# *Uncaria tomentosa* in the Treatment of the Herpes Labialis: Randomized Double-Blind Trial

## *Uncaria tomentosa* no Tratamento de Herpes Labial: Estudo Duplo-Cego Randomizado

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**ABSTRACT**

**Introduction**: the lesions caused by herpes simplex are common and have symptoms affecting the quality of life of affected people. **Objective**: this study aims to assess the safety efficacy of cream with *Uncaria tomentosa* (cat's claw), for topical treatment of the herpes labialis. **Methods**: a clinical investigation was undertaken by means of controlled, randomized, double-blinded protocol in humans. According to the regulatory procedures, 74 patients were selected based on inclusion/exclusion criteria previously submitted to the Local Ethical Committee (nº 144/02) whenever herpes labialis lesion appeared. Following, those selected through medical evaluation received either the test (Uncaria) or the reference (Acyclovir) drug. **Results**: fifty-four episodes of herpes labialis lesions ecloded in 31 volunteers. After their clinical assessment, one showed 4 episodes, two had 3 episodes and six had 2 infections. Hence, 27 patients received the reference drug while 27 applied the Uncaria cream four times a day. Overall, there were not significant differences between either responses. Although, the Uncaria group showed lower scores on the first two days of treatment ($p < 0,005$; $t = 0,028$), on day 3, it was even to Acyclovir. **Conclusion**: the assessment of clinical efficacy of either treatment demonstrated that both drugs were safe as no adverse reactions were reported. Futher, there was no difference ($p > 0,05$) in the overall period infections as well as in the inflammatory process or crost formation. Regarding the severity of inflammatory reaction, the clinical efficacy of *Uncaria tomentosa* was significantly better than acyclovir. Rather than the being antiviral drug, the *Uncaria tomentosa* may act as an anti-inflammatory agent and this would possibly represent an advantage of not inducing viral resistance for long use.

**Keywords**: Uncaria tomentosa; herpes simplex; double-blind clinical trial

**RESUMO**

**Introdução**: as lesões causadas por herpes simples são comuns e apresentam sintomatologia que altera a qualidade de vida das pessoas acometidas. **Objetivo**: este estudo visa avaliar a eficácia da segurança de creme com *Uncaria tomentosa* (unha-de-gato) para o tratamento tópico de herpes labial. **Métodos**: a pesquisa clínica foi realizada por meio de protocolo controlado, randomizado e duplo-cego. De acordo com os procedimentos de regulamentação, 74 pacientes foram selecionados com base em critérios de inclusão e exclusão previamente submetidos à Comissão de Ética Local (nº 144/02), sempre a lesão de herpes labial apareceu. Em seguida, os selecionados através de avaliação médica receberam o produto-teste (*Uncaria*) ou o de referência (aciclovir). **Resultados**: cinquenta e quatro episódios de lesões de herpes labial eclodiram em 31 voluntários. Após a avaliação clínica, um apresentou quatro episódios, dois tiveram três episódios e seis tinham duas infecções. Assim, 27 pacientes receberam a droga de referência, enquanto 27 aplicaram o creme *Uncaria* quatro vezes por dia. Em geral, não houve diferença significativa entre as respostas. Contudo, o grupo de Uncaria apresentou escores inferiores nos dois primeiros dias de tratamento ($p < 0,005$ $t = 0,028$), depois do dia 3, foi similar ao aciclovir. **Conclusão**: a avaliação da eficácia clínica dos tratamentos demonstraram que ambas as drogas foram seguras, bem como não foram notificadas reações adversas. Além disso, não houve diferença significativa ($p > 0,05$) no período total de infecções, bem como no processo inflamatório ou na formação de crosta. Quanto à gravidade da reação inflamatória, a eficácia clínica da *Uncaria tomentosa* foi significativamente melhor do que o aciclovir. Em vez de a droga ser antiviral, a *Uncaria tomentosa* pode atuar como um agente anti-inflamatório e isso, possivelmente, representa uma vantagem de não induzir resistência viral para uso por muito tempo.

**Palavras-chave:** *Uncaria tomentosa*, herpes simples, estudo clínico duplo-cego

## INTRODUCTION

Herpes simplex virus type 1 and type 2 (HSV-1, HSV-2) is a nuclear replicating enveloped DNA virus which transmission is typically through body fluids as well as infected lesions[1]. Primary infection mostly presents as gingivostomatitis and pharyngitis while approximately 90% recurrent HSV-1 and 10% by HSV-2 infections manifest as herpes labialis, with vesiculo-ulcerative lesions at mucocutaneous junction of lip and/or perioral skin[2].

Infection with HSV, besides its high prevalence, has an important psychosocial impact as a result of frequent recurrences. Therefore, further understanding of herpes labialis natural history is worthwhile, in order to enable speedy management of patients, providing early treatment and minimizing clinical manifestations[3,4].

The primary objective of this study was to evaluate the safety and efficacy of a topical drug for treatment of herpes labialis. It is a topical phytotherapeutic compound, based on Uncaria tomentosa, obtained by Herbarium Laboratório Botânico Ltda.

Uncaria tomentosa extract was standardized to 5% of mitrafilina. This herb, known as cat's claw (uña-de-gato, unha-de-gato) – is one of the best known medical herbs from Amazon[5,6]. Its medical properties have largely been used within this area with a significant amount of scientific articles written on its pharmacological potential[7,8]. Among cat's claw assigned pharmacological actions, its anti-inflamatory actions are prominent[6,9-11]. An intense immunomodulation is induced by its alkaloidal fraction: TNF-alpha and IFN-alpha levels are significantly reduced and there is a tendency towards IL-10 modulation[12-15]. Therefore, cat's claw seems to act as an inhibitor of TNF-alpha, a pro-inflammatory cytokine, and as an antioxidan t as it has anti-apoptotic properties as well as enhance DNA repair[14-18].

## OBJECTIVE

The object of the study had a systematic methodological approach, validated through a prospective, comparative, random, double blind study. The used methodology has the same patterns as other published studies about topical products efficacy for herpes labialis

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treatment[1-4], as those defined by Resolução da Agência Nacional de Vigilância Sanitária (ANVISA) RDC nº 17; on April, 24th, 2000[19].

## METHODS

The clinical trial protocol was submitted to the Research Ethics Committee, which analysed and approved it. The protocol was referred to CONEP, which registered and countersigned the local approval.

Seventy four volunteers were included in the study, with a positive history of herpes simplex labialis, according to the previously established criteria for selection. These volunteers were informed about the research's objectives and procedures, signed an informed consent, were evaluated by clinical and laboratorial tests and included in the study by intention to treat herpes simplex labialis relapse episodes, whenever they occurred, informing the Center about these events.

The primary outcomes referred to: I. time for complete resolution (therapy lenght in days); II. time to drying or to start crust formation (in days); III. clinical course and intensity of signs and symptoms (pruritus, tension, pain, swelling, erosion, diameter of largest lesion) at scheduled evaluation visits.

Secondary criteria of evaluation consisted of:

- treatment failure;
- complications (superinfection);
- subjective (volunteers) and objective (clinicians) judgement of overall effectiveness;
- judgement of tolerability.

According to the legislation (RDC 17/00)[19], these volunteers were submitted to a clinical evaluation, consisting of anamnesis and physical examination, 12-lead ECG, and laboratorial exams (complete blood count, glycemia, urea, creatinine, uric acid, triglyceride, total cholesterol, sodium, potassium, CPK, AST, ALT, total bilirubin and fractions, gamma GT, besides urinalysis). The clinical and laboratorial evaluation objective was to select volunteers otherwise healthy with positive history of recurrent herpes simplex labialis.

Whenever the volunteers reported the Research Center about a relapsing outbreak of herpes labialis, they were invited for an appointment with a dermatologist. At that time, they were evaluated, oriented, and randomly assigned, in a double blind way, to receive either the trial drug (Uncaria) or the reference drug (Zovirax®). They also received a notebook to register symptoms and medicine use. The achieved data were recorded on a case registration form (CRF). After this initial assessment, patients were scheduled for two more follow up visits, until complete resolution of the lesions. The obtained data were statistically analyzed.

The medications administered in a double-blind way were provided in identical containers, indentified only by numbers 1 or 2. Their identification codes (as well as their respective manufacturing batches and expiration dates) remained sealed, deposited with a representative from Laboratório Universitário Rodolfo Albino (LURA) at Universidade Federal Fluminense (UFF).

## RESULTS

A total of 54 episodes of herpes labialis in 31 volunteers was evaluated, as some volunteers have presented more than one episode during the study time period. Among the volunteers who were treated more than once, 1 had 4 episodes, 2 had 3 episodes, and 6 volunteers had 2 episodes. New relapses in volunteers previously included were treated with alternating medicines.

Twenty-seven volunteers received drug 1 and twenty-seven received drug 2. The **Table 1** presents the description by gender and age of each group:

**Table 1** – Group description according to gender and age.

| | Group 1 (Drug 1) | Group 2 (Drug 2) |
|---|---|---|
| N (= 54) | 27 | 27 |
| Gender (M/F) | 4/23 | 3/24 |
| Age (± SD) | 28.1 (± 9.5) | 30.6 (± 12.4) |

All volunteers used the assigned drug at least 4 times a day, and were encouraged to record on their notebooks every detail they would consider relevant regarding the use of the medication or clinical course.

When discharged, volunteers were asked if they would use the same medication again, if necessary. They were all positive. Both drugs were, overall, well tolerated, and no adverse events were reported.

Median episode lenght was 8.4 days for drug 1 and 8.1 days for drug 2, according to **Chart 1**. The inflammatory period was 6.7 days and 7 days for groups 1 and 2, respectively. The last stage, when crust formation takes place, was 2.7 and 3 days, for groups 1 and 2, respectively. In summary, there was no significant difference between the analyzed groups.

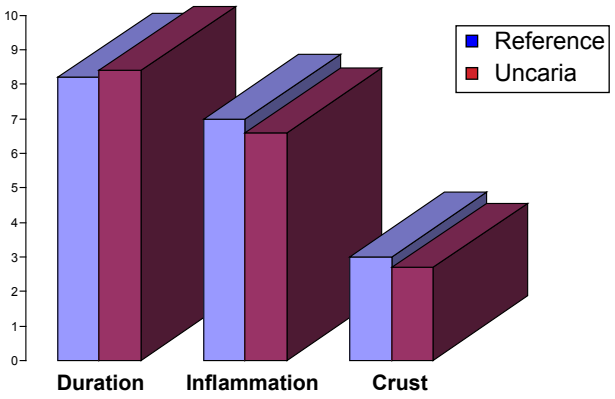


**Chart 1 –** Evaluation of the time, inflammation and crust.

Besides the aesthetic inconvenience, inflammatory signs and symptoms (pain, swelling, erythema) account for patients greatest discomfort. Analyzed altogether, regarding the symptom scores registered by patients reflecting their intensity, Uncaria group (whose marketing name was Imuno-Max®) showed, during clinical course, significantly lower scores on the first two days of treatment ($p < 0.005$; $t = 0.028$), when these symptoms were more intense. From third day on, there was no statistically significant difference (**Chart 2**).

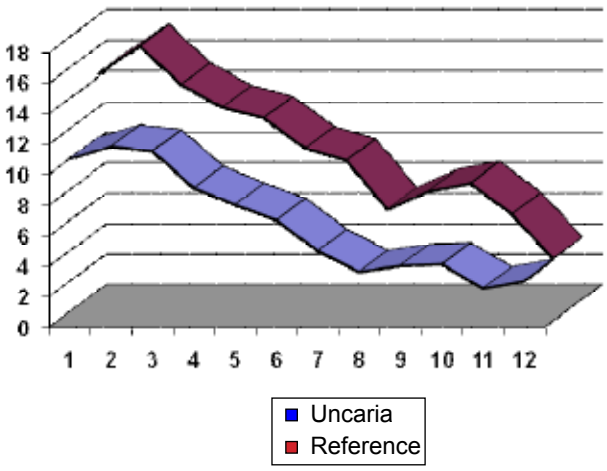


**Chart 2 –** From third day on, there was no statistically significant difference.

## DISCUSSION

Obtained results showed that both drugs used in the study were effective and safe for herpes labialis treatment. There was no statistically significant difference neither in total episode lenght nor in inflammatory or crust formation time course. However, in terms of intensity of inflammatory signs (swelling, erythema) and symptoms (pain) drug 1 efficacy (test, Uncaria – Imuno-Max®) was significantly superior to drug 2 (reference, Zovirax ®), providing more comfort to patients on the first two days of clinical course.

While the reference drug's mechanism of action is based on its antiviral activity, Uncaria tomentosa seems to act mostly as an anti inflammatory agent. In that case, using this drug, with safety and efficacy similar to the reference drug, could be an advantage, as its prolonged use would not drive viral resistance, which many authors have pointed out as a concern.

Considering the safety and clinical response to herpes simplex lesions, that this herbal medicine has, believe it is worth to invest in clinical trials for genital herpes. This is because shortening the symptoms, improves quality of life of patients and may reduce local vulnerability to acquisition of other sexually transmitted diseases including HIV.

## CONCLUSION

The assessment of clinical efficacy of either treatment demonstrated that both drugs were safe as no adverse reactions were reported. Futher, there was no difference ($p > 0,05$) in the overall period infections as well as in the inflammatory process or crust formation. Regarding the severity of inflammatory reaction, the clinical efficacy of Uncaria tomentosa was significantly better than acyclovir. Rather than the being antiviral drug, the Uncaria tomentosa may act as an anti-inflammatory agent and this would possibly represent an advantage of not inducing viral resistance for long use.

### Conflict of interest

This study was sponsored by the Herbaruim Foudation.

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