Preclinical evaluation of antiarthritic activity of ultra-diluted preparations of capsaicin alkaloids (CP-10), tumor necrosis factor-alpha, and Magnesium phosphoricum in wistar rats

Rajesh Shah1*, Sadhana Sathaye2
1Department of Research and Development, Life Force, 2Department of Pharmaceutical Sciences and Technology, ICT, Mumbai, Maharashtra, India

Abstract

Background: The use of animal models in the development of new medicine and research is common in the conventional medicine. Animal model for new drug discovery and efficacy testing for preclinical research is explored in Homoeopathy only by a few. This study explores the possibility to test in a controlled way the effects of homeopathic remedies on experimental model of acute inflammation in rats. Methods: Wistar rats were divided into seven groups (seventy rats of 6–8 weeks’ age); medicines were evaluated by oral administration in the Complete Freund’s adjuvant (CFA)-induced arthritis. Two new homeopathic preparations, a combination of Capsaicin and Dihydrocapsaicin (CP-10), tumor necrosis factor-alpha (TNF-α), and one existing homeopathic medicine, Magnesium phosphoricum (0.6 ml oral), were evaluated against vehicle control using Diclofenac as a standard. Edema was measured using a water-based plethysmometer, before and at different times after arthritis induction. Results: Magnesium phosphoricum showed good results, almost similar to Diclofenac at days 7 and 21, whereas CP-10 and TNF-α showed nonsignificant results. The body processes reversed the inflammatory condition on day 7 onward indicated by similar paw volume of all the treatments. Arthritic index was higher with negative control, which was decreased by CP-10 although nonsignificantly on days 7 and 21. Diclofenac and Magnesium phosphoricum showed significant reduction in arthritic index on days 7 and 21. Conclusion: Ultra-diluted homeopathic preparations of Magnesium phosphoricum exhibited definite antiarthritic activity. The same could have been confirmed studying the levels of inflammatory biomarkers in a study with longer treatment period.

Keywords: Arthritic index, Capsaicin, Complete Freund’s adjuvant, Magnesium Phosphoricum, Tumor necrosis factor-alpha, Homoeopathy, Ultra-dilute potency

INTRODUCTION

Homoeopathy is a system of alternative medicine based on the principle of “like cures like” Homoeopathy rests on the premise of treating diseases with extremely ultra-diluted medicinal agents that, in undiluted doses are deemed to produce similar disease symptoms in healthy individuals. Acceptance in the effectiveness of Homoeopathy in general is widespread and growing among the physicians and public.1 The present study was undertaken to investigate the antiarthritic, anti-inflammatory effect of three homeopathic preparations in ultra-dilute 30C potencies in animal model: (1) a combination of Capsaicin and Dihydrocapsaicin, (2) tumor necrosis factor-alpha (TNF-α), and (3) Magnesium phosphoricum. For blinding, the formulations were coded as formulation I, II, and III, respectively. Capsaicin and Dihydrocapsaicin are the plant alkaloids, potentized up to 30c potency using a standardized potentiator.2,3 TNF-α (cachexin or cachectin) is a cell signaling protein (cytokine) involved in systemic inflammation. This particular preparation is sourced from human TNF-α procured from Sigma Aldrich. Homoeopathic potencies were prepared by a serial dilution of 1:99, where one part of the drug substance is mixed with 99 parts of vehicle (alcohol) and exposed to ten mechanical strokes, to make 1c potency. Again, one part of 1c potency is mixed with 99 parts of vehicle to undergo the same process to arrive at 2c potency.

Access this article online

Quick Response Code: Website: www.ijrh.org DOI: 10.4103/0974-7168.200848

*Address for correspondence: Dr. Rajesh Shah, Life Force, 411 Krushal Commercial Complex, GM Road, Chembur, Mumbai - 400 089, Maharashtra, India. E-mail: sanjivvak@gmail.com

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms. For reprints contact: reprints@medknow.com

How to cite this article: Shah R, Sathaye S. Preclinical evaluation of antiarthritic activity of ultra-diluted preparations of capsaicin alkaloids (CP-10), tumor necrosis factor-alpha, and Magnesium phosphoricum in wistar rats. Indian J Res Homoeopathy 2017;11:34-40.
2C potency. Likewise, 30C, 200C, and more potencies were prepared.

In this study, the antiarthritic activity of the three potentized (30C) medicines was compared with Diclofenac (10 mg/kg, source - Sigma Aldrich). The selection of medicines was based on the fundamental principle of Homoeopathy “like cures like” and the phenomenon of homeresis, which state that the substance known to produce inflammation or pain may have built-in capacity to relieve the same, if administered in small dose. The author had done anecdotal work using the new homoeopathic preparations used in this study, where he had observed activity against inflammation and arthritis.

 Materials and Methods

Animals
Male and female Albino Wistar rats (180–200 g) were procured from Haffkine Bio Pharmaceutical, Parel, Mumbai, and housed under a controlled environment (room temperature: 23 ± 2°C, relative humidity: 60 ± 5%, 12 h day/night cycle) with balanced diet and water ad libitum. The animals were acclimatized for a period of 1 week and were kept under pathogen-free conditions. All animal experiments were approved by the Institutional Animal Ethics Committee (IAEC), Department of Pharmaceutical Sciences and Technology, ICT, Mumbai (ICT/IAEC/2012/P-39).

Complete Freund’s adjuvant-induced arthritis
Arthritis was induced in rats by injecting 0.1 ml of fine emulsion of complete Freund’s adjuvant (CFA) in olive oil (1:2, v/v) (at a concentration of 0.25 mg heat-killed Mycobacterium tuberculosis per milliliter of emulsion) in the subplantar surface of rats’ left hind foot. Equal amount of salina was injected at the same site of the right foot. Arthritis was induced in all the animals except normal control. A volume of 0.1 ml saline was injected in both paws of the normal control animals. All rats were randomly divided into seven groups each containing 5 males (M) and 5 females (F). Group I: normal control (distilled water), Group II: vehicle control (dispensing alcohol), Group III: untreated control (CFA), Group IV: homoeopathic formulation I Capsaicin and Dihydrocapsaicin 30C, Group V: homoeopathic formulation TNF-α 30C, Group VI: homoeopathic formulation Magnesium phosphoricum 30C, and Group VII: Diclofenac.

Dosage preparation and administration
Homoeopathic formulations Capsaicin and Dihydrocapsaicin and TNF-α in 30C potency and the vehicle control (Curative Power Lab Ltd., dispensing alcohol 91% v/v, Batch number: HD-18, Mfg. date: February 2013) were supplied by Life Force Homeopathy, Mumbai, India. Formulation Magnesium phosphoricum in 30C potency, liquid dilution, was sourced from Dr. Willmar Schwabe India Pvt Ltd. (Batch Number: 2981299, Mfg. date: November 2009). CFA was obtained from Haffkine Biopharmaceuticals, Parel, Mumbai (Lot number 098K8729). The rats received 0.6 ml of homoeopathic formulation or vehicle, in each respective group, and 10 mg/kg of Diclofenac every day for 21 days by oral route. Animals were kept nil by mouth for 15 minutes before the drug administration.

Evaluation of the severity of arthritis
Severity of arthritis was evaluated based on the following parameters, namely, body weight, paw volume, arthritic index, and mechanical pain threshold. All animals were treated with CFA except normal control animals, and evaluation parameters were assessed before adjuvant injection and then on days 7, 14, and 21 after adjuvant injection. The body weights of all the rats were recorded, and the paw volumes were measured using a Digital Plethysmometer (UGO Basile [SRL], biological research apparatus, 21025 Comerio VA Italy, Model 71411). For arthritic index, the physical symptoms of arthritis were evaluated by the Arthritic Index Grading System [Table 1]. The animals were sacrificed as per the approved method of euthanasia at the end of study.

Arthritis index for each group was calculated by adding the scores for each rat. Mechanical pain threshold was assessed using external mechanical force. The mechanical pain threshold of hind paw was determined by compressing the paw using a custom-designed balance pressure apparatus consisting of conical tip of 1 mm diameter. The load on the conical tip was gradually increased and the load cell allowed visualization on the digital display of the force applied at each moment of the test in grams. The threshold force of rats squeaking or struggling was expressed in grams.

Statistical analysis
The results were expressed as the mean for the parametric data sets and as the median minimum, maximum for the nonparametric data sets. The significant difference between the means (parametric) was evaluated by one-way ANOVA followed by Dunnett’s post hoc multiple comparison test for normal data.

Results
CFA-induced arthritis in rats is used as a model to evaluate the antiarthritic activity of drugs in preclinical research. CFA induces a chronic immune-mediated inflammation similar to arthritis characterized by elevation of pro-inflammatory mediators and development of swelling, pain, and deformity of joints. Inflammation was indicated by increase in paw volume. The reduction in inflammation due to treatment was indicated by decreased paw volume for evaluation of therapeutic efficacy of the drug, administered in the ultra-diluted form.

Table 1: Arthritic index grading system

<table>
<thead>
<tr>
<th>Parameter</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Redness and nodules in ear</td>
<td>None</td>
<td>visible</td>
<td>moderate</td>
<td>marked</td>
</tr>
<tr>
<td>Swelling of connective tissue of nose</td>
<td>None</td>
<td>visible</td>
<td>moderate</td>
<td>marked</td>
</tr>
<tr>
<td>Nodules in tail</td>
<td>None</td>
<td>visible</td>
<td>moderate</td>
<td>marked</td>
</tr>
<tr>
<td>Forepaw inflammation</td>
<td>None</td>
<td>slight</td>
<td>moderate</td>
<td>marked</td>
</tr>
<tr>
<td>Hind paw inflammation</td>
<td>None</td>
<td>slight</td>
<td>moderate</td>
<td>marked</td>
</tr>
</tbody>
</table>
Body weight
No significant difference was observed with respect to negative control in both male and female rats, and a good increase in weight on days 7, 14, and 21 indicated normal growth in all the groups.

Paw volume
In the acute phase of arthritic inflammation on day 1, homoeopathic formulation Magnesium phosphoricum indicated a significant reduction in inflammation by reduced paw volume, similar to standard Diclofenac. Homoeopathic formulations Capsaicin and Dihydrocapsaicin and II also showed a nonsignificant reduction in inflammation similar to negative control. The body processes reversed this inflammatory phase as seen by decrease in inflammation by the negative control on day 7. A nonsignificant rise in the inflammation was seen with homoeopathic formulations on day 21, especially with the formulation TNF-α, which was not seen with Diclofenac, suggestive of the continued primary action of the formulation. Such an increase is peculiar of ultra-dilute homoeopathic formulation, as per the homoeopathic principle of “like cures like,” where initial effect (inflammation index) caused by the medicinal substance gets reduced subsequently by secondary effect\(^6\) (which could be body’s defense mechanism), leading to anti-inflammatory effect [Figures 1 and 2]. This study has demonstrated the initial (primary) effect of formulation TNF-α by increasing the inflammation, which could have possibly reversed on further continuation of treatment.

Formulation Capsaicin and Dihydrocapsaicin 30C is an alkaloid which is known to produce pain and inflammation, not only in crude form but also in high dilution dose as seen in a Homoeopathic Pathogenetic Trial (HPT).\(^7\) The same compound has also demonstrated anti-pain and anti-inflammatory effects with 30C potency on a range of painful conditions in a clinical trial.\(^8\) The current study has produced similar effects in an animal model. Longer study to explore this phenomenon can be conducted in future.

Arthritic index
Arthritic index was higher with negative control which was decreased by formulation Capsaicin and Dihydrocapsaicin on days 7 and 21 although not significantly. Diclofenac and formulation Magnesium phosphoricum showed a significant reduction in arthritic index on days 7 and 21 [Table 2]. Formulation Magnesium phosphoricum exhibited similar response as that of standard Diclofenac on day 7.

Similar to the paw volume, a trend in nonsignificant rise in the arthritic index was seen in all the groups, probably due to the immunological process systemically. It is extremely important to plan a further study with an increase in the duration of administration of the homoeopathic formulation to evaluate if on a longer administration the symptoms could reverse significantly.

\(P\) value was calculated using paired \(t\)-test for all the three formulations as compared to vehicle control and negative control. It was noted that the statistical significant results \((P < 0.05)\) were obtained with formulation Magnesium phosphoricum as compared to vehicle control in male rats. In case of Diclofenac, statistical significant results \((P < 0.05)\) were observed in female rats as compared to vehicle control and negative control.

Mechanical pain
A decreased pain threshold in negative control (CFA) on day 7 indicated induction of arthritic process, i.e., immune-mediated inflammation. No drug treatment could reverse this significantly as compared to negative control on day 7, indicating induction of arthritis and subsequent pain. Reversal of mechanical pain threshold in negative control group on day 14 indicated natural body process toward recovery although none of the drugs could alleviate the decreased pain threshold. On day 21, negative control groups almost reversed back the decreased pain threshold to normal. Diclofenac, too, increased the pain threshold, indicating good analgesic, anti-inflammatory activity. None of the homoeopathic formulations could alleviate the pain threshold to normal by day 21 [Figures 3 and 4]. Continuation of treatment further could probably alleviate the pain threshold, relieving the arthritic symptoms. This corresponds to the other parameters as discussed before, where a rise in paw volume and arthritic index was seen in the homoeopathic treatment groups.
**Discussion**

The medicinal substances sourced from different materials (herbs, minerals, and biological) are known to act differently, as observed in clinical homoeopathic practice. It is a common observation that medicines from herbs have quicker and shorter span of action; medicines from minerals and metals (depending on the exact ingredient) have slow or fast but longer duration of action; while those from animal source (many subvarieties) may take longer time to act and the action may last longer.\(^9\)\(^{10}\) Of course, there are many other factors that determine the duration of action. Usually, the medicines sourced from biological materials take longer duration to set in action, as compared to the mineral and plant materials. Different formulations having different actions need further exploration.\(^11\)

Our understanding about formulation *Magnesium phosphoricum* (a tissue salt) is based on clinical experience, where it is known to work quickly. It has been in use as an analgesic. It seems that the primary action of this magnesium compound may have been quick and short, quickly followed by the secondary action. Formulation *Magnesium phosphoricum* did not undergo HPT.\(^12\) Interesting to note that magnesium compounds showed efficacy in pain relief when administered in crude form.\(^13\)\(^{14}\) Intravenous MgSO\(_4\) infusion has shown analgesic effect. The magnesium compound showed anti-inflammatory efficacy in ultra-diluted form in this study. This calls for further study.

The significant reduction in paw volume by homoeopathic formulation *Magnesium phosphoricum* indicated its anti-inflammatory activity during the acute phase of inflammation. Administration of ultra-dilute potency of TNF-\(\alpha\), which is a pro-inflammatory cytokine, exhibited an increase in paw volume on day 21 [Figure 1]. Although this increase is not statistically significant, a trend toward rise in inflammation is seen as compared to the vehicle control and also to its own activity on days 7 and 14, indicating that the formulation in ultra-dilute potency was capable of producing inflammation showing that it acted and produced biological changes, as compared to the control.

High-dilution medicinal substances are known to induce biological changes and hence symptoms as primary action, which are observed in HPTs.\(^7\) As per the homoeopathic principle and hypothesis, the therapeutic effect of the medicinal substance is through the secondary action of the organism, which is observed once the primary stimulus (formulation) is withdrawn. The constant increase in inflammation in case of TNF-\(\alpha\) till day 21, in comparison with the control group, could be the continued primary action of the formulation. It may be hypothesized that on discontinuing the stimulus, there could have been possible reduction in inflammation as a secondary action of the organism. Further studies in this direction alone could bring insight in this phenomenon.

It was noted that the homoeopathic formulations were administered three times a day, while *Diclofenac* was administered only once a day. Since the handling of animals is known to tire the animals, it might affect the results. In future studies doses may be maintained identical.

<table>
<thead>
<tr>
<th>Table 2: Arthritic Index for different groups</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Days</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Day 0</td>
</tr>
<tr>
<td>Day 7</td>
</tr>
<tr>
<td>Day 14</td>
</tr>
<tr>
<td>Day 21</td>
</tr>
</tbody>
</table>

Figure 3: Mechanical pain (male)  
Figure 4: Mechanical pain (female)
CONCLUSION

The study was undertaken to evaluate the antiarthritic activity of ultra-dilute potencies of homoeopathic formulations from different origins on CFA-induced arthritic model in rats. A significant decrease in inflammation as well as arthritic index was seen by high-dilution homoeopathic formulation Magnesium phosphoricum similar to Diclofenac, demonstrating evidence that small dose of substance having a capacity to produce inflammation could work against inflammation, as per like cures like, the fundamental principle of Homoeopathy.

No such effect was seen on the mechanical pain threshold by the homoeopathic formulations.

Further study needs to be designed with longer duration of administration of these formulations to study whether these formulations could reverse the arthritic index and resultant pain and inflammation on long-term administration.

Acknowledgment

We thank the members of IAEC, sponsor, and subject experts for their technical, ethical, legal, and medical inputs; and the department staff for their cooperation.

Financial support and sponsorship

Nil.

Conflict of interest

None declared.

REFERENCES

Präklinische Bewertung der anti-arthritischen Wirkung hochverdünnter Präparate von Capsaicin-Alkaloiden (CP-10), TNF-α und Magnesium phosphoricum bei Wistar-Ratten

**Auszug**


**Methoden:** Wistar-Ratten wurden in sieben Gruppen (siebzig Ratten im Alter von 6-8 Wochen) aufgeteilt; Arzneimittel wurden evaluiert durch orale Anwendung bei CFA-induzierter Arthritis. Zwei neue homöopathische Präparate, eine Kombination von Capsaicin und Dihydrocapsaicin (CP-10), Tumornekrose-Faktor-α (TNF-α) und ein bekanntes homöopathisches Arzneimittel – Magnesium phosphoricum (0,6 ml oral) - wurden als Standard gegenüber der Lehreprobe unter Verwendung von Diclofenac bewertet. Ödeme wurden mit einem wasserbasierten Pletysmometer vor und während verschiedener Zeitpunkte nach der Arthritisinduktion gemessen.

**Ergebnisse:** Magnesium phosphoricum zeigte gute Ergebnisse, fast ähnlich dem von Diclofenac am 7. und 21. Tag, während CP-10 und TNF-α nicht signifikante Ergebnisse erbrachten. Der körpereigene Prozess ließ den entzündlichen Zustand vom siebten Tag an abklingen, angezeigt durch ein ähnliches Pfotenvolumen aller Behandlungen. Der arthritische Index war höher mit einer negativen Kontrolle, was durch CP-10, obwohl nicht signifikant, am 7. und 21. Tag abnahm. Diclofenac und Magnesium phosphoricum zeigten eine signifikante Reduktion des arthritischen Index am 7. und 21. Tag.

**Fazit:** Ein hochverdünntes homöopathisches Magnesium phosphoricum Präparat zeigte definitiv eine anti-arthritische Wirkung. Das gleiche konnte in einer Studie, die über einen längeren Behandlungszeitraum ging und bei der der Gehalt an entzündlichen Biomarkern untersucht wurde, bestätigt werden.

Evaluación preclínica de la actividad antiartrítica de las preparaciones ultradiluidas de los alcaloides de la Capsaicina (CP10), TNF-α y Magnesium phosphoricum en ratas wistar

**RESUMEN**

**Fundamento**

El uso de modelos animales en el desarrollo de nuevos fármacos y en la investigación es una práctica habitual en medicina convencional. El sistema de medicina homeopática se practica desde hace más de dos siglos. En homeopatía, únicamente unos pocos investigadores aplican un modelo animal para el descubrimiento de nuevos medicamentos y la comprobación de la eficacia en la investigación preclínica. En este estudio, se explora la posibilidad de examinar de forma controlada los efectos de los remedios homeopáticos en un modelo experimental de inflamación aguda en ratas.

**Método:** Las ratas Wistar fueron divididas en siete grupos (setenta ratas de 6 a 8 semanas de edad); los medicamentos se evaluaron por administración oral en la artritis inducida por CFA. Se evaluaron dos preparados homeopáticos nuevos, una combinación de capsaicina y dihidrocapsaicina (CP-10), y el factor de necrosis tumoral α (TNF α), así como un medicamento homeopático existente, Magnesium phosphoricum (0,6 ml por vía oral) frente al control con vehículo, utilizando el diclofenac como control. Se midió el edema utilizando un pletysmómetro de agua antes y en diferentes momentos tras la inducción de la artritis.

**Resultados:** Magnesium phosphoricum mostró buenos resultados, casi similares al diclofenac en los días 7 y 21, mientras que CP-10 y TNF-α mostraron resultados no significativos. Los procesos corporales invirtieron la inflamación a partir del día 7 en adelante, lo cual quedaba reflejado en un volumen de pata similar en todos los tratamientos. El índice artrítico fue superior en el control negativo, lo que descendió con CP-10, aunque no de forma significativa en los días 7 y 21. Diclofenax y Magnesium phosphoricum mostraron una reducción significativa del índice artrítico en los días 7 y 21.

**Conclusiones:** Uno de los preparados homeopáticos ultradiluidos de Magnesium phosphoricum mostró una actividad antiartrítica definida. Esto mismo pudo confirmarse al estudiar los niveles de biomarcadores inflamatorios en un estudio con un periodo de tratamiento más prolongado.
विस्तार छूटों में कैप्सीडिन एल्क्लाइड (सीपी—10), टीएनएफ—α और मैनीशियम फोसफोरिकम का अल्टों—तनुकृत निमित्त की प्रतिसंदिहिथता गतिविधि का पूरा नैदानिक मूल्यांकन

सार

पृष्ठभूमि: आधुनिक विकिल्सा और अनुसंधान के विकास के लिए पारंपरिक विकिल्सा में पन्जु मॉडल का उपयोग आम है। विकिल्सा क्षेत्र में होम्योपैथिक प्रणाली गत दो शारदाओं से उपयोग में लाई जा रही है। होम्योपैथी जगत में नई औषधियों की खोज और पूर्ण नैदानिक अनुसंधान हेतु भ्रमणकार्य परीक्षण, पन्जु मॉडलों की सहायता से कम ही लोगों द्वारा किया गया है। इस अध्ययन हेतु छूटों में तीन शीर्ष के प्रयोगान्वयक मॉडल पर होम्योपैथिक उपचार के प्रभाव का एक नियंत्रित तत्काल से परीक्षण की संभावना का प्रमाण करता है।

विवेचन: विस्तार छूटों को सात समूहों में विभाजित किया गया (6–8 सपाट उम के सतार छूटों); सीपीएफ जिसमें गतिविधि भी शामिल है में नैदानिक प्रयोग द्वारा औषधियों का मूल्यांकन किया गया। दो नई होम्योपैथिक निमित्त, कैप्सीडिन और डाइहाइड्रोकैप्सीडिन (सीपी—10) का एक संयोजन, टूपर नेक्रोसिस कारक—ए (टीएनएफ—α) तथा एक मौजूदा होम्योपैथिक औषधि, मैनीशियम फोसफोरिकम (0.6 मिलिलॉटर मैक्सिक) का मूल्यांकन वाहक नियंत्रण के बनाम डाइब्लॉकेनाक का एक मानक के रूप में उपयोग करते हुए किया गया। उद्ध शीर्ष का मापन एक जल आधारित प्लास्टिमेटर का उपयोग कर, गतिविधि प्रयोग के पहले और बाद के अलग-अलग समय पर किया गया।

परिणाम: मैनीशियम फोसफोरिकम ने अच्छे परिणामों का प्रदर्शन किया, लगभग डाइब्लॉकेनाक के समान सातवें और इक्कीसवें दिन जबकि सीपी—10 और टीएनएफ—α ने गैर-महत्वपूर्ण परिणामों का प्रदर्शन किया। शरीर प्रक्रिया द्वारा सूजन की रिखित सातवें दिन के बाद सामान्य हो गई, जो सभी उपचारों में समान पंजा (प) मात्रा द्वारा इंगित था। गतिविधि सूचकांक और मैक्सिक नियंत्रण के साथ उच्च था, जो सीपी—10 द्वारा कम था, हालाँकि सातवें तथा इक्कीसवें दिन गैर महत्वपूर्ण था। डाइब्लॉकेनाक और मैनीशियम फोसफोरिकम द्वारा सातवें तथा इक्कीसवें दिन, गतिविधि सूचकांक में महत्वपूर्ण कमी का प्रदर्शन किया गया।

विवेचन: एक अल्टों—तनुकृत मैनीशियम फोसफोरिकम द्वारा निरंजन प्रतिसंदिहिथता गतिविधि का प्रदर्शन किया गया। उपज्ञात की पुष्टि लंबी उपचार अवधि के साथ सूजन के बायोमार्कर्स के एक अध्ययन विशेष के कर से किया जा सकता है।