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Herbal Alternatives for Pain Relief: Evaluating the Effectiveness of Violet Flower Oil and Bitter Almond Oil Compared to Diclofenac Gel in Animal Models

Reza Kazemi[1], Mahdi Mashhadi Akbar Boojar[1,2]*, Gholamreza Poorheidari[2], Seyed Mohammad Zarei[3] and Mehdi Saberi[2]

1. Student Research Committee, Baqiyatallah University of Medical Sciences, Tehran, Iran
2. Department of Pharmacology and Toxicology, Faculty of Pharmacy, Baqiyatallah University of Medical Sciences, Tehran, Iran
3. Department of Pharmacognosy and Traditional Pharmacy, Faculty of Pharmacy, Baqiyatallah University of Medical Sciences, Tehran, Iran

*** Corresponding author**
Mahdi Mashhadi Akbar Boojar, PharmD
Department of Pharmacology and Toxicology, Faculty of Pharmacy, Baqiyatallah University of Medical Sciences, Tehran, Iran
Tel: +98 9124401322
Email: mahdimashhadi@yahoo.com

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Abstract

Background: Inflammatory and local pains are common issues. People often use Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) like diclofenac or herbal products for relief, and some studies suggest that herbal oils may work better than NSAIDs. This study compared the pain-relieving and anti-inflammatory effects of Violet Flower (*Viola odorata*) Oil (VFO) and Bitter Almond (*Prunus amygdalus*) Oil (BAO) with diclofenac gel in animal models.

Methods: Tail-flick, hot-plate, and formalin tests were used to compare the local analgesic and anti-inflammatory effects of studied herbal oils and diclofenac. The experiments were performed in 6 groups (N=8), including the control, paraffin, diclofenac, VFO, BAO, and VFO+BAO. Each experiment's data were analyzed with one-way ANOVA.

Results: In the tail-flick test, 30 *min* after administrating the studied agents, the latency of all groups receiving diclofenac, VFO, BAO, and VFO+BAO was significantly increased ($p<0.05$). 60 *min* after administration, in diclofenac, VFO, and BAO, and after 120 *min* in VFO and BAO groups, pain latency elevated significantly. The results of the hot-plate test for BAO were somewhat similar to the tail-flick test, but VFO could not significantly increase the latency. In the inflammatory phase of formalin fest, all four groups that received diclofenac, VFO, BAO, and VFO+BAO reduced the grooming time ($p<0.001$).

Conclusion: This study found that BAO works similarly to diclofenac gel. BAO takes longer to start working but lasts longer than diclofenac. Both VFO and BAO show good pain-relieving and anti-inflammatory effects, indicating they could be effective alternatives to traditional NSAIDs for managing pain and inflammation.

Keywords: Analgesics, Diclofenac, Flowers, Inflammation, Non-steroidal anti-Inflammatory agents, Oils, Prunus dulcis, Viola

Introduction

The world's elderly population is increasing, and physical disability and related pain are among the most common problems in this period of life (1). Inflammatory and local pains are major complications that people may experience during their lives, especially in old age, for various reasons (2). These pains may occur in different parts of the body, such as a specific muscle, joint, and other areas due to factors including trauma, osteoarthritis, and autoimmune diseases such as rheumatoid arthritis (3). In these cases, according to the recommendations of international guidelines, the use of topical painkillers is preferred because patient acceptance is higher, they are easier to use, have limited systemic absorption, and, as a result, have fewer side effects (4,5). This makes topical analgesics a crucial component of pain management strategies for the elderly, ensuring both efficacy and safety.

Common topical products for regional pain relief often include Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and some herbal products. Patients should pay attention to the side effects of NSAIDs, including gastrointestinal bleeding, decreased kidney function, Increased blood pressure, and cardiovascular disease, even when used topically (6,7). Unfortunately, there have been reports of gastrointestinal bleeding after chronic use of topical NSAIDs (8). This highlights the need for safer alternatives, such as herbal products, which may offer effective pain relief with fewer adverse effects.

Among local analgesic agents, herbal oils have been of great interest, and some studies have shown that herbal oils can be more effective than common NSAIDs (6). Medicinal plants have been one of the oldest topical agents for pain relief and have attracted the attention of researchers worldwide due to their availability and acceptance by the public (9,10). This growing interest in herbal oils underscores their potential as viable alternatives in pain management, particularly for those seeking safer, more natural options.

Herbal topical analgesics suppress pain through several mechanisms, primarily involving the modulation of peripheral nociceptive pathways and inflammatory responses. One key mechanism is the activation of peripheral opioid receptors, which can inhibit pain signal transmission at the site of application (4). Additionally, topical products may block voltage-gated sodium channels, reducing neuronal excitability and the conduction of pain signals (6). Furthermore, many topical formulations contain anti-inflammatory agents that inhibit the release of pro-inflammatory cytokines and mediators, thereby decreasing inflammation and associated pain (6,10).

Bitter Almond Oil (BAO)(*Prunus amygdalus* var. amara) and Violet Flower Oil (VFO) (*Viola odorata*) are among the most conventional herbs used in traditional Persian medicine (11). BAO has been noted for its pharmacological properties, such as antispasmodic, analgesic, anti-inflammatory, and sedative effects (12,13). Unsaturated fatty acids in this oil, such as oleic acid, can relieve pain by inhibiting the activity of the cyclooxygenase enzyme (14). VFO is used systemically and locally to treat headaches, cough, and fever in ethnobotany and ethnopharmacology (15). Generally, these biological effects have been attributed to salicylate derivatives and some flavonoid compounds (11,15). Several studies have been conducted on therapeutic doses, and results indicated their low toxicity and high safety (16,17). This evidence supports the potential of these herbal oils as effective and safe options for pain management in clinical settings.

Considering the importance of using herbal medicinal oils as a complementary treatment, alongside the side effects of NSAIDs such as diclofenac for the elderly, this study aimed to compare the analgesic effects of BAO and VFO with diclofenac gel in reducing pain in animal models. To achieve this, three distinct pain assessment tests: the hot plate test, the tail-flick test, and the formalin test were employed. The hot plate test evaluates thermal nociception by placing mice on a heated surface and measuring the time taken for them to exhibit a pain response, such as licking or jumping; this test is particularly useful for assessing central pain mechanisms. In contrast, the tail-flick test measures reflexive responses to a noxious thermal stimulus applied to the tail, offering a rapid assessment of pain sensitivity and the efficacy of analgesic treatments. Lastly, the formalin test involves injecting a small amount of formalin into the paw, eliciting a biphasic pain response characterized

by acute and inflammatory pain phases, which allows researchers to study both immediate and prolonged pain behaviors. Together, these tests provide a comprehensive overview of analgesic effects, highlighting the differences in pain modalities and mechanisms targeted by various analgesic agents (17,18).

Materials and Methods

Animals

To carry out this research, 48 male mice of NMRI strain, weighing 20 to 30 *g*, were used in 6 groups of 8, which were obtained from the laboratory animal center of Baqiyatallah University of Medical Sciences. The animals were kept in special cages in the pharmacology laboratory of the Faculty of Pharmacy and weighed before the experiment. All experiments were performed during the illumination period.

Reagents and devices

VFO in a standardized form based on 1.9 *mg* of flavonoid percentage and bitter almond oil in a standardized form based on 22% weight-volume of Oleic acid were prepared from Barij Essential Pharmaceutical Co, Iran. Diclofenac as a final product, in the form of a 1% weight-volume gel, was prepared by Iran Najo Pharmaceutical Co, Iran. Formalin (formaldehyde) was obtained as a 1% solution from Kimia Alcohol Zanjan Co, Iran. Liquid paraffin was obtained from Farabi Pharmaceutical Co, Iran. Other items included: Mouse restraints, animal cages with sizes 24x13.5x13 *cm*, Tail-flick, and Hot-plate devices made by Tajhiz-gostar Omid Iranian Co, Iran.

Groups and experiments

In the present study, animals were tested in six groups (n=8).

The first group (control): Mice did not receive medication before the pain measurement test.

The second group: Before performing the tail-flick test, 0.5 *g* of paraffin was applied to the tails of the mice with 50 finger movements, first on two *cm* of the end of the tail, and then the entire tail was rubbed. In the hot plate and formalin tests, the amount of paraffin applied was 0.3 *g* per mice paw.

The third group: 0.5 *g* of diclofenac gel was applied to the tail before performing the tail-flick test, and 0.3 *g* of diclofenac gel was applied to the paw before conducting the hot plate and formalin tests.

The fourth group: 0.5 *g* of VFO was applied on the tail before performing the tail-flick test, and 0.3 *g* of VFO was applied on the paw before conducting the hot plate and formalin tests.

Fifth group: 0.5 *g* of BAO was applied on the tail before performing the tail-flick test, and 0.3 *g* of bitter almond oil was applied on the paw before conducting the hot plate and formalin tests.

The sixth group: 0.5 *g* of a mixture of BAO and VFO (in equal proportion) on the tail before performing the tail-flick test and 0.3 *g* of a mixture of BAO and VFO (in equal proportion) on the paw before performing the hot plate and formalin tests.

The method and amount of administration in the third to sixth groups were similar to the second group.

Paraffin was used as a neutral agent in the control group to ensure that any changes in pain responses were due to the active ingredient itself (herbal oils), and this is a standard approach in pharmacological studies to isolate specific drug effects.

In this study, the 30, 60, and 120-*min* evaluation intervals were strategically selected based on pharmacokinetic/dynamic mechanisms of topical analgesics and standardized pain response patterns in animal models. The timeline was optimized to assess three key phases: onset (30 *min* for initial drug absorption and analgesic initiation), peak efficacy (60 *min* reflecting maximum local concentration), and duration (120 *min* evaluating therapeutic persistence and drug half-life in tissues). This framework accommodates both rapid-acting agents (*e.g.*, diclofenac) and delayed-onset compounds (*e.g.*, herbal oils). Standardized tests were employed: Tail-flick (spinal reflex) and Hot-plate (supraspinal response) for pain threshold changes, alongside the formalin test differentiating acute (0-5 *min*) and inflammatory (15-30 *min*) phases to isolate analgesic *vs.* anti-inflammatory effects. The intervals align with prior studies, enabling robust cross-study comparisons of topical analgesic profiles (17).

Pain assessment tests

The behavioral assays in this study comprised

hot-plate, tail-flick, and formalin tests, executed sequentially on separate days following compound administration. To ensure methodological rigor, a 72-*hr* washout period was systematically implemented between consecutive tests to mitigate potential pharmacological interference. The formalin test, which induces localized inflammation and tissue injury, was deliberately positioned as the terminal assay following the completion of the preceding two tests. This staggered design minimized confounding effects from inflammatory sequelae on prior nociceptive evaluations, thereby preserving the integrity of comparative analgesic assessments.

Tail-flick test

In the tail-flick test, a heat stimulus of the type of light rays with an intensity of 5 (8.5 *V*) was used on the tails of the mice. The duration of the delay in the occurrence of the spinal reflex that leads to the removal of the tail from the radiation path was expressed as tail-flick latency. The sudden and quick movement of the animal's tail to get out of the path of light radiation indicates the threshold of pain, and the time of this response was recorded. To prevent tissue damage in case of no response of the tail reflex, the treatment was stopped ten *s* after the start of the thermal radiation according to the previous setting of the device. This experiment was performed 30, 60, and 120 *min* after topical administration (17). These time intervals allow for the assessment of the analgesic effects of the treatment over different durations, providing valuable insights into its efficacy.

Hot plate test

This experiment is a response to an acute thermal and generally non-inflammatory stimulus. The circular plate is heated with the help of an electric current, its temperature can be controlled, and it is heated up to 55±0.5°*C*. The device is equipped with a timer and thermostat. After setting the temperature, the mice were placed on the hot plate of the device, and the time required to observe the reaction of the animal to the thermal stimulus (leg raising) was recorded. To adapt the animals to the conditions, the day before the experiment, the animals were placed in the machine's environment. In this test, the time to stop the test was 50 *s* after the start of the test. This experiment was done 30, 60, and 120 *min* after topical application (17). These time points are crucial for assessing the analgesic efficacy of the topical treatment, providing insights into both its immediate and sustained effects.

Formalin test

This experiment is one of the examples of pain assessment tests to measure inflammatory and nociceptive pain thresholds. 50 μL of 1% formalin solution were poured into the sole of the mice's left foot using a syringe. In the first phase of the experiment, the total foot-licking (grooming) time was recorded from 0 to 5 *min*, and in the second phase of this test, after 15-30 *min* of formalin administration, the foot-licking time was recorded by a camera. Before the formalin test, the animals were transferred to the test site at the same time of the day for 3-4 *hrs* before the start of the experiment to reduce stress and acclimatize (17,18). This approach enables a comprehensive evaluation of both inflammation and pain responses, providing valuable insights into pain thresholds and the efficacy of analgesic treatments in inflammatory conditions.

The method of carrying out the current study is illustrated in figure 1.

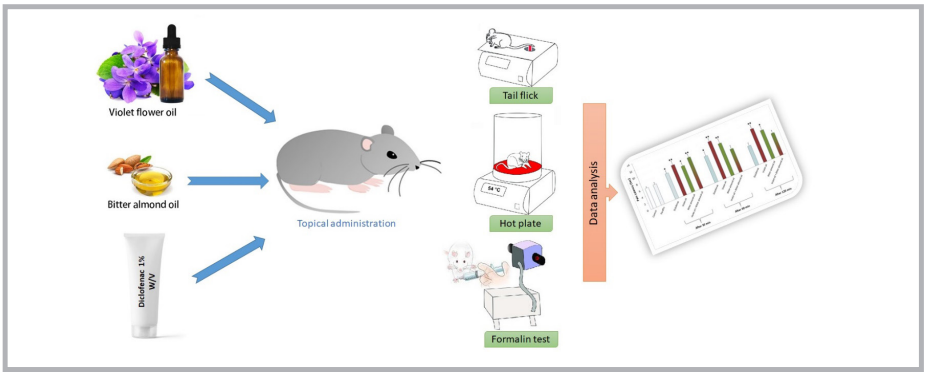

Figure 1. The procedure for conducting the study has been depicted.

Statistical analysis

All data were expressed as mean±standard error (SE) of 8 mice in each separate group. For statistical analysis, a one-way analysis of variance (ANOVA) and SPSS software (version 20) were used, and $p<0.05$ was considered significant in each test. Also, in this research, Microsoft Excel 2016 software was used to draw graphs. The researchers conducted a Kolmogorov-Smirnov test and found a p-value of 0.084, which exceeds the alpha level of 0.05, suggesting that the data conforms to a normal distribution.

Ethics considerations

This research was carried out under standard conditions in terms of light (12 *hrs* of light and 12 *hrs* of darkness), temperature conditions of 22 to 25°*C*, and free access to water and food for the mice. The animals were kept in cages with the number of 6 mice in each cage. They were kept in compliance with the ethical considerations protocols of the Ethics Committee of Baqiyatallah University of Medical Sciences in storage and transportation. In addition, all the principles of safety, health, and ethics in working with laboratory equipment and materials, as well as working with laboratory animals (such as gloves, appropriate and separate gowns, and regular washing of hands, *etc*.) have been observed during the conduct of this research. This study has been approved with the code of ethics number IR.BMSU.AEC.1400.008.

Results

Tail-flick test

In this experiment, the control and the paraffin groups did not have a significant difference in pain latency at any of the investigated times after the start of the test ($p=0.145$). Therefore, the statistical comparison of the studied oils and diclofenac groups was made with the paraffin group (Figure 2).

The pain latency of the response to the stimulus, 30 *min* after administrating the studied compounds, in all four groups receiving diclofenac, VFO, BAO, and the group receiving BAO and VFO at the same time was considerably increased compared to the paraffin group [$F(1,14)=15.62$, $p<0.05$]. This increased response was more considerable in the groups receiving VFO and the group receiving a mixture of VFO and BAO [$F(1,14)=10.45$, $p<0.001$].

60 *min* after the application of the investigated agents, the analgesic effects of the group that simultaneously received VFO and BAO disappeared. However, in the other three groups, the analgesic effects continued significantly [$F(1,14)=11.09$, $p<0.05$]. Finally, 120 *min* after administration, the effects of diclofenac gel in increasing latency time disappeared, but the groups receiving VFO [$F(1,14)=12.44$, $p<0.001$] and BAO [$F(1,14)=10.37$, $p<0.05$] (separately) still had an increase in latency.

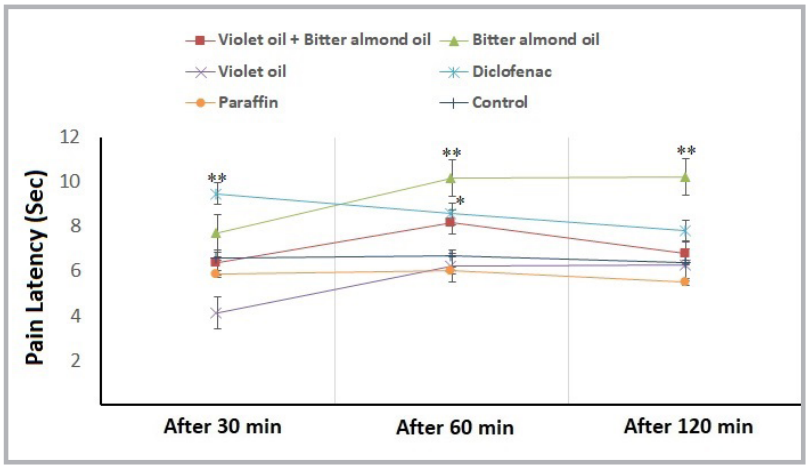

Figure 2. Comparing the analgesic effects of topical diclofenac administration, VFO and BAO, and their mixture with the control and paraffin groups using the tail-flick test at 30, 60, and 120 *min* after administration in mice. Data were expressed as mean±standard deviation (n=8), and the results obtained from each group were analyzed separately using the control group as the reference by one-way analysis of variance and SPSS software. * and ** indicate a significant difference compared to the paraffin group ($p<0.05$ and $p<0.001$, respectively).

Hot plate test

Local application of paraffin did not affect the onset time of the response to the thermal stimulus, and therefore, other groups were compared with the group receiving paraffin (p=0.429). At 30 *min* after administration, only the group receiving diclofenac was able to considerably increase the duration of the onset of the response to the nociceptive stimulus [F(1,14)=9.31, p<0.001]. 60 *min* after treatment, the analgesic effects of bitter almond oil appeared significantly as much as diclofenac [F(1,14)=11.25, p<0.05]. Finally, 120 *min* after administration, the analgesic effects of diclofenac had disappeared, and only the animals in the group receiving BAO still showed an increase in the response threshold to pain [F(1,14)=10.30, p<0.001]. The analgesic effect of BAO appeared delayed but more prolonged than that of diclofenac (Figure 3).

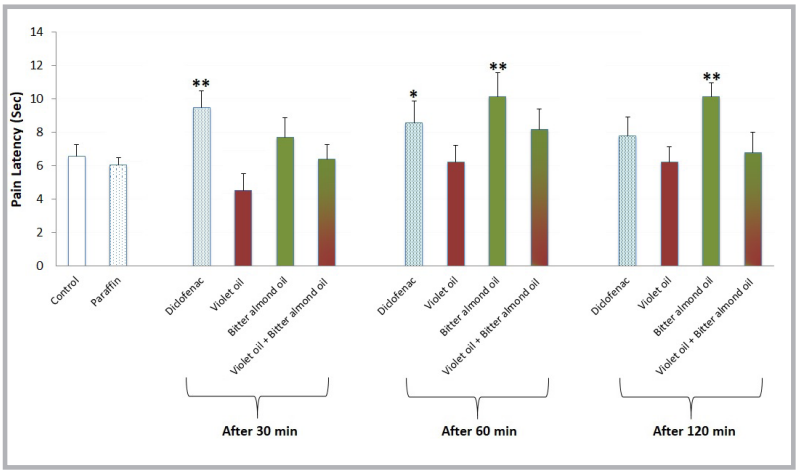

Figure 3. Comparing the analgesic effects of topical diclofenac administration, VFO and BAO, and their mixture with the control and paraffin groups using the hot plate test at 30, 60, and 120 *min* after treatment in mice. Data were expressed as mean±standard deviation (n=8), and the results obtained from each group were analyzed separately using the control group as the reference by one-way analysis of variance and SPSS software. * and ** indicate a significant difference compared to the paraffin group (p<0.05 and p<0.001, respectively).

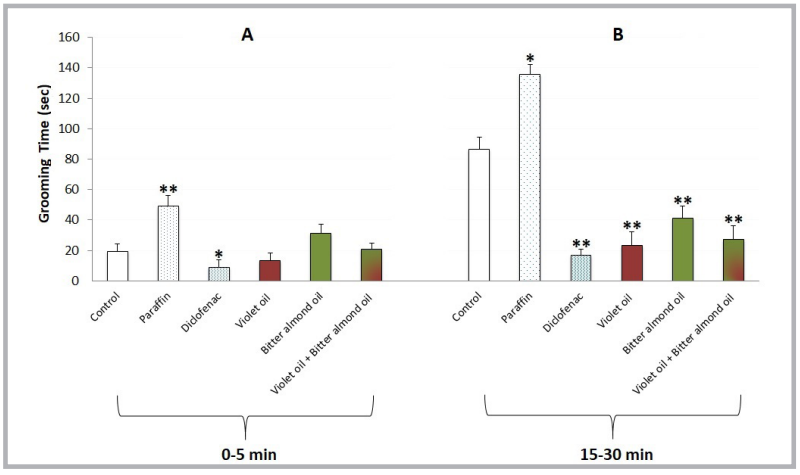

Figure 4. Comparison of the analgesic (A) and anti-inflammatory (B) effects of diclofenac and VFO and BAO and their mixture compared to the control using the formalin test in the acute (0-5 *min*) and chronic (15-30 *min*) phase after formalin administration in mice. Data were expressed as mean±standard deviation (n=8), and the results obtained from each group were analyzed separately with the control group by one-way analysis of variance and SPSS software. * and ** indicate a significant difference from the control group (p<0.05 and p<0.001, respectively).

Formalin test

In the assessment of 0 to 5 *min* after formalin administration (acute), the grooming time in the group receiving paraffin increased greatly [$F(1,14)=12.69$, $p<0.001$], so a comparison was made with the control group. In this period, only the group receiving diclofenac could significantly reduce the grooming time following formalin administration [$F(1,14)=10.85$, $p<0.001$].

In the inflammatory or chronic phase (15 to 30 *min* after treatment), the administration of paraffin significantly increased the irritability caused by inflammation compared to the control group [$F(1,14)=13.44$, $p<0.05$]. In this situation, all four groups that received diclofenac, VFO and BAO and VFO+BAO were able to reduce the grooming time [$F(1,14)=11.72$, $p<0.001$]. In this phase, the effects of BAO were significantly greater than those of diclofenac [$F(1,14)=10.01$, $p<0.05$] (Figure 4).

Discussion

Localized pain is a common health problem at different stages of life, especially in old age (19). Previous studies have shown that topical products as a "smart choice for multimodal pain relief," can be as effective as systemic medications in controlling pain and reducing unwanted side effects (20). Herbal analgesics have long been of interest, and some studies have even shown their higher efficacy than common analgesics such as NSAIDs (21). In this regard, the present study, focusing on the selection of indigenous Iranian plants, investigated the analgesic effects of VFO and BAO in comparison with diclofenac. The choice of these two herbal oils was based on their extensive use in traditional Iranian medicine, the presence of active anti-inflammatory compounds such as oleic acid in BAO and salicylates in VFO, and preliminary evidence from previous studies indicating analgesic efficacy similar to NSAIDs (22). This comparison aims to provide safer herbal alternatives with fewer side effects than common drugs such as diclofenac and analyzes their potential role in improving pain management strategies, especially for people seeking alternatives to traditional medications.

The results of the tail-flick test (which mainly produces a spinal response) showed that both evaluated herbal oils were able to increase the delay in response to the thermal stimulus as much as diclofenac. In this test, while the local analgesic effect of diclofenac continued up to 60 *min* after administration, the duration of action of both VFO and BAO continued for more than 120 *min* after separate treatment. However, it is important to note that administering a mixture of the two investigated oils resulted in a short analgesic effect, which was even shorter than that of diclofenac (23). This suggests that while individual herbal oils may provide prolonged relief, their combined use may not yield the same efficacy, highlighting the complexity of interactions between different analgesic agents.

The findings of the hot-plate test on BAO and diclofenac were completely consistent with the tail-flick test. Data from the hot-plate test revealed that VFO has no analgesic effect. It seems that the pain-relieving effects of VFO are only applied peripherally, while BAO can exert central pain-relieving effects as well. Also, the analgesic effects of BAO started with a delay (compared to the tail-flick test), which is a reason for the requirement of distribution before the onset of its central effects. It has been demonstrated that BAO can have pain-relieving effects in primiparous women by increasing beta-endorphin levels (24). These findings suggest that while VFO may have limited utility in pain management, BAO presents a promising option for achieving both peripheral and central analgesic effects.

The delayed onset of analgesia observed with BAO may suggest that it facilitates central mechanisms, possibly through the modulation of neurotransmitter systems involved in pain processing. Studies have indicated that certain fatty acids, including those found in BAO, can influence the release of endogenous opioids, which play a crucial role in descending pain modulation pathways. This dual action-peripheral inhibition of nociceptive pathways and central modulation-may explain the prolonged analgesic effects of BAO compared to diclofenac (13).

In the acute phase of the formalin test, none of the studied oils could have analgesic effects, or in other words, their effects had not begun. While in the delayed phase of this experiment (a persistent pain model), when the process of inducing inflammation also appeared, each of the investigated two oils (administered separately or mixed) was able to

exert an analgesic and anti-inflammatory effect. The application of paraffin increased the total grooming time, probably by increasing the availability of formaldehyde at the site of administration in both phases. Also, potential interactions between paraffin and formalin could alter the pharmacokinetics of the latter, resulting in prolonged nociceptive responses. A previous study reported that in lung inflammation conditions caused by formalin, an aqueous extract of *Viola odorata* has an anti-inflammatory effect as much as hydrocortisone and can be used as a safer alternative (25). These findings suggest that while the oils may not provide immediate relief, they could offer significant benefits in managing inflammation-related pain over time.

Based on previous studies, almond oil contains a considerable proportion of oleic acid as a monounsaturated fatty acid, and also a great amount of vitamin E and phytosterols (26). The possible neuroprotective roles of oleic acid and the reduction of oxidative stress have been noted by several investigations (16). The suppression of enzymes involved in prostaglandin biosynthesis and Inhibition of inflammatory cytokines such as Tumor Necrosis Factor-alpha (TNF-α) have been reported as a major mechanism of the pain-relieving and anti-inflammatory effect of oleic acid (14,27). Consequently, the incorporation of almond oil into therapeutic strategies may not only alleviate pain but also enhance overall cellular health through its multifaceted biochemical properties.

Local therapeutic products containing VFO used to control pain and inflammation and antioxidant properties have been of interest in modern phytotherapy (15). Flavonoids, saponins, salicylates, and alkaloids are responsible for the main therapeutic effects of VFO (11). It seems that the set of these components together is involved in the observed analgesic and anti-inflammatory effects by suppressing oxidative stress and inhibiting cyclooxygenase (COX)-2 (28). This synergistic action not only enhances the efficacy of VFO in pain management but also underscores its potential as a holistic treatment option in integrative medicine.

This study provided a direct comparative analysis of the analgesic and anti-inflammatory effects of VFO and BAO against diclofenac, adding significant insight into their potential efficacy. By investigating the combined effects of these herbal oils, the research explores interactions between different analgesic agents, a topic less examined in existing literature. Additionally, given the known side effects of NSAIDs, this study highlights the potential of herbal oils as safer, more natural alternatives, contributing to the development of complementary treatment options in holistic and integrative medicine.

Conclusion

This comparative investigation revealed that BAO was mostly similar in the analgesic effects of topical diclofenac. In contrast to prescribed oils, topical diclofenac exhibits a faster onset of action, but its duration of effect is shorter. Furthermore, the co-administration of a mixture of VFO and BAO does not compromise their efficacy.

Unlike VFO, the pain-relieving effects of BAO are mediated by both peripheral and central mechanisms. These findings suggest that while BAO may serve as an effective alternative or complementary option to diclofenac, further research is necessary to fully understand the mechanisms of action and optimize its therapeutic applications in pain management.

Additionally, the potential for integrating these herbal oils into multimodal analgesic strategies could enhance patient outcomes and minimize reliance on conventional pharmaceuticals.

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Conflict of Interest

There was no conflict of interest in this manuscript.

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