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## The case for cat's claw: Peru



### GENERAL INFORMATION

- ◆ **Implementing institution**  
Immunology Section, Department of Microbiology,  
Faculty of Sciences and Philosophy, Universidad Peruana  
Cayetano Heredia
- ◆ **Head**  
Oswaldo Zegarra (rector)
- ◆ **Details of institution**  
*Address:* Immunology Section, Department of Microbiology,  
Faculty of Sciences and Philosophy, Universidad Peruana  
Cayetano Heredia, Box 4314, Lima 100, Peru  
*Tel.:* (+51) 1 319 0000  
*Fax:* (+51) 1 319 0003  
*E-mail:* jaguilar@upch.edu.pe  
*Web site:* [www.upch.edu.pe/facien/microweb/inmuno/  
principal.htm](http://www.upch.edu.pe/facien/microweb/inmuno/principal.htm)
- ◆ **Implementation period**  
Several different studies have developed over  
a three-year period.

### ◆ Costs

Approximately US\$25,000 was provided by the Immunology Section in terms of funds from different sources. Government contributions from a national project that provided some reagents and laboratory animals amounted to around US\$2,000. Contributions from private funds totalled US\$15,000 and provided partial support for some small projects, such as the determination of toxicity parameters. Foreign funds (US\$3,000) helped to buy some experimental reagents. The Section's own funds (around US\$5,000) were used to procure consumable reagents and laboratory and office equipment.

## SUMMARY

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Chronic inflammatory diseases are a major public health problem around the world, a problem that is worsening because of the increasing percentage of older people in both developed and developing countries. Traditionally, several natural products with attributed anti-inflammatory properties exist, including cat's claw (*Uncaria tomentosa*), the bark of which is widely used in Peru.

The aim of the current project was to verify the anti-inflammatory properties using an alcoholic extract of cat's claw and a combination of cellular and molecular experiments. Following these basic tests, clinical studies were designed to demonstrate the scientifically proven usefulness of the extract.

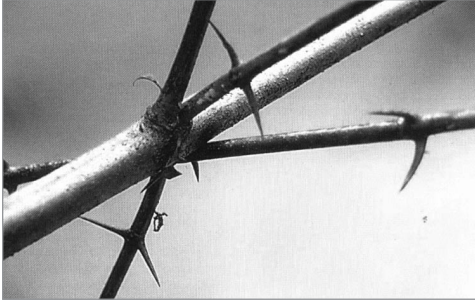
## BACKGROUND AND JUSTIFICATION

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Throughout the world, the number of

people with chronic inflammatory diseases is increasing. For the most part, developed countries have the capacity to cope with this situation. In developing countries, however, there is a critical need to allocate as many resources as possible to production issues, leaving little for older people. This situation puts a large part of the population in developing countries beyond the reach of pharmaceutical products. There is, therefore, a critical requirement to develop therapeutic alternatives from readily available regional resources. Not only will such locally developed pharmaceutical products assist the elderly — and others — but their development will also reduce the amount spent on costly imported alternatives.

In today's global economy, the application of traditional knowledge can be useful. However, for a pharmaceutical product derived from a botanical source to gain wide support, its worth must be proved scientifically with data based on molecular, cellular and clinical trials in accordance with the current concepts of evidence-based medicine.



**Figure 1** | Cat's claw (*Uncaria tomentosa*) showing the characteristic paired thorns.

Cat's claw (*Uncaria tomentosa*, family Rubiaceae) is a woody vine that can grow up to 30 metres into the forest canopy of Peru. It derives its name from the thorns that grow in pairs at regular intervals along the stem and resemble the claws of a cat (fig. 1). The plant has been exploited for its medicinal properties by various Peruvian tribes for at least 2,000 years. Traditionally, it has been used to treat such ailments as arthritis, asthma, cancer, gastric ulcers and rheumatism. It is also used to control inflammation, help to heal wounds and alleviate pain and therefore has the potential to treat a wide range of chronic inflammatory diseases, especially if the active ingredients can be identified and isolated.

In addition, other, unrelated species of plants in Mexico and Latin America are commonly called cat's claw, or *uña de gato*. Several of them, however, have toxic properties, making the verification and standardization of "true" cat's claw (*U. tomentosa*) preparations a vital issue.

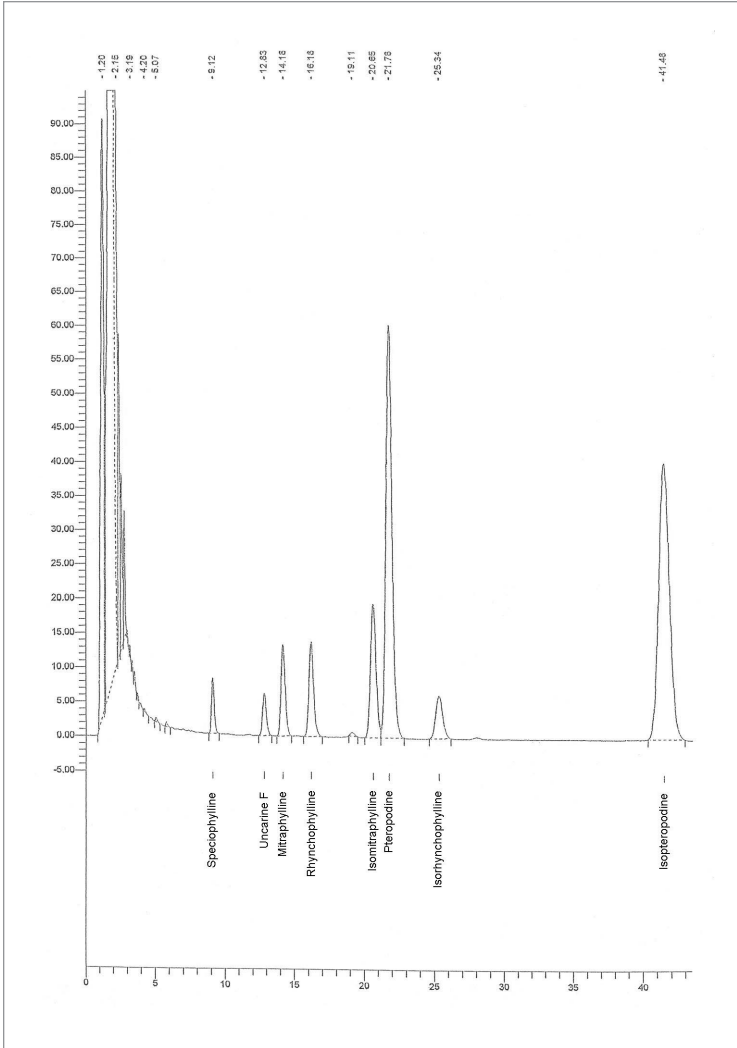
## DESCRIPTION

The project is part of a wider investigation of the properties of Peruvian natural products. In this case study, a standardized hydro-alcoholic extract of cat's claw (Uncitolina<sup>®</sup>) was evaluated.

Collaborative research with a local private company (Naturalfa) helped to develop a protocol based on high performance liquid chromatography (HPLC) to standardize the Uncitolina<sup>®</sup> extract (fig. 2).

The toxicity of the Uncitolina<sup>®</sup> extract was evaluated in cell culture and animal (mouse) models using standard LD<sub>50</sub> assays (the dose required to kill 50 per cent of the cells or mice). In both systems, the extract demonstrated no toxicity. Uncitolina<sup>®</sup> was tested against human peripheral blood mononuclear cells using the flow cytometry technique. No increase in apoptosis (cell death) was detected for doses between 10 to 300 microgrammes per millilitre, demonstrating that the cells can tolerate relatively high concentrations of the extract. In the animal experiment, the LD<sub>50</sub> was established as 10.8 grammes of the extract per kilogramme bodyweight, putting Uncitolina<sup>®</sup> in the standard William's category V, i.e., essentially non-toxic.

Next, the anti-inflammatory properties of the extract were tested on an animal model, that is, its ability to reduce the swelling induced in mouse paws caused by the application of carrageenan. On assessment of the swelling 2 and 4



**Figure 2** | High performance liquid chromatography (HPLC) analysis of oxindole alkaloids in a hydro-alcoholic extract (Uncitolina®) of cat's claw.

hours later, the Uncitolina® extract showed good anti-inflammatory effects at low doses (50 milligrammes per kilogramme bodyweight), when its effect was comparable to synthetic non-steroidal anti-inflammatory drugs (NSAIDs), and at higher doses (500 milligrammes per kilogramme bodyweight), when the extract was more effective than NSAIDs (table 1).

Other molecular and cellular experiments corroborated this anti-inflammatory effect and provided clues for determining the location of the activity of Uncitolina® extract along molecular pathways in the body. Among the experiments carried out were:

- inhibition of the production of a pro-inflammatory cytokine;

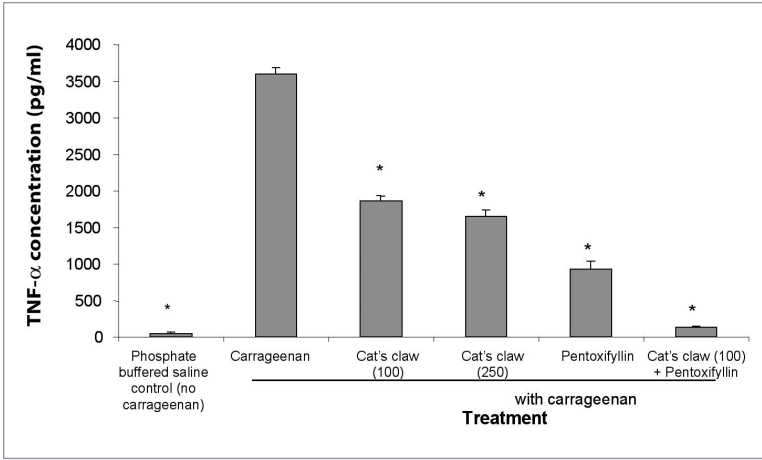
**Table 1** | Anti-inflammatory effect of a hydro-alcoholic and an aqueous cat's claw extract compared to a standard dose of indomethacin (a synthetic non-steroidal anti-inflammatory drug) on mouse paw oedema after 4 hours (means of 8 replicates).

DOSE (MG/KG)	ANTI-INFLAMMATORY ACTIVITY (per cent reduction in swelling)		
	HYDRO-ALCOHOLIC EXTRACT	AQUEOUS EXTRACT	INDOMETHACIN
7	—	—	37.8
50	35.3	21.9	—
100	37.3	23.8	—
200	43.0	33.0	—
500	51.7	26.7	—

- inhibition of the activation of the transcription factor NF- $\kappa$ B in animal Jurkat T cell culture;
- inhibition of the production of tumour necrosis factor alpha (TNF $\alpha$ ) in the air pouch model in mice (fig. 3);
- inhibition of the production of the inflammatory enzyme cyclooxygenase in cell culture; and
- inhibition of the adhesion molecule ICAM-1 expression on human macrophages.

A Phase I clinical study was also performed to evaluate the safety of the extract on human volunteers. In this 8-week study, during which patients received 300 milligrammes of the extract, no side effects were detected. A Phase II clinical study demonstrated a significant

response in 52 patients with acute inflammation, with no side effects when Uncitolina<sup>®</sup> was used at recommended pharmacological doses. At the beginning of the trial, more than 70 per cent of patients had major inflammatory responses that limited joint articulation (Class III of the functional class limitation scores of the American College of Rheumatology, ACR) caused by such ailments as rheumatism, and none were regarded as having mild (Class I) limitation. For the majority of patients, there were clear improvements after both 3 and 6 weeks of treatment. By the sixth week, the number of Class III patients had fallen to 16 per cent, while more than half of the patients were regarded as having only mild symptoms (table 2).



**Figure 3** | Inhibition of the production of tumour necrosis factor alpha (TNFα) by an extract of cat’s claw in the mouse air pouch model, a method for observing an inflammatory response whereby irritants such as carrageenan are injected into subcutaneous pockets of air on the animals’ backs.

**Table 2** | Percentage of patients with different classes of limitation ACR score after treatment with Uncitolina® (Class III = large limitation ACR score, Class I = minor limitation score).

FUNCTIONAL CLASS	TIME OF EVALUATION		
	0 WEEKS	3 WEEKS	6 WEEKS
III	70.5	40.0	16.6
II	29.5	35.0	33.3
I	0	25.0	50.1

**PATENTING AND COMMERCIALIZATION**

Uncitolina®, the alcoholic extract of cat’s claw, is registered by Naturalfa, Quimica Suiza, and is commercially available in Peru.

**PARTNERSHIPS**

The local community participated in the

clinical trials (with previous informed consent). In the longer term, the community should also benefit from being able to produce a scientifically proven, effective product, which should help to guarantee higher prices.

The participation of private companies, in particular Naturalfa, Quimica Suiza, has been — and continues to be — critical in supporting several of the steps that have led to the development of this product.

## REPLICABILITY

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The strategy and methodologies used in this case study can easily be reproduced and applied to other natural products from around the world. The idea is to add value to local resources, thus averting the need to import costly alternative products.

## LESSONS LEARNED

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Initially, the main obstacle to be overcome was the lack of financial support to develop the project. Funds were obtained slowly and with great difficulty. Another obstacle was the problem of introducing a natural botanical extract to health professionals in Peru, who prefer synthetic products.

## IMPACT

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Following these studies, there is now sufficient scientific data to support the incorporation of extracts of cat's claw into therapeutic strategies that can be promoted to medical doctors and prescribed to the general population. The data supporting the clinical use of Uncitolina® will also facilitate the introduction of the use of cat's claw extract into medical school curricula. In addition, the scientific evaluation of cat's claw is allowing non-medical, traditional healers to use their traditional products more effectively and with improved benefits for patients.

## FUTURE PLANS

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Efforts are now under way to obtain funding to carry out a Phase III clinical trial with a large number of patients to demonstrate further the benefits of the cat's claw product.

In addition, there are plans to continue the basic cellular and molecular investigations to elucidate further the mechanisms by which the plant's active ingredients work as anti-inflammatory agents. Preliminary studies have also demonstrated potential anti-cancer properties of cat's claw extracts, and these will also be investigated further, perhaps in collaboration with international partners.

Finally, there is still a great need for local pharmaceutical corporations to take an interest in developing products derived from indigenous plants and indigenous knowledge. The sustainability of such products will depend not only on the marketing of the product but also on how the use of traditional products is taught in both undergraduate and post-graduate medical school programmes. This is true not only in Peru but in many other countries in South America and elsewhere.

## PUBLICATIONS

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## Case study prepared by:

*Jose L. Aguilar*

Head of Immunology Section,  
Department of Microbiology, Faculty of  
Sciences and Philosophy, Universidad  
Peruana Cayetano Heredia, Box 4314,  
Lima 100, Peru

Tel: (+51) 1 319 0000 ext. 2511

E-mail: jaguilar@upch.edu.pe

## Project participants:

*Percy Rojas*: Biologist, associate investigator in the Immunology Section, responsible for the animal experiments.

*Adolfo Marcelo*: Biologist, associate investigator in the Immunology Section, responsible for cellular and molecular studies.

*Patricia Hurtado*: M.D., associate investigator in the Immunology Section, participated in clinical trials.

*Fidel Barrantes*: Medical student, participated in the clinical trials.