Cerrahpaşa Med J 2025; 49: 1-6 ORIGINAL ARTICLE

Clinical Outcomes of Propolis-Supplemented Therapies in Verruca Vulgaris: A Prospective Observational Study

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Cite this article as: Huseynova C, Yücesoy SN, Kutlubay Z. Clinical outcomes of propolis-supplemented therapies in verruca vulgaris: a prospective observational study. *Cerrahpaşa Med J.* 2025, 49, 0031, doi: 10.5152/cjm.2025.25031.

What is already known on this topic?

- *Verruca vulgaris is a common and often treatment-resistant skin infection caused by human papillomavirus.*
- *Standard destructive treatments such as cryotherapy and electrocauterization have moderate success rates and are frequently associated with recurrence.*
- *Propolis has demonstrated antiviral and immunomodulatory properties in limited studies, but its clinical efficacy in verruca vulgaris remains underexplored.*

What does this study add on this topic?

- *This study suggests that systemic oral propolis, when combined with destructive methods such as cryotherapy and electrocauterization, may improve treatment outcomes and help reduce recurrence.*
- *The addition of topical propolis to oral supplementation appeared to contribute to lesion reduction, with no side effects observed in this cohort.*
- *Compared to previous studies, the combined use of propolis with standard treatments showed relatively higher cure rates in this sample, indicating that propolis could be considered a promising adjunctive option in the management of verruca vulgaris, though further controlled trials are needed.*

Abstract

Objective: Verruca vulgaris is a common infectious dermatosis for which treatment alternatives have gained importance. In this study, the aim was to evaluate the efficacy of systemic propolis, an alternative treatment modality, when used with both destructive treatments and topical propolis, and to monitor the recurrence in the long term.

Methods: This study is a prospective study that included 58 patients with verruca vulgaris. Of the 58 patients, 20 received electrocauterization with propolis supplementation, 21 received cryotherapy with propolis supplementation, and 17 received propolis cream with propolis supplementation.

Results: The decrease in the number of lesions in the 3 treatment groups was statistically significant in the third and sixth months compared to pretreatment. The total cure rates of the patient groups at the third and sixth months were 35% and 70% in the cryotherapy + oral propolis group, 42% and 71% in the electrocauterization + oral propolis group, and 29% and 41% in the propolis cream + oral propolis group, respectively. The main limitations of this study are small sample size and lack of control group.

Conclusion: This study suggests that oral propolis supplementation, when combined with destructive or topical treatments, appears to improve treatment outcomes and may help reduce recurrence. While these findings are encouraging, the absence of a control group and the inability to isolate the effect of oral propolis alone warrant cautious interpretation. Further randomized controlled trials with larger populations are needed to confirm the efficacy and safety of propolis in verruca vulgaris.

Keywords: Cryotherapy, electrocauterization, propolis, verruca vulgaris

Introduction

Verruca vulgaris is a skin condition caused by the human papillomavirus (HPV) that affects skin and mucous membranes. There are various destructive and immunomodulatory treatment options in the treatment of verrucas. The patient's age, type, extent, and duration of lesions should be considered when determining the treatment. Propolis is a flavonoid molecule consisting of approximately 50% resin, 30% wax, 10% essential oil, 5% pollen, and 5% various minerals, vitamins, and poly- and oligosaccharides.[1]In vivo and in vitro studies have shown that propolis increases macrophage activity and stimulates antibody production.[2] The flavonoid structure of propolis explains its antitumoral, antioxidant, antimicrobial, anti-inflammatory, and immunomodulatory effects.[3] In a limited number of studies, it has been found that propolis has an antiviral effect in addition to its antibacterial effect.[4,5]In this study, the aim was to evaluate the efficacy of propolis in HPV treatment based on its antiviral effect.

Methods

This prospective study included 58 verruca vulgaris patients admitted to the outpatient clinic. Informed consent forms were obtained from all patients. Ethics committee approval was received from İstanbul University-Cerrahpaşa, Cerrahpaşa Medical Faculty ethics committee (20.05.2022-384717). The study was conducted between June 2022 and December 2022. Immunocompetent

Received: May 8, 2025 **Revision Requested:** September 29, 2025 **Last Revision Received:** October 21, 2025 **Accepted:** November 11, 2025 **Publication Date:** December 31, 2025
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DOI: 10.5152/cjm.2025.25031

individuals between 18 and 65 years of age without comorbidities were included. Exclusion criteria were age under 18 years, pregnancy, breastfeeding, known immunosuppression (due to disease or medication), and the presence of significant systemic comorbidities. The patients who participated in the study were examined in 3 groups: Group A: patients receiving oral propolis + electrocauterization; Group B: patients receiving oral propolis + cryotherapy; and Group C: patients receiving oral propolis + propolis cream treatment. Patients were randomly allocated into the 3 treatment groups. This approach minimized potential selection bias. All patients received 360 mg (40 drops) of pure Anatolian propolis 30% daily for 3 months. Propolis cream 30% was applied to the lesion area 2 times a day for 3 months. All propolis products (oral drops and topical cream) were provided to the patients free of charge by the investigators to ensure standardization of treatment. In the patient groups receiving electrocauterization and cryotherapy, destructive treatments were applied at the beginning of treatment and the 12th week. During the 6-month follow-up, clinical photographs were taken at 0, 3, and 6 months, and the number of lesions was compared. Cure was defined as complete clinical disappearance of all verruca lesions with no recurrence observed during the 6-month follow-up period. Treatment compliance was assessed by direct questioning at each follow-up visit and by checking the remaining amount of oral drops and cream tubes that patients brought to visits. Adverse events were monitored through systematic questioning at each follow-up visit, and patients were also instructed to report any unexpected symptoms spontaneously. Written informed consent was obtained from all participants in accordance with the principles of the Declaration of Helsinki.

SPSS 15.0(SPSS Inc.; Chicago, IL, USA) Windows program was used for statistical analysis. Descriptive statistics were given as numbers and percentages for categorical variables and mean, SD, minimum, and maximum for numerical variables. Independent comparisons of numerical variables of more than 2 groups were performed by the one-way ANOVA test when the numerical variables met the normal distribution condition in the groups and the Kruskal–Wallis test when they did not. In the nonparametric test, subgroup analyses were performed with the Mann–Whitney *U*-test and interpreted with Bonferroni correction. In independent groups, proportions were compared using chi-square analysis. Dependent group analyses were performed with Friedman's test since the differences did not meet the normal distribution condition. Subgroup analyses were performed with the Wilcoxon test in the nonparametric test and interpreted with Bonferroni correction. The statistical alpha significance level was accepted as $P < .05$.

Table 1. Demographical Features

		Treatment			*P*
		Group A	**Group B**	**Group C**	
Age	Mean ± SD	31.8 ± 12.6	27.6 ± 9.9	36.8 ± 16.0	.179
	Min-Max (Median)	18-64 (27)	18-52 (24)	18-65 (32)	
Gender, n (%)	Male	11 (55.0)	12 (57.1)	7 (41.2)	.580
	Female	9 (45.0)	9 (42.9)	10 (58.8)	
Location, n (%)	Hand	17 (85.0)	16 (76.2)	16 (94.1)	.352
	Periungual	5 (25.0)	3 (14.3)	2 (11.8)	.621
	Finger	4 (20.0)	7 (33.3)	3 (17.6)	.580
	Abdomen	1 (5.0)	0 (0.0)	0 (0.0)	.634
	Extremities	1 (5.0)	1 (4.8)	2 (11.8)	.671

Results

Demographic data and treatment groups of the patients who participated in the study are shown in Table 1. Of the 58 patients who participated in the study, Group A (n = 20) received oral propolis + electrocauterization treatment; Group B (n = 21) received oral propolis + cryotherapy treatment, and Group C (n = 17) received oral propolis + propolis cream treatment. There was no statistically significant difference in the mean age and sex ratios of the patients in the study groups. Lesion locations of Group A were 85% (n = 17) on the hand, 25% (n = 25) periungual, 20% (n = 4) finger, 5% (n = 1) abdomen, and 5% (n = 1) knee-elbow. Lesion duration was 45% (n = 9) 0-6 months, 40% (n = 8) 7-12 months, 15% (n = 3) 13-24 months. Lesion locations of Group B were 76.2% (n = 16) on the hand, 14.3% (n = 3) periungual area, 33.3% (n = 7) finger, 4.8% (n = 1) knee-elbow, while the disease duration was 28.6% (n = 6) 0-6 months, 33.3% (n = 7) 7-12 months, 38.1% (n = 8) 13-24 months. Lesion locations of Group C were 94.1% (n = 16) on the hand, 11.8% (n = 2) in the periungual region, 17.6% (n = 3) on the fingers,

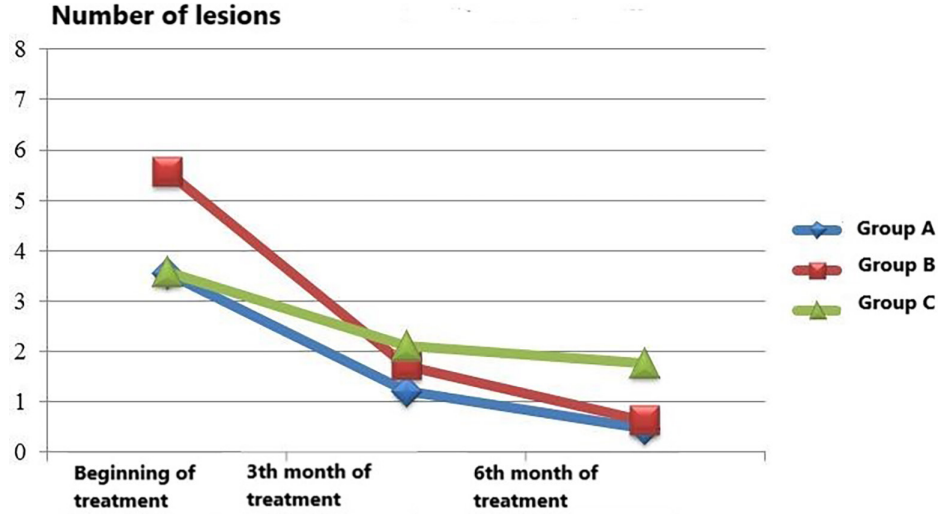

Figure 1. Number of lesions in the treatment groups at baseline and at 3rd- and 6th-month follow-up.

Table 2. Comparison of the Number of Lesions in the Treatment Groups Before and After Treatment

	Treatment			
	Group A	Group B	Group C	
Number of Lesions (n)	Mean ± SD Min-Max (Median)	Mean ± SD Min-Max (Median)	Mean ± SD Min-Max (Median)	*P*
Beginning of treatment	3.55 ± 1.70 1-7 (4)	5.57 ± 2.40 1-9 (6)	3.59 ± 2.00 1-7 (3)	.421*
3rd month of treatment	1.20 ± 1.32 0-4 (1)	1.71 ± 2.15 0-6 (1)	2.12 ± 2.26 0-7 (2)	.519**
6th month of treatment	0.45 ± 0.83 0-3 (0)	0.62 ± 1.07 0-3 (0)	1.76 ± 2.36 0-7 (1)	.081**
P#	<.001	<.001	<.001	

*One-way ANOVA.
**Kruskal–Wallis test.
#Friedman test.

Table 3. Comparison of the Reduction in the Number of Lesions in the Treatment Groups at 3 and 6 Months Follow-Up, ***P***-Value

		Number of Lesions		
		Beginning of Treatment – 3rd Month *P***	Beginning of Treatment – 6th Month *P***	3rd Month – 6th Month *P***
Group A vs.	Group B	.004	.004	.834
	Group C	.036	.008	.055
Group B vs.	Group C	<.001	<.001	.166

**Mann–Whitney *U*-test (Bonferroni correction $P < .017$).

11.8% (n = 2) in the knee-elbow, and the disease durations were 29.4% (n = 5) 0-6 months, 35.3% (n = 6) 7-12 months, and 35.3% (n = 6) 13-24 months. There was no significant difference between the groups regarding lesion duration, lesion location, and number of lesions. There was no statistically significant difference between the groups' third and sixth-month lesion counts ($P = .519$, $P = .081$). The decrease in the number of lesions with treatment in all groups was statistically significant ($P < .001$ for all) (Figure 1). In the 3 treatment groups, the decrease in lesions in the third and sixth months compared to pretreatment was statistically significant (Table 2). In the Group A and Group B patients, the decrease in the number of lesions in the sixth month compared to the third month was statistically significant ($P = .001$, $P = .015$). In the Group C patients, the decrease in the number of lesions in the sixth month compared to the third month was not statistically significant ($P = .077$).

The difference at pretreatment–third month was statistically significantly higher in the Group B patients than in the Group A patients ($P = .004$, $P < .001$). The pretreatment–sixth month difference was statistically significantly higher in Group B than in Group A and in Group A than in Group C patients ($P = .004$, $P < .001$, $P = .008$) (Table 3). There was no statistically significant difference between the groups in that the number of lesions decreased in the sixth month of treatment compared to the third month ($P = .177$).

The total cure rates of the patient groups at the third and sixth months were 7/21 (33.3%) and 14/21 (66.7%) in Group B, 8/20 (40%) and 14/20 (70%) in Group A, and 5/17 (29.4%) and 7/17 (41.2%) in Group C, respectively. No recurrence was observed in any patient at the sixth month of treatment. No secondary side effects related to propolis or destructive methods have been observed in patient groups. Pretreatment and posttreatment third-month and sixth-month control photographs of some of the patients belonging to the treatment groups are given in Figures 2, 3, and 4.

Discussion

Verruca vulgaris is a commonly encountered dermatological problem in the community, and due to its potential resistance to treatment, alternative therapeutic options have gained importance for this infectious dermatosis. In addition to destructive methods, antiviral treatments and immunotherapy also play a significant role in its management. The lack of a definitive cure, treatment failures with current therapies, and the possibility of recurrences pose challenges in the treatment of verruca vulgaris. Propolis has emerged as an alternative treatment option for verruca vulgaris, but there needs to be more research available regarding its effectiveness in the literature.

In this study, all patient groups received oral propolis supplementation, and a significant reduction in lesion count was

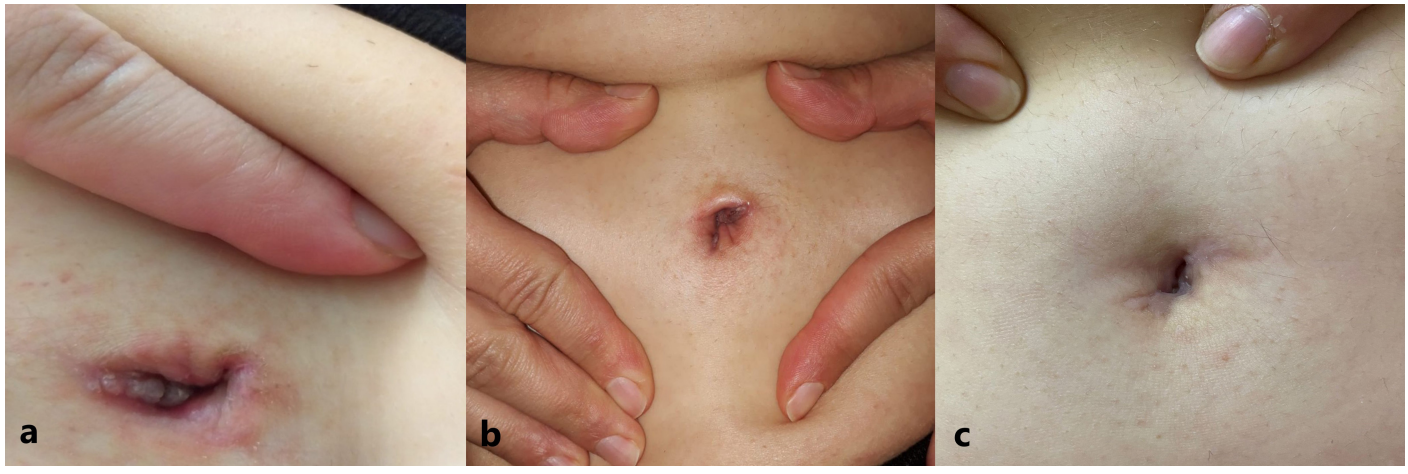

Figure 2. Patient with verruca vulgaris receiving electrocauterization with propolis supplementation. (a) Before treatment. (b) Third month of follow-up. (c) Sixth month of follow-up.

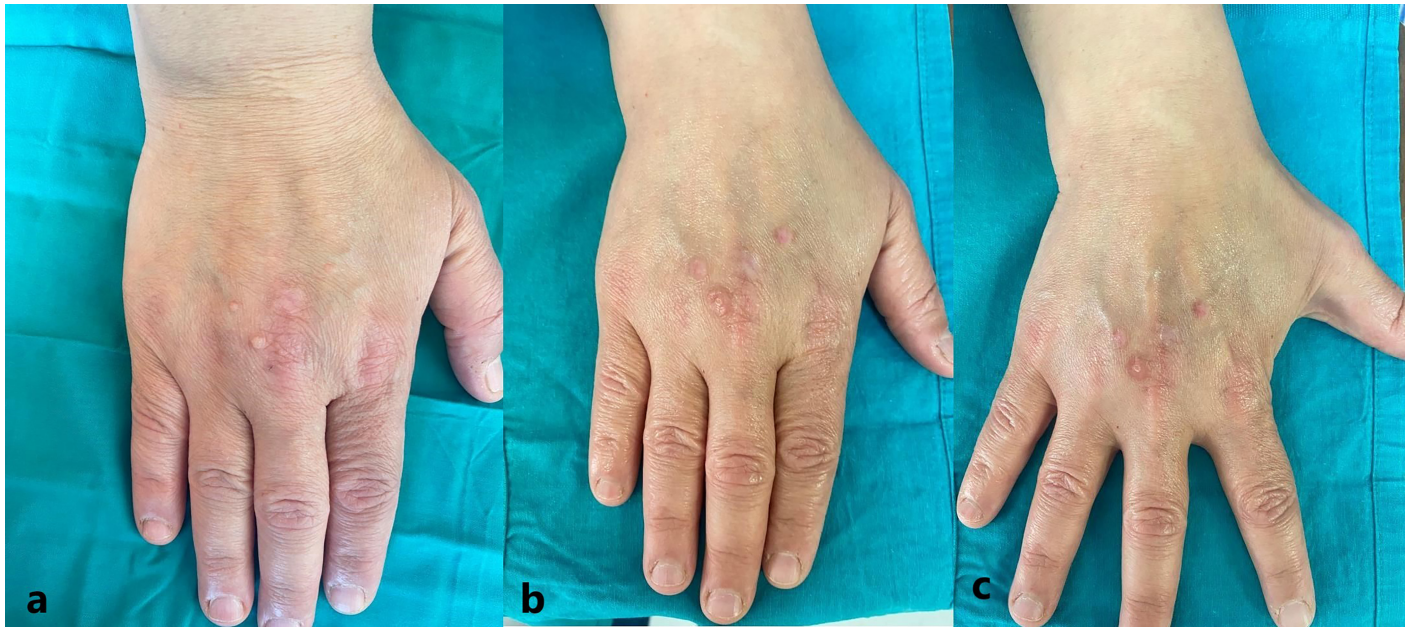

Figure 3. Patient with verruca vulgaris receiving cryotherapy with propolis supplementation. (a) before treatment. (b) Third month of follow-up. (c) Sixth month of follow-up.

observed at the third- and sixth-month follow-ups in all treatment groups compared to baseline. Additionally, patients who used topical propolis cream concurrently with oral propolis supplementation showed a significant decrease in verruca vulgaris lesion count during the treatment follow-up. At the sixth month of treatment, patients receiving cryotherapy with propolis supplementation had statistically higher treatment success than those receiving electrocauterization with propolis supplementation. Also, patients receiving electrocauterization with propolis supplementation had higher treatment success than those receiving propolis cream with propolis supplementation. In a study conducted by Zedan et al,[6] patients with verruca vulgaris and verruca plana were given 500 mg/day single dose of pure propolis or 600 mg/day Echinacea purpurea propolis for 12 weeks and compared with patients receiving placebo treatment. As a result of the study, it was determined that the treatment efficacy of pure propolis treatment was significantly higher than that of placebo, especially in patients with verruca vulgaris. At the same time, no difference was observed between the Echinacea purpurea propolis and placebo group.[6]

Cryotherapy is one of the most commonly used destructive methods in treating verrucae, and its advantages include its easy applicability and low cost. Many studies in the literature support cryotherapy as an effective treatment for verrucae.[7,8] However, in most of the studies, it is seen that the recurrence rate is high with destructive treatments, especially cryotherapy.[9]

Cockayne et al[10] investigated the effectiveness of cryotherapy and salicylic acid in treating plantar verrucae. A total of 240 patients were included in the study: 117 received cryotherapy

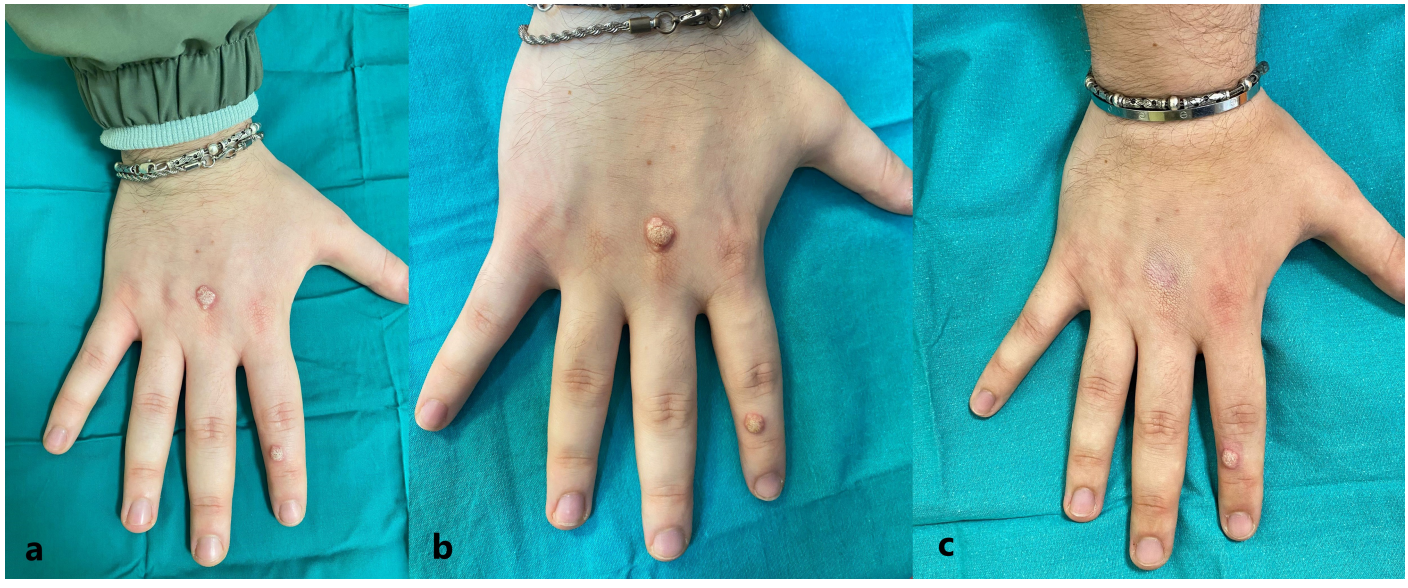

Figure 4. Patient with verruca vulgaris receiving propolis cream with propolis supplementation. (a) before treatment. (b) Third month of follow-up. (c) Sixth month of follow-up.

treatment and 123 received salicylic acid treatment. The total cure rate of the group treated only with cryotherapy was 14% and 31% at 3 and 6 months, respectively, and the cure rate of the group treated only with salicylic acid was 14% and 34% at 3 and 6 months, respectively.[10] In this study, the total cure rate of the group receiving cryotherapy + oral propolis treatment was 35% and 70% at 3 and 6 months, respectively. Based on this, it can be interpreted that oral propolis treatment may be potentially effective in preventing recurrence after cryotherapy. Another study by Anwar et al[11] compared electrocauterization and cryotherapy in treating non-genital verrucae. A total of 50 patients were included in the study; half were evaluated at the eighth week of treatment with cryotherapy and the other half with electrocauterization, receiving a maximum of 8 weekly treatment sessions. In this study, a total cure rate of 76% with electrocauterization and 44% with cryotherapy was achieved, and electrocauterization was found to be superior to cryotherapy in the treatment of verrucae.[11]However, in this study, patients were evaluated only at the end of the eighth week, and long-term recurrence and total cure rates were not analyzed. In this study, patients were evaluated at the 12th and 24th week of treatment, and total cure rates were 71% in the electrocauterization + oral propolis group and 70% in the cryotherapy + oral propolis group. Although the total cure rate was similar in the electrocauterization + oral propolis group compared to the electrocauterization group in this study, the total cure rate was higher in the cryotherapy + oral propolis group compared to cryotherapy alone in this study, and this result supports that oral propolis supplementation may be successful in preventing long-term recurrence.

Ablative and vascular laser treatments, another destructive treatment method, have been shown to have a variable total cure rate of 10%-100% in verruca vulgaris, and recurrence rates vary between 10% and 40%.[12-15] Although laser treatment is considered to be an effective treatment in the study results, its disadvantages include the fact that it is costly, requires long sessions, and has risks such as pain, bleeding, secondary infection, persistent erythema, ulceration, and cicatrix formation at the procedure site, which limit its use. In this study, the 6-month total cure rate of patients treated with cryotherapy or electrocauterization with oral propolis was around 70%, which is a higher cure rate than most of the studies in the literature in which only laser was used in the treatment of verrucae. In addition, the fact that no recurrence was observed in any of the patients in this study shows the effectiveness of oral propolis in preventing recurrence. It supports the view that combined use with laser treatment may effectively increase treatment success.

Immunomodulatory agents constitute an essential alternative in treating verruca vulgaris, especially in cases with treatment-resistant and diffuse lesions.[16,17] There are a limited number of studies on the efficacy of oral propolis treatment in the treatment of verrucae, and there are no studies evaluating the efficacy of topical propolis treatment as an immunomodulatory agent. This study observed that topical propolis cream treatment given simultaneously with oral propolis treatment caused a significant decrease in verruca vulgaris. In addition, no side effects related to topical propolis treatment were reported. Imiquimod is another immunomodulatory agent in 5% cream form commonly used in treating both genital and non-genital verrucae. It shows antiviral and antitumoral effects by increasing cellular IFN-alpha(Interferon-alpha), TNF-alpha (Tumor necrosis factor-alpha), and IL-6(Interleukin-6) levels.[18] In studies, imiquimod's efficacy in treating non-genital verrucae varies between 27% and 89% in immunocompetent patients and a 33%-50% total cure rate in immunosuppressed patients.[19] In addition to the differences in study results, tenderness, erythema, and vitiligo-like depigmentation are the side effects limiting its use.[20] This study observed no side effects related to topical propolis cream. The fact that it is easy to use and devoid of side effects compared to many topical agents is among the factors that increase the survival in treatment.

The limitations of this study include its relatively small sample size, the absence of a control group, and its single-center design. The lack of a control group, in particular, limits the ability to draw definitive conclusions regarding the efficacy of propolis, as the observed outcomes cannot be directly compared to standard treatments or placebo. Although various therapeutic modalities exist for verruca vulgaris, cases that are resistant, extensive, or located in anatomically challenging areas continue to necessitate the exploration of alternative options. Propolis is one such emerging agent, and current literature offers only limited data on its clinical utility in the treatment of viral warts. In this study, oral propolis appeared to play a significant role in reducing recurrence rates when combined with destructive methods, while the addition of topical propolis further contributed to lesion reduction. Because all patients received oral propolis, it was not possible to isolate the specific contribution of oral versus topical or destructive therapies. Therefore, the conclusion that oral propolis prevents recurrence should be interpreted cautiously. Although the products were provided by the investigators to ensure standardization and minimize variability, potential reporting bias regarding patient adherence cannot be fully excluded.

This study suggests that oral propolis supplementation, especially when combined with destructive methods, appears to be a promising adjunctive therapy for verruca vulgaris. However, randomized controlled trials with larger cohorts are required to confirm these findings.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of İstanbul University-Cerrahpaşa, Cerrahpaşa (Approval No.: 384717 Date: 20.05.2022.

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: .Concept – C.H., S.N.Y.; Design – C.H., S.N.Y.; Supervision – S.N.Y., Z.K.; Resources – S.N.Y., Z.K.; Materials – C.H., S.N.Y.; Data Collection and/or Processing – C.H., S.N.Y.; Analysis and/or Interpretation – C.H., S.N.Y., Z.K.; Literature Search – C.H., S.N.Y.; Writing – C.H., S.N.Y.; Critical Review – S.N.Y., Z.K.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

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