

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

5
6 **ABSTRACT**

Aims:

Commercial formulas for the treatment of warts use salicylic acid in concentrations above 100 mg/ml, which causes skin irritation, and the results are often unsatisfactory. To address this problem, we developed a new formula with a low concentration of salicylic acid (20 mg/ml) and with the addition of virucidal compounds (metallic iodine and benzoic acid) and compared it to a formula currently on the market (Verrux®) containing 165 mg salicylic acid (0.165 g) and 145.2 mg lactic acid (0.145 g) per ml collodion.

Study design: a randomized double-blind study was conducted.

Location and Duration of Study: Department of Biotechnology, 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 were treated with the formula with salicylic acid (20mg), benzoic acid (20mg) and metallic iodine (2.5mg) per ml (group A) and 95 received treatment with Verrux® (salicylic acid 165mg, lactic acid 145.2mg per ml collodion) (group B).

Results: All patients in Group A (100%) reported complete resolution of signs and symptoms after 13 weeks of treatment. In contrast, 67 subjects (70.5%) in group B reported regression of symptoms during the same period.

Conclusion:

There was a statistically significant difference between the groups studied here ($P < 0.05$). This new formulation with a low level of salicylic acid and two virucidal agents promotes healing of recalcitrant cutaneous warts without significant side effects. The price of the two formulas is virtually the same (about \$8 to \$10 each bottle).

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

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10 **1. INTRODUCTION**

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12 Common wart (*Verruca vulgaris*) is an infection of the uppermost layer of the skin caused by the human papillomavirus (HPV) and characterized by cauliflower-like papules with a rough, papillomatous and hyperkeratotic surface, ranging in size from 1 mm to 2 cm. It is seen equally in both sexes and almost all races (twice as common in whites as in blacks or Asians) and can occur at any age, but is most common 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].

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17 There are more than 100 strains for *Verruca vulgaris* (types 2 and 4 are most common, followed by types 1, 3, 27, 29, and 57; HPV types 5, 8, 20, and 47 have the potential to cause the development of a tumor or tumors leading to epidermodysplasia verruciformis). Cutaneous HPV have been associated with the development of non-melanoma skin cancer, particularly in patients with HIV [2 - 6].

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21 Cutaneous warts are diagnosed by examination.

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23 There are several therapies for warts. Some of them are: Silver nitrate, adhesive tape, cryotherapy, monochloroacetic acid, podophyllin, cantharidin and 5-fluorouracil, topical salicylic acid and lactic acid [7 - 16].

In general, none of the above treatments will result in a cure without the patient experiencing discomfort (moreover, some are only mildly effective). For this reason, there is a constant need for new wart treatments, which should preferably be easy to produce, inexpensive, stable in storage, effective, and act as quickly as possible after application to eliminate warts in a short time. In addition, it should preferably be easy to apply without the help of medical professionals, nontoxic, and not cause discomfort to the patient, i.e., it should not have a repulsive odour or be painful to the patient during or after application. Some patients complain that acid-based treatments for warts are ineffective, take several weeks to work, are smelly, and can be painful to use.

A safe, effective treatment for skin warts with few side effects is not yet available. Despite the introduction of various treatment methods, salicylic acid is the most commonly used ingredient. This organic acid has various side effects such as irritation, itching, hives, tingling or stinging. Generally, these effects are tolerable until the end of treatment (13 to 15 weeks).

Until then, there was no substance (or mixture of substances) that could quickly and safely promote a true cure and a complete reversal of the signs; this is now presented in this article.

A formulation containing benzoic acid (20 mg), salicylic acid (20 mg) and metallic iodine (2.5 mg) per ml was developed to promote the regression of the signs and symptoms of skin warts. This formulation is based on information from the medical literature, which reports that pure benzoic acid (and its derivatives) and metallic iodine have antiviral properties (17 - 20). The potential mechanisms of action of benzoic acid may be related to the degradation of the viral envelope, as its integrity is essential for the conduct of cellular infection (21). Salicylic acid at a concentration of 5% is marketed for desquamation of corns and keratinized artificial skin (22). Some techniques reveal methods to attenuate its irritating properties by combining it 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 antiviral agents (iodine and benzoic acid) was performed to achieve the most effective viral effect and avoid the irritant properties of salicylic acid. Due to the low salicylic acid dosage in this formulation, the associated side effects are less than other formulations currently used in clinical medicine.

The aim of this study was to investigate whether this new combination of benzoic acid, salicylic acid and iodine helps patients with recurrent skin warts and to compare it with a commercially available preparation containing salicylic acid (Verrux®).

2. PATIENTS AND METHODS

2.1 Patients and inclusion criteria

Male and female patients suffering from skin warts were included in the study.

Patients aged 12 to 65 years were enrolled in this prospective, randomized, parallel-group, double-blind, multicenter study between December 2004 and October 2016. They were randomly divided into two groups (A and B) using free software "Generate Random Groups" written in Python (from GitHub Repository). Group A of 95 patients received the formulation containing benzoic acid 20 mg, salicylic acid 20 mg, and metallic iodine 2.5 mg per ml and Group B of 95 patients received Verrux® (salicylic acid 165mg, lactic acid 145.2mg per ml collodion) daily for 13 weeks. Patients were followed up every 4 weeks until 13 weeks.

2.2 Exclusion criteria

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

2.3 Statistical analysis

Treatment outcomes were assessed by per-protocol (PP) analysis (which included only patients who completed the study) and intention-to-treat (ITT) analysis (which included patients who did not complete the study). Demographic and clinical characteristics of the two groups (A and B) were compared using Chi-square test or Fisher's exact test. Treatment outcomes were compared using the Chi-square test. $P < 0.05$ was considered statistically significant.

2.4 Randomization

Patients who qualified were randomized using the free software GENERATE RANDOM GROUPS using PYTHON (GitHub repository: <https://github.com/AIRGG/Generate-Random-Groups>): 95 patients received the formulation with benzoic acid 20mg, salicylic acid 20mg, and metallic iodine 2.5mg per ml (Group A) daily for 13 weeks and Group B of 95 patients received Verrux® (salicylic acid 165mg, lactic acid 145.2mg per ml collodion) daily for 13 weeks (Group B). It was recommended that the drug be applied twice daily. No other medications were allowed to be used during treatment.

2.5 Symptom severity

84 Patients were evaluated every 4 weeks up to 13 weeks. Safety and tolerability were assessed by recording adverse
85 events for both groups (16).
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89 **2.6. Materials**

90 **2.6.1. Use of organic acids and metallic iodine**

91 Chemical compounds were obtained from Galena (Campinas, SP, Brazil). Manipulation was performed by a trained
92 pharmacist. Both formulations were filled in identical bottles to ensure a double-blind study. One kit, containing 150 ml,
93 was used to treat one patient for 13 weeks (topical application twice a day). The composition was applied as drops to a
94 wart with a cotton swab or a dropper. Patients received a supply of medication for 90 days. A total of 190 kits were
95 prepared for use in 190 patients. Patient compliance was assessed at each consultation. The date of therapy initiation
96 was recorded for each patient. Photographs were taken of some patients. Symptoms and signs were recorded in a diary,
97 and changes in severity of signals noted.
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125 **Chart 1: CONSORT (CONsolidated Standards Of Reporting Trials)** 126 **FLOW DIAGRAM** 127 128 129 130 131 132 133 134 135 136 137 138

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3. RESULTS AND DISCUSSION

3.1 RESULTS

A total of 190 patients with cutaneous warts were enrolled in the surveillance programme between December 2005 and December 2016. The mean age at enrollment was 31 ± 14 years, with a range of 12 to 65 years; 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 recruitment was 2009. Geographically, subjects were from 9 different cities and municipalities in 4 Brazilian states and 1 city in Paraguay: 85 patients (44.74%) were 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 about 2,864 km apart. Regarding social class: 15 patients (7.9%) are rich, 72 (37.9%) belong to the middle class, and 103 (54.2%) are poor. Regarding education: 124 (35.32%) have university degrees [of which 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%) are illiterate.

The subjects were divided into two groups: 95 patients were allowed to use the formulation described in this paper with benzoic acid 20mg, salicylic acid 20mg and metallic iodine 2.5mg per ml for 13 weeks without further medication (group A) and for comparison the other half (95 volunteers) with salicylic acid 165mg, lactic acid 145.2mg per ml collodion (group B). Thus, 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.

At the end of 13 weeks of treatment, complete regression of symptoms (significant improvement) was observed in 100% of the subjects in group A. They reported relief of symptoms after 9 to 12 weeks of using the formulation. These results indicate that warts can be regressed with the organic acids and iodine of the formulation presented here. Completed adverse event and compliance questionnaires were obtained from all 190 patients. A total of 67 patients in group B (70.5%) reported complete regression of signs and symptoms (marked improvement) after 10 to 13 weeks of treatment, while the remaining patients continued to experience symptoms described 90 days before the start of treatment.

199 Three patients (3.15%) in Group B withdrew from the study due to burning sensation and skin irritation
 200 There was a statistically significant difference between groups A and B with regard to the regression of all symptoms: the
 201 active cure rate was 100% (95/95) in group A (subjects using the formulation with benzoic acid, salicylic acid, and iodine)
 202 and 65.7% (67/95) in group B (subjects using salicylic acid and lactic acid) ($P < 0.05$) (see Table 2).
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204 3.2 DISCUSSION

205 The regression and cure of the signs and symptoms of skin warts is probably due to the following facts: The first
 206 compound of this formula is benzoic acid, which has antiviral properties (25), including its derivatives (17, 18). Pure
 207 benzoic acid is a common preservative for food and beverages and an effective acidifier for weaned piglets and fattening
 208 pigs (20, 26).

209 The second compound is iodine, an active and potent virucidal agent (19, 27) that has been used for more than 150 years
 210 to prevent infections and treat wounds and exists as a complex mixture of many species (e.g., I₂, I⁻, I₃⁻, IO⁻, IO₃⁻) in
 211 equilibrium in water.

212 Our previous results (data not shown) have demonstrated that the use of iodine in combination with pure benzoic acid
 213 reduces the amount of pure benzoic acid needed for virucidal activity, suggesting that there is a synergistic effect when
 214 pure benzoic acid and iodine are combined.

215 Most likely, virucides such as benzoic acid and iodine damage the virion protein capsid or supercapsid membrane or
 216 penetrate the virion and destroy the viral genome. The integrity of the viral particles could also be affected (28).

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

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

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

226 In our formulation, we decreased the concentration of salicylic acid to about 2% to maintain minimal keratolytic properties
 227 and avoid side effects. In other words, we use salicylic acid to desquamate the skin, which allows better penetration of
 228 benzoic acid and iodine and facilitates virucidal action.

229 The Verrux® formula contains two keratolytic (or desquamating) active ingredients: salicylic acid (about 14%) and lactic
 230 acid (about 12.5%).

231 Although the virucidal effect of salicylic acid (34, 35) and lactic acid (36) is well known, the results of this article show that
 232 this effect is less than that of iodine and benzoic acid.

233 Fig. 1 shows photographs of the leg and hands of a patient (of group A) with skin warts who used the formulation with
 234 benzoic acid, salicylic acid, and metallic iodine in two different periods. This patient had tried several other treatments: first
 235 salicylic acid and lactic acid and lastly cryotherapy with liquid nitrogen - without success. The patient was 12 years old and
 236 traumatized by the side effects of previous treatments (especially the severe pain caused by the liquid nitrogen). After 13
 237 weeks of treatment with benzoic acid, iodine, and salicylic acid, the warts were completely removed and the skin was
 238 healthy again (Fig. 1B), and no side effects were observed.

239 Fig. 2 shows photos of the left hand of a patient (of group A) with skin warts who used the formulation with benzoic acid,
 240 salicylic acid, and iodine in two different periods. This patient had not taken any medication before. The warts were
 241 removed after 12 weeks of treatment with benzoic acid, salicylic acid, and iodine. No side effect was observed.
 242 Previously, this patient had used Duofilm®, Duofort®, Verrux®, sulfuric acid, and nitric acid. All of these treatments were
 243 unsuccessful. Two months had passed since the last treatment.
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245 **Table 1. Physical, chemical and biological properties of experimental soil (0-20 cm)**

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

	Group A (n=95)	Group B (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%)

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

	Group A (n=95)	Group B (n=95)	P	χ^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

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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%)

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

(A) December 7, 2005: during the onset of the warts (indicated by arrows). The patient consulted a dermatologist, who applied cryotherapy (with liquid nitrogen), which did not lead to any improvement. Conventional treatment was suspended, and after 4 weeks she began to treat with the formulation described here;

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



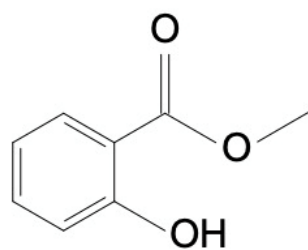
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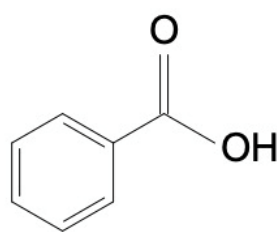
Fig. 2. Photographs of the left hand of a patient (of group A) with palmoplantar warts who used the formulation with benzoic acid, salicylic acid, and metallic iodine in two different periods:

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

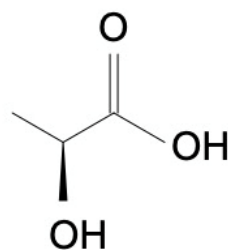
(B) April 2, 2007: after 12 weeks of treatment with benzoic acid, salicylic acid, and metallic iodine.



Salicylic Acid



Benzoic Acid



Lactic Acid

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

4. CONCLUSION

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

Ethical Approval and Consent

The data were reviewed and approved by the Ethics Committee of Universidade Vale do Rio Verde (UNINCOR - Três Corações - MG - Brazil) in November 2005 and by the Ethics Committee of Universidad Politécnica y Artística del Paraguay (UPAP) in November 2018. The study was conducted in accordance with the ethical principles of the 1964 Declaration of Helsinki, written by the World Medical Association.

The authors state that "informed consent form" was obtained from participating patients (or other approved parties) for publication of this study and accompanying images. A patent application has been filed in I.N.P.I. (Brazil) for intellectual property protection (BR 10 2022/008401-7).

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314 **COMPETING INTERESTS**

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316 The authors have no conflict of interest to declare.

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318 **AUTHORS' CONTRIBUTIONS**

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320 Prof. Dr. Ricardo de Souza Pereira designed the study, drafted the protocol, performed the statistical analysis and wrote
321 the manuscript; Dr. Nayana Mendes Monteiro supervised the patients, directed the literature search and analyses of the
322 study. All authors read and approved the final version of the manuscript.

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