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Research Article

The Efficacy of Combined Olive Leaf and Curcumin Extract on Healing Human Papillomavirus: A Randomized Clinical Trial

Fatemeh Mehrabi rad,[1] **Farahnaz Changaee**,[2] **Tahereh Toulabi**,[3] **Fatemeh Yari**,[4] **Marzieh Rashidipour**,[5] **Rasool Mohammadi**,[6] **Sajad Yarahmadi**,[3,7] **and Mohammad Almasian**[8]

[1]*Student Research Committee, School of Nursing and Midwifery, Lorestan University of Medical Sciences, Khorramabad, Iran*
[2]*Razi Herbal Medicines Research Center, School of Nursing and Midwifery, Lorestan University of Medical Sciences, Khorramabad, Iran*
[3]*Cardiovascular Research Center, School of Nursing and Midwifery, Lorestan University of Medical Sciences, Khorramabad, Iran*
[4]*Social Determinants of Health, School of Nursing and Midwifery, Lorestan University of Medical Sciences, Khorramabad, Iran*
[5]*Nutritional Health Research Center, Lorestan University of Medical Sciences, Khorramabad, Iran*
[6]*Nutritional Health Research Center, School of Health and Nutrition, Lorestan University of Medical Sciences, Khorramabad, Iran*
[7]*Student Research Committee, Semnan University of Medical Sciences, Semnan, Iran*
[8]*Social Determinants of Health, School of Medicine, Lorestan University of Medical Sciences, Khorramabad, Iran*

Correspondence should be addressed to Farahnaz Changaee; farahnazchangavi@yahoo.com

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Background. Genital warts are sexually transmitted diseases for which there is no definitive cure. This study aimed to determine the effect of the combination of olive leaf extract and curcumin on the number of lesions and the duration of recovery in patients with external anogenital warts. *Methods*. This study is a three-blind randomized controlled clinical trial conducted in 2020. In this study, women with external anogenital warts were enrolled by the consecutive nonprobability sampling method and then assigned by stratified block randomization to two groups: placebo ($n = 28$) and intervention ($n = 26$). In the intervention group, the combined olive leaf and curcumin extract was applied topically three times a day until recovery and up to 12 weeks. Routine treatment was administered to both groups in addition to the interventions. The number of warts, the duration of recovery, and the severity and duration of treatment side effects were assessed in all participants. *Results*. The results showed that the mean number of warts was significantly lower in the intervention group (5.65 ± 5.223) than in the placebo group (7.61 ± 5.245) from the fifth day of treatment onwards ($p = 0.027$). The mean duration of recovery in days in the intervention group (14.73 ± 9.735)) was significantly less than the placebo group (34.25 ± 18.863) ($p = 0.001$). In addition, there was no significant difference between the two groups in the frequency of drug side effects such as burning ($p = 0.083$), redness ($p = 0.413$), and itching ($p = 0.706$). The intervention group experienced side effects for a shorter duration of time (1.50 ± 1.924) compared to the placebo group (4.93 ± 8.366) ($p = 0.043$). *Conclusion*. The combined 10% olive leaf and curcumin extract can be effective in reducing the number of warts, duration of healing, and reducing the duration of complications in patients with external anogenital warts and is recommended as a complementary treatment for these patients. This trail is registered with IRCT20200509047350N1

1. Introduction

Human papillomavirus (HPV) is one of the most common causes of sexually transmitted diseases [1]. Human papillomavirus is a virus with two strands of deoxyribo-nucleic acid (DNA) from the Papillomaviridae family that is only hosted by humans. Human papillomavirus is transmitted through the skin or mucous membranes. It often affects squamous tissues and causes hyperplastic lesions called warts, which remain latent infections in tissues [2–4]. Statistics show that the prevalence of HPV in the world is increasing. The prevalence of HPV in developing countries is 42.4%, and it is 22.6% in developed countries [5, 6]. Most HPV infections resolve on their own [7]. Clinical manifestations of HPV include burning, itching, wart-like lesions, severe discomfort, and vaginal discharge. Larger lesions may be associated with bleeding [5]. There is currently no definitive treatment for genital warts [8]. Temporary treatments for genital warts include topical medications such as podophyllin, trichloroacetic acid, interferon, green tea extract, and surgical and invasive methods such as cryotherapy, surgical removal of warts, and laser therapy [9, 10].

Despite the positive effect of these treatments on genital warts, each of the above methods has disadvantages. For example, laser therapy and cryotherapy are expensive methods that are difficult to access and sometimes require long-term follow-up. Podophyllin also causes patients to discontinue treatment due to the many topical side effects it leaves behind. On the other hand, the recurrence rate of these methods is very high [10, 11]. Although studies have shown the vaccine to be effective in preventing genital warts, not everyone has access to the vaccine. Moreover, there is no accurate information about the effectiveness and acceptability of the vaccine in the prevention of cervical cancer. Therefore, other alternative therapies should be sought [12].

The World Health Organization (WHO) recommends the use of herbal medicines due to their availability and low cost [13]. There are many plants with antiviral properties. *Curcumin, Praneem*, and *Epigallocatechin Gallate* are among the plant-derived drugs that play a role in the treatment of genital warts [14]. Olive leaf is an available substance and has rich sources of polyphenols such as oleuropein, rutin, verbose oxide, apigenin 7-glucoside, luteolin 7-glucoside, glystrozide, tyresol, and hydroxy tyrazole. The oleuropein in olives has anti-inflammatory, skin protective, antioxidant, antiatherogenic, anticancer, antibacterial, antiviral, antiaging, and vasodilating properties [15–17]. Viral diseases, such as papillomavirus, hepatitis B and C virus, herpes simplex virus (HSV) types 1 and 2, influenza type A, and coronavirus can be ameliorated by the antiviral activity of polyphenols found in olive leaves [18–21]. The immune response to viruses can be improved by the stimulating effect of olive leaf extract on phagocytosis [22].

Polyphenols can curb the progression of aggressive tumors by inhibiting DNA synthesis and cell growth and by inducing apoptosis [23]. Visa et al.'s in vitro study demonstrated for the first time that olive leaf extract may improve cervical cancer, which is mainly caused by HPV [24]. Moreover, the antiviral activity of curcumin has been demonstrated in recent studies [25] against hepatitis and influenza among other diseases. It has also been reported to inhibit Human Immunodeficiency Virus (HIV), HSV-2, and HPV, indicating the effect of curcumin on suppressing sexually transmitted diseases [26, 27]. According to the results of studies on the effect of 10% olive leaf extract and curcumin in the treatment of viral diseases, the combination of these two drugs seems to be more effective than either drug alone. In addition, due to the anti-inflammatory effects of this drug combination, it can be anticipated to reduce side effects such as pain, burning, and redness caused by Podophyllin as the routine drug. Few studies have been performed in this field, so the present study aimed to determine the effect of olive leaf and curcumin extract ointment on the number of warts and the recovery period of patients with external anogenital warts.

2. Materials and Methods

2.1. Trial Design. This study was a triple-blind controlled randomized clinical trial (IRCT20200509047350N1) conducted in 2020.

2.2. Participants. This study was performed on women with external anogenital warts referred to Lorestan University of Medical Sciences, Khorramabad, Iran. The inclusion criteria were the diagnosis of external anogenital warts by the midwife, being 18 years old or older, willingness to participate in the study, and access to a mobile phone or landline. The exclusion criteria were pregnancy and lactation, cancer, metabolic and chronic diseases; a compromised immune system; pelvic inflammatory diseases and other infectious diseases of the genital tract; and the use of corticosteroids, antiviral drugs, and immunosuppressant drugs during research and participation in another study that affected the results of the current study in any way. Moreover, patients who did not want to continue participating in the research and did not follow the treatment, patients who were allergic to the drugs, and patients who did not answer their phones for self-reporting were excluded from the study.

2.3. Sample Size. The sample size was estimated based on a study by Kafaei and Torabipour [28] and taking into account a type 1 error rate of 5% ($\alpha = 0.05$), the statistical power of 90% ($\beta = 0.1$), and the following formula ($P_1 = 1.00$, $P_2 = 0.74$, $Z\ (1-\alpha/2) = 1.96$, $Z\ (1-\beta) = 1.28$), and a target population of fewer than 30 people in each group.

$$n = \frac{\left(z_{1-(a/2)} + z_{1-\beta}\right)^2 \left(p_1\left(1-p_1\right) + p_2\left(1-p_2\right)\right)}{\left(p_1 - p_2\right)^2}. \quad (1)$$

2.4. Participant Assignment to Groups. Participants who met the inclusion criteria were entered into the study using a nonprobability method and then randomly assigned to the intervention ($N = 30$) and placebo ($N = 30$) groups by stratified block randomization. In this method, the strata included age group (less than or equal to 30 years/over

30 years) and lesion severity (mild/severe). The size of each block was 4 cases so 6 different combinations of 4 blocks were created and selected randomly by placing the blocks.

2.5. The Preparation of the Olive Leaf Extract. *Olea europaea* is a member of the *Oleaceae* family [29]. To make the olive leaf extract (*Olea europae L*), first, the olive leaves of the Solana cultivar were collected in the second half of February 2020 from the countryside of Khorramabad and transferred to the laboratory of the Health and Nutrition Research Center, Khorramabad, Iran. After being dried in the shade, the leaves were ground into a soft powder using an electric grinder and extracted using acetone in two steps. The resulting extract was concentrated using a rotary apparatus and dried completely. After drying, the resulting powder was washed with dichloromethane and methanol solution in a ratio of 98 : 2. Insoluble parts were separated and completely dried using a freeze dryer. High-performance liquid chromatography (HPLC) showed that oleuropein, hydroxytyrosol, and tyrosol were the main phenolic compounds of the olive leaf extract [30]. Acetone is a solvent that, after extraction, is rapidly separated by vacuum distillation and dried completely at ambient temperature.

2.6. Preparation of the Curcumin Extract. *Curcuma longa*, a perennial herb, is a member of the *Zingiberaceae (ginger)* family [31]. The HPLC showed that in *Curcuma longa* rhizome extract 15 phenolic compounds were identified, namely, digalloyl-hexoside, caffeic acid hexoside, curdione, coumaric, caffeic acid, sinapic acid, qurecetin-3-D-galactoside, casuarinin, bisdemethoxycurcumin, curcuminol, demethoxycurcumin, isorhamnetin, valoneic acid bilactone, curcumin, and curcumin-O-glucuronide [32].

To prepare the curcumin extract (*Curcuma longa*), the turmeric rhizome was ground into a soft powder using an electric grinder. Turmeric was extracted using 95% ethanol by the reflux method. After being filtered with Whatman filter paper number 3, the obtained extract was concentrated under a vacuum at 50°C.

2.7. Preparation of the Drug and the Placebo. A topical formulation containing olive leaf extract and turmeric was prepared, containing 10% of each ingredient under sterile conditions in a eucerin base. eucerin was melted at 65 to 70°C, and the other components of the formulation were added after cooling to 40°C. This formulation contained 10% propylene glycol as a moisturizer and extract carrier and 0.1% ascorbic acid. The placebo was made from a mixture of water, glycerin, and eucerin. The process of manufacturing, packaging and coding of the study drugs was carried out by the Health and Nutrition Research Center, Khorramabad, Iran. The patients were also routinely treated with 20% podophyllin applied topically once a week. Podophyllin is a plant compound that causes cells to arrest in mitosis, leading to tissue necrosis. Podophyllum resin 10% to 25% in compound tincture of benzoin used to be the standard provider-administered therapy for genital warts [33].

2.8. Blinding. Patients, researchers, and the statistician were not aware of group assignments. The placebo and the olive leaf extract and curcumin combined ointment had the same appearance, consistency, and scent and were poured into similar-looking aluminum tubes and coded with the letters *A* and *B*. At the end of the study and after data analysis, the codes were decoded for the research team.

2.9. Data Collection Instruments

(1) The demographic questionnaire included items on age, marital status, occupation, level of education, place of residence, and date of onset of illness.

(2) The patient self-report questionnaire was delivered to patients at the beginning of the study and included the presence of clinical symptoms, such as itching, burning, redness, and pain (answered with "yes" or "no"), the exact time and date of starting the treatment, the healing of the lesions, and the occurrence of drug side effects (redness, itching, and burning).

(3) The specialist evaluation questionnaire included items on the number of single lesions; the number of cauliflower-shaped lesions before, during, and after treatment; and the number of weekly treatment sessions.

2.10. Intervention. In the intervention group, a combination of 10% olive leaf-curcumin extract ointment and in the placebo group a placebo ointment with eucerin base was applied topically to each wart at the amount of two mm three times a day until complete recovery and for a maximum of 12 weeks. Before the ointments were applied for the first time, a thin layer of the drug was placed on the inside of the forearm for 20 minutes, and the area was examined for signs of allergies such as redness, itching, burning, swelling, and skin lesions. Before application, the lesion site was washed with water. The lesion site was then dried, and the patients swabbed the 10% target ointment according to their groups (the placebo and olive leaf-curcumin extracts) and refrained from washing it until the next dose. The exact time and date of starting the treatment were recorded by the researcher, and the patient was given the necessary instructions for using the drugs. Both treatment groups received the 20% Podophyllin solution once a week from a midwife. The researcher also followed the correct and timely use of drugs, their side effects, self-reports from the first day of treatment until the next visit (once a week to a midwife) and until complete recovery for a maximum of 12 weeks using a mobile phone. Necessary instructions such as the duration and method of using ointments as well as storage conditions of drugs at room temperature away from sunlight and how to wash the lesion before using ointments were given to patients by the researcher on the first day of referral.

2.11. Outcomes. The severity of the initial symptoms was assessed before the intervention as mild (less than 10 warts) and severe (10 warts and more). Additionally, the number of

warts was counted, recorded, and reported by the patients daily from the start of the study until full recovery or the completion of the 12 weeks and also weekly by a midwife. Moreover, the exact time (hour and day) when the first lesion disappeared and the recovery time were assessed and recorded until the time when all lesions had completely healed. The disappearance of all warts was considered a full recovery, the disappearance of 50% of the warts was regarded as a relative recovery, and the disappearance of less than 50% was considered a lack of recovery [34]. Finally, the side effects of the drugs, including burning, itching, and redness, were recorded by patients daily and by a specialist every week for up to 12 weeks.

2.12. Data Analysis. Demographic information and the frequency of side effects were analyzed by the chi-squared test. The initial duration of time for a reduction in the number of lesions, recovery time in days, and the number of days on which side effects were experienced were analyzed by the independent *t*-test. The number of warts was analyzed by the Mann–Whitney test. The data analysis was conducted by the SPSS software version 22. The significance level was set at 0.05.

3. Results

The study flow diagram is shown in Figure 1. The mean age of the placebo group participants was 34.46 ± 8.048 and it was 36.81 ± 9.687 in the olive leaf/curcumin extract group, which was not significantly different ($p = 0.337$).

No significant difference was observed between the groups in terms of demographic information (Table 1).

Symptoms such as pain, redness, burning, and itching were not observed in any of the patients before the intervention and participants only complained of the presence and number of genital warts. The mean number of lesions before the intervention in the olive leaf/curcumin group was 7.38 ± 5.933 and it was 7.71 ± 5.297 in the placebo group. This figure was not significantly different before the intervention ($p = 0.807$).

Patients were not significantly different before the intervention in terms of the severity of the symptoms based on Table 2 ($p = 0.999$).

Moreover, the time since the appearance of the first lesion was three months or less in 19 patients (35.18%). It was between three and six months in 21 patients (38.88%) and more than six months in 14 patients (25.92%). The mean time since the appearance of the symptoms in days was not significantly different between the two groups, the time being 126.30 ± 75.47 days in the placebo group and 147.69 ± 142.16 days in the extract group ($p = 0.502$).

The mean number of warts was not significantly different during the first five days in the intervention group (7.38 ± 5.39) and the placebo group (7.75 ± 5.25), ($p = 0.740$). However, from the fifth day on, the number of warts was significantly lower in the group treated with the olive leaf and curcumin extract (5.65 ± 5.22) than in the placebo group (7.61 ± 5.245), ($p = 0.027$) (Table 3).

Additionally, patients treated with the olive leaf/curcumin extract ointment (52.96 ± 16.665) responded to treatment faster than the placebo group (194.29 ± 53.621) and improvement in the first lesion occurred earlier in them in hours. The number of warts in the olive leaf/curcumin extract ointment group reached zero in 14.73 ± 9.73 days and healed completely, while the recovery lasted 34.25 ± 18.86 days in the placebo group ($p = 0.001$), (Figure 2).

There was no significant difference between the two groups in terms of the frequency of side effects (burning, redness, and itching), (Table 4). Furthermore, the intervention group patients experienced side effects on fewer days (1.50 ± 1.924) than the placebo group (4.93 ± 8.366), ($p = 0.043$).

4. Discussion

This study was a clinical trial comparing the effects of 10% olive leaf and curcumin extract ointment and placebo on the healing of genital warts. The results showed that after the treatment was initiated, the elimination of the first lesion as well as complete healing in the group receiving olive leaf and curcumin extract occurred in a shorter time than in the placebo group. In addition, the number of genital warts was lower in the intervention group than in the control group. The results showed that the severity of the side effects of the treatments was not different in the intervention group from the placebo group, but the number of days that the participants in the intervention group suffered from side effects was less.

The results showed that the number of warts reached zero in the intervention group on the fourteenth day on average. However, this number reached zero on the thirty-fourth day in the placebo group. The effectiveness of treatment in the intervention group was likely due to the antiviral properties of olive leaf and curcumin. The oleuropein present in olive leaves possesses anti-inflammatory, skin-protective, antioxidant, anticancer, antibacterial, and antiviral properties [16]. Evidence suggests that polyphenols exert their antiviral effects by inhibiting viruses from binding to receptors, signal transduction, and antiproliferative effects, as well as inducing cellular apoptosis [34]. In one study, olive leaf extract was reported to block viruses from attaching to the cell and thus eliminate the viruses' access to the cell [30]. In a study by Gorzynik et al. on the benefits of plant polyphenols, it was stated that polyphenols have antiviral activity against viral diseases such as papillomavirus, hepatitis B and C virus, HSV 1 and 2, and influenza type A [35]. The results of another study showed that curcumin also demonstrates antiviral activity [25]. On curcumin as an antiviral agent, Jennings et al. stated that curcumin has a variety of biological functions, including anticancer, antioxidant, and antimicrobial properties. Curcumin can act not only as an antifungal and antibacterial compound but also as an antiviral compound that prevents virus replication by several mechanisms [36]. One study found that Indian areca palm leaves could be effective in treating male genital warts. Due to their anti-inflammatory properties, areca palm

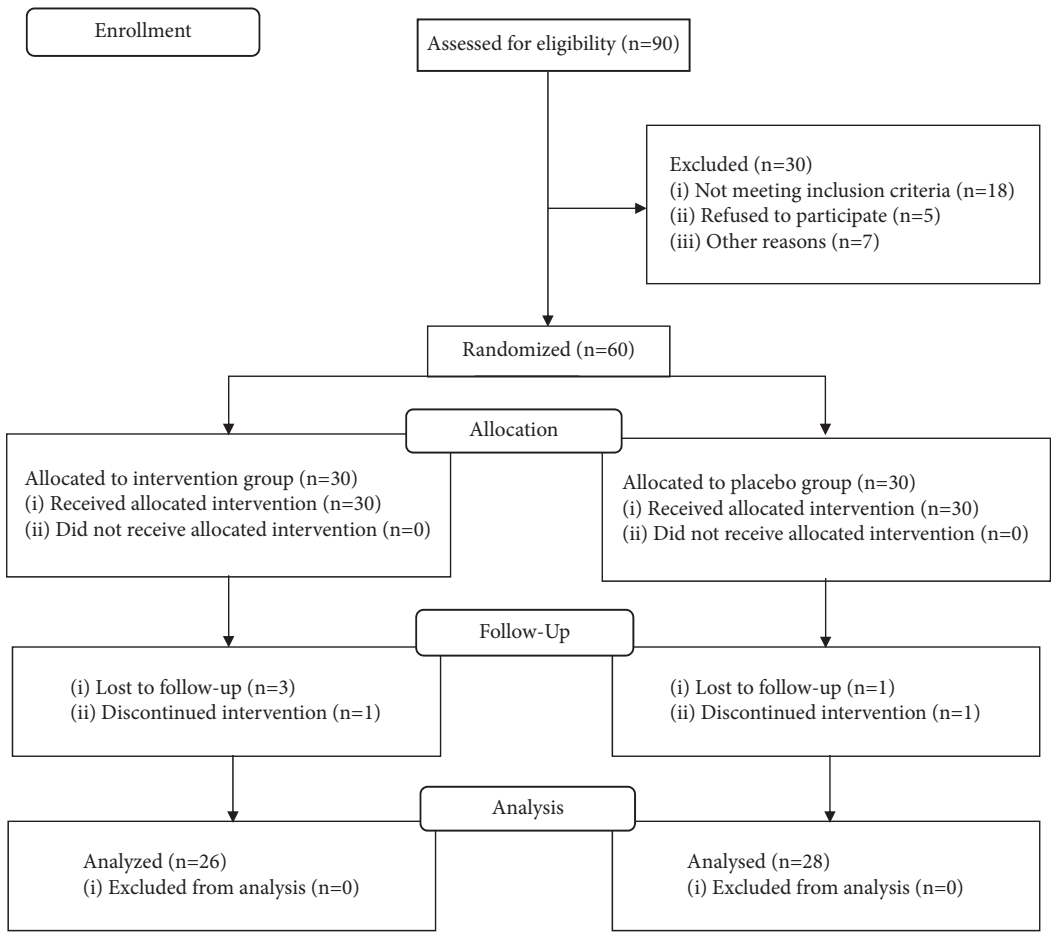

Figure 1: Study flow diagram.

Table 1: Comparison of demographic information between study groups.

Variables	Intervention *N* (%)	Placebo *N* (%)	Total *N* (%)	*p* value*
Marital status				
Married	22 (84.6)	24 (85.7)	46 (85.2)	
Single	2 (7.7)	0 (0)	2 (3.7)	0.261
Divorced	2 (7.7)	4 (14.3)	6 (11.1)	
Education				
Primary or high school	10 (38.5)	9 (32.1)	19 (35.2)	
High school diploma	9 (34.6)	15 (53.6)	24 (44.4)	0.317
University	7 (26.9)	4 (14.3)	11 (20.4)	
Location				
Urban	20 (76.9)	18.524 (85.7)	44 (81.5)	0.494
Rural	4 (14.3)	10 (18.5)	14 (18.5)	
Occupational status				
Housewife	21 (80.8)	22 (78.6)	43 (79.6)	
Self-employed	2 (7.7)	5 (17.9)	7 (13)	0.327
Employee	3 (11.5)	1 (3.6)	4 (7.4)	

*The chi-squared test.

Table 2: Comparison of baseline symptoms in study groups before the intervention.

Symptoms	Intervention *N* (%)	Placebo *N* (%)	Total *N* (%)	*p*-value*
Severe	13 (50)	14 (50)	27 (50)	0.999
Discoloration	13 (50)	14 (50)	27 (50)	
Cauliflower lesions				
Yes	3 (11.5)	3 (10.7)	6 (11.1)	0.999
No	23 (88.5)	25 (89.3)	48 (88.9)	

*The chi-squared test.

Table 3: Comparison of the number of warts between the two groups during the study.

Days	Intervention mean (SD)	Placebo mean (SD)	p value*
1	7.38 (5.93)	7.75 (5.25)	0.740
5	5.65 (5.22)	7.61 (5.24)	0.027
10	3.23 (3.44)	6.04 (4.67)	0.004
15	2.08 (2.85)	5.32 (4.57)	0.002
20	1.19 (1.98)	4.25 (3.84)	0.001
25	0.42 (0.94)	3.43 (3.62)	0.001
30	0.12 (0.43)	2.89 (3.17)	0.001
35	0.00 (0.00)	1.96 (2.57)	0.001
40	0.00 (0.00)	1.46 (2.30)	0.001
45	0.00 (0.00)	1.04 (1.83)	0.004
50	0.00 (0.00)	0.79 (1.59)	0.013
55	0.00 (0.00)	0.54 (1.20)	0.025
60	0.00 (0.00)	0.32 (0.81)	0.047
65	0.00 (0.00)	0.18 (0.67)	0.169
70	0.00 (0.00)	0.00 (0.00)	0.999

*The Mann–Whitney test.

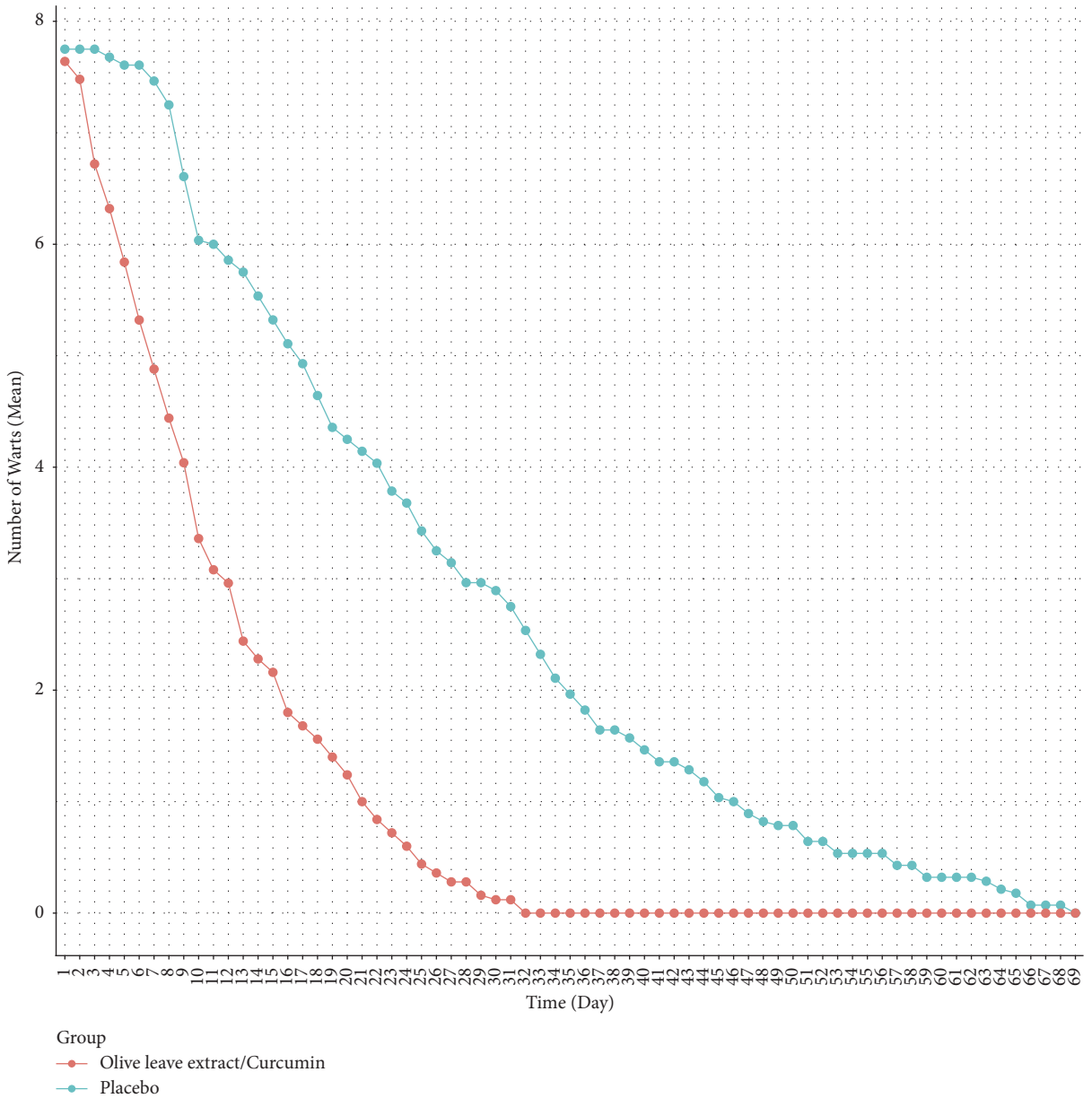

Figure 2: Comparison of the number of warts between groups during the study.

Table 4: Comparison of the frequency of drug side effects between groups during the study.

Drug side effects	Intervention *N* (%)	Placebo *N* (%)	Total *N* (%)	*p* value*
Burning				
Yes	12 (46.2)	6 (21.4)	18 (33.3)	0.083
No	14 (53.8)	22 (78.6)	36 (66.7)	
Itching				
Yes	3 (11.5)	5 (17.9)	8 (14.8)	0.706
No	23 (88.5)	23 (82.1)	46 (85.2)	
Redness				
Yes	4 (15.4)	2 (7.1)	6 (11.1)	0.413
No	22 (84.6)	26 (92.9)	48 (88.9)	

*The chi-squared test.

leaves can be effective in treating warts and healing lesions. Olive leaf extract and curcumin also have anti-inflammatory properties [37]. A clinical trial showed that the use of 10% garlic extract can be effective in the treatment of genital warts in terms of reducing the treatment period and the number of warts. Garlic extracts, such as olive leaf and curcumin extracts, have been shown to have antioxidant properties [38]. However, garlic contains sulfur compounds, and some studies have stated that garlic application usually results in local inflammation and, if there is poor wound care or a secondary infection, it can cause a severe dermal reaction and a deep chemical burn [39]. Nevertheless, in the present study, the side effects in the intervention group were minor side effects such as itching or redness.

The results showed that the intervention group participants experienced the drug side effects including burning, itching, and redness for a shorter period. In line with the current study, another clinical trial showed that patients with HSV experienced less pain, itching, burning, and discoloration followed by the application of topical olive leaf extract [30]. The results of another clinical trial also showed patients with genital warts who received shallot extract topically experienced less burning, itching, and pain than those who received podophyllin [40], which may be due to its anti-inflammatory properties [41]. There have also been reports of increased local inflammation following the use of curcumin, although these reports claim to improve healing due to the increased severity of inflammation. The evidence is consistent with the results of the researcher's study in this experiment in terms of rapid healing of the lesion site [42, 43]. A review study showed that the use of plants rich in polyphenols and antioxidants has been approved and recommended as an acceptable treatment for external genital warts, which is consistent with the results of the present study [44].

Numerous studies have shown that olives and their products decrease inflammation and accelerate wound healing by increasing antioxidant activity [45, 46]. Since antioxidant therapy strengthens the cell's antioxidant defense mechanisms, it may reduce the damage from free radicals, minimize tissue damage during injury, and may accelerate wound healing [47].

The present study showed that during the fourth week, 100% of patients in the combined 10% olive leaf extract and curcumin group recovered completely. In the intervention group, treatment with podophyllin was not stopped. In the control group that received just podophyllin, 100% of patients recovered completely during the ninth week. In comparison, a study comparing the effects of 10% garlic extract and cryotherapy on genital warts in men showed that only 69.7% of patients who received 10% garlic extract recovered completely. Moreover, in the cryotherapy group, 78.8% of patients improved by the eighth week [38]. Another study comparing the effect of shallot extract and podophyllin on female genital warts showed that in the sixth week, only 56.5% of the shallot extract group and 50% of the podophyllin group experienced complete recovery [40]. These results indicate that the use of olive leaf extract and curcumin can be a more effective treatment than garlic extract, cryotherapy [38], shallot extract, and podophyllin alone [40]. It can also be concluded that the use of a combination of chemical drugs and complementary medicine can be effective in a short time compared to monotherapy in patients with genital warts.

This is a study to investigate the effects of a combination of 10% olive leaf extract and curcumin in the treatment of genital warts, and there were naturally some limitations in this study. Among the limitations of this study were the low sample size and the lack of serological tests to confirm genital warts. Furthermore, in this study, we could not investigate the absolute effects of olive leaf extract and curcumin because we were not able to eliminate routine treatment due to ethical issues, so routine treatment was received in both groups. We used only a 10% dose of a combination of olive leaf extract and curcumin, and it is recommended that other doses be evaluated as well. Since genital warts are a recurrent disease, it is recommended that the long-term effects of the combined olive leaf extract and curcumin be evaluated. In this study, we could not investigate the effects of curcumin and olive leaf extract alone, so it is suggested that in future studies, these compounds be evaluated in factorial design studies.

5. Conclusion

The combination of 10% olive leaf and curcumin extract as a complementary treatment along with routine treatments can be effective in reducing the number of external anogenital warts in women and reducing the duration of the disease and the duration of side effects caused by drug use and is recommended as a complementary treatment for these patients.

Data Availability

The [DATA TYPE] data used to support the findings of this study are included within the article.

Ethical Approval

The current research was approved by the Research Ethics Committee of Lorestan University of Medical Science in 2020 (IR.LUMS.REC.1399.045). Before the start of the study, the objectives of the study were explained to the patients and written informed consent was obtained from them. The privacy of the participants was observed during the enrollment and the study. The whole treatment course was free for the participants. To ensure confidentiality, the names of the participants were not recorded on the data collection instruments. The participants were free to leave the study at any stage of the study. The participants were not deprived of routine care and treatment. On request, the participants received the results of the study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Tahereh Toulabi, Farahnaz Changaee, Fatemeh Mehrabi rad, Sajad Yarahmadi, Mohammad Almasian, Fatemeh Yari, Marzieh Rashidipour, Rasool Mohammadi contributed to the study design, data collection, and manuscript writing. Fatemeh Mehrabi rad, Sajad Yarahmadi, Rasool Mohammadi have contributed to the data analysis. All authors have read and approved the final version and added a statement confirming this.

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