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Original Article

The Effect of Oleuropein on the Healing of Recurrent Aphthous Stomatitis

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Abstract

Background: In recent years, the use of herbal remedies has grown increasingly popular, attracting not only patients exploring alternative treatment options but also gaining interest from both patients and healthcare professionals alike. Recurrent aphthous stomatitis is a prevalent condition affecting the oral cavity, with various treatments proposed by researchers over time. This study aimed to investigate the effectiveness of oleuropein on healing recurrent aphthous stomatitis.

Methods: The research involved 60 participants, aged 19–45 years, all with a history of oral ulcers. They were randomly divided into three groups: a control group using 0.2% chlorhexidine mouthwash, an oleuropein mucoadhesive paste group, and a base (placebo) group. Statistical analysis was carried out using the paired sample t-test, ANOVA, and the Kruskal-Wallis test (Wilcoxon signed-rank test).

Results: At the start of the study, no significant differences were observed in the average wound pain scores among the three groups ($P>0.05$). However, on days 2, 4, and 6, a significant reduction in pain was noted in both the mucoadhesive paste group and the control groups compared to the base group. On the second day, the efficacy index of the control was higher than that of the mucoadhesive paste and the base material. Also, there was a significant difference between the adhesive mucus and the control groups with the base material. The recovery rate was significantly higher in the control group than in the mucoadhesive paste and base group. All treatments were well-tolerated by the patients, with no complications reported throughout the study.

Conclusion: This study showed that oleuropein has beneficial effects on healing recurrent aphthous stomatitis. Therefore, it is suggested as a substance for healing wounds in the mouth.

Keywords: Oleuropein, Healing, Recurrent aphthous stomatitis, Olives

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Introduction

Traditional medicine has been used to treat human pain for thousands of years. This treatment instrument remains one of the most innovative medication supply sources. The popularity of herbal remedies has increased among patients seeking conventional treatment approaches, as well as among patients and physicians.[1,2]

In Germany, a regulatory agency known as Commission E investigated the quality, clinical efficacy, and applications of 300 herbal products as part of a comprehensive study of common herbs. These surveys have contributed to the standardization of herbal medicines.[3] Currently, herbal products in the United States are subject to stringent restrictions. Herbal remedies have been effectively utilized to treat skin diseases in Europe and Asia for thousands of years. Now, these treatments are the subject of scientific inquiry. Several herbal remedies for dermatological diseases are now under investigation, many of which have demonstrated substantial scientific proof of efficacy.[4] The olive tree's leaves, fruit, wood, and bark contain the bitter substance oleuropein, some fatty acids, nitrogen, phosphorus, calcium, and magnesium, as well as sugars. Oleuropein is a phenolic chemical with various blood vessel and blood pressure-lowering, anti-inflammatory, anti-rheumatic, diuretic, anti-atherogenic, and antipyretic activities.[5]

According to nutrition experts, olive is a very beneficial plant for human health which helps prevent heart disease. Olive leaves are known to contribute to reducing blood pressure. Even though this plant's fruit is heavy in fat, it is an excellent source of oleic acid, omega-9 unsaturated fatty acids, and vitamin A. Olives can also stimulate hunger. Olive leaf decreases blood pressure, and its decoction is effective for toothache relief. Olive oil was primarily employed as

a laxative and to alleviate nervous symptoms in ancient medicine. Olive oil reduces the deposition of cholesterol on the walls of blood vessels and arteries, as well as their constriction, in addition to reducing bad blood cholesterol and preventing the formation of vascular issues. This plant and its oil contain anti-cancer and anti-inflammatory capabilities to prevent intestinal irritation to the greatest extent feasible. Olives are also recognized for their ability to prevent and treat asthma and arthritis. The majority of these pharmacological activities are related to antioxidant capabilities of oleuropein. This compound possesses potent antibacterial, antifungal, and antiviral activities. Additionally, this combination is good at enhancing the immunological response.[5]

Some individuals use oleuropein for medical purposes, believing it kills only dangerous germs. Comparing with industrial antibiotics, it eradicates both helpful and dangerous microorganisms without discrimination. Oleuropein has also powerful antioxidant effects. This characteristic supports improved health since it inhibits free radicals from destroying cells. This compound inhibits excessive oxidation.[5]

First, oleuropein searches the body for infectious organisms. Then, it attacks them and destroys their outside lining. This results in structural variations within the infectious mass. As a result, the crime cannot serve any purpose and cannot be rebuilt. Typically, it is administered orally for medicinal purposes. It is utilized generally for many days. This quantity ingested is absorbable by the body. To be successful, this mixture must be used with substances and quantities that are compatible with it. Therefore, there is a larger chance of compositional compatibility if all European items are bought from a single source. In the early twentieth century, oleuropein was initially extracted. It was believed that this combination confers disease resistance to olive trees. Scientists thought that this substance might have the same impact on people. In the latter part of the 20th century, further laboratory experiments on this chemical were done. These investigations demonstrated that this chemical lowers blood pressure in experimental animals; thus, it was widely utilized (5). This study's objective was to examine the influence of oleuropein on the healing of RAS.

Methods

Preparation of oleuropein extract

The necessary olive fruit sample was gathered during the harvest season, between late September and early October, and immediately frozen following transfer. This olive was picked from the olive tree collecting research station in the city of Kazeroon, which is linked with the Agricultural and Natural Resources Research Center of Fars province. In this study, oleuropein was isolated using the Bradford and Malik technique. Using surgical blades, the kernels of frozen olives were separated using this procedure. Then, using a scale with four decimal places, one gram of seedless olive fruit was weighed and pulverized and softened in a mortar. Next, the pulverized tissue was extracted in 10 ml of 80% methanol for 30 seconds using a Brinkam Model PT 3100 mixer at maximum speed. This was repeated three times, each time for 10 seconds, and the resulting mixture was centrifuged at 39,000 g for 20 minutes. After centrifugation, the floating liquid was spilled onto the far surface, and its sediment was extracted a second time with 10 ml of methanol containing 80% methanol, bringing the total amount of methanol extraction to 25 ml. The extracted material was then strained through a filter with a pore size of 20 microns and stored at -20 degrees until the tests were conducted.[6]

Preparation of the plastic base

Oral sticky mucus paste is produced by mixing sodium carboxymethyl cellulose, pectin, and gelatin with a plastic base. By rapidly chilling a heated mixture of 5% low-density polyethylene in liquid paraffin, plastic base gel is produced. To this end, polyethylene was added to Boshari, and liquid paraffin at a temperature of 80°C was added in a quantity equal to two times the weight of polyethylene. The gel was agitated at 130°C until it reached the required viscosity. The remaining heated paraffin was then added gradually to the mixture while stirring continued until all of the paraffin had been added. After one hour of stirring, swiftly transfer the liquid into an aluminum foil container that has been chilled with salt ice until it is absolutely cold. The resultant substance is known as plastic base gel.[7]

Formulation of mucus-sticky base

The proposed formula for the base consists of 16,6% gelatin, 16,6% pectin, and 16,6% sodium carboxymethyl cellulose, and the plastic base can reach a maximum of 100%. Gelatin, pectin, and sodium carboxymethyl cellulose powders were initially sieved via a 200-mesh screen. Adding sodium carboxymethyl cellulose, pectin, and lastly gelatin to a plastic foundation while continually stirring until a homogeneous base is created is the ideal approach for producing sticky mucus.[8]

Medicinal formulation for mucus adhesive with oleuropein

To create the sticky mucus paste containing oleuropein, the extract prepared evenly in the initial step of manufacture was added to the plastic base and stirred until the mixture was well combined. Then, the remaining formula components were added to the plastic base containing the medication according to the manner described in the section on producing sticky mucus paste, and mixing was maintained until the manufacture of a uniform adhesive mucus paste.[8]

Study Design

The study population included 60 volunteer students from Kerman and Bahonar University of Medical Sciences with a history of RAS. Participants were randomly divided into three groups of 20: the oleuropein mucoadhesive group, the mucus sticky base group, and the control group. Oral ulcers were defined as those that recur at least twice annually and heal within 10 days without leaving a scar.

Inclusion Criteria

- Adults aged 18 years or older.
- Ulcers less than or equal to 1 cm in size.
- Ulcers healing within 10 days without medication.

Exclusion criteria

- Ulcers caused by sharp tooth edges, broken restorations, orthodontic appliances, or partial dentures.
- Known medical conditions such as anemia, unusual skin lesions, recurrent respiratory tract infections, similar wounds in the genital area, or swelling and pain in the joints.
- Symptoms involving the eyes (e.g., blurring, redness, tearing).
- Use of medications to treat ulcers before enrollment or after 72 hours of ulcer development.
- Drug allergies.
- Pregnancy or lactation.
- History of immune-related issues or recent treatment with systemic steroids or immunosuppressive agents within the past month.
- Use of nonsteroidal anti-inflammatory drugs (NSAIDs), oral antihistamines, or antibiotics in the month preceding enrollment.
- Participation in another clinical trial in the previous three months.

Consent and Preliminary Assessments

Before enrollment, all participants provided informed consent. It was explained to them that they might be placed in one of four treatment groups, with detailed explanations about oral ulcers provided. Reference images of oral ulcers were shared to help volunteers identify their condition accurately. An intraoral examination was performed for all participants to document ulcer characteristics, which were recorded in a dedicated form.

The study materials

A mucoadhesive paste containing oleuropein and a placebo paste devoid of active ingredients were packaged in coded containers by individuals uninvolved in the research to maintain the double-blind nature of the trial. The control group was administered standard treatments (Benzydamine mouthwash, Chlorhexidine mouthwash, and Betamethasone lotion).

Participants were instructed to apply the prescribed paste to their ulcers four times daily (after breakfast, lunch, dinner, and before bed). Clinical assessments were conducted on days 0, 1, 4, 6, and 10. Ulcer diameters were measured with a periodontal probe, focusing on the most prominent ulcer or one located in an easily accessible area if multiple ulcers were present.

Pain intensity over the 10-day observation period was measured using the Visual Analogue Scale (VAS), where 0 represented no pain, and 10 indicated the worst imaginable pain.[9] Patients received instructions for proper documentation of daily pain levels and were asked to record their pain intensity one hour after taking their morning dose of medication.

The severity of erythema and exudate was evaluated using criteria developed by Greer et al. [10] (Erythema Scoring: 0: No erythema, 1: Pink/light red, 2: Red (not dark), 3: Dark red). Exudate Scoring: 0: No exudation, 1: Light exudation, 2: Moderate exudation, 3: Heavy exudation with pseudomembrane formation.[10]

Also, in this study, 3 indices are examined and calculated: Efficacy Indices (EI), Marked Improvement Rate (MIR), and Improvement Rate (IR).[11] To evaluate EI, the wound size on days 0, 4, 6, and 10 is put into the following formula:

Desired day EI = Wound size on desired day - Wound size on day 0: Wound size on day 0 * 100%Accordingly,

1. EI equals 100% as improvement
2. ≤ 70% EI < 100% indicates significant improvement
3. ≤ 30% EI < 70% indicates moderate improvement
4. EI < 30% indicates no improvement.

The averages for cases 1 and 2 on days 4, 6, and 10 reflect MRI results recorded on those specific days, while the averages for cases 1, 2, and 3 in the same timeframe represent the improvement rate (IR). Additionally, data on variables such as age, gender, annual ulcer recurrence frequency, common sites of involvement, ulcer formation duration, average number of ulcers per period, ulcer size, and recurrence intervals were collected.

Statistical analyses were performed using a two-paired-sample t-test, ANOVA, the Kruskal-Wallis test, Wilcoxon signed-rank test, and Chi-squared test via SPSS version 26.

This study adhered to the International Guidelines for Human Research. It was carried out under the oversight of the Ethics Committee of Kerman University of Medical Sciences (Ethical Code: 940648).

Results

In this study, three groups were evaluated as follows: Group A: Mucoadhesive paste containing oleuropein; Group B: Mucoadhesive paste without oleuropein; Group C: Control group.

A total of 60 patients participated in the study, distributed evenly across the groups (20 per group based on random numbers). The study included 37 women and 23 men, with ages ranging from 19 to 45 years, and an average age of 27.31 ± 4.23 years (Table 1).

At the start of the study, no significant differences were observed in the average wound pain scores among the three groups ($P > 0.05$). However, on days 2, 4, and 6, a significant reduction in pain was noted in both the mucoadhesive paste (Group A) and control groups (Group C) compared to Group B ($P < 0.05$) (Table 2).

On the second day, the efficacy index of the control was higher than that of the mucoadhesive paste and the base material ($P = 0.03$). Also, there was a significant difference between the groups of the adhesive mucus and the control with the base material ($P = 0.002$). The control group had a significantly higher recovery rate compared to the adhesive and base mucus groups; this recovery rate was significant in the positive control and base material groups ($P = 0.03$).

Over time, pain scores decreased more significantly in Groups A and C, with no considerable difference between these two groups. The base group (Group B), however, showed less substantial improvement in pain scores.

On the second day, the efficacy index of the control group was significantly higher than that of both the adhesive mucus and base material groups ($P=0.03$). A notable difference was also observed between Groups A and C compared to Group B ($P=0.002$). The recovery rate was significantly higher in the control group than in Groups A and B, with statistical significance noted between the control group and Group B as well ($P=0.03$). By the fourth day, the control group maintained a higher efficacy index and recovery rate than both Groups A and B. Additionally, Group A demonstrated significantly higher efficacy and recovery compared to Group B ($P<0.05$).

On the sixth day, as more patients recovered, the control group continued to show significant improvements compared to Group B ($P<0.05$). While improvements were observed in Group A compared to Group B, these differences were not statistically significant. At the start of the study, no significant differences were found in wound size among the three groups ($P>0.05$). However, by days 4 and 6, a significant reduction in average wound size was seen in the control group compared to both Groups A and B ($P<0.05$). There was no statistically significant difference in wound size between Groups A and B during this period ($P>0.05$((Table 3).

On day 2, the control group showed a considerably greater efficacy index than Group B ($P<0.05$), but no significant differences were noted between Groups A and C ($P>0.05$). Recovery rates among all groups appeared similar at this point ($P>0.05$). By day 4, the control group demonstrated both a much higher efficacy index and a statistically significant recovery rate compared to other groups ($P<0.05$). No notable differences were found between Groups A and B regarding these parameters ($P>0.05$). On day 6, the control group consistently outperformed Groups A and B in terms of efficacy and achieved statistically significant improvement rates compared to both groups ($P<0.05$). While slight differences were observed between Groups A and B, these was no statistically significance ($P>0.05$).

All treatments were well-tolerated by the patients, with no complications reported throughout the study.

Table 1. Demographic profile of the study participants

Variable		Mucoadhesive Group	Control Group	Base Group	Total	*P*-value
Age	Min	19	21	20	19	
	Max	43	41	45	45	0.124
	Mean	26.55±3.11	27.61±5.10	27.77±4.48	27.31±4.23	
Gender	Male	7(30.4)	8(34.8)	8(34.8)	23(61.7)	0.113
	Female	12(32.4)	13(35.2)	12(32.4)	37(38.3)	

Table 2. The mean and standard deviation of pain intensity, as measured by the Visual Analog Scale (VAS)

Pain Intensity (VAS)	Mean±SD Mucoadhesive Group	Mean±SD Control Group	Mean±SD Base Group	* *P*-value
First day	1.13±7.22	1.21±7.21	1.19±7.25	0.11
Day 2	1.21±6.81	1.09±6.15	1.02±6.05	0.01***
Day 4	1.00±4.45	1.10±5.12	1.11±6.05	0.001***
Day 6	1.00±2.45	1.12±3.32	1.29±6.35	0.02***
**Day 1 compared to day 2	***0.02	0.01***	0.14	
**Day 1 compared to day 4	***0.02	0.01***	0.16	
**Day 1 compared to day 6	***0.01	0.01***	0.09	

*Kruskal-Wallis Test- ** Wilcoxon sign test- *** $P<0.05$

Discussion

Recurrent aphthous stomatitis (RAS) are prevalent oral disorders that affect 12 to 20% of the population. Numerous compounds have been studied for their ability to heal oral wounds and decrease postoperative sequelae (11). Wound healing is a complicated process involving a number of regulated elements. Several chemicals that only occur during embryonic development are present in the bud tissue during this stage. The regenerated bud tissue contains fibroblast cells with a particular phenotype. After tissue injury disrupts the epithelium, re-epithelialization occurs rapidly to preserve tissue integrity.[12]

Wound healing begins at the time of damage and can last for varying amounts of time, depending on the severity of the wound and its three-phase healing process. 1- inflammatory phase, 2- phase of proliferation, and 3- phase of remodeling.[13,14]

This study demonstrated that topical oleuropein promotes RAS healing. The study revealed that oleuropein exhibits positive effects on wound healing. Additionally, findings indicated that using adhesive mucus, compared to the standard base treatment, helps alleviate pain and decrease wound size.

The hunt for natural wound-healing therapies has brought attention to plant extracts. About sixty percent of the world's population prefers traditional medicine for basic treatment, particularly wound care.[15,16]

Table 3. Mean and standard deviation of wound size in millimeters in three studied groups

Wound Size	Mean±SD Mucoadhesive Group	Mean±SD Control Group	Mean±SD Base Group	**P*-value
First day	3.71±27.31	4.51±.27.25	4.21±24.82	0.65
Day 2	3.61±22.82	4.21±21.76	3.75±22.52	0.51
Day 4	3.41±15.31	3.42±14.02	3.61±16.54	0.001***
day 6	2.21±8.52	2.61±4.82	2.51±12.84	0.001***
**Day 1 compared to day 2	0.001***	0.001***	0.001***	
**Day 1 compared to day 4	0.001***	0.001***	0.001***	
**Day 1 compared to day 6	0.001***	0.001***	0.001***	

*One-way ANOVA, **Test Two-Paired Sample t test, $P<0.05$***

Oleuropein is one of the most significant of the 98 phytochemical compounds found in olive leaf extract. A Bitter-tasting phenolic glycoside found in olive leaves possesses anti-inflammatory and antioxidant characteristics and has been launched as a blood pressure-lowering medication.[17]

In Iran, herbal treatments have long been utilized to prevent and treat sickness. Olive trees are mostly cultivated in northern Iran.[18]

Oleuropein possesses therapeutic qualities including cardiac protection, suppression of platelet aggregation, anticancer and antibacterial properties, neuroprotective effects, vasodilator, antirheumatic, diuretic, antiatherogenic, and antipyretic activities.[19] It appears that many of these therapeutic benefits of oleuropein are attributable to this substance's powerful antioxidant impact.[20]

Studies have demonstrated that oleuropein has a significant impact on blood sugar management. Numerous researchers have explored the hypoglycemic action of oleuropein, and laboratory tests on animals have demonstrated its hypoglycemic activity. This substance indirectly decreases oxidative stress and produces hypoglycemia by reducing blood sugar levels in diabetic mice.[21] This component has also demonstrated antidiabetic action in rats with diabetes caused by alloxan. This component's hypoglycemic effect is due to two mechanisms: (1) the capacity to boost insulin production and (2) the increase in peripheral glucose consumption. In addition, the hypoglycemic action of oleuropein in diabetic rabbits revealed that the ethanol product of this drug reduces blood glucose levels, and it does so independently of insulin to boost glucose metabolism.[22]

In a study done by Mehraein et al[23] in 2014, investigating the impact of oleuropein on the healing of rat skin wounds, it was discovered that this chemical enhances the rate of reepithelialization, the formation of collagen fibers, and blood flow to the region. It becomes hurt by increasing the expression of the VEGF protein production gene.

In addition, research has demonstrated that oleuropein increases proteasome activity and the creation of fibroblasts to produce new collagen strands, influences collagen metabolism, and promotes wound healing. An increase in collagen deposition stabilizes and strengthens the wound, which aids in wound healing.[24]

In addition, research done by Gardner et al[25] on the healing of skin wounds in aged mice revealed that this chemical accelerates wound healing. Also, on days 3 and 7, the infiltration of inflammatory cells was reduced in the oleuropein group compared to the control group, while the accumulation of fibroblast cells and collagen synthesis increased.

The study done by Jessup et al[26] revealed that the use of oleuropein cream topically in diabetic patients for the treatment of foot and bed sores has a high degree of healing effect compared to the control group, and that 98.71% of the use group experienced the healing of chronic wounds. The effect of this substance was observed in comparison to hyaluronic acid treatment.

The study conducted by Del Boccio et al[27,28] indicated that three formulations of oleuropein compounds—cream, gel, and ointment—promoted wound healing in elderly individuals. This positive effect was observed despite the significantly higher concentration and purity of the active ingredient in these formulations compared to other products. Notably, none of the patients reported adverse effects or abnormalities associated with the placebo.

Similarly, Al-Rimawi et al[29] highlighted the potent antimicrobial properties of oleuropein against gram-negative and gram-positive bacteria as well as yeasts and molds. Although some studies suggest that this activity may be attributed to the ortho-diphenolic system (catechin) in oleuropein, the exact mechanism remains unclear.[28,30-32] Supporting this, Sudjana et al[33] observed the antimicrobial activity of oleuropein against Staphylococcus aureus, Salmonella typhimurium, Escherichia coli, Klebsiella pneumoniae, and Bacillus cereus, which is compatible with other studies.[34-37]

Atai et al[15] reported that olive leaf extract provides significant healing benefits for oral aphthous ulcers compared to standard dexamethasone mouthwash. The extract effectively reduced both the size of ulcers and associated pain without causing any adverse reactions. Unlike corticosteroids, which can cause discomfort during administration, olive leaf extract is easy to use, cost-effective, and derived from a straightforward preparation process.

Showraki[38] illustrated the healing potential of daily application of olive leaf extract ointment in treating 5-fluorouracil-induced oral mucositis in hamsters. This beneficial effect was attributed to the extract's antioxidant and anti-inflammatory properties, alongside its antimicrobial activity, which could further enhance its wound-healing capabilities. The wound-healing function of oleuropein may also be tied to its antioxidant and anti-inflammatory actions.[27] Furthermore, Motawea et al[39] demonstrated that olive leaf extract possesses intestinal anti-inflammatory, antioxidant, and anti-apoptotic effects in an experimental model of ulcerative colitis.

Alirezaei et al[40] examined the preventive effects of oleuropein against ethanol-induced liver damage in rats. Their research demonstrated that oleuropein improved the activity of the antioxidant enzyme catalase and prevented toxicity in the liver following ethanol consumption, as measured by a decrease in ALT and AST levels and TBARS concentration in the liver. The findings of these researchers demonstrate that oleuropein has positive effects on ethanol-induced liver damage.

In addition, Pirzadeh et al.[41] showed that doses of 5 and 10 mg oleuropein effectively reduce the effects of alcohol on the duodenum of mice. Therefore, they hypothesized that oleuropein in low doses may have a protective effect against ethanol on duodenal tissue.

Alirezaei et al. [40] found that histological abnormalities such as coagulative necrosis, inflammatory changes, and wounds are considerably more prevalent in mice treated with ethanol and oleuropein than in mice treated with

ethanol alone. This study demonstrated that oleuropein reduces intestinal oxidative damage caused by ethanol.

Studies have demonstrated that this chemical also protects stomach tissue from the harmful effects of NSAIDS.[42]

Alirezaei et al[40] found that oleuropein has a protective effect against oxidative stress-induced liver cell damage. Multiple studies have demonstrated that olive oil can decrease oxidative stress in the liver via a variety of methods.[43]

Many modern medications are directly or indirectly produced from plants, as plants have always been a source for the creation of medicines. Ethnobotanical research has identified over 1200 plant species that may have anti-diabetic properties.[44,45]

Four steps comprise the wound healing process: homeostasis, inflammation, proliferation, and regeneration. These activities need the coordination of inflammatory cells, fibroblasts, keratinocytes, biochemical mediators, and extracellular matrix molecules.[46,47] In nations with a long history of traditional medicine, such as China and India, there is vital knowledge regarding the use of several unidentified plants in the healing of wounds. Therefore, the development of novel chemicals to accelerate wound healing is welcome.[48-50]

Conclusion

The study revealed that oleuropein exhibits positive effects on wound healing. Additionally, the findings indicated that using adhesive mucus, compared to the standard base treatment, helps alleviate pain and decrease wound size. However, the adhesive mucus was less effective in pain relief and wound size reduction when compared to routine treatment methods. Consequently, further research is required to explore these outcomes in a greater depth.

Limitations

- Non-cooperation of some patients
- Incorrect use of medicine in several patients

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Competing Interests

None.

Ethical Approval

The study was approved by the ethics committee of Kerman University of Medical Sciences by the research deputy of Kerman University of Medical Sciences. The authors would like to express their gratitude to the Vice Deputy of Research at Kerman University of Medical Sciences for their financial support (Reg. No. 940648). This project was approved by the Ethics Committee of the university with the code IR.KMU.REC.1394. 940648.

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References

1. Scherrer MM, Zerbe S, Petelka J, Säumel I. Understanding old herbal secrets: the renaissance of traditional medicinal plants beyond the twenty classic species? Front Pharmacol 2023;14:1141044. doi:10.3389/fphar.2023.1141044
2. Thin SM, Thet D, Li JY, Nakpun T, Nitadpakorn S, Phanudulkitti C, et al. A systematic review of community pharmacist practices in complementary medicine. Pharm Pract (Granada) 2022;20(3):2697. doi:10.18549/PharmPract.2022.3.2697
3. Ünlüyol D, Gökçekuş H, Kassem Y, Tezer M, Meriçli F, Yavuz D. Complementary and alternative medicines in Northern Cyprus: public awareness, patterns of use, and attitudes. Healthcare (Basel) 2023;11(7):977. doi:10.3390/healthcare11070977
4. Abdel-Kawi SH, Hashem KS, Saad MK, Fekry G, Abdel-Hameed EM. The ameliorative effects of cinnamon oil against ethanol-induced gastric ulcer in rats by regulating oxidative stress and promoting angiogenesis. J Mol Histol 2022;53(3):573-87. doi:10.1007/s10735-022-10072-y
5. Yimam M, Burnett BP, Brownell L, Jia Q. Clinical and preclinical cognitive function improvement after oral treatment of a botanical composition composed of extracts from *Scutellaria baicalensis* and *Acacia catechu*. Behav Neurol 2016;2016:7240802. doi:10.1155/2016/7240802
6. Abbattista R, Losito I, Calvano CD, Cataldi TRI. Exploring the isomeric precursors of olive oil major secoiridoids: an insight into olive leaves and drupes by liquid-chromatography and fourier-transform tandem mass spectrometry. Foods 2021;10(9):2050. doi:10.3390/foods10092050
7. Ben-Amor I, Musarra-Pizzo M, Smeriglio A, D'Arrigo M, Pennisi R, Attia H, et al. Phytochemical characterization of *Olea europea* leaf extracts and assessment of their anti-microbial and anti-HSV-1 activity. Viruses 2021;13(6):1085. doi:10.3390/v13061085
8. Salinas-Arellano ED, Castro-Dionicio IY, Jeyaraj JG, Mirtallo Ezzone NP, Carcache de Blanco EJ. Phytochemical profiles and biological studies of selected botanical dietary supplements used in the United States. Prog Chem Org Nat Prod 2023;122:1-162. doi:10.1007/978-3-031-26768-0_1
9. Fani MM, Ebrahimi H, Pourshahidi S, Aflaki E, Shafiee Sarvestani S. Comparing the effect of phenytoin syrup and triamcinolone acetonide ointment on aphthous ulcers in patients with Behcet's syndrome. Iran Red Crescent Med J 2012;14(2):75-8.
10. Greer RO Jr, Lindenmuth JE, Juarez T, Khandwala A. A double-blind study of topically applied 5% amlexanox in the treatment of aphthous ulcers. J Oral Maxillofac Surg 1993;51(3):243-8. doi:10.1016/s0278-2391(10)80164-8
11. Liu J, Zeng X, Chen Q, Cai Y, Chen F, Wang Y, et al. An evaluation on the efficacy and safety of amlexanox oral adhesive tablets in the treatment of recurrent minor aphthous ulceration in a Chinese cohort: a randomized, double-blind, vehicle-controlled, unparallel multicenter clinical trial. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2006;102(4):475-81. doi:10.1016/j.tripleo.2005.12.014
12. Zhuang WB, Li YH, Shu XC, Pu YT, Wang XJ, Wang T, et al. The classification, molecular structure and biological biosynthesis of flavonoids, and their roles in biotic and abiotic stresses. Molecules 2023;28(8):3599. doi:10.3390/molecules28083599
13. Pang QQ, Lee S, Cho EJ, Kim JH. Protective effects of *Cirsium japonicum* var. *maackii* flower on amyloid β(25-35)-treated

C6 glial cells. Life (Basel) 2023;13(7):1453. doi:10.3390/life13071453
14. Aloo SO, Ofosu FK, Kim NH, Kilonzi SM, Oh DH. Insights on dietary polyphenols as agents against metabolic disorders: obesity as a target disease. Antioxidants (Basel) 2023;12(2):416. doi:10.3390/antiox12020416
15. Atai Z, Ansari M, Torabi N. Efficacy of olive leaf extract in the treatment of minor oral aphthous ulcers. Am J Infect Dis 2007;3(1):24-6. doi:10.3844/ajidsp.2007.24.26
16. Lamichhane G, Pandey J, Devkota HP. Bioactive chemical constituents and pharmacological activities of *Ponciri Fructus*. Molecules 2022;28(1):255. doi:10.3390/molecules28010255
17. Alimenti C, Lianza M, Antognoni F, Giusti L, Bistoni O, Liotta L, et al. Characterization and biological activities of in vitro digested olive pomace polyphenols evaluated on ex vivo human immune blood cells. Molecules 2023;28(5):2122. doi:10.3390/molecules28052122
18. Gorzynik-Debicka M, Przychodzen P, Cappello F, Kuban-Jankowska A, Marino Gammazza A, Knap N, et al. Potential health benefits of olive oil and plant polyphenols. Int J Mol Sci 2018;19(3):686. doi:10.3390/ijms19030686
19. Ibrahim D, Halboup A, Al Ashwal M, Shamsher A. Ameliorative effect of *Olea europaea* leaf extract on cisplatin-induced nephrotoxicity in the rat model. Int J Nephrol 2023;2023:2074498. doi:10.1155/2023/2074498
20. Yan X, Li Q, Jing L, Wu S, Duan W, Chen Y, et al. Current advances on the phytochemical composition, pharmacologic effects, toxicology, and product development of *Phyllanthi Fructus*. Front Pharmacol 2022;13:1017268. doi:10.3389/fphar.2022.1017268
21. Ivanova A, Gerasimova E, Gazizullina E. Study of antioxidant properties of agents from the perspective of their action mechanisms. Molecules 2020;25(18):4251. doi:10.3390/molecules25184251
22. Shah NA, Khan MR. Antidiabetic effect of *Sida cordata* in alloxan induced diabetic rats. Biomed Res Int 2014;2014:671294. doi:10.1155/2014/671294
23. Mehraein F, Sarbishegi M, Aslani A. Evaluation of effect of oleuropein on skin wound healing in aged male BALB/c mice. Cell J 2014;16(1):25-30.
24. Bai L, Zhang X, Li X, Wang S, Zhang Y, Xu G. Impact of a novel hydrogel with injectable platelet-rich fibrin in diabetic wound healing. J Diabetes Res 2023;2023:7532637. doi:10.1155/2023/7532637
25. Serena TE, Snyder RJ, Bowler PG. Use of fluorescence imaging to optimize location of tissue sampling in hard-to-heal wounds. Front Cell Infect Microbiol 2022;12:1070311. doi:10.3389/fcimb.2022.1070311
26. Hoang LQ, Pal S, Liu Z, Senkowsky J, Tang L. A time-dependent survival analysis for early prognosis of chronic wounds by monitoring wound alkalinity. Int Wound J 2023;20(5):1459-75. doi:10.1111/iwj.14001
27. Nikou T, Sakavitsi ME, Kalampokis E, Halabalaki M. Metabolism and bioavailability of olive bioactive constituents based on in vitro, in vivo and human studies. Nutrients 2022;14(18):3773. doi:10.3390/nu14183773
28. Ahmed KM. The effect of olive leaf extract in decreasing the expression of two pro-inflammatory cytokines in patients receiving chemotherapy for cancer. A randomized clinical trial. Saudi Dent J 2013;25(4):141-7. doi:10.1016/j.sdentj.2013.09.001
29. Al-Rimawi F, Sbeih M, Amayreh M, Rahhal B, Mudalal S. Evaluation of the effectiveness of natural extract as a substituent for synthetic preservatives and antioxidants in pharmaceutical preparations. Saudi Pharm J 2024;32(5):102014. doi:10.1016/j.jsps.2024.102014
30. Sousa A, Ferreira IC, Calhelha R, Andrade PB, Valentão P, Seabra R, et al. Phenolics and antimicrobial activity of traditional stoned table olives 'alcaparra'. Bioorg Med Chem 2006;14(24):8533-8. doi:10.1016/j.bmc.2006.08.027
31. Casas-Sanchez J, Alsina MA, Herrlein MK, Mestres C. Interaction between the antibacterial compound, oleuropein, and model membranes. Colloid Polym Sci 2007;285(12):1351-60. doi:10.1007/s00396-007-1693-x
32. Hemeg HA, Moussa IM, Ibrahim S, Dawoud TM, Alhaji JH, Mubarak AS, et al. Antimicrobial effect of different herbal plant extracts against different microbial population. Saudi J Biol Sci 2020;27(12):3221-7. doi:10.1016/j.sjbs.2020.08.015
33. Sudjana AN, D'Orazio C, Ryan V, Rasool N, Ng J, Islam N, et al. Antimicrobial activity of commercial *Olea europaea* (olive) leaf extract. Int J Antimicrob Agents 2009;33(5):461-3. doi:10.1016/j.ijantimicag.2008.10.026
34. Malik SN. Antibacterial activity of olive (*Olea europaea*) leaves and arugula (*Eruca sativa*) seeds extract. Int J Pharmacogn Phytochem Res 2015;7(2):307-10.
35. Pereira AP, Ferreira IC, Marcelino F, Valentão P, Andrade PB, Seabra R, et al. Phenolic compounds and antimicrobial activity of olive (*Olea europaea* L. *Cv*. Cobrançosa) leaves. Molecules 2007;12(5):1153-62. doi:10.3390/12051153
36. Korukluoglu M, Sahan Y, Yigit AY. Antifungal properties of olive leaf extracts and their phenolic compounds. J Food Saf 2008;28(1):76-87. doi:10.1111/j.1745-4565.2007.00096.x
37. Lee OH, Lee BY. Antioxidant and antimicrobial activities of individual and combined phenolics in *Olea europaea* leaf extract. Bioresour Technol 2010;101(10):3751-4. doi:10.1016/j.biortech.2009.12.052
38. Borjan D, Leitgeb M, Knez Ž, Hrnčič MK. Microbiological and antioxidant activity of phenolic compounds in olive leaf extract. Molecules 2020;25(24):5946. doi:10.3390/molecules25245946
39. Showraki N, Mardani M, Emamghoreishi M, Andishe-Tadbir A, Aram A, Mehriar P, et al. Topical olive leaf extract improves healing of oral mucositis in golden hamsters. J Dent (Shiraz) 2016;17(4):334-42.
40. Motawea MH, Abd Elmaksoud HA, Elharrif MG, Desoky AA, Ibrahimi A. Evaluation of anti-inflammatory and antioxidant profile of oleuropein in experimentally induced ulcerative colitis. Int J Mol Cell Med 2020;9(3):224-33. doi:10.22088/ijmcm.Bums.9.3.224
41. Taamalli A, Feriani A, Lozano-Sanchez J, Ghazouani L, El Mufti A, Allagui MS, et al. Potential hepatoprotective activity of super critical carbon dioxide olive leaf extracts against CCl4-induced liver damage. Foods 2020;9(6):804. doi:10.3390/foods9060804
42. Morovvati H, Najafzadeh H, Dezfoolian O, Pirzadeh SA. Histological and histometrical changes of rat deodenum following administration of ethanol and oleuropein. Iran Vet J 2017;12(4):100-8. doi:10.22055/ivj.2017.43041
43. Karakoç MD, Sekkin S. Effects of oleuropein on epirubicin and cyclophosphamide combination treatment in rats. Turk J Pharm Sci 2021;18(4):420-9. doi:10.4274/tjps.galenos.2020.69008
44. Hassan AA, Bel Hadj Salah K, Fahmy EM, Mansour DA, Mohamed SA, Abdallah AA, et al. Olive leaf extract attenuates chlorpyrifos-induced neuro- and reproductive toxicity in male albino rats. Life (Basel) 2022;12(10):1500. doi:10.3390/life12101500
45. Scicchitano S, Vecchio E, Battaglia AM, Oliverio M, Nardi M, Procopio A, et al. The double-edged sword of oleuropein in ovarian cancer cells: from antioxidant functions to cytotoxic effects. Int J Mol Sci 2023;24(1):842. doi:10.3390/ijms24010842
46. De la Ossa JG, Danti S, Esposito Salsano J, Azimi B, Tempesti V, Barbani N, et al. Electrospun poly(3-hydroxybutyrate-co-3-hydroxyvalerate)/olive leaf extract fiber mesh as prospective bio-based scaffold for wound healing. Molecules 2022;27(19):6208.

doi:10.3390/molecules27196208
47. Niu H, Guan Y, Zhong T, Ma L, Zayed M, Guan J. Thermosensitive and antioxidant wound dressings capable of adaptively regulating TGFβ pathways promote diabetic wound healing. NPJ Regen Med 2023;8(1):32. doi:10.1038/s41536-023-00313-3
48. Khalil MA, Al-Ghamdi SM, Dawood US, Ahmed Khamis SS, Ishida H, Chong VH, et al. Mammalian target of rapamycin inhibitors and wound healing complications in kidney transplantation: old myths and new realities. J Transplant 2022;2022:6255339. doi:10.1155/2022/6255339
49. Siamandoura P, Tzia C. Comparative study of novel methods for olive leaf phenolic compound extraction using NADES as solvents. Molecules 2023;28(1):353. doi:10.3390/molecules28010353
50. Abdel-Aziz ME, Darwish MS, Mohamed AH, El-Khateeb AY, Hamed SE. Potential activity of aqueous fig leaves extract, olive leaves extract and their mixture as natural preservatives to extend the shelf life of pasteurized buffalo milk. Foods 2020;9(5):615. doi:10.3390/foods9050615