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Update

Pilot study on the assessment of the effect of fig (Ficus carica L.) latex on cutaneous papillomas

Étude pilote sur l'évaluation de l'effet du latex de figuier (Ficus carica L.) sur les papillomes cutanés

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Abstract:

Introduction: Cutaneous warts are benign epidermal proliferations caused by the Human Papillomavirus (HPV), often requiring invasive or painful treatments such as cryotherapy or surgical excision. *Ficus carica* L. (fig tree) latex, traditionally used for its medicinal properties, has shown potential antiviral and keratolytic effects. This pilot clinical study aimed to evaluate the therapeutic efficacy of crude latex and its main fractions (ficin enzyme and gum), extracted from two fig varieties (*bifera* and *caprifig*), in the treatment of human cutaneous warts. **Materials and methods:** Twenty-four patients from the dermatology unit of a public health facility in Tazmalt (Bejaia, Algeria) were randomly assigned to six treatment groups, without a placebo control. **Results:** The heated crude latex from *caprifig* produced the highest complete regression rate (100%), followed by the gum fraction (83%), whereas the purified ficin fraction showed minimal activity. Treatments were applied topically once daily for six to eight weeks, covering the entire lesion area. The treatment was non-invasive, well tolerated, and demonstrated a remarkably short duration of action, with complete regression observed after only five applications in some patients. **Conclusion:** Despite limitations related to the small sample size and lack of a placebo control, these preliminary findings suggest that heated *caprifig* latex represents a promising, safe, and plant-derived alternative for the management of cutaneous warts. Ethical approval was obtained, and all participants provided written informed consent.

KEYWORDS: latex; *Ficuscarica* L.; cutaneous wart; clinical trial; gum.

Résumé

Introduction: Les verrues cutanées sont des proliférations épidermiques bénignes causées par le papillomavirus humain (HPV), nécessitant souvent des traitements invasifs ou douloureux tels que la cryothérapie ou l'exérèse chirurgicale. Le latex de *Ficus carica* L. (figuier), utilisé traditionnellement pour ses propriétés médicinales, a montré un potentiel antiviral et kératolytique. Cette étude clinique pilote avait pour objectif d'évaluer l'efficacité thérapeutique du latex brut et de ses principales fractions (enzyme ficine et gomme), extraites de deux variétés de figuier (bifère et caprifiguier), dans le traitement des verrues cutanées humaines. **Matériels et méthodes :** Vingt-quatre patients de l'unité de dermatologie d'un établissement public de santé à Tazmalt (Béjaïa, Algérie) ont été répartis de manière aléatoire en six groupes de traitement, sans groupe placebo. **Résultats:** Le latex brut chauffé de caprifiguier a induit le taux de régression complète

le plus élevé (100 %), suivi de la fraction gomme (83 %), tandis que la fraction de ficine purifiée a montré une activité minimale. Les traitements ont été appliqués par voie topique une fois par jour pendant six à huit semaines, en couvrant l'ensemble de la surface lésionnelle. Le traitement s'est révélé non invasif, bien toléré et a présenté une durée d'action remarquablement courte, avec une régression complète observée après seulement cinq applications chez certains patients. **Conclusion:** Malgré des limites liées à la taille réduite de l'échantillon et à l'absence de groupe placebo, ces résultats préliminaires suggèrent que le latex chauffé de caprifiguier constitue une alternative prometteuse, sûre et d'origine végétale pour la prise en charge des verrues cutanées. Une approbation éthique a été obtenue et tous les participants ont fourni un consentement éclairé écrit.

MOTS CLES: latex ; *Ficus carica* L. ; verrue cutanée ; essai clinique ; gomme

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Introduction

Cutaneous papillomas, commonly referred to as warts, are benign epithelial proliferations caused by various types of human papillomavirus (HPV), especially types one, two, and four. These infections affect individuals of all ages and are primarily transmitted through direct skin contact or autoinoculation. While spontaneous regression is possible, many patients seek treatment due to discomfort, cosmetic concerns [01], or persistent lesions. Conventional therapies include cryotherapy, chemical cauterization, and immunotherapy. However, these methods often have limitations, such as pain, scarring, recurrence, or cost. Therefore, there is a growing interest in exploring alternative, natural-based treatments that are effective, accessible, and minimally invasive.

The prevalence of viral warts ranges from seven to 12%. There are more than 200 different varieties of HPV, a double-stranded DNA virus. Given their potential to cause cancer, HPVs can be broadly classified as either low-risk or high-risk. The HPV life cycle is intimately linked to epithelial differentiation and proliferation [02].

The majority of cutaneous HPV infections result in benign proliferative lesions; squamous cell carcinoma and other skin malignancies are uncommon outcomes [03].

The virus infects skin cells called keratinocytes, and if not eliminated by the individual's immune system, it causes them to proliferate. The incubation period varies from one to 21 months, with an average of 4 months. Transmission of the virus occurs through direct or indirect contact [04]. Skin-to-skin or skin-to-mucosa contact is the main way that HPV is spread. Although non-sexual routes have been suggested by several studies, sexual transmission is the most well-documented. Fomites, fingers, mouths, and skin contact (apart from sexual contact) are all examples of horizontal HPV transmission [05].

Appropriate measures for prevention, diagnosis, treatment, and long-time management of cutaneous HPV infection are mandatory for physicians and general practitioners [02].

Current treatments, including chemical and physical methods such as salicylic acid, cryotherapy, silver nitrate, phenol, cantharidin, glycolic acid, pyruvic acid, citric acid, formic acid, trichloroacetic acid, monochloroacetic acid, zinc, laser, surgery and electrocautery, they areoften involve pain and the risk of recurrence[06].

Ficus carica L., or the common fig tree, is a member of the Moraceae family renowned for its medicinal properties [07]. Its latex is composed of enzymes, polysaccharides, alkaloids, phenols, tannins and other organic compounds, it has medicinal properties. It exhibits anti-inflammatory, antibacterial, antioxidant and wound healing characteristics, making it useful in various medical and dermatological applications [08].

Topically, fig latex is often used to treat skin problems such as burns, rashes, insect bites, and wounds. It can reduce inflammation, relieve pain, and promote healing of damaged tissues. In addition, it has antiparasitic and insect repellent properties, making it a remedy for parasitic infections, including infections caused by intestinal worms [09-10]. In particular, it has been traditionally employed during fruit picking for the treatment of skin tumors and warts [11-08].The primary active compound, ficinor ficain (EC 3.4.22.3), is the cysteine protease with keratolytic properties [12-08].

Studies have shown that *Ficus carica* latex inhibits DNA synthesis in cancer cells, causing their apoptosis and preventing their proliferation [13]. A potent cytotoxic compound called 6-O-acyl-β-D-glucosyl-β-sitosterol complex has been isolated from fig latex. In vitro, this agent exhibits inhibitory effects on the proliferation of various cancer cells, as well as inhibition of 3H-benzo α-pyrene, a carcinogenic chemical [14].

It should be noted that an allergic reaction to fig latex may occur in some people [15]. Therefore, it is recommended to perform a skin test before prolonged use to avoid any risk of allergy.

Latex derived from fig tree *Ficus carica* L. has been traditionally used in folk medicine. Nevertheless, scientific evidence supporting its clinical efficacy against cutaneous warts remains limited. This study aims to assess the therapeutic potential of crude latex and its purified fractions from both male (caprifig) and female (bifera) fig trees in treating human papillomas through a pilot randomized topical intervention trial.

Material and methods

Study Design and Ethical Approval

This pilot clinical study was conducted between March and July 2023 at the University of Bouira (Algeria), Department of Agricultural Sciences, in collaboration with the dermatology unit of a public health facility in Tazmalt (Bejaia, Algeria). The study protocol was reviewed and approved by the Institutional Ethics Committee (Approval No. 23-ETH/2023), and written informed consent was obtained from all participants before enrollment.

Patient Selection and Allocation

Twenty-four adult patients (aged 18–60 years) diagnosed with common cutaneous warts (non-genital, non-facial) persisting for at least two months were recruited. Exclusion criteria included immune suppression, pregnancy, lactation, recent wart treatment (within the last three months), chronic dermatological disorders, or known latex allergy.
Participants were randomly assigned to six treatment groups (n = 4 per group) using a computer-generated randomization list :

- **G1:** Fresh *caprifig* latex
- **G2:** Heated *caprifig* latex
- **G3:** *Caprifig* gum fraction (supernatant)
- **G4:** *Caprifig* ficin fraction (precipitate)
- **G5:** Heated *bifera* latex
- **G6:** Control (no treatment)

Blinding was maintained for both participants and clinical evaluators during the treatment and assessment phases.

Latex Collection and Preparation

Latex, a milky exudate from *Ficus carica* L., was collected early in the morning from immature fruits, young stems, and leaves by making shallow incisions. Samples were obtained from two fig varieties traditionally used in local medicine: the male *caprifig* ("Adokkar") and the female *bifera* ("Abbakor"), collected from three regions of Bouira Province (Aghbalou, Chorfa, Bouira).
Fresh latex was collected in sterile vials and immediately centrifuged at 3200 rpm for 15 min at 4 °C to obtain two fractions (figure 1).:

- the **supernatant** (gum fraction), and
- the **precipitate** (ficin enzyme fraction).

For the *heated latex* preparation, crude *caprifig* latex was briefly exposed to microwave heating (5 seconds) to test the effect of thermal activation

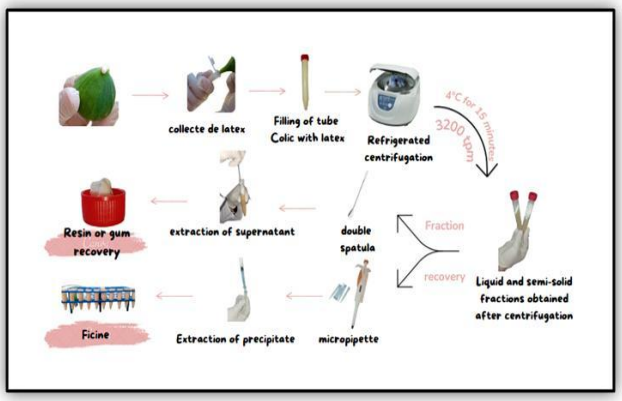


Figure 1: The diagram showing the steps followed for recovering latex and its fractions

Treatment Protocol

Each treatment was applied topically twice daily for 6–8 weeks. Approximately 0.2 mL of the assigned preparation was applied directly to each lesion using a sterile cotton swab, covering the entire wart surface. The treated area was left uncovered to dry naturally.
Patients received clear written and verbal instructions regarding proper application, hand hygiene, and monitoring for local reactions. They were asked to

avoid other topical or systemic wart treatments during the study period.

Clinical Assessment and Monitoring

Participants attended weekly follow-up visits for clinical evaluation and documentation. At each visit:

- Lesion size (mm) was measured with a digital caliper,
- Number, color, and texture of warts were recorded,
- Photographs were taken for comparative evaluation,
- Adverse effects were systematically reported and recorded.

Treatment adherence was verified at each visit through direct questioning and inspection of remaining samples.

Outcome Measures

Treatment response was categorized as follows:

- **Complete regression:** total disappearance of the wart and normalization of the skin surface,
- **Partial regression:** ≥ 50 % reduction in lesion size,
- **Stationary:** < 50 % reduction or no visible change.

Statistical Analysis

Data were analyzed using SPSS software version 26.0. Results were expressed as percentages (%) of complete, partial, or stationary regression within each treatment group. Categorical data were compared across groups using the Chi-square test or Fisher's exact test when appropriate. A p-value < 0.05 was considered statistically significant.

Safety and Patient Withdrawal

Patients were closely monitored throughout the treatment period for any adverse events. No participants withdrew from the study. Mild, transient local irritation occurred in two subjects and resolved spontaneously without discontinuation of treatment.

Results

The therapeutic response varied across treatment groups. Complete regression was observed in all patients in Group two (heated caprifig latex), demonstrating a 100% clearance rate. Group 3 (caprifig gum) showed an 83% complete regression rate, with the remaining case showing partial regression. Group one (fresh caprifig latex) exhibited a 50% complete and 50% partial regression rate. Group four (caprifig ficin) demonstrated minimal activity, with only one case of partial regression and the rest stationary. Group five (heated bifera latex) showed moderate efficacy, with 50% complete and 50% partial regressions. No changes were observed in the control group (figure 2).

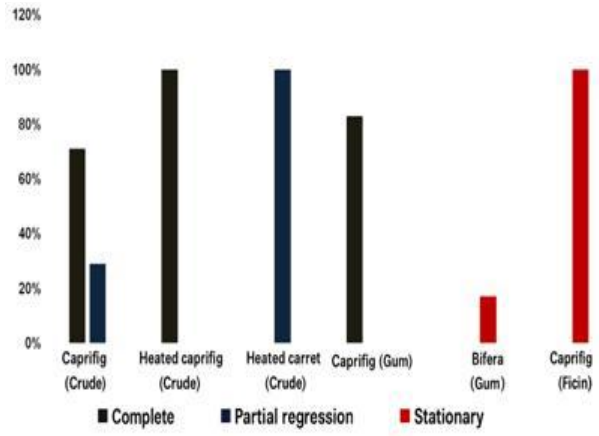
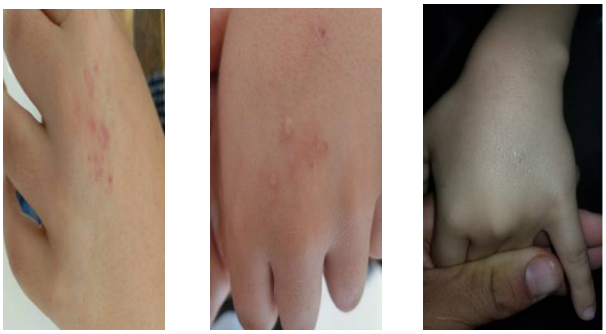


Figure 2: Results of the 06 treatment groups with latex of Ficuscarica

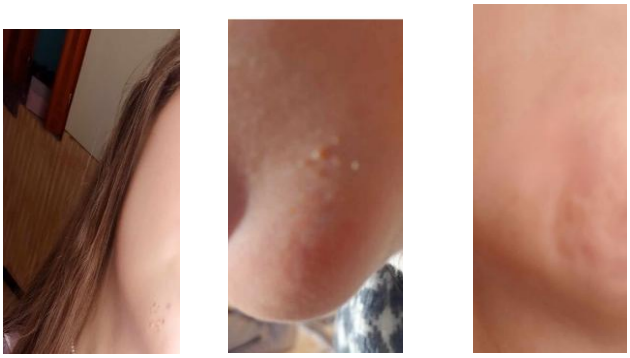
Statistical analysis revealed significant differences between treatment and control groups ($p < 0.05$), particularly in Groups two and three, confirming the efficacy of heat-treated latex and latex gum (figure 3).

The superior efficacy of heated caprifig latex may be attributed to thermal modification of active compounds, possibly enhancing their bioavailability or activity. The gum fraction retained strong therapeutic properties, likely due to enrichment in polyphenols and other non-enzymatic components. Interestingly, the ficin fraction alone showed limited activity, suggesting that other constituents in the latex matrix contribute significantly to wart resolution.

Caprifig Latex: complete regression of flat wart



Caprifig Gum: complete regression of flat wart



Heated Crude Caprifig Latex: complete regression of common wart

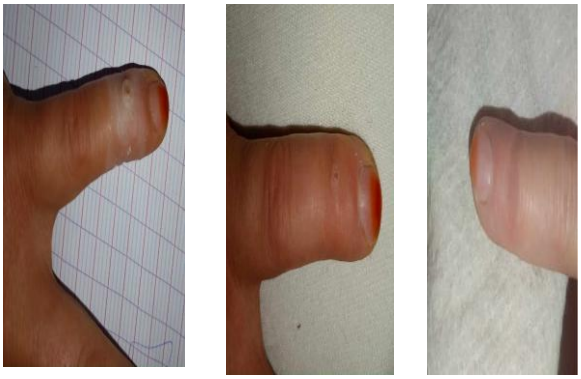


Figure 3: Photographs of patients subjected to treatment with Ficuscarica latex

Discussion

The limited activity of the ficin fraction indicates that ficin alone is not sufficient to induce wart regression. This finding suggests that a synergistic interaction among latex constituents, rather than a single enzymatic mechanism, contributes to the observed efficacy. These results align with prior reports describing the multifactorial bioactivity of *Ficus carica* latex, involving both proteolytic and phenolic pathways **[16].**

This study highlights the potential of *Ficuscarica* latex, particularly heated crude caprifig latex, as a treatment for cutaneous warts. The heated latex led to complete regression in all patients, while caprifig gum also showed significant efficacy. However, the ficin fraction exhibited no therapeutic effect. The exact mechanisms behind the efficacy of the gum and heated latex remain unclear, but they could involve proteolytic and antiviral actions. The gum appears to contain bioactive compounds that contribute to wart regression, while heating the crude latex may enhance the activity of these compounds. The overall lack of side effects among the participants further underscores the potential of *Ficuscarica* latex as a non-invasive treatment option.

Compared to conventional non-surgical therapies—such as salicylic acid (48–87%)**,** topical 5-fluorouracil (47–68%)**,** intralesional interferon (36–63%), or imiquimod (37–57%), the overall efficacy rate (62%) observed with heated *caprifig* latex and gum is within the same range or superior. Additionally, the short treatment duration in this study (complete clearance after five applications of heated latex or 16 applications of gum, corresponding to 3–8 days) represents a clear advantage over standard treatments, which generally require two weeks or more **[17].**

Other advantages after the use of latex were observed: The duration of application required which was three days after five applications of heated caprifig latex and eight days after 16 applications of caprifig latex gum in this study, be lower than two weeks which is the duration of treatment required for the majority of other treatments **[17]**. Importantly, no adverse effects or complications were reported, except for mild transient irritation in two participants. This contrasts with invasive modalities such as laser therapy or cryotherapy, often associated with pain, bleeding, or scarring **[18].**

Although ficin has known proteolytic and keratolytic activity, its limited efficacy here suggests that additional non-enzymatic compounds : such as polyphenols or polysaccharides, contribute to the antiviral or immunomodulatory effects. Heating may facilitate the release or structural modification of these molecules, enhancing their bioavailability and activity. Further biochemical and molecular characterization of the latex components is needed to elucidate these mechanisms. Additionally, larger-scale clinical trials are needed to confirm the results and explore the latex's effectiveness against other types of warts.

This study has several limitations that must be acknowledged:

1. **Small sample size (n = 24):** As a pilot trial, the findings cannot be generalized. A larger clinical study is currently being designed to confirm these results.
2. **Absence of a placebo or vehicle control:** The present study was exploratory, focusing

on comparisons among latex fractions. Future studies will include a placebo or vehicle group to rule out non-specific effects.

3. **Short follow-up period:** The present evaluation covered 6–8 weeks; recurrence beyond this period was not assessed. Future trials should include 6–12 months follow-up to evaluate relapse rate.
4. **Unclear mechanism of action:** While plausible biochemical hypotheses have been proposed, further in vitro and analytical studies are necessary to identify the active compounds and define their specific antiviral and keratolytic pathways.

Conclusion

This pilot study provides promising preliminary evidence that heated *Ficus carica* (caprifig) latex is an effective, safe, and natural topical therapy for cutaneous warts. The results support the traditional medicinal use of fig latex and highlight the importance of thermal processing in enhancing its therapeutic potential. Future research should aim to:

- isolate and characterize the bioactive molecules responsible for efficacy,
- verify reproducibility in larger randomized controlled trials**,** and
- evaluate long-term recurrence rates and mechanistic pathways**.**

These findings position *Ficus carica* latex as a low-cost, non-invasive alternative in the management of human cutaneous papillomas, deserving of further clinical and pharmacological exploration.

Conflicts of interest

"The authors declare that they have no competing interests".

Acknowledgement

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