Hindawi
Dermatologic Therapy
Volume 2024, Article ID 8814508, 9 pages
https://doi.org/10.1155/2024/8814508

Research Article

Efficacy and Safety of *Phoenix dactylifera* L. Leaf Extract (WartOver®) in the Treatment of Cutaneous Warts: A Randomized, Double-Blind, Placebo-Controlled Trial

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Received 31 October 2023; Revised 23 March 2024; Accepted 26 March 2024; Published 24 April 2024

Academic Editor: Marc Zachary Handler

Background. Cutaneous warts are caused by the human papillomavirus that can affect a patient's quality of life. Current treatments have high cost, low efficacy, adverse effects, and recurrence. Therefore, novel therapeutic approaches are needed. Complementary and Alternative Medicines (CAMs) are gaining popularity as a therapeutic approach. *Phoenix dactylifera* L. (date palm) is used in folk medicine to treat warts. Antiviral effects of *P. dactylifera* L. have been demonstrated due to its polyphenolic compounds, especially gallic acid and tannins in various studies. So, this trial evaluates the efficacy and safety of *P. dactylifera* L. leaf extract (formulated as WartOver®) as a novel treatment for cutaneous warts. *Study Design*. Based on the results of our previously published pilot clinical trial and the CONSORT guideline, this randomized, double-blind, and placebo-controlled study was performed on 70 eligible patients divided into intervention and placebo groups ($N = 35$/per group). Every 2 weeks, patients were examined to assess the rate of complete clearance, duration of treatment, patient satisfaction (measured using a Likert scale), and occurrence of any adverse effects and recurrence in a maximum of 12 weeks of treatment and at the 6-month follow-up. *Results*. Based on the intention-to-treat (ITT) analysis approach, complete clearance was achieved in 24 patients in the intervention group (68.57%; confidence interval 95% = 0.51–0.81), which was significantly higher than that in the placebo group (8.57%; CI 95% = 0.02–0.23, $p < 0.0001$). The time to complete clearance was 7.6 weeks (mean ± SD: 53.30 ± 17.17 days). The treatment was very satisfactory (Likert score of 4.24 ± 1.15 (mean ± SD)) with no recurrence or adverse effects. *Conclusion*. WartOver® is a novel efficacious treatment for cutaneous warts with minimal risk for adverse events or recurrence. Due to the rising popularity of CAM approaches in medicine, including herbal medicines, WartOver® can be a valuable choice for clinicians against cutaneous warts. This trial is registered with IRCT20200509047352N2.

1. Introduction

Human papillomavirus (HPV) is the source of benign epithelial lesions known as cutaneous warts [1]. The high-risk HPV subtypes 16 and 18 cause high-grade intraepithelial lesions that develop into cancers [2]. Warts affect approximately 10% of the global population. It is more common among school-aged children, immunosuppressed patients, and meat handlers. During lifetime, almost all unvaccinated individuals who engage in sexual activity, more than 90% of sexually active men and 80% of sexually active women, get involved with HPV. Approximately 13 million Americans, including teenagers, are annually infected with HPV. Approximately 50% of HPV infections involve certain high-risk HPV types, which can cause cancer. Most of the time, the body clears these infections and prevents the development of cancer, but it may take at least 6 months [1, 3–5].

Warts are treated using different approaches such as destructive techniques, immunotherapy, antimitotic drugs, and other remedies [6]. Given the high incidence of HPV infection across various age cohorts and its associated morbidity and the suboptimal efficacy of current therapies with high recurrence rates, there is an unmet need for highly efficacious and safe treatments.

Herbal remedies are becoming more and more common in Complementary and Alternative Medicines (CAMs), due to their minimal side effects and high efficacy. 36% of American adults over the age of 18 use CAM, a trend that is spreading throughout the world. One of the world's earliest Arecaceae plants is *P. dactylifera* L. (date palm). North Africa and the Middle East are where it primarily grows [7]. *P. dactylifera* L. exhibits antioxidant, antibacterial, antiviral, antifungal, and antiproliferative properties due to its phenolic acids and flavonoids [8].

Our pilot clinical study on WartOver®, a formulation based on the extract of the leaves of *P. dactylifera* L., demonstrated the efficacy and safety of this herbal product in the treatment of cutaneous warts, with no recurrence or side effects during the follow-up period [9]. As our pilot study was the first study to investigate the efficacy of date palm leaves for treating cutaneous warts, further research was required to arrive at a reliable conclusion on this matter. These facts encouraged us to investigate the efficacy and safety of WartOver® in a larger sample and with a longer follow-up period in mostly difficult-to-treat patients who have not responded to other treatments or who have relapsed to better assess our formulation as a therapeutic method for cutaneous warts.

2. Materials and Methods

2.1. Study Design. Our CONSORT-based randomized, double-blind, placebo-controlled experiment included a 6-month follow-up after the maximum 12-week treatment phase, in the dermatology clinic of the Tehran University of Medical Sciences, Iran-affiliated Center for Research and Training in Skin Diseases and Leprosy. The Helsinki Declaration and Good Clinical Practice were all followed in the conduct of the research. Prior to the collection and reporting of clinical data and photographs, all participants signed informed consent forms before recruitment which clarify all the procedures of the trial such as reporting unidentifiable images of patients and results of the intervention. The Tehran University of Medical Sciences ethical committee examined and approved the study protocol (IR.TUMS.MEDICINE.REC.1401.416), and the trial was registered on the Iranian Registry of Clinical Trials (IRCT20200509047352N2).

2.2. Plant Collection and Extraction. Leaves of *P. dactylifera* L. were gathered from 25 to 30 individual trees during the optimal season. Any dried or infested leaves were identified and excluded from the collection at this stage. Following this, the spine and rachis of the collected leaves were discarded, leaving only the leaflets for extraction. The collected leaflets were milled and then subjected to extraction in a solution of 80% methanol, at a ratio of five times the volume of the milled leaflets. This extraction was carried out at room temperature for six days using the maceration method. The extract was then filtered and dried by a vacuum drier.

2.3. Phytochemical Study. The total phenolic content was determined quantitatively using the Folin–Ciocalteu reagent, with gallic acid (GA) as the standard, using a spectrophotometric (UV method) method. Each gram of *Phoenix dactylifera* L. leaf extract ointment contains 11.27 milligrams of GA equivalent as the active ingredient.

2.4. Preparation of Interventions. We developed WartOver® as a 10% ointment after obtaining a dried powder from an 80% methanol extract of *P. dactylifera* L. leaves. This product also contains inactive ingredients such as petrolatum, lanolin, and glycerin. The placebo ointment was formulated using the same ointment base, a brown colorant, and an ineffective odorant to mimic the appearance and smell of the intervention ointment.

2.5. Eligibility Criteria. After screening 87 patients, 17 patients were excluded according to inclusion and exclusion criteria and 70 eligible subjects between the ages of 18 and 65 years were assessed for randomization. The inclusion criteria were 18–65 years of age, clinically diagnosed cutaneous wart(s), maximally up to 5 cutaneous warts with an area of up to 1 cm, at least four weeks passed from other treatments, understanding the conditions and guidelines of the clinical study, and the patients consenting to participate in the clinical trial. The exclusion criteria were breastfeeding and pregnancy, history of malignant and premalignant skin disease (e.g., actinic keratosis), congenital or acquired immunodeficiency, genital lesions or eyelid involvement, complicated infections, HPV vaccination in the six months prior to study entry, current diagnosis of atopic dermatitis, psoriasis, eczema, or other skin conditions, and any

conditions that in the opinion of the researcher could expose the participant to unnecessary risks by participating in the study or that interfere with the assessment. Participants may withdraw from the study for any reason, e.g., if they are not willing to continue the study, if they take the drug less than twice a day for one month, if the disease worsens and the patient is diagnosed with skin cancer, if severe allergic reactions (e.g., severe urticaria) occur with the drug, use of another standard treatment for warts, in case of severe and unpredictable complications attributable to the intended treatment, failure to participate in the specified time intervals for more than two visits, and participation in other clinical trials.

2.6. Sample Size, Randomization, and Blinding. In our preliminary study [9], we estimated the treatment's effect size to be 0.5. With an α of 0.05 and a power of 95%, we used G* Power software to calculate a total sample size of 52 individuals. Another study which evaluated complete clearance of warts by using topical ointment, considered a type 1 error rate of 5% ($\alpha = 0.05$), statistical power of 90% ($\beta = 0.1$), and the formula ($P1 = 1.00$, $P2 = 0.74$, $Z\ (1 - \alpha/2) = 1.96$, $Z\ (1 - \beta) = 1.28$) and determined a target population of fewer than 30 people for each group. Given these evaluations and the potential 15% dropout rate observed in wart studies, we decided on a total sample size of 70 (35 patients in each arm) in this study. This decision was made to enhance the precision of the treatment effect estimate [10]. Randomization was employed using a block size of four to allocate subjects who fulfilled the inclusion criteria to either the intervention or placebo group. Online randomization was conducted using four permuted balanced blocks, resulting in 70 patients with a 1 : 1 allocation ratio. A contract research organization created randomization codes for this study. To ensure the validity of the results, a third-party expert prepared and labeled the ointment tubes containing either the intervention drug or placebo and delivered them to the researcher. The investigators and patients were blinded to the treatment allocation and followed the same protocol for applying the ointment.

2.7. Interventions. Owing to the topical formulation's uniqueness, skin sensitivity tests were performed on each patient 48 hours following the initial ointment application. The patients would be invited to take part in the trial if they experienced no complications. Following the skin irritation evaluation during the second screening visit, a 30-day treatment-free interval was assessed for admission. Before starting treatment, clinical and demographic information was documented, photos were taken, and participants were randomly assigned to the placebo or intervention groups. During the study, the enrolled patients were mandated not to receive any other treatments. Patients were informed that the ointment must be applied to the entire wart area three times a day for 12 weeks or until total clearance was attained. The patients were monitored all the time through telephone calls. After the wart had completely cleared up or after 12 weeks of starting treatment, the patients were checked on again at 1, 3, and 6 months. A follow-up study was conducted using digital imaging, and patient data were assessed for recurrence and adverse effects of WartOver®.

2.8. Outcomes. The clinical improvement is considered as a decrease in the number of warts and a significant size reduction. Every 2 weeks, patients were examined to assess the rate of complete clearance, duration of treatment, patient satisfaction (measured using a Likert scale) [11, 12], and occurrence of any adverse effects at a maximum of 12 weeks of treatment and 6-month follow-up. The proportion of patients who achieved complete clearance (according to clinical diagnosis or measurement of 0 mm wart in taken photographs) of target warts within 12 weeks or less in the intervention and placebo groups was considered as the primary outcome, and for the secondary outcomes, significant reduction of the wart area, the time to complete clearance of warts, the level of satisfaction measured using Likert scale, and the intervention safety were evaluated. Also, the incidence of side effects and recurrence in intervention and placebo groups is reported.

2.9. Statistical Analysis. The SPSS software, version 25.0 (SPSS Inc., Chicago, IL, USA), was used for all statistical analysis. The chi-squared and *t*-test were employed for qualitative and quantitative variables, respectively. Also, data were expressed as mean ± standard deviation (SD). For all tests, the significance level was set at 0.05.

3. Results

During the study period, 87 patients with clinically diagnosed cutaneous warts were assessed for their eligibility to be included in the study. Based on specific inclusion and exclusion criteria, a total of 70 patients were enrolled in the interventional phase of the study.

3.1. Demographic and Baseline Analysis Results. The baseline parameters for the two groups did not show any statistically significant difference ($P > 0.05$), indicating the homogeneity of the intervention and control groups prior to the trial (Table 1 and Figure 1).

3.2. Clearance of Warts. Two patients in the intervention arm and three patients in the placebo arm withdrew from the study because they did not adhere to the treatment (using the medication less than two times a day, not attending more than two doctor's visits, stopped using the ointment for more than one week or wanted immediate and on-the-spot treatment due to concerns about the transmission and complications of the disease, and did not receive a response in the first week) and were considered nonresponders. In the intervention arm, 24 of the remaining 33 patients experienced complete clearance, and nine patients experienced partial clearance and a remarkable decrease in the extent of lesions (Table 2, Figure 2). There were no adverse effects or recurrence of warts observed in the patients with complete clearance ($N = 24$) in

Table 1: Demographic and baseline clinical data of the studied subjects.

Characteristics	Patients ($N = 70$)	Intervention group ($n = 35$)	Placebo group ($n = 35$)	P value
Age (years)	18–65	30.94 ± 11.8 (mean ± SD)	33.97 ± 9.19 (mean ± SD)	0.235
Gender				
Male	34 (48.57%)	16	18	
Female	36 (51.42%)	19	17	0.811
Male : female	1 : 1.06			
Types of warts				
Verruca vulgaris	36	17	19	
Plantar	17	11	6	0.8762
Plane	15	5	10	
Periungual	2	2	0	
Wart number	70	35	35	
1 or 2 warts	47 (67.14%)	27	20	0.085
3 or 4 warts	8 (11.43%)	1	7	
5 warts	15 (21.43%)	7	8	

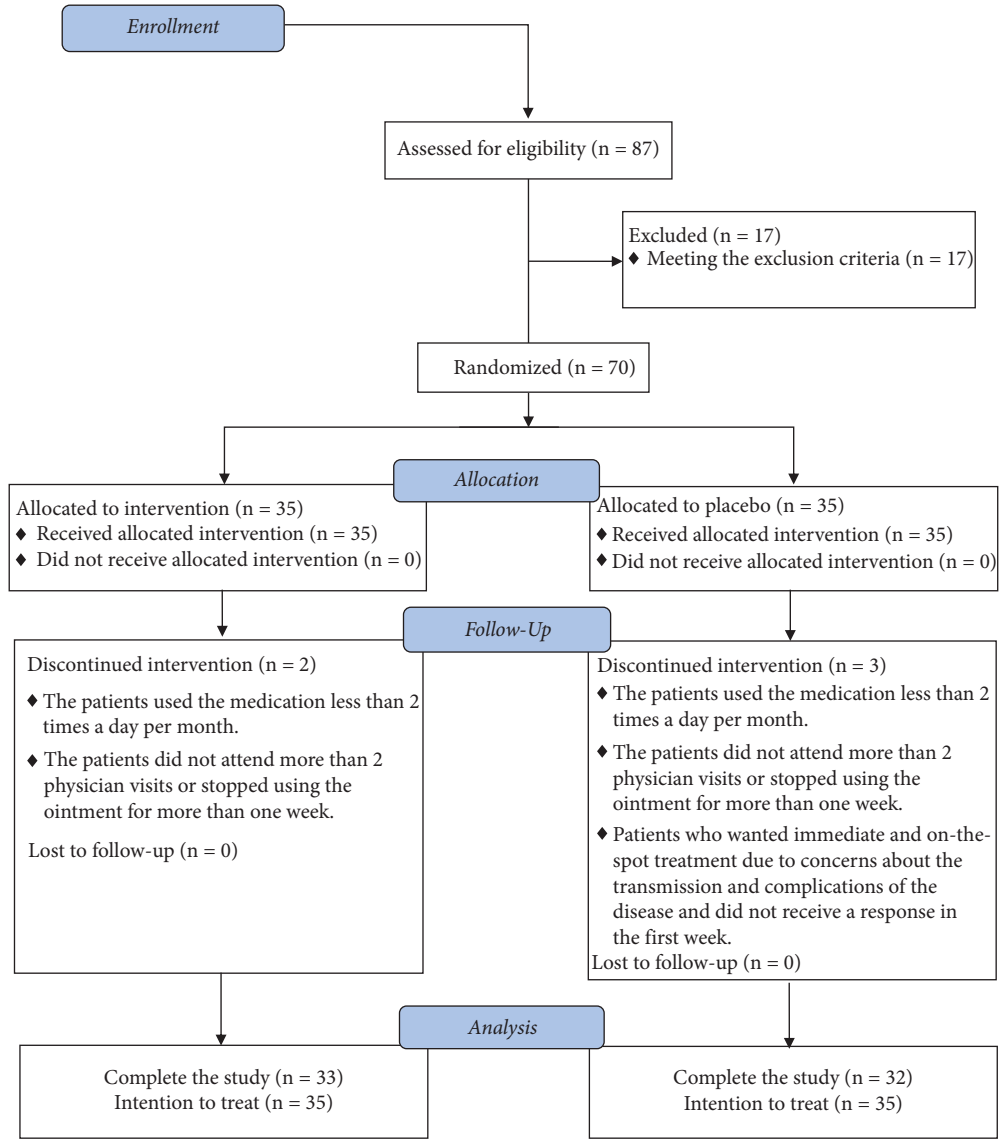

Figure 1: The flowchart of the participants' selection and allocation.

Table 2: Clinical improvement and recurrence of warts in the studied groups.

Clinical improvement	Outcomes Intervention group		Placebo group
	35; CI: 95%		35; CI: 95%
Complete clearance	24 (68.57%); 0.51–0.81		3 (8.57%); 0.02–0.23
Partial clearance	9 (25.71%); 0.14–0.42		2 (5.71%); 0.006–0.19
No response	2 (5.71%); 0.006–0.196		30 (85.71%); 0.70–0.94
	Value	*df*	Asymptotic significance (2-sided)
Pearson chi-square	45.288	2	<0.001
Likelihood ratio	52.810	2	<0.001
Recurrence rates Patients with complete clearance	Intervention group $N = 24$		Placebo group $N = 3$
Number of patients with recurrence	0		3 (8.57%); 0.02–0.23
	Value	*df*	Asymptotic significance (2-sided)
Pearson chi-square	27	1	<0.001
Likelihood ratio	18.837	1	<0.001

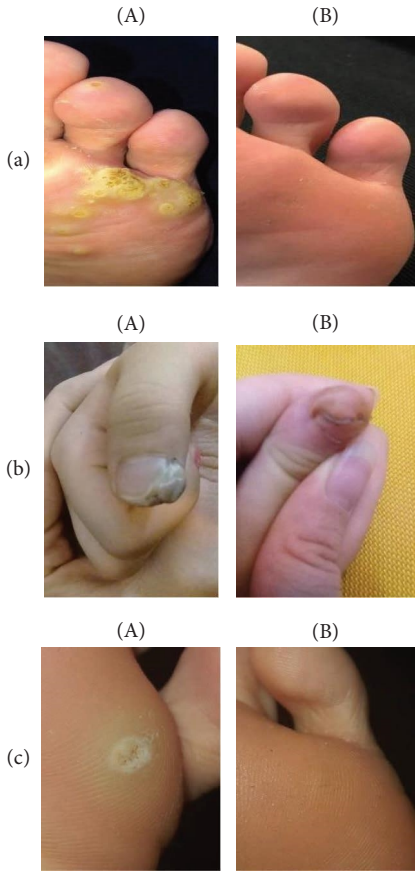

Figure 2: Plantar wart before therapy ((a)(A), (c)(A)), showing complete clearance at 12 weeks after treatment with topical *Phoenix dactylifera* L. leaf extract ((a)(B), (c)(B), respectively). Also, periungual wart before therapy ((b)(A)), showing complete clearance at 12 weeks after treatment with topical *Phoenix dactylifera* L. leaf extract ((b)(B)).

the intervention group. Among the remaining 32 participants assigned to the placebo group, three achieved complete clearance of warts, two showed partial reduction of lesion area, and the others showed no changes. In addition, all participants in the placebo group with complete clearance ($N = 3$) showed recurrence of warts during the follow-up period (Table 2, Figure 3).

3.3. Time to Complete Clearance. The time to complete clearance in the placebo group was significantly higher than that in the intervention group (Table 3). On average, the duration of complete wart clearance in the intervention group was 7.61 weeks (53.30 ± 17.17 days).

3.4. Clearance Rate Based on Wart's Type. The most prevalent wart type in the intervention group was verruca vulgaris, with a cure rate of 64.7% after the trial period. All plantar warts in the intervention group were cured by the end of the study (cure rate: 100%). 20% of plane and 50% of periungual warts were also completely cleared (Table 4). In the placebo group, the most common wart type was verruca vulgaris, with a cure rate of 5.26%. Plane and plantar warts in this group showed more significant response than verruca vulgaris (10% and 16.66% cure rates, respectively). No periungual warts were observed in the placebo group at the baseline (Table 4).

3.5. Patient's Satisfaction and Likert Scale Score. In the intervention group, 28 patients were very satisfied with their treatment (Likert scale score = 5). In comparison, five patients were almost satisfied with the partial removal of warts at the end of the study period (Likert scale score = 4) (Table 5) (Figure 4). The mean Likert scale score was 4.24 ± 1.15 (mean ± SD) in the intervention group, indicating probable increase in quality of life (QOL) and patient compliance. Most participants in the placebo group reported low satisfaction due to lack of significant improvement (Table 5). No adverse effects or recurrence were observed during the intervention or follow-up periods.

4. Discussion

The efficacy and safety of WartOver® were evaluated in our pilot clinical study that was conducted on 30 patients with skin warts. Patients used WartOver® 3 times a day for

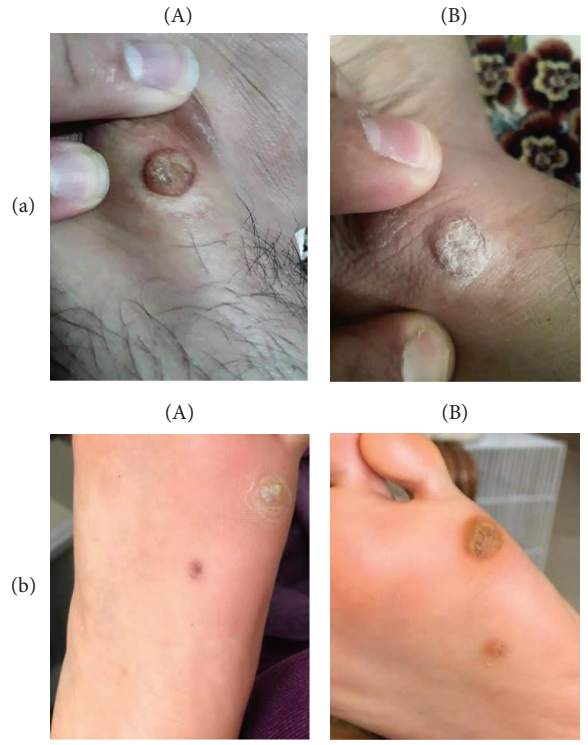

Figure 3: Plantar wart before therapy ((a)(A), (b)(A)), showing no complete, even partial clearance at 12 weeks after treatment with topical placebo ((a)(B), (b)(B), respectively).

Table 3: Time to complete clearance among intervention and placebo groups in days.

Characteristics	Intervention group ($N = 24$)	Placebo group ($N = 3$)	P value; CI: 95%
Time to complete clearance	53.30 ± 17.17 (mean ± SD)	76.33 ± 15.92 (mean ± SD)	0.031; 0.02 to 0.43

Table 4: The complete clearance rate among intervention and placebo groups.

Wart types	Outcome			
	Intervention group		Placebo group	
	Baseline	Clearance (%)	Baseline	Clearance (%)
Verruca vulgaris	17	11 (64.7)	19	1 (5.26)
Plantar	11	11 (100)	6	1 (16.66)
Plane	5	1 (20)	10	1 (10)
Periungual	2	1 (50)	0	0 (0)
Total	35	24 (68.57)	35	3 (8.57)
	Value		*df*	Asymptotic significance (2-sided)
Pearson chi-square	5.248		3	0.154
Likelihood ratio	6.075		3	0.108

maximally 8 weeks. Out of 24 patients who completed the study, 19 patients recovered completely (63%) with 3.9 ± 1.76 (mean ± SD) of Likert score and no complications or recurrence of the disease. Considering that the previous study was conducted only in the patient group and there was no control group for comparison and also the short follow-up period, it was necessary to design a two-armed drug and placebo study with a longer follow-up for a more accurate evaluation.

According to the results of our current study, compared with the placebo group, complete clearance of warts due to the intervention was significant (68.57% versus 8.57%; p value: <0.0001). Use of WartOver® ointment for 12 weeks or to complete clearance of warts showed no significant adverse reaction; besides, the patient satisfaction based on the Likert score was very promising and hopeful (p value <0.0001). Also, no recurrence was observed during the therapy period with WartOver® and at the 6-month follow-up. These results were obtained while most of these patients did not respond to their previous treatments or had recurrence of warts after those.

Table 5: The placebo and intervention groups' Likert scale score.

Outcomes	Intervention group		Placebo group
Patients' satisfaction	$N = 35$; CI: 95% 4.24 ± 1.15 (mean ± SD)		$N = 35$; CI: 95% 2.54 ± 1.29 (mean ± SD)
Excellent (score: 5)	28 (80%); 0.63–0.90		3 (8.57%); 0.02–0.23
Good (score: 4)	5 (14.28%); 0.05–0.29		6 (17.14%); 0.07–0.33
I did not decide (score: 3)	2 (5.71%); 0.006–0.196		8 (22.85%); 0.11–0.39
Unsatisfied (score: 2)	0		8 (22.85%); 0.11–0.39
Very unsatisfied (score: 1)	0		10 (28.57%); 0.16–0.45
Characteristics	Value	*df*	Asymptotic significance (2-sided)
Pearson chi-square	41.852	4	0.001
Likelihood ratio	52.162	4	0.001

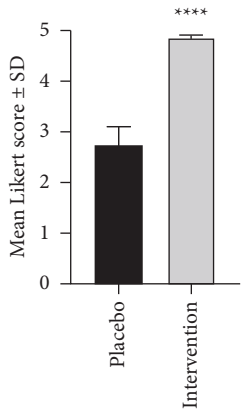

Figure 4: The patient satisfaction comparison between the intervention and placebo groups based on the Likert score. **** showed significant difference.

Patient satisfaction with therapy and quality of life are interconnected elements of healthcare. Effective treatment not only addresses specific health concerns but also contributes to an individual's overall well-being and satisfaction with life. Open communication, empathy, and positive treatment outcomes are essential for fostering patient satisfaction, while factors like health status, social relationships, and psychological well-being influence the broader concept of quality of life [13, 14]. Based on the effectiveness and the satisfaction of patients from the therapeutic effect of WartOver®, we expect that it can increase patient's quality of life.

In terms of mechanism of action, the phenolic acids of *P. dactylifera* L. particularly GA and tannins exhibit antitumor, anti-inflammatory, antiviral, and antioxidant properties against HPV [15]. Antiviral activity has been demonstrated for different tannin-rich plant extracts. The in vitro antiproliferative activity of a phenolic-rich extract from *Lycium barbarum* fruits against head and neck HPV16 squamous-cell carcinoma (OSCC) has been demonstrated, indicating that *L. barbarum* extract inhibits human papillomavirus (HPV) type 16 cell lines [16]. Tannins may be able to inhibit several aspects of viral replication, such as the extracellular virions themselves, their cellular attachment and penetration, the host cell's replication process, and the assembly of fresh viral particles. Tannins from *Hamamelis virginiana* bark extract show antiviral efficacy against influenza A virus and HPV [17]. It was also observed that a cream containing 5% date palm kernel ethanol extract exhibited potent antiviral activity against herpes simplex virus type 1 (HSV-1) infection. This formulation was demonstrated to be one of the most effective therapeutic agents for treating HSV-1-infected mice [18]. GA, as a phenolic acid, has been shown in a recent study to be effective against the RNA viruses parainfluenza-3 and herpes simplex-1 [19]. A study showed that GA inhibited HPV-positive cell proliferation (human cervical epithelial cells containing HPV) dose-dependently. GA induced apoptosis in HPV and HeLa cells, resulting in reduced viability, as well as activation of p53 transcripts in HPV and HeLa cells [20]. It has been shown that GA induces apoptosis in human cervical epithelial cells containing human papillomavirus type 16 episomes [20].

Kemp et al. [21] found higher levels of proinflammatory cytokines among women with persistent HPV infection than women without HPV infection. Inflammation and its associated diseases are mainly caused by cycloxygenase-2-(COX-2-) catalyzed prostaglandin E2 synthesis [22, 23]. Several studies have demonstrated that *P. dactylifera* L. contents can inhibit COX-2 activity [24, 25].

Considering the efficacy and safety of WartOver® due to its antiviral, anti-inflammatory, and antioxidative effect in the treatment of skin warts in our both clinical studies, we suggest it as a novel therapeutic option for skin warts.

5. Conclusion

Topical application of WartOver® ointment, a novel drug based on date palm (*Phoenix dactylifera* L.) leaf extract, has been found to be effective, safe, and relatively cheap treatment for cutaneous warts. The safety and efficacy of our formulation in the pediatric, pregnant, and lactating populations remain unknown. Further studies are warranted to evaluate the potential of our formulation in this population, given the high prevalence and skin-to-skin transmission ability of warts. We excluded patients with genital warts from this study because the topical formulation required specific considerations for this region, such as unique microbial controls, specific pH, and higher sensitivity to probable irritants. Future clinical trials with a formulation tailored for the genital application may determine the efficacy and safety of palm date leaf extract for genital warts as well.

Data Availability

Data are available on request from the authors.

Additional Points

Highlights. (i) Cutaneous warts are benign epithelial proliferations caused by human papillomavirus infection. (ii) Leaves of *Phoenix dactylifera* L. have been demonstrated to possess antiviral effects and have been used to treat warts in Iran's folk medicine. (iii) WartOver®, which is based on the extract of *P. dactylifera* L. leaves, caused 68.57% complete clearance. (iv) There was no recurrence of warts or any adverse effects with WartOver®.

Conflicts of Interest

N. Aramipour is the inventor and patent holder of the WartOver® botanical drug. N. Aramipour, M. Saber, N.A. Lashgari, M.R. Niavand, and F. Tavakoli-Far worked at Aras Pharmaceuticals LTD. at the time of writing the manuscript.

Authors' Contributions

A. Ayatollahi, A. Firooz, S. Shokouie, M. Fattahi, R.M. Robati, and S. Sadeghi were responsible for visualization, supervision, and review and editing. N. Aramipour was responsible for conceptualization, resources, and investigation. M.R. Niavand and F. Tavakoli-Far were responsible for original draft preparation, formal analysis, visualization, and review and editing. M. Saber and A. Sadri were responsible for methodology, visualization, supervision, and review and editing. N.A. Lashgari was responsible for original draft preparation, formal analysis, methodology, visualization, supervision, and review and editing.

Acknowledgments

The authors thank Tehran University of Medical Sciences and Aras Pharmaceuticals LTD. for their cooperation. Aras Pharmaceuticals LTD. provided WartOver® samples as part of this research; provided funding and support for the trial; drafted the manuscript; created the figures for publication; sponsored the design and conduct of the study; collected, managed, analyzed, and interpreted the data; and coordinated the preparation, review, and approval of the manuscript.

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