Original Research Article

Successful treatment of recalcitrant non-genital warts (*Verruca vulgaris*) with a topical solution containing two antivirals and low concentration of salicylic acid

ABSTRACT

Aims: Commercial formulas to treat warts use salicylic acid concentrations above 100mg/mL causing skin irritation and results are often unsatisfactory. In order to solve this problem, we designed a new formula with low concentration of salicylic acid (20mg/mL) and with the addition of virucidal compounds (metallic iodine and benzoic acid) and compared it with a current formula sold in the market (Verrux®) which contains salicylic acid 165mg (0.165g) and lactic acid 145.2 mg (0.145g) per ml of collodion.
Study design: double blind randomized study was performed.
Place and Duration of Study: Department of Biotechonology, UNINCOR, Chácara das Rosas, Três Corações, MG, Brazil; School of Pharmacy, Universidade Federal do Amapá - Campus Universitário Marco Zero do Equador, Rod. Juscelino Kubitschek, KM-02, Jardim Marco Zero, Macapá, AP, Brazil and School of Medicine, Universidad Politécnica y Artística del Paraguay (UPAP), Km 10, Ciudad del Este, Paraguay, between December 2004 and October 2016.
Methodology: 95 patients underwent treatment using the formula with salicylic acid (20mg), benzoic acid (20mg) and metallic iodine (2.5mg) per ml (group A) and 95 received treatment of Verrux® (salicylic acid 165mg, lactic acid 145.2mg per ml of collodion) (group B).
Results: All patients of the group A (100%) reported a complete regression of signs and symptoms after 13 weeks of treatment. On the other hand, 67 subjects (70.5%) of the group B reported regression of symptoms in the same period.
Conclusion: There was statistically significant difference between the groups ($P < 0.05$). This new formulation, with low salicylic acid and two virucidal compounds, promotes healing of recalcitrant cutaneous warts with no significant side effects.

Keywords: warts (non-genital), viral infection, human papilloma virus (HPV), benzoic acid, metallic iodine, salicylic acid, skin cancer, Verruca vulgaris.

1. INTRODUCTION

Common wart (Verruca vulgaris) is an infection in the top layer of skin caused by the human papilloma virus (HPV) and it is also characterized by a cauliflower-like papules with a rough, papillomatous and hyperkeratotic surface ranging in size from 1 mm to 2 cm. It is observed equally in both sexes and nearly all races (twice as common in Whites as in Blacks or Asians) and it may appear at any age but commonly occur in children and young adults. The

World Health Organization (WHO) estimates that the prevalence of HPV infection is between nine and thirteen percent or about 630 million [1].
Verruca vulgaris has more than 100 strains (types 2, 4, are the most common, followed by types 1, 3, 27, 29, and 57; HPV types 5, 8, 20, and 47 have oncogenic potential leading to epidermodysplasia verruciformis). Cutaneous HPV are associated with the development of non-melanoma skin cancer, especially in patients with HIV [2 – 6].
Diagnosis of cutaneous wart is by examination.
Several treatments are available for warts management. Some of them include: silver nitrate, duct tape, cryotherapy, mono-chloroacetic acid, podophyllin, cantharidin, and 5-fluorouracil, topical salicylic acid and lactic acid [7 – 16].
In general, none of these treatments mentioned above promotes a cure without patient complaints (besides some have low efficacy). For this reason, there is a continuing need for new treatments for warts that should preferably be: easy to manufacture, inexpensive, stable in storage, effective and should work as quickly as possible after application, allowing warts to be eradicated in a short amount of time. In addition, it should preferably be easy to apply without the help of medical experts, non-toxic and not associated with discomfort for the patient, that is, it should not have a repulsive smell or be painful for the patient during or after administration. Some patients complain that acid-based treatments for topical warts are ineffective, take several weeks to work, are smelly, and can be painful to apply.
A safe and effective treatment, with low side effects, for cutaneous warts is still lacking. Despite the introduction of different treatments, salicylic acid is the most used ingredient. This organic acid has several side effects such as irritation, itching, hives, tingling or stinging. In general, those effects are tolerable until the end of treatment (13 to 15 weeks).
Until then, there was no substance (or mixture of substances) that could promote real healing and total reversal of signs, quickly and safely; which is now presented in this article.
In order to promote the regression of the signs and symptoms of cutaneous wart, a formulation with benzoic acid (20mg), salicylic acid (20mg) and metallic iodine (2.5mg) per ml was developed. This formulation is based on information accumulated by the medical literature which reports that pure benzoic acid (and its derivatives) and metallic iodine have antiviral properties (17 – 20). The potential mechanisms of benzoic acid can be related to the viral envelop being degraded, since its integrity is indispensable for accomplishing the cellular infection (21). Salicylic acid at a concentration of 5% is marketed for desquamating corns and cornified synthetic skin (22). Some techniques disclose methods to lessen their irritating properties by combining with ascorbic acid (23) and pantothenic acid (24). Based on these techniques, a combination of salicylic acid, at the lowest possible concentration (1.9%), and two antivirals (iodine and benzoic acid) was performed for maximum effective viral action, in order to avoid the irritating properties of salicylic acid. Due to the low doses of salicylic acid present in this formula, the associated side effects are lesser than other formulations currently used in clinical medicine.
The aim of this study was to investigate if this new combination containing: benzoic acid, salicylic acid and iodine would help patients with recalcitrant cutaneous warts, and compare with a preparation with salicylic acid commercially available (Verrux®).

2. MATERIAL AND METHODS

2.1 Use of organic acids and metallic iodine

Chemical compounds were obtained from Galena (Campinas, SP, Brazil). The manipulation was made by a trained pharmacist. Both formulations were inserted into identical capsules to ensure double-blind study. A set, containing 150ml, was used to treat one patient for 13 weeks (topical application twice a day). The composition was applied on a wart as a drop, with a cotton stick or a dropper. Patients received 90 days of medication supply. A total of

190 sets were prepared for use by 190 patients. Patient compliance was checked at each consultation. The starting date of the therapy was recorded for each patient. Pictures of some patients were taken. Symptoms and signs were recorded in a diary and changes in severity of signals noted.

2.2 Patients and inclusion criteria

Male and female patients who had cutaneous warts were eligible for inclusion.
Patients in the age range between 12 and 65 years were enrolled into this prospective, randomized, parallel-group comparative, double blind, multi-center study between December 2004 and October 2016. They were randomly divided into two groups (A and B). Group A with 95 patients was given the formulation containing [benzoic acid 20mg, salicylic acid 20mg and metallic iodine 2.5mg per ml] and Group B with 95 patients had Verrux® (salicylic acid 165mg, lactic acid 145.2mg per ml of collodion) daily for 13 weeks. Patients were followed up every 4 weeks, till 13 weeks.

2.3 Exclusion criteria

Exclusion criteria were seborrheic keratoses, plane or anogenital warts, immune compromised patients, pregnant, or lactating women.

2.4 University Ethics Committee

The data were evaluated and approved by Universidade Vale do Rio Verde (UNINCOR – Três Corações – MG - Brazil) Ethics Committee in November 2005 and by Universidad Politécnica y Artística del Paraguay (UPAP) Ethics Committee in November 2018. The study was conducted in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki.
The authors declare that “written informed consent form” was obtained from the enrolled patients (or other approved parties) for publication of this study and accompanying images. In order to protect intellectual property, a patent was registered (BR 10 2022/008401-7).

2.5 Statistical analysis

The results of treatment were evaluated with per-protocol (PP) analysis (which included only patients who completed the study) and intention-to-treat (ITT) analysis (which included also patients who did not complete the study). The demographic and clinical characteristics of the two groups (A and B) were compared by Chi-square test or Fisher’s exact test. The results of treatment were compared by Chi-square test. $P < 0.05$ was considered statistically significant.

2.6 Randomization

Patients who qualified were randomized: 95 patients received the formulation containing benzoic acid 20mg, salicylic acid 20mg and metallic iodine 2.5mg per ml (Group A) had daily for 13 weeks and Group B with 95 patients received Verrux® (salicylic acid 165mg, lactic acid 145.2mg per ml of collodion) daily for 13 weeks (group B). It was recommended topical application twice a day. No other medication was allowed during the treatment.

2.7 Symptom severity

Assessment of the patients was done using acceptable physician assessment scale every 4 weeks till 13 weeks. Safety and tolerability were evaluated by recording adverse events for both groups.

3. RESULTS AND DISCUSSION

3.1 RESULTS

A total of 190 patients with cutaneous warts entered the surveillance program between December 2005 and December 2016. Mean age at enrollment was 31 ± 14 yr, with a range from 12 to 65 yr; 52.10% were women. The number of patients recruited per year increased over the course of the study as the practice grew; the median year of enrollment was 2009. In terms of geographical area, the subjects are from 9 different cities and towns from 4 Brazilian states and 1 city of Paraguay: 85 patients (44.74%) are from São Paulo, 68 (35.8%) from Minas Gerais, 20 (10.52%) from Paraná, 9 (4.74%) from Espírito Santo, 4 (2.1%) from Amapá and 4 (2.1%) from Paraguay. Some of them are separated one another about of 2,864 km. In terms of social class: 15 patients (7.9%) are rich, 72 (37.9%) are from middle class and 103 (54.2%) are poor. In terms of education: 124 (35.32%) have university degree [from these, 2 (1.05%) are university professors and scientists, 7 have university education (3.7%), 116 (61.05%) have high school, 63 (33.15%) have incomplete high school and 2 (1.05%) re illiterate.

The subjects were divided in two groups: it was allowed to 95 patients use the formulation with benzoic acid 20mg, salicylic acid 20mg and metallic iodine 2.5mg per ml described in this paper, during 13 weeks without using any other medication (group A) and, for comparison, the other half (95 volunteers) used salicylic acid 165mg, lactic acid 145.2mg per ml of collodion (group B). So, there were significant differences in eradication rates between the two groups ($P<0.05$). The demographic and clinical characteristics of the 190 subjects in the two groups are shown in Table 1.

After finishing the 13 weeks of treatment, total regression of the symptoms (markedly improved) was observed in 100% of the subjects of the group A. They reported relief of the symptoms after 9 to 12 weeks using the formulation. These results indicate that warts can be regressed with organic acids and iodine of the formulation presented in this paper. Completed questionnaires about the adverse events and compliance were obtained from all the 190 patients. A total of 67 patients of group B (70.5%) reported total regression of the signs and symptoms (markedly improved) after 10 – 13 weeks of treatment and the remainder continued to feel all symptoms described 90 days before starting the treatment.

Three patients (3.15%) of group B withdrew from the study because of burning sensation and irritation of skin.

In terms of regression of all symptoms, there was a statistically significant difference between groups A and B: the active healing rate was 100% (95/95) in group A (subjects who used the formulation with benzoic acid, salicylic acid and iodine), and 65.7% (67/95) in group B (subjects who used salicylic acid and lactic acid) ($P < 0.05$) (see Table 2).

3.2 DISCUSSION

Probably, the regression and healing of cutaneous warts signs and symptoms was based on the following facts: the first compound of this formula is benzoic acid which has antiviral properties (25) including its derivatives (17, 18). Pure benzoic acid is a common preservative for foods and beverages and is an efficacious acidifier for weaned piglets and fattening pigs (20, 26).

The second compound is iodine, an active and powerfully-virucidal agent (19, 27), used for more than 150 years for the prevention of infection and for the treatment of wounds, exists as a complex mixture of many species (e.g. I_2, I^-, I_3^-, IO^-, IO_3^-) at equilibrium in water.

Our previous results (data not shown) the use of iodine in combination with pure benzoic acid has been shown to reduce the amount of pure benzoic acid needed for virucidal effect, indicating that there is a synergistic effect when combining pure benzoic acid and iodine.

Most likely, virucidals, such as benzoic acid and iodine, damage the virion protein capsid or supercapsidal membrane, or penetrate into the virion destroying the viral genome. The viral particle integrity could also be affected (28).

The third compound, salicylic acid, has been used for more than 2,000 years to treat various skin disorders. Salicylic acid is keratolytic agent (22).

Keratolytics (or desquamating) agents are compounds that break down the outer layers of the skin and can decrease the thickness of psoriatic plaques. This class of compounds includes salicylic acid (2%–10%), urea (20%–40%), and alpha-hydroxy acids (glycolic and lactic acids) (22).

Salicylic acid is destructive to tissue at concentrations above 6%. Concentrations of 6%-60% are used to remove corns and warts (29, 30). Concentrations of 15% - 17% is commercially available for treating warts. Side effects of salicylic acid include: redness and crusting of the skin; if the product is absorbed, diarrhea may occur; psychic disturbances; nausea; hearing loss; accelerated breathing; somnolence; dizziness; vomiting; tinnitus (31-33).

In our formulation we lowered the concentration of salicylic acid around 2% in order to maintain minimal keratolytics properties and avoid side effects. In other words, we use salicylic acid in order to desquamate the skin which allowed for enhanced penetration of benzoic acid and iodine, facilitating the virucidal action.

The Verrux® formula contains two keratolytics (or desquamating) agents : salicylic acid (approximately 14%) and lactic acid (approximately 12.5%).

Although salicylic (34, 35) and lactic (36) acids have known virucidal action, the results of this article demonstrate that this action is inferior to iodine and benzoic acid.

Fig. 1 shows photographs of the leg and hands of a patient (of the group A), with cutaneous warts, who used the formulation with benzoic acid, salicylic acid and metallic iodine, in two different time periods. This patient tried several other treatments: first, salicylic acid and lactic acid and lately, cryotherapy with liquid nitrogen with no success. This patient was 12 years old and was traumatized because the side effects of previous treatment (mainly intense pain caused by liquid nitrogen). After 13 weeks of treatment using benzoic acid, iodine and salicylic acid, the warts were completely removed and skin was healthy again (Fig. 1B) and no side effects were observed.

Fig. 2 shows photographs of the left hand of a patient (of the group A), with cutaneous warts, who used the formulation with benzoic acid, salicylic acid and iodine, in two different time periods. This patient used no medication before. The warts were removed after 12 weeks of treatment using benzoic acid, salicylic acid and iodine. No side effect was observed. Previously, this patient had used Duofilm®, Duofort®, Verrux®, sulfuric acid and nitric acid. All of them were not successful. Two months had passed since the last treatment.

Table 1. Physical, chemical and biological properties of experimental soil (0-20 cm)

Table 1. Baseline characteristics of patients enrolled in the current study

	Group A	Group B

	(n=95)	(n=95)
Gender (M / F)	45 / 50	46 / 49
Age (yr) (S.D.)	30 ± 13	32 ± 14
Previous medication for warts	52 (54.7%)	23 (24.21%)

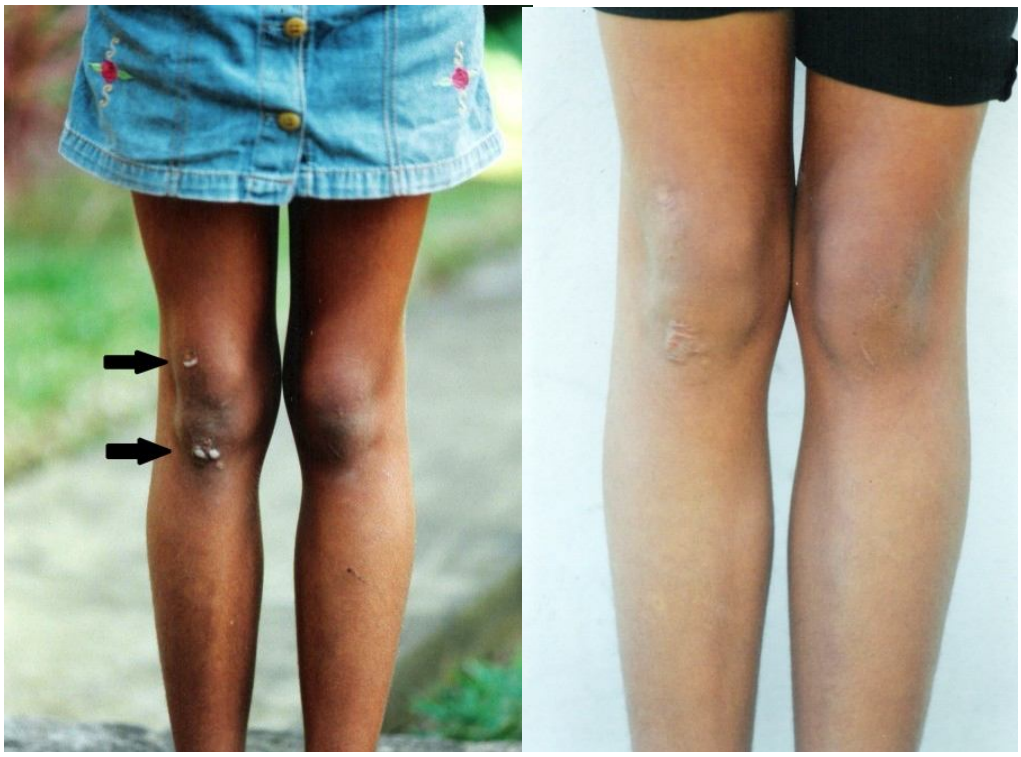
Table 2. Healing rates of patients in the two treatment groups

	Group A (n=95)	Group B (n=95)	*P*	X^2
PP analysis (%)	95/95 (100%)	67/92 (72.8%)	$5e^{-8}$	29.79
ITT analysis (%)	95/95 (100%)	67/95 (70.5%)	$8e^{-8}$	28.78

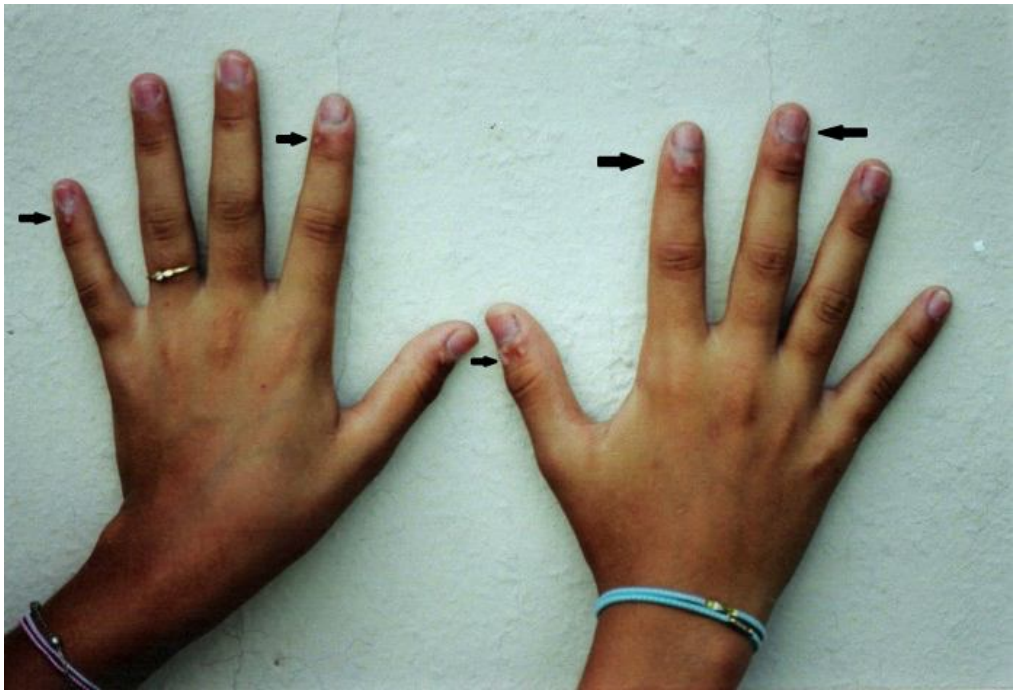
Table 3. Adverse events during the treatments used in the current report

	Group A (n=95)	Group B (n=95)
Blistering	1 (1.05%)	33 (33.7%)
Burning sensation	4 (4.21%)	21 (22.1%)
Dryness	86 (90.52%)	89 (93.7%)
Erythema	4 (4.21%)	12 (12.6%)
Itching	1 (1.05%)	6 (6.13%)
Pain	0 (0%)	7 (7.36%)
Peeling	88 (92.63%)	92 (96.84%)
Scarring	0 (0%)	2 (2.10%)
Skin infection	0 (0%)	0 (0%)
Skin irritation	7 (7.36%)	8 (8.4%)
Skin pigmentation	0 (0%)	4 (4.2%)

A **B**



A



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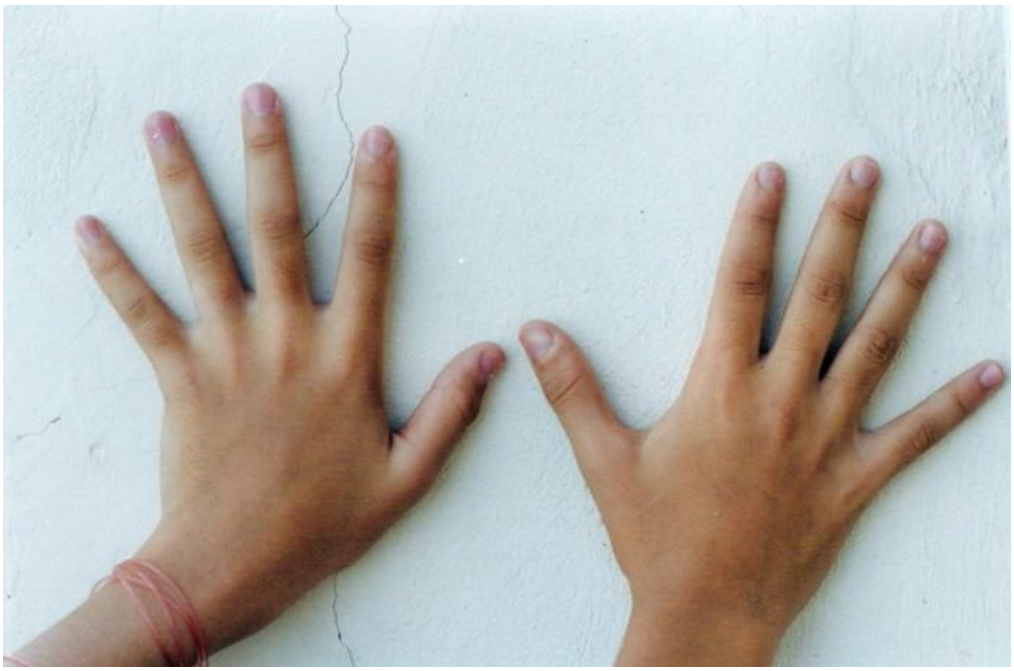
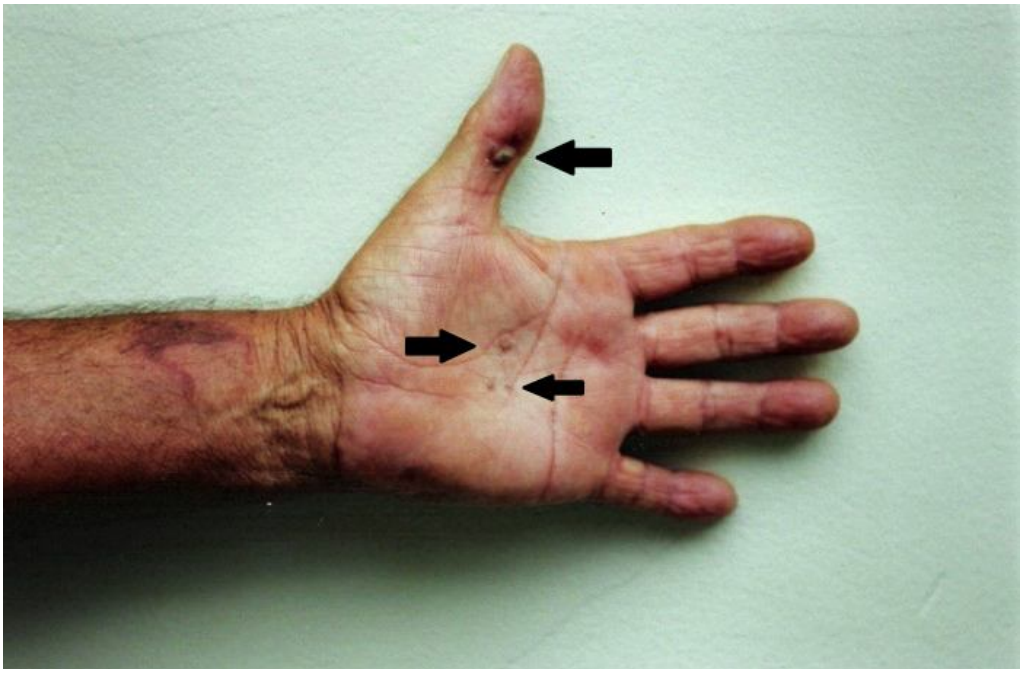


Fig. 1. Photographs of the leg and hands of a patient (of the group A), with cutaneous warts, who used the formulation with benzoic acid, salicylic acid and metallic iodine, in two different time periods:

(A) December 7, 2005: during the period of the warts (indicated by the arrows). Patient consulted a dermatologist who used cryotherapy (with liquid nitrogen) and nothing was resolved. Conventional treatment was suspended and, after 4 weeks, she started treatment with the formulation above described;

(B) March 8, 2006: after 13 weeks of treatment with benzoic acid, salicylic acid and metallic iodine. The scar that appears on the leg (photo 2) was due to previous treatment with liquid nitrogen.

A



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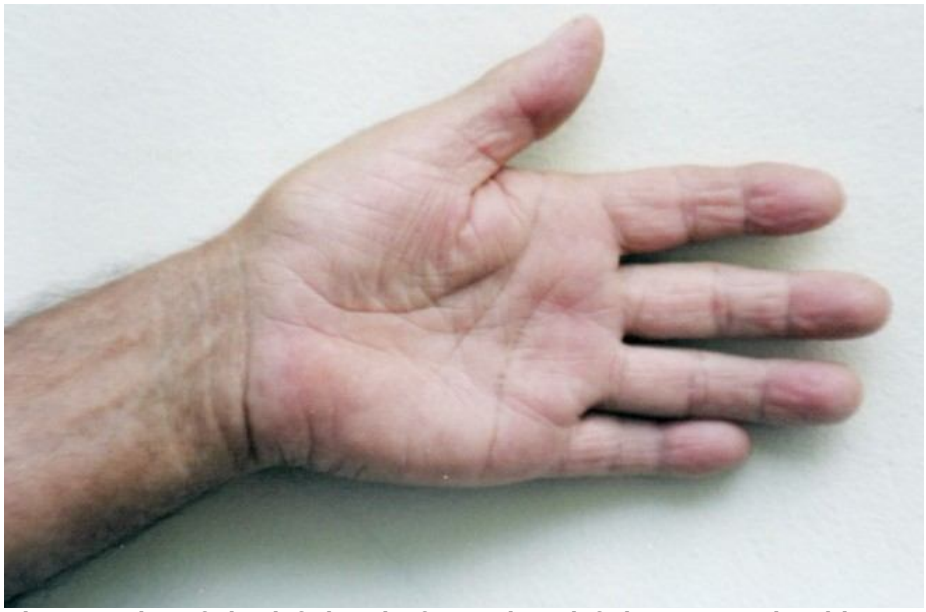

Fig. 2. Photographs of the left hand of a patient (of the group A), with cutaneous warts, who used the formulation with benzoic acid, salicylic acid and metallic iodine, in two different time periods:

(A) January 8, 2006: during the period of the warts (indicated by the arrows);

(B) April 2, 2007: after 12 weeks of treatment with benzoic acid, salicylic acid and metallic iodine.

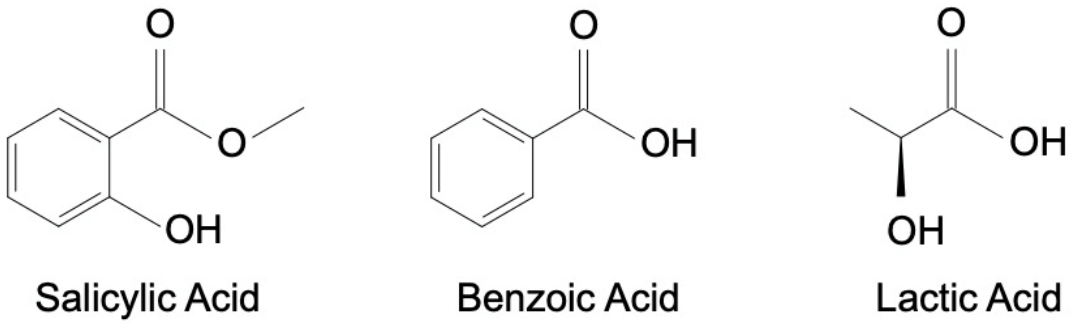

Fig. 3. Chemical structure of organic acids used in this study.

4. CONCLUSION

The results shown in this paper are highly significant, because the patients, who used the formulation with benzoic acid, salicylic acid and iodine reported fewer side effects than patients of group B. The formulation is cheap and reliable.

CONSENT AND UNIVERSITY ETHICS COMMITTEE

The data were evaluated and approved by Universidade Vale do Rio Verde (UNINCOR – Três Corações – MG - Brazil) Ethics Committee in November 2005 and by Universidad Politécnica y Artística del Paraguay (UPAP) Ethics Committee in November 2018. The study was conducted in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki.

The authors declare that “written informed consent form” was obtained from the enrolled patients (or other approved parties) for publication of this study and accompanying images. In order to protect intellectual property, a patent was registered (BR 10 2022/008401-7).

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