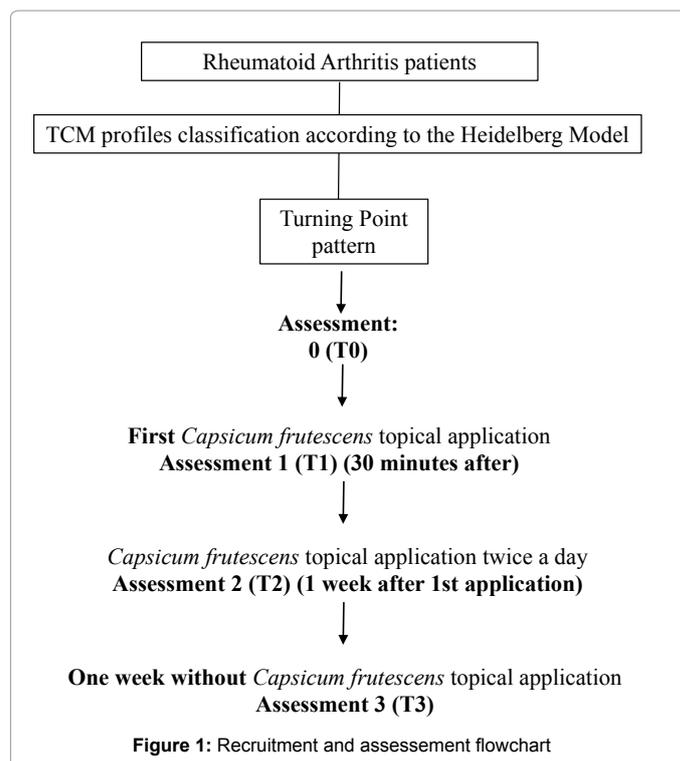
The final product obtained, capsicum pepper oleoresin, was stored in 70 ml amber flasks at $5^{\circ}\text{C} \pm 1^{\circ}\text{C}$. The ointment was then packed in plastic jars and the weight checked and stored at a temperature of $5^{\circ}\text{C} \pm 1^{\circ}\text{C}$.

Design

Patients were instructed to apply the topical solution of *Capsicum frutescens* twice a day for seven consecutive days. All patients kept the pharmacological plan defined by their rheumatologist.

The patients were directed to apply a thin layer (approximately 2 g/cm² of skin) of *C. frutescens* ointment on the hands after that to put on the gloves and wait 30 min. They would then remove the gloves and rinse thoroughly with cold water and soap. We considered four assessments. The first moment (T0), performed before the first application; the second (T1), 30 min after the first topical application; the third (T2), seven days after the first session, and the last assessment was one week after the end of the treatment (T3).

The outcomes assessed were: the pain self-reported assessed by VAS; the pressure tolerated by hand compression, evaluated quantitatively by the algometer device, that was developed in strict cooperation with the Biomedical Engineer department of the Engineer Faculty of the University of Porto, specifically to measure the tolerated force, considering the hand tissue compression; the force, evaluated by the Jamar dynamometer; and the physical incapacity, evaluated by the Health Assessment Questionnaire (HAQ) (Figure 1).



Sex (Male:Female)			0 (0.0%): 4 (100.0%)
Age, mean			58.00
Disease duration, mean			14.75
Body Mass Index (mean)			24.80
Bone erosions (yes:no)			2 (50.0%): 2 (50.0%)
Tender joints (0:2:6)			3 (75.0%): 1 (25.0%)
Swollen Joints (0:2:4)			0 (00.0%) : 1 (25.0%) : 3 (75.0%)
Current medication	NSAIDs (yes:no)		4 (100 %): 0 (00.0%)
	Biological agents (yes:no)		0 (00.0%): 4 (100.0%)
	DMARD's (yes:no)		4 (100.0%): 0 (00.0%)
	Analgesics (yes:no)		3 (75.0%): 1 (25.0%)
Pain (VAS, 0–10) (mean)			5
Pain sensation	Cold exposure	Indifferent	2 (50.0%)
		Worsens	2 (50.0%)
	Heat exposure	Relieves	1 (25.0%)
		Indifferent	2 (50.0%)
	Worsens		1 (25.0%)
		Indifferent	2 (50.0%)
	Cold application	Worsens	2 (50.0%)
		Relieves	1 (25.0%)
	Heat application	Worsens	1 (25.0%)
		indifferent	2 (50.0%)
Frozen		1 (25.0%)	
Hands temperature		Cold	3 (75.0%)
		Heat	0 (0, 0%)
		Frozen	0 (0, 0%)
Feet temperature		Cold	3 (75.0%)
		Heat	1 (25.0%)

Table 1: Clinical characteristics of the patients (n=4).

Results

Recruitment rate and baseline characteristics

A group of four patients, with features of the traditional Chinese medicine *Turning Point* syndrome and RA in a remission stage that fulfilled the inclusion and exclusion criteria were recruited between June and September of 2016. Data of the demographics and clinical characteristics of the participants are summarized in Table 1.

We compared the pain data assessed by self-report (VAS) and by a physically measurable parameter (using the Pressure Algometer), before and after all the treatments. The variability of the VAS score and PA at baseline, 30 min after the first application (T1), one week after the first assessment (T2) and one week after to finish the application of *C. frutescens* (T3) are presented in Figure 2. The improvements induced by the treatment, expressed by the difference between the values obtained after T3 and before the first treatment (T0), are represented in the graphs (Figure 2). We assessed the force by dynamometry and also for this parameter we had an improvement of the values during the time that the patients applied the *C. frutescens* preparation, as represented in Figure 3. HAQ reflects the patient's symptoms and the impacts the disease has on their health and life. The results, based on patient-reported measures, to the HAQ instrument are representing in the graph of the Figure 4.

During the application of the *C. frutescens* prepared, there was a decrease in the self-reported pain here evaluated by the VAS, improvement of the pressure tolerated by the compression of the hand, and improvement of the hand strength. The HAQ is one of the most important patient-reported outcome measures in RA clinical trials, but is also commonly used by rheumatologists in daily practice. The HAQ yields a disability index score between 0 and 3, where 0 means no

disability and 3 represents total dependence on others [23]. The HAQ scores of our sample at baseline were already >1, a value that indicates the presence of disability. The application of the *Capsicum frutescens* had a positive impact to the HAQ index score to 75% (n=3) of the patients, what means the favorable impact of the prepared effect in the necessity of support and health status. After applying the solution, there was a slight increase in pain for all patients, though the force decreased from T2 to T3 in two patients. The pressure tolerated by hand compression continued to improve for three patients, and even after a week without *Capsicum frutescens* application, the patients did not report signs of aggravation compared to the assessment before to start the treatment (T0). One patient (A) showed the lowest increase of the force assessed by dynamometry, and also the could only tolerate the lowest increase of the pression. Interestingly, the same patient expressed pain relief and their health status, as assessed by HAQ instrument, had a better score after the use of *Capsicum frutescens*. The subjective and self-reported pain evaluated by the VAS, the tolerance to the hand compression pressure, as well as the hand strength exerted by the patient himself showed favorable results immediately (T0 and T1). After the first week (T2), the same behavior was observed, with a tendency to increase the force exerted by the hand evaluated by the dynamometer. After finishing the application of the topical solution, VAS scores decreased and the tolerated pressure increasingly slowed down. From the analysis of T0 to T2, we can see that in general the pain self-reported decreased, the pressure tolerated and the force increased. From T0 to T3, despite regression in clinical behavior, the results are higher in T3 when compared with the results in T0 for all variables. Throughout the period of application of *C. frutescens*, no complications were found.

Discussion

RA is a disease affecting many aspects of a patient's life, associated

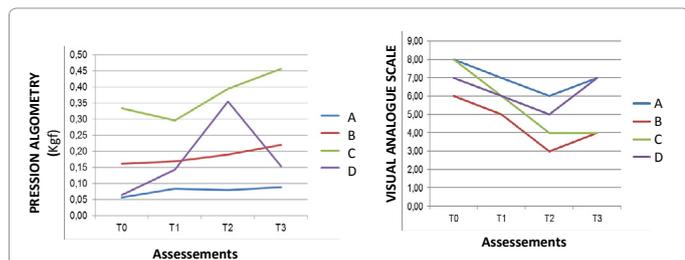


Figure 2: Pain variability assessed by Pression algometry and VAS (n=4).

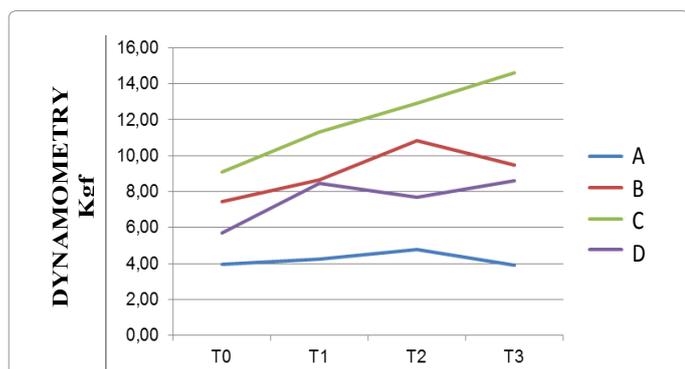


Figure 3: Force variability assessed by dynamometer (n=4).

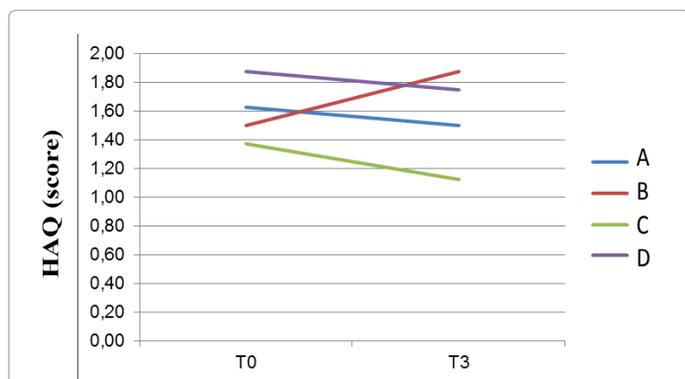


Figure 4: HAQ assessment by patient-reported.

with severe morbidity and permanent disability [5,6]. A broad approach to assess different RA disease features is necessary, as it is a major goal in the management of RA to relieve the pain and maintain functional capacity.

We assessed the effects of the application of *Capsicum frutescens* prepared in RA remission patients (according EULAR criteria's), with pain and lack of strength of the hands. The sample was selected according to the HM of TCM. We chose patients with signs and symptoms of *algor* (external agent) and lack of microcirculation (as guiding criteria) features. Tongue and pulse main tools of TCM diagnosis, hand skin temperature, type of pression hand tolerance, as signs and symptoms self-reported, were essential to determine the *Turning Point* TCM diagnose. Our results demonstrate that for the sample, the application of *Capsicum frutescens* was effective in relieving self-reported pain assessed by VAS. The pressure tolerated by hand compression and the strength improved 30 min after the first application (T0 to T1). After the first week of application (T2), RA symptoms continued to improve,

with a marked increase in hand strength evaluated by the dynamometer.

On the basis of their need for personal care and/or their difficulties with mobility, assessed by HAQ, the reports of the patients from baseline to last assesment (T3) were promising. At the end of the application of the *Capsicum frutescens*, there was a setback in the clinical behavior. The scores of self-reported pain increased and the pressure tolerated decreased when compared to the parameters after one week of application (T2) however, the strength continued, slower, but positive increase. Even after a week without application of the topical solution, the self-reported pain, tolerance of pressure to the hand, and the hand's strength, are still superior to T0. Capsaicin, the alkaloid derivative from plants that include common pepper, when applied topically has analgesic effects, acting on substance P and peripheral sensory receptors [9]. The effects of capsaicin on pain relief in RA patients have been already demonstrated in randomized controlled trials [10-12].

Some of the results found that the percentage of capsaicin correlates directly to faster pain relief but, [10] capsaicin from chili, it seems, does not always get results from to all RA types due to the recognized alkaloid effects in local temperature and microcirculatory flow increase [11].

In a larger double-blind, randomized, vehicle-controlled, multicenter study patients (n=113) received either topical capsaicin or vehicle four times daily during 12 weeks. The results support the beneficial effects of application of 0.025% capsaicin cream as a first-line was superior to vehicle in providing pain relief. Drawbacks to the application of Capsaicin are the delay of onset of action (three to four weeks) and it requires multiple applications (three to four times daily).

Adverse reactions related to this treatment are mostly local, and most commonly the studies reported erythema, heat/burning sensation and burn-like pain, risk of mucosal irritation, namely mouth and eyes, by inadvertent application [10-12]. However, in the studies cited above, these effects were temporary. When applied in safe conditions (such as wearing protective gloves and washing hands after the treatment is finished), side effects are greatly diminished. In our study, all patients completed the recommended time of application of *Capsicum frutescens* with a concentration of 0.25 mg/g, with no reported side effects. This allows us to infer that the adverse reactions, when present, were not of significant relevance to the participants and not either were a barrier to treatment adherence. Expectations regarding the efficacy of this therapy and the fact that it can provide long-term relief may influence patients to tolerate the application of the cream and its possible adverse reactions.

A recognized advantage for the topical application of capsaicin it is the possibility of to reduce the necessity of supplementary systemic medication for relief RA symptoms and may also be useful as an adjunctive treatment for patients who are intolerant or who do not respond to the conventional therapy [24,25]. The combination of non-pharmacological strategies, as acupuncture, moxibustion or biofeedback therapies as qigong, with the application of *Capsicum frutescens* may be a future research hypothesis. Our results are limited by the small sample and lack of a control group. Concomitant analgesic medication may induce bias regarding the effectiveness of *Capsicum frutescens* application, as well as, the frequency of application of two times a day, needs to be better analyzed. This treatment is not recommended for children under the age of 16, pregnant or lactating women. Acceptation from the patient to oft topical application may interfere with the efficacy of the preparation. Also, the effects of this topical therapy versus oral medications have not been adequately studied.

The skin's condition can interfere with absorption and distribution

of the medication applied topically. In addition, its effectiveness also depends on the rate, amount and depth of penetration into the skin. Capsaicin is insoluble in water than, the depth of skin penetration is minimal. Higher concentrations may benefit the desirable depth and functional sensory denervation of nerve fiber nerve.

Conclusion

The analysis of four clinical cases showed us that the topical preparation of *Capsicum frutescens* relieves pain and increases the hand's strength, as well as its overall physical health. The topical solution was well tolerated without any relevant secondary reactions. To use *C. frutescens* means a low-cost choice with few side effects, thus making it a viable investment that can be presented in the form of cream, gel, liquid, lotion or transdermal system. Future, randomized, controlled, double-blind study, with three-arms (verum, placebo and no *C. frutescens* application), should be designed to assess, in a representative population sample, the effects and tolerability of long-term topical application of *C. frutescens*. A follow up of at least 21 days is suggested in several studies. In any way, assessments every 7 days of application can be important to understand the beginning of effects and possible stability. Similar clinical cases could be developed to analyze the clinical behavior of patients in other RA stages.

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