scientific reports

Check for updates

OPEN

# Evaluating the effectiveness of topical olive leaf extract emulgel in managing recurrent herpes labialis: a randomized controlled clinical study

Mai Adnan Gaizeh Al-Hallak[1]✉, Jamileh Ali Hsaian[2] & Abeer Ahmad Aljoujou[1]

**Recurrent herpes labialis (RHL) is a lifelong oral health issue that affects about one-third of the world's population, causing frequent, painful, and discomfort lesions. This randomized, triple-blinded study aimed to evaluate the effectiveness of olive leaf extract (OLE) compared to acyclovir cream (Veramid 5%) in managing vesicular stage of RHL lesions. Forty patients were randomly divided into two equal groups and were instructed to apply the prescribed medication five times a day for five consecutive days. The evaluation was carried out by measuring the pain intensity on the first day before the treatment was applied (T0), 48 h (T1), and 7 days later (T2). Additionally, the day when the pain completely healed and the day when the lesion's crust fell off spontaneously were recorded. Statistical analysis was conducted using the Mann-Whitney test at a significance level of $\alpha = 0.05$. The study results indicated that there were no significant differences in pain intensity between the two groups during the three evaluation times: T0 ($P = 920$), T1 ($P = 0.596$), and T2 ($P = 1.00$). Furthermore, there was no significant difference in the day when the pain was completely healed ($P = 0.697$). However, the OLE showed a statistically significant advantage regarding the day the lesions' crust fell off ($P = 0.040$). In conclusion, OLE may be a potential alternative treatment for RHL.**

**Trial registration: isrctn.com ID: ISRCTN87606522, 04/09/2023.**

**Keywords** Recurrent herpes labialis, Herpes simplex virus, Olive leaf extract, Emulgel, Acyclovir

Herbal medicine is a form of alternative medicine that uses plant extracts to treat and prevent diseases. Its growing popularity stems from the safety, efficacy, and abundance of medicinal herbs[1,2].

Plants of the Mediterranean region are particularly well-known for their unique medicinal properties. This region is home to Olea europaea L., commonly known as the olive tree, which is one of the oldest tree species. The fruit of the olive tree, known as olives, and its by-products, such as olive oil, have historically formed the basis of nutrition for the Indigenous people of the Mediterranean region[1,3].

Olive leaves have gained substantial attention in the human diet due to their diverse health benefits, which include antioxidant, hypoglycemic, antihypertensive, antimicrobial, antiviral, and anti-atherosclerotic properties. Such health benefits are primarily attributed to the presence of phenolic compounds in olive leaves, with oleuropein, hydroxytyrosol, and verbascoside being the most notable. Olive trees synthesize these phenols as a natural response to pathogen and insect attacks[1,4].

Recurrent herpes labialis (RHL) is a viral infection caused by the reactivation of herpes simplex virus type 1 (HSV-1). Primary infection with this virus occurs mainly during childhood through direct exposure to infected patients' saliva or secretions from lesions. The virus then establishes a latent state in the nerve ganglia, particularly the trigeminal nerve ganglion, where it remains dormant until reactivated by various triggers[5,6].

The development of RHL usually involves multiple clinical stages. In the early stage, a feeling of pain, tingling, or burning may occur in the affected area, followed by the formation of small vesicles. The vesicles may rupture,

[1]Faculty of Dentistry, Oral Medicine Department, Damascus University, Damascus University, Damascus, Syria. [2]Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, Damascus/Syria University, Damascus University and Yarmouk Private University, Damascus, Syria. ✉email: maighallak@gmail.com; mai95.hallak@damascusuniversity.edu.sy

forming a soft crust that later turns into a hard crust. Eventually, the crust falls off, allowing the lesion to heal without leaving scars. During the healing process, pain and discomfort may occur, and complete recovery may take 7 to 10 days[5,7].

The reactivation of the HSV is typically triggered by various factors, including stress, trauma, menstrual or hormonal changes in women, fever, exposure to sunlight or ultraviolet radiation, and immunosuppression resulting from radiation or chemotherapy[5,8].

Spontaneous healing may occur, but topical antiviral medications are preferred for their ability to reduce the viral load and its ability to infect.

Oral HSV-1 infection remains a highly prevalent viral infection that affects a large proportion of the world's population. According to the World Health Organization (WHO), approximately 67% of people under the age of 50, which equates to around 3.7 billion people, suffer from HSV-1 infection worldwide[5]. According to statistics from the National Health and Nutrition Examination Survey (NHANES) conducted in the United States between 2015 and 2016, among individuals aged 14 to 49 years, the prevalence of antibodies to HSV-1 was 50.9% in females and 45.2% in males[9].

There is no definitive cure for HSV infection, however antiviral medications such as acyclovir and its derivatives, which are nucleoside analogues, are considered the gold standard for the management of HSV infections and are commonly administered for mitigation of the severity and duration of the outbreak[10]. Nevertheless, due to the chronic and recurrent nature of HSV infection, prolonged use of antiviral drugs has led to the development of high viral resistance due to mutations in the viral genes encoding thymidine kinase, especially among immunocompromised individuals[11].

Some studies suggest that Olive Leaf Extract (OLE) has antiviral effects due to its ability to interfere with the virus's ability to attach and enter cells. Evidence shows that OLE interacts with the surface of the phospholipid bilayer, supporting this theory. Studies also have demonstrated that OLE can prevent viral envelope fusion, acting as a viral inhibitor during the early stages of replication[12–14].

Plant extracts may present novel and efficacious remedies for the management of RHL lesions. The active ingredients contained in these extracts operate through diverse mechanisms, making it difficult for viruses to develop resistance. Furthermore, natural treatments generally exhibit fewer side effects and lower toxicity in comparison to pharmaceutical treatments[15].

Considering the widespread occurrence of HSV-1 infection globally, in addition to the growing interest in finding alternative treatments that are less toxic and reduce viral resistance to chemical drugs, and due to the increasing use of herbal remedies and medicinal plants that prove their effectiveness and considerable contribution to human health[16], we conducted this study to compare the effectiveness of topical application of acyclovir cream 5% and emulgel as pharmaceutical dosage form contain OLE in the management of RHL. The null hypothesis states that olive leaf extract emulgel would not be superior to 5% acyclovir cream in accelerating healing or relieving pain.

## Methods

### Sample and study protocol

This was a triple-blind, randomized controlled clinical trial, following the Helsinki Convention. The protocol was reviewed and approved by the Scientific Research Ethics Committee at the University of Damascus (Date 02/08/2021/No 2640) and registered in the International Standard Randomised Controlled Trial Number (ISRCTN-No.87606522, Date: 04/09/2023). All study participants provided informed consent.

The clinical section of this study was conducted at the Department of Oral Medicine, Faculty of Dentistry, while the laboratory section was conducted at the Faculty of Pharmacy. The research work was carried out between April 2022 and June 2023.

This study focused on patients over 18 years old with good general health, who visited the Department of Oral Medicine complaining of one or more RHL lesions in the vesicular stage that had appeared no more than 24 h before the examination. Pregnant and breastfeeding, patients who took anti-inflammatory medications, antibiotics, or antivirals during the four weeks before treatment were excluded, along with immunocompromised patients, diabetics, smokers, and patients who had allergic reactions to the drug used.

The sample size calculation was performed using G*Power 3.1.9.2 software, based on the mean values and standard deviations of the pain index in Gürbüz et al. study[17]. To achieve significant results with a standard α error of 0.02 and a power of 0.98, forty patients were required for the entire sample. The expected effect size was considered to be 0.5.

The patients were randomly divided into two groups: A and B. A simple randomisation method was employed using an envelope containing cards coded with the code corresponding to the treatment group. Patients in group A received acyclovir cream, while those in group B received OLE emulgel.

The control group ($n=20$) received acyclovir cream (Veramid 5%), while the study group ($n=20$) received OLE in the form of an emulgel. Patients from both groups were instructed to use their respective medication five times daily for five days. This was a triple-blind trial, which ensured that the treatment used was concealed from all the participants, researchers, and the statistician. The CONSORT flowchart of the trial is shown in Fig. 1.

### Laboratory procedures

*Plant preparation*

Olive leaves were collected in April 2022 in Damascus, Syria. An expert has identified the plant specimen. The leaves were dried in a dry environment, at room temperature, away from sunlight. After that, they were ground into powder with an electric grinder. We obtained 40 g of powder that was stored in a dark, tightly sealed glass container.

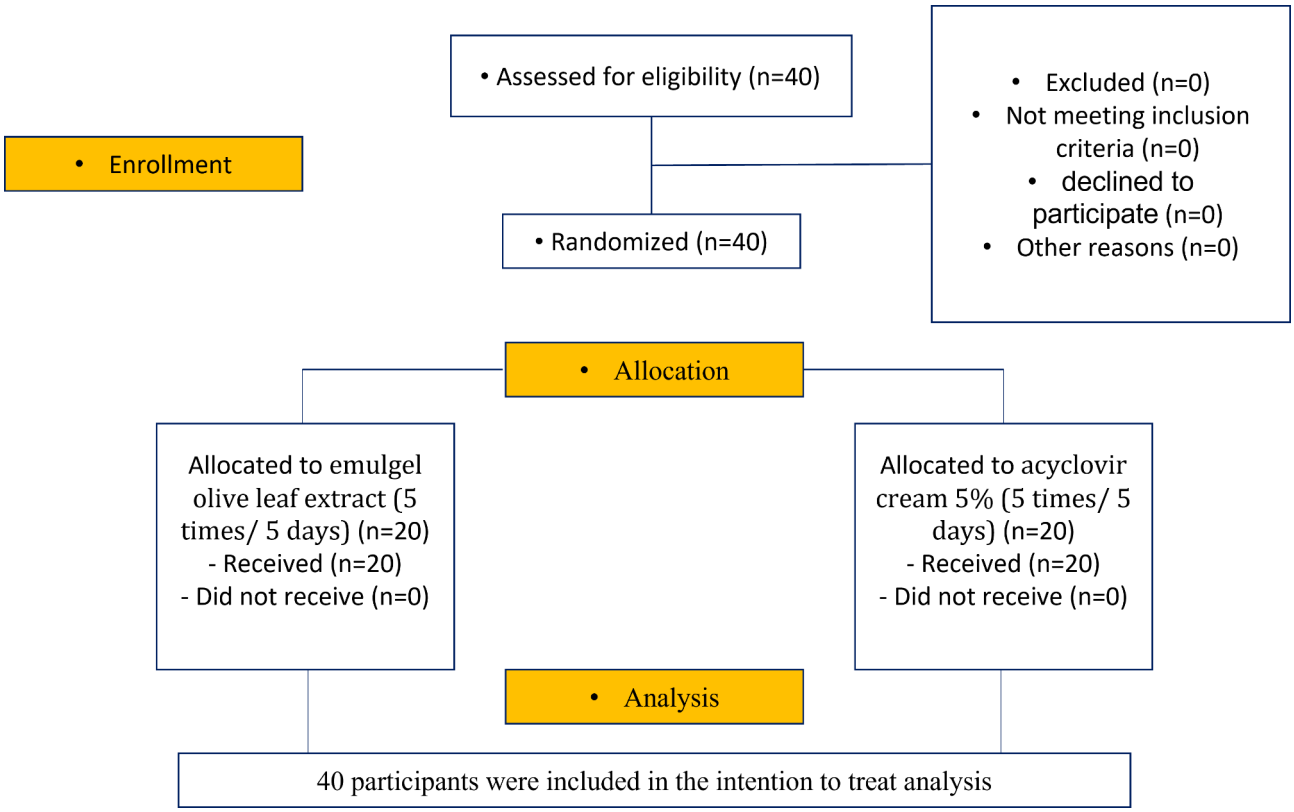



**Fig. 1**. The CONSORT flowchart of the trail.

*Extraction*

An ultrasonic bath was used to prepare a hydroalcoholic extract as mentioned by Cifá et al.[18] with some modifications. The process involved mixing 20 g of olive leaf powder with 30 ml of distilled water and 70 ml of absolute ethanol at 40 °C. The vibration was activated for 30 min, Afterwards, the extract was filtered using sterile gauze, filter paper, and micron discs. Subsequent to filtration, the extract was diluted with distilled water to obtain a total volume of 100 ml. The extract's total phenolic (TP) content was assayed using the Folin-Ciocalteau method as described in Waterhouse et al. study[19], and it was $24.20 \pm 0.84$ mg/g of dried extract.

*Prepare olive leaf extract emulgel*

Emulgel is a combination of emulsion and gel. Preparing 50 g of emulsion requires a two-phase approach, involving both an aqueous and an oily phase. The oily phase dissolved 1 g of span80 in 12.5 g of liquid paraffin, which was then mixed thoroughly. The aqueous phase was created by dissolving 2.5 g of tween80 in 5 ml of distilled water, followed by the addition of 0.075 g of methylparaben and 0.025 g of propylparaben, dissolved in 4 g of propylene glycol. Subsequently, 0.1 g of EDTA was added to the mixture, which was then combined with 25 ml of extract and thoroughly mixed. Once the aqueous and oily phases had been prepared, the oily phase was added to the aqueous phase with rapid stirring to achieve a fully emulsified product. The gel component of the final product was prepared by dissolving 1.5 g of Carbopol in 48.5 W/V of distilled water, which was stirred for 15 min. The emulsion was then gradually added to the gel and stirred continuously until the two components achieved complete homogeneity. The end product is a light yellow OLE emulgel that possesses a subtle herbal odor, which is deemed acceptable without the incorporation of any additional fragrance.

The OLE emulgel and acyclovir cream were stored in identical containers and coded with symbols A or B. The assignment of codes was solely known by the pharmacist who prepared Emulgel, while the patients and researchers were blinded to the codes throughout the study phases.

## Clinical procedures

Following the diagnosis of active RHL lesions at the vesicular phase by the researcher, participants were ensured that they met the inclusion criteria. Then they were asked to provide informed consent after learning about the aims and phases of the study. Afterward, participants were given a container of medication that was coded according to the treatment group to which they belonged.

The participants received detailed instructions on how to administer the prescribed medications. The instructions comprised washing hands, cleaning and drying the affected area delicately without applying any pressure or force. Subsequently, they were advised to apply a layer of the medication to cover the affected skin and rub it gently, taking care not to wash the medication off the skin. Furthermore, it was recommended to repeat the application approximately every 5 h for 5 days. The daily dosage equated to roughly 1 gr of Acyclovir

| Parameter | Explanation |
|---|---|
| Pain intensity | Evaluation of pain intensity from 0 to 10 according to the VAS scale, where 0 is no pain and 10 is the most severe pain possible. |
| Healing of pain | The day the patient realizes that the pain has completely disappeared. |
| Healing of the lesion | The day the crust fell off spontaneously from the lesion |

**Table 1**. Operationalization of the variables studied in patients with herpes labialis.

| | | Acyclovir group | | OLE group | | |
|---|---|---|---|---|---|---|
| | | Number | Percent % | Number | Percent % | *P*-value |
| Gender | Male | 1 | 5.0 | 2 | 10.0 | 0.249[a] |
| | Female | 19 | 95.0 | 18 | 90.0 | |
| | Total | 20 | 100.0 | 20 | 100.0 | |
| Age | Mean ± SD | 27.70 ± 9.35 | | 25.40 ± 4.25 | | 0.997[b] |

**Table 2**. Demographic profile and clinical characteristics of patients. The tests used: [a]Chi-Square, [b]Mann-Whitney U to compare the means of the two groups. *The difference is significant at the 5% significance level. Acyclovir group: using treatment with acyclovir cream 5%. OLE Group: using treatment with olive leaf extract emulgel.

cream and about 0.5 gr of OLE emulgel. To ensure compliance, the participants received a written copy of the instructions. They were also asked to immediately cease application of the medication in question and notify the researchers should any anomalous side effects manifest.

Throughout the study, patients were reminded daily through phone calls and messages to adhere to their prescribed medication regimen.

Pain intensity was measured during the first visit before treatment (T0), as well as during the second (T1) and third visits (T2), 48 h and 7 days after treatment, respectively. To accomplish this, a Visual Analogue Scale (VAS) from 0 to 10 was employed (where 0 means no pain and 10 is the most severe pain possible). In addition, the day when the pain disappeared completely and the day when the lesion crust spontaneously fell off were recorded. (Table 1)

### Statistical study

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 25. The distribution of study variables in both groups was tested using the Shapiro-Wilk test, which showed that they were not normally distributed. Therefore, a non-parametric test (Mann-Whitney) was used to compare the means of the study variables between the two groups. Furthermore, the Chi-Square test was performed to determine the independence of the variables. The significance level was set at 0.05.

## Results

The study involved 40 participants who were randomly assigned into two groups. The OLE group comprised 18 females (90%) and 2 males (10%) with an average age of 25.40 ± 4.25, while the acyclovir group consisted of 19 females (95%) and 1 male (5%) with an average age of 27.70 ± 9.35. There was no statistically significant difference between the two groups concerning gender (P-value = 0.249) or age (P-value = 0.997). as shown in Table 2.

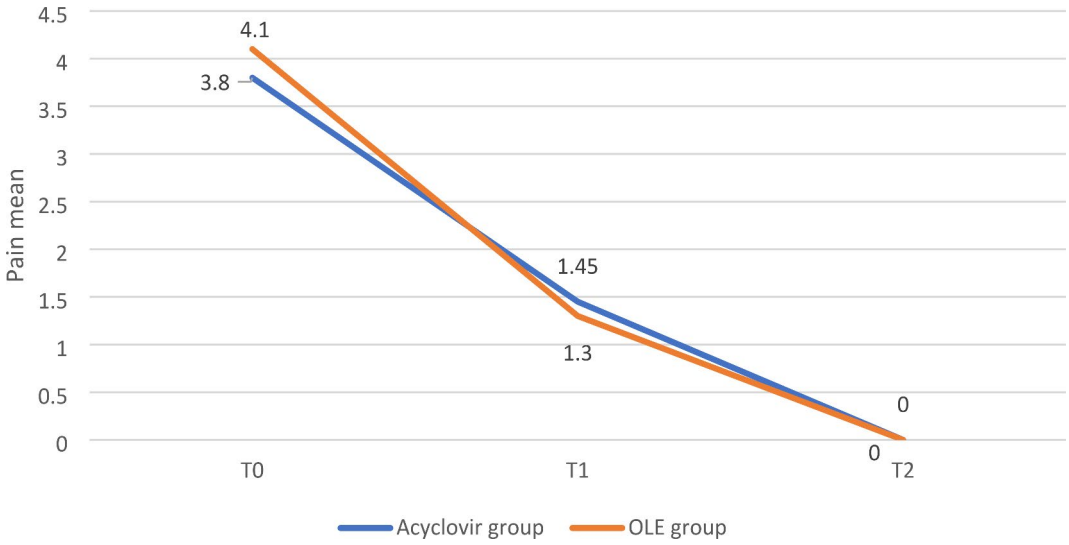
The results of the Mann-Whitney test showed that there were no significant differences in pain intensity between the two study groups at the three assessment time points: before treatment (T0) ($P = 0.920$), after 48 h (T1) ($P = 0.596$), and after 7 days (T2) ($P = 1.00$). The median pain levels were also equal in both groups at T0 and T2, recording 4 and 0, respectively. However, there was a difference at T1, where the median pain level was 0 in the OLE group and 1 in the acyclovir group. Graph 1 shows the average pain levels in both groups at the three assessment times.

The findings of the study also indicate that there were statistically significant differences between the two treatment groups concerning the day of spontaneous crust fell-off and initial lesion healing ($P = 0.040$), where the OLE group presented a faster rate of healing in comparison to the acyclovir group. Conversely, there was no significant difference between the two groups in terms of the day of complete pain relief ($P = 0.697$), as presented in Table 3.

There were no adverse effects in this study, such as superinfections, skin irritation, allergic reactions, or local intolerance. Both preparations were well tolerated.

## Discussion

This clinical study aimed to assess the effectiveness of olive leaf extract (OLE) in managing recurrent herpes labialis compared to acyclovir cream 5%, which is the standard treatment for this condition.




**Graph 1**. The average pain levels in both groups at the assessment times.

| | Acyclovir group ($n=20$) | | | | | OLE group ($n=20$) | | | | | *P*-value[a] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Min | Max | Median | Mean | SD | Min | Max | Median | Mean | SD | |
| Healing of pain | 0 | 5 | 3.5 | 2.70 | 1.63 | 0 | 5 | 2 | 2.50 | 1.61 | 0.697 |
| Healing of the lesion | 3 | 8 | 5 | 4.85 | 1.23 | 2 | 8 | 4 | 4.05 | 1.34 | *0.040 |

**Table 3**. Results of the difference test in the healing index. The test used: [a]Mann-Whitney U to compare the means of the two groups. *The difference is significant at the 5% significance level. Acyclovir group: using treatment with acyclovir cream 5%. OLE Group: using treatment with olive leaf extract emulgelc.

Extraction is considered the first step for the analysis and utilization of bioactive compounds present in medicinal plants. In our study, ultrasound-assisted extraction (UAE) was used to extract active compounds from olive leaves. This method has become increasingly popular in recent years due to its effectiveness and speed in extracting polyphenols with minimal dissociation, compared to other methods. Additionally, UAE is cost-effective as it requires less quantity of solvent and less extraction time[20,21].

This extract has been formulated as an emulgel for dermatological use. This pharmaceutical form offers numerous benefits, including thixotropic properties, greaseless texture, easy to spread and remove, moisturizing effect, non-pigmenting, relatively long shelf life, environmental friendliness, transparency, and an attractive appearance[22,23].

Topical acyclovir has been the gold standard for treating RHL for over 20 years and is available without a prescription. There is moderate scientific evidence that it reduces the healing time and reported pain of herpes labialis attacks[24]. Accordingly, it was considered as a control group treatment in our study.

The findings of this study indicate that OLE was superior in accelerating the healing process of RHL lesions, with a significant reduction in healing time observed when compared to the control group treated with acyclovir cream. This outcome aligns with the research conducted by Toulabi et al.[25], which is the only previous clinical investigation assessing the efficacy of OLE on RHL. Nevertheless, the effect size calculated in the present study, measured at 0.6, is classified as moderate and is smaller than the effect size reported in Toulabi's study, which was 1.2. This discrepancy may be attributed to the differing methodologies employed to evaluate healing in the two studies. In our research, healing was assessed by recording the duration necessary for crust to fell off, whereas Toulabi's assessment focused on measuring the dimensions of the lesions rather than observing the stages of healing. However, both methodologies are recognized within the literature for assessing the healing of RHL.

The unique therapeutic properties of (OLE) are attributed to its high polyphenol content, primarily oleuropein, followed by hydroxytyrosol and tyrosol[26]. These active ingredients provide OLE with antioxidants, anti-inflammatory, and antiviral properties[12,27].

It is believed that OLE has an inhibitory effect on HSV-1. Unlike acyclovir, OLE does not require conversion into an active form by the HSV thymidine kinase enzyme. Consequently, viruses that are resistant to acyclovir due to mutations that inhibit the production of this enzyme may still be sensitive to OLE[12].

OLE phenols, especially oleuropein, possess free-radical scavenging properties, and they can inhibit the oxidation of low-density lipoprotein and lipoxygenase, reducing inflammation, improving blood flow, and preventing cell damage, thus promoting better healing[28].

The measured differences in pain intensity were very minimal and did not conflict with the hypothesis of non-superiority, which contrasts with the results reported by Toulabi et al.[25]. The observed variation in the

therapeutic effectiveness of OLE may be attributed to differences in the concentration of phenolic compounds found in olive leaves, influenced by various factors including climatic conditions, moisture content, plant maturity, cultivar, harvest timing, geographic region, and agricultural practices[29,30].

Phenols relieve pain by inhibiting pro-inflammatory enzymes such as cox-2 and Lox, as well as inducible nitric oxide synthase (iNOS) enzymes. Additionally, they can inhibit cell signalling pathways such as phosphoinositide 3 kinase (PI 3-kinase), tyrosine kinases, NF-kB, and AP-1. Olive phenols also down-regulate various pro-inflammatory cytokines including chemokines, tumor necrosis factor-alpha (TNFα), interleukins (IL-8, IL-6, IL-1b), and monocyte chemotactic protein-1 (MCP-1)[31–36].

In addition to OLE, numerous studies have investigated the efficacy of various medicinal plants and natural substances in treating HSV-1. Some of these studies were controlled clinical trials that used acyclovir 5% cream. Where the effectiveness of lavender cream[37] and special propolis extract (GH2002)[38,39] were studied, and all of these trials found superiority of the natural substance over acyclovir, whether in accelerating healing or relieving pain, while in a study on the effect of Mellisa gel[40], did not find any considerable differences between the two groups in accelerating healing, while the superiority of Mellisa gel over acyclovir cream in relieving pain was obvious.

Olive leaves represent a significant source of biologically active compounds that can be utilized rather than discarded as organic waste. The transition towards the extraction of these compounds for application in the pharmaceutical industry offers substantial environmental, economic, and health advantages. Olive leaves serve as natural sources for the treatment of various diseases, thereby decreasing reliance on synthetic medications that may have adverse side effects[41,42]. Furthermore, this sector contributes to the establishment of a more sustainable pharmaceutical industry that prioritizes renewable natural resources.

The production costs associated with olive leaf extracts are anticipated to be lower than those for chemical pharmaceuticals due to the abundant availability of the raw material (olive leaf), which can be harvested in substantial quantities from a single tree (25 kg per olive tree)[42]. The UAE process is straightforward, and there is no requirement for complex or costly chemical additives[30].

Additionally, the formulation of emulgel involves streamlined and expedited procedures, thereby enhancing production feasibility. The materials necessary for this process are widely available and economically viable, which further contributes to the reduction of production costs associated with emulgel[43].

The potential for a placebo effect in this trial was mitigated by implementing a blinded study design, in which patients were not informed about the medications prescribed to them or any potential benefits associated with the treatments. Given that RHL is a self-limiting disease care was also taken to apply clear criteria for assessing healing and pain, and patients were followed until the crusts fell off and symptoms completely disappeared.

We believe that the current study design allows us to compare the effectiveness of the two treatments fairly and accurately, and to determine any additional benefits of the experimental treatment compared to the standard treatment.

The safety and tolerability of the OLE emulgel were evaluated by monitoring any changes or adverse experiences reported by participants during both the treatment and follow-up periods. Notably, no undesirable side effects were observed, nor were there any allergic reactions to the materials utilized in the study. The findings of this research indicate that the emulgel was safe and well-tolerated by all participants involved.

Based on the aforementioned considerations, OLE emulgel may be regarded as a viable alternative to acyclovir cream for the treatment of RHL lesions. Its advantages encompass low cost, minimal side effects, environmental sustainability, and enhanced healing.

### Limitations

The study faced limitations because it was not possible to fully blind the patients as the emulgel and the cream had distinguishable forms. To address this issue, patients were not explicitly told about the contents of the containers given to them. Additionally, the researcher who administered the treatment was different from the one who evaluated its effectiveness.

## Conclusion

Olive leaf extract (OLE) offers a promising alternative for the treatment of RHL, particularly in cases where patients may develop viral resistance to traditional antiviral drugs. Our research has demonstrated that OLE exhibits superiority to acyclovir cream in expediting the healing process of RHL lesions, suggesting its potential as an effective alternative treatment for Individuals experiencing this recurrent infection. Further randomized clinical studies are necessary to assess the effectiveness of OLE at different stages of infection, such as the prodromal phase. It is also important to study the effect of the extract on the recurrence of outbreaks by applying it during lesion-free periods. Conducting these studies will enhance our understanding of the antiviral properties of olive leaf extract and its influence on the course of herpes labialis infection. This knowledge could lead to the development of new and more effective treatments for patients.

## Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Received: 2 September 2024; Accepted: 29 November 2024
Published online: 02 December 2024

## References


1. Pennisi, R. et al. Analysis of Antioxidant and Antiviral Effects of Olive (Olea europaea L.) Leaf Extracts and Pure Compound Using Cancer Cell Model. *Biomolecules* 13, (2023).
2. Ben-Amor, I. et al. Phytochemical characterization of olea europea leaf extracts and assessment of their anti-microbial and anti-hsv-1 activity. *Viruses* **13**, 1085–1100 (2021).
3. Rocha, J., Borges, N. & Pinho, O. Table olives and health: A review. *J. Nutr. Sci.* **9**, 452–463. https://doi.org/10.1017/jns.2020.50 (2020).
4. Kermanshah, Z., Samadanifard, H., Moghaddam, M. & Hejrati, A. O. *Olive Leaf and Its Various Health-Benefitting Effects: A Review Study*. 14.
5. Gopinath, D., Koe, K. H., Maharajan, M. K. & Panda, S. A. Comprehensive Overview of Epidemiology, Pathogenesis and the Management of Herpes Labialis. *Viruses* **15**, 255–267. https://doi.org/10.3390/v15010225 (2023).
6. Roizman, B. & Whitley, R. J. An inquiry into the molecular basis of HSV latency and reactivation. *Annu. Rev. Microbiol.* **67**, 355–374 (2013).
7. Chen, F. et al. Efficacy and safety of nucleoside antiviral drugs for treatment of recurrent herpes labialis: a systematic review and meta-analysis. *Journal of Oral Pathology and Medicine* **46**, 561–568. https://doi.org/10.1111/jop.12534 (2017).
8. Cole, S. Herpes Simplex Virus: Epidemiology, Diagnosis, and Treatment. *Nursing Clinics of North America* **55**, 337–345. https://doi.org/10.1016/j.cnur.2020.05.004 (2020).
9. Mcquillan, G., Kruszon-Moran, D., Flagg, E. W. & Paulose-Ram, R. *Prevalence of Herpes Simplex Virus Type 1 and Type 2 in Persons Aged Key Findings Data from the National Health and Nutrition Examination Survey*. https://www.cdc.gov/nchs/data/databriefs/db304_table.pdf#3 (2018).
10. Crimi, S. et al. Herpes virus, oral clinical signs and qol: Systematic review of recent data. *Viruses* **11**. https://doi.org/10.3390/v11050463 (2019).
11. Jiang, Y. C., Feng, H., Lin, Y. C. & Guo, X. R. New strategies against drug resistance to herpes simplex virus. *International Journal of Oral Science* **8**, 1–6. https://doi.org/10.1038/ijos.2016.3 (2016).
12. Motamedifar, M., Nekooeian, A. A. & Moatari, A. *The Effect of Hydroalcoholic Extract of Olive Leaves against Herpes Simplex Virus Type 1*. (2007).
13. Paiva-Martins, F., Gordon, M. H. & Gameiro, P. Activity and location of olive oil phenolic antioxidants in liposomes. *Chem. Phys. Lipids* **124**, 23–36 (2003).
14. Khan, M. Y., Panchal, S., Vyas, N., Butani, A. & Kumar, V. *Olea Europaea: A Phyto-Pharmacological Review. Pharmacognosy Reviews* vol. 1. http://www.phcogrev.com (2007).
15. Hassan, S. T. S., Masarčíková, R. & Berchová, K. Bioactive natural products with anti-herpes simplex virus properties. *Journal of Pharmacy and Pharmacology* **67**, 1325–1336. https://doi.org/10.1111/jphp.12436 (2015).
16. Balkrishna, A. et al. Exploring the Safety, Efficacy, and Bioactivity of Herbal Medicines: bridging traditional wisdom and Modern Science in Healthcare. *Future Integr. Med.* **3**, 35–49 (2024).
17. GÜRBÜZ, M. C., KIRTAK, N. & TAŞ ÖZYURTSEVEN, B. Comparison of topical acyclovir and penciclovir in recurrent herpes labialis treatment. *Cukurova Med. J.* **46**, 927–933 (2021).
18. Cifá, D., Skrt, M., Pittia, P. & Di Mattia, C. Poklar Ulrih, N. enhanced yield of oleuropein from olive leaves using ultrasound-assisted extraction. *Food Sci. Nutr.* **6**, 1128–1137 (2018).
19. Waterhouse *Determination of Total Phenolics*. (2002).
20. Alara, O. R., Abdurahman, N. H. & Ukaegbu, C. I. Extraction of phenolic compounds: A review. *Current Research in Food Science* **4**, 200–214. https://doi.org/10.1016/j.crfs.2021.03.011 (2021).
21. Oreopoulou, A., Tsimogiannis, D. & Oreopoulou, V. Extraction of Polyphenols from Aromatic and Medicinal plants: an overview of the methods and the effect of extraction parameters. in Polyphenols in Plants. Pp. 243–259. doi:https://doi.org/10.1016/b978-0-12-813768-0.00025-6 (Elsevier, 2019).
22. Parihar, N., Saini, M., Soni, S. L. & Sharma, V. Emulgel: A Topical Preparation. *Asian J. Pharm. Res. Dev.* **8**, 196–201 (2020).
23. Vanpariya, F., Shiroya, M., Malaviya, M. & Emulgel A review. *Int. J. Sci. Res.* **10**, 263–270 (2021).
24. Worrall, G. *Herpes Labialis*. www.clinicalevidence.com (2009).
25. Toulabi, T. et al. The efficacy of olive leaf extract on healing herpes simplex virus labialis: a randomized double-blind study. *Explore* **18**, 287–292 (2022).
26. Xie, P., jun, Huang, L., xin, Zhang, C. & Zhang, Y. hong lei. Phenolic compositions, and antioxidant performance of olive leaf and fruit (Olea europaea L.) extracts and their structure-activity relationships. *J. Funct. Foods* **16**, 460–471 (2015).
27. Torrecillas-Baena, B. et al. Comparative study of the efficacy of EHO-85, a Hydrogel Containing Olive Tree (Olea europaea) Leaf Extract, in skin Wound Healing. *Int. J. Mol. Sci.* **24**, 136–152 (2023).
28. Borjan, D., Leitgeb, M., Knez, Ž. & Hrnčič, M. K. Microbiological and Antioxidant Activity of Phenolic Compounds in Olive Leaf Extract. *Molecules* **25**, 946–973. https://doi.org/10.3390/MOLECULES25245946 (2020).
29. Ghomari, O. et al. Phenolic profile (HPLC-UV) of olive leaves according to extraction procedure and assessment of antibacterial activity. *Biotechnol. Rep.* **23**, 245–255 (2019).
30. Martín-García, B. et al. Comparative extraction of Phenolic compounds from Olive leaves using a Sonotrode and an Ultrasonic bath and the evaluation of both antioxidant and antimicrobial activity. *Antioxidants* **11**, 558–570 (2022).
31. Beauchamp, G. K. et al. Ibuprofen-like activity in extra-virgin olive oil. *Nature* **437**, 45–46 (2005).
32. Cuzzocrea, S. et al. PPAR-contributes to the anti-inflammatory activity of verbascoside in a model of inflammatory bowel disease in mice. *PPAR Res.* https://doi.org/10.1155/2010/917312 (2010).
33. Speranza, L. et al. Antiinflammatory effects in THP-1 cells treated with verbascoside. *Phytother. Res.* **24**, 1398–1404 (2010).
34. Pastore, S. et al. Blackwell Publishing Inc.,. Plant polyphenols effectively protect HaCaT cells from ultraviolet C-triggered necrosis and suppress inflammatory chemokine expression. In: *Annals of the New York Academy of Sciences* **1171**, 305–313 (2009).
35. Zhang, X., Cao, J. & Zhong, L. Hydroxytyrosol inhibits pro-inflammatory cytokines, iNOS, and COX-2 expression in human monocytic cells. *Naunyn Schmiedebergs Arch. Pharmacol.* **379**, 581–586 (2009).
36. Laaboudi, W., Ghanam, J., Aissam, H., Merzouki, M. & Benlemlih, M. *ANTI-INFLAMMATORY AND ANALGESIC ACTIVITIES OF OLIVE TREE EXTRACT*. www.olivie.ma (2016).
37. Altaei, T., Shaheen & Ahmed, A. *Topical treatment oral diagnosis 70. J. Bagh Coll. Dentistry* **24** (2012).
38. Jautová, J. et al. Lip creams with propolis special extract GH 2002 0.5% versus aciclovir 5.0% for herpes labialis (vesicular stage): Randomized, controlled double-blind study. *Wien. Med. Wochenschr.* **169**, 193–201 (2019).
39. Arenberger, P., Arenbergerova, M., Hladíková, M., Holcova, S. & Ottillinger, B. Comparative study with a lip balm containing 0.5% Propolis Special Extract GH 2002 versus 5% aciclovir cream in patients with Herpes Labialis in the Papular/Erythematous Stage: a Single-blind, randomized, two-arm study. *Curr. Ther. Res. Clin. Exp.* **88**, 1–7 (2018).
40. Ahadian, H., Akhavan Karbassi, M. H., Ghaneh, S. & Hakimian, R. Therapeutic effect of melissa gel and 5% acyclovir cream in recurrent herpes Labialis: a double-blind randomized clinical trial. *Jundishapur J. Nat. Pharm. Prod.* **10**, 261–266 (2015).
41. Espeso, J. et al. Olive Leaf Waste Management. *Frontiers in Sustainable Food Systems* **5**, 112–127. https://doi.org/10.3389/fsufs.2021.660582 (2021).
42. Rahmanian, N., Jafari, S. M. & Wani, T. A. Bioactive profile, dehydration, extraction and application of the bioactive components of olive leaves. *Trends in Food Science and Technology* **42**, 150–172. https://doi.org/10.1016/j.tifs.2014.12.009 (2015).
43. Haneefa, K., Easo, S., Prasad Mohanta, G. & Nayar, C. *Emulgel: Adv. Rev.* (2013).

## Acknowledgements
This paper and the research behind it would not have been possible without the exceptional support of all authors, their institutions, and department staff.

## Author contributions
All authors contributed to drafting and reviewing the manuscript and approving its final version. M.G.H participated in the study concept, design, registration, clinical work, data registration, and statistical analysis. Professor J.H participated in the preparation of the pharmaceutical extract and manufacture of the emulsion, as well as designing and registering the study. Associate Professor A.J contributed to the study design, registration, and supervision of clinical work.

## Funding
This study research is funded by Damascus University – funder No. 501100020595.

## Declarations

## Competing interests
The authors declare no competing interests.

## Ethics approval and consent to participate
The study was carried out following the ethical standards established in the 1964 Declaration of Helsinki. The Ethics Committee of Damascus University approved the protocol (Date 02/08/2021/No 2640), and all patients provided written consent to participate in the present study.

## Additional information
**Correspondence** and requests for materials should be addressed to M.A.G.-H.