CellMed
Orthocellular Medicine and Pharmaceutical Association

Original Article

Enhanced Analgesic Efficacy of Flurbiprofen Plaster Supplemented with Natural Berry Herb Oil in a CFA-Induced Inflammatory Pain Model

Bong-Keun Jang[1,2*], Seong-Hoon Yun[1], Hye-Yeon Kang[1], Sunyoung Park[1], Gun-Woo Lee[1]

[1]*JBK-LAB, Inc., 17 Techno 4-ro, Yuseoung-gu, Daejeon 34013, Republic of Korea*
[2]*JBK-LAB, Inc., 464 Dunchon-daero, Jungwon-gu, Seongnam-si, Gyeonggi-do 13229, Republic of Korea*

ABSTRACT

Objective: This study evaluated the analgesic efficacy of "Flucoxfen", a flurbiprofen plaster enriched with natural berry-herb oils, compared to a conventional plaster in a Complete Freund's Adjuvant (CFA)-induced rat model.

Materials and Methods: Twenty rats were assigned to Normal, Control (CFA), Flucoxfen, and J Plaster groups. Daily applications of plasters were made to the inflamed paw. Mechanical hyperalgesia (von Frey test) and functional weight-bearing were assessed on days 4 and 10.

Results: Flucoxfen significantly alleviated pain, increasing the paw withdrawal threshold by 122% (Day 4) and 193% (Day 10) compared to the Control group (*$p < 0.05$). Additionally, it restored weight-bearing balance by 44% on Day 10 and markedly reduced edema. In contrast, the conventional plaster exhibited minimal therapeutic effects.

Conclusion: The incorporation of berry-herb oils significantly enhances the transdermal delivery and anti-inflammatory efficacy of flurbiprofen. Flucoxfen presents a potent therapeutic alternative for severe inflammatory pain where standard topical formulations are insufficient.

Keywords Osteoarthritis, Flurbiprofen, Essential Oils, Inflammatory Pain, Transdermal Drug Delivery, Permeation Enhancer

INTRODUCTION

Osteoarthritis (OA) is a degenerative disorder characterized by the loss of articular cartilage, leading to debilitating pain and functional impairment.[1] According to the 2021 Global Burden of Disease Study, OA affects approximately 595 million people worldwide, representing 7.6% of the global population.[2] As a prevalent condition among the elderly, OA significantly impacts overall health and the ability to perform daily activities.[3] Since a definitive cure for OA remains elusive, current therapeutic strategies focus primarily on alleviating pain and modulating inflammation to delay functional decline.[4]

Flurbiprofen, a potent non-steroidal anti-inflammatory drug (NSAID), is widely utilized due to its high efficacy in managing OA symptoms.[5] However, its clinical application is often constrained by significant adverse effects; systemic administration can lead to central nervous system symptoms, such as headache and dizziness, as well as gastrointestinal complications ranging from nausea to severe ulceration and renal impairment.[6,7] To circumvent these systemic risks, transdermal plasters have been employed for localized delivery.[8] Nevertheless, their clinical utility is often hindered by poor skin permeability and low percutaneous absorption rates, which limit the drug's overall therapeutic bioavailability.[9]

To address these delivery challenges and enhance the safety-efficacy profile of topical treatments, there is growing interest in essential oils (EOs) as natural adjunctive therapies and potential penetration enhancers.[10] EOs are complex mixtures of volatile compounds, predominantly terpenes, which act as powerful antioxidants, free-radical scavengers, and metal chelators.[11] Preclinical studies have demonstrated that these secondary metabolites possess significant analgesic, neuroprotective, and anti-inflammatory properties.[12-14] Specifically, the anti-inflammatory and antipyretic potential of various plant-derived EOs has been validated in both in vitro and in vivo models.[15,16]

However, most existing research on the synergistic effects of EOs and flurbiprofen has focused on gel-based

*Correspondence: Bong-Keun Jang
E-mail: jbk@jbklab.co.kr
Received Feb 24, 2026; **Revised** Feb 25, 2026; **Accepted** Feb 27, 2026; **Published** Feb 27, 2026
doi: http://dx.doi.org/10.5667/CellMed.2026.003

formulations.[17] There remains a paucity of evidence regarding their efficacy in plaster-type delivery systems, which are often preferred for sustained release and patient convenience. Therefore, the present study aims to investigate whether the incorporation of 'Natural Berry-Herb Oil' into a flurbiprofen plaster (Flucoxfen plaster) can enhance its therapeutic efficacy in reducing pain and edema, thereby providing a more effective and safer intervention for OA management.

MATERIALS AND METHODS

Test Materials

The Flucoxfen plaster, provided by JBKLAB Co., Ltd. (Republic of Korea), is a modified flurbiprofen formulation enriched with a proprietary blend of essential oils—including peppermint, eucalyptus, rosemary, and lavender—and berry aroma oils (raspberry and blueberry). For comparative analysis, a conventional flurbiprofen plaster (J Plaster, Company G, Republic of Korea) was utilized as the standard control.

Animal Preparation and Acclimatization

Twenty female Sprague-Dawley (SD) rats (6 weeks old) were housed in a climate-controlled facility under a 12 h light/dark cycle, with ad libitum access to standard chow and water. Before any intervention, all animals underwent handling and behavioral training to acclimatize to the von Frey filament and weight-bearing apparatus. During this phase, baseline measurements for paw withdrawal threshold (PWT) and static weight-bearing balance were recorded for each rat (Fig. 1). All animal handling procedures and experimental protocols were approved by the Institutional Animal Care and Use Committee of JBKLAB Co., Ltd (JBK-26-02-001).

Induction of Inflammatory Pain

To simulate the pathological conditions of osteoarthritis, the CFA-induced model is widely employed due to its ability to reliably replicate inflammatory responses and joint degradation.[18] The animals were randomly assigned to four groups: Normal (n=4), Control (CFA-induced, n=4), Flucoxfen (CFA + berry herb-oil supplemented flurbiprofen plaster, n=6), and J Plaster (CFA + standard flurbiprofen plaster, n=6). To establish the inflammatory pain model, 5 mg/ml of Complete Freund's Adjuvant (#7027, CFA; Chondrex, USA) was injected intraplantarly into the metatarsal region of the left hind paw. Following the injection, the rats were closely monitored for the development of localized inflammation and mechanical hypersensitivity.

Treatment Application

Upon confirmation of clinical inflammation, the therapeutic plasters (Flucoxfen or J Plaster, 2 × 2 cm) were applied directly to the inflamed site of the left hind paw.[19] To ensure the integrity of the treatment and prevent self-trauma, such as licking, biting, or oral ingestion of the drug, an Elizabethan collar (E-collar) was secured around the neck of each rat for the duration of the treatment.[20] The plasters were maintained for approximately 5 hours and subsequently removed once daily.

Measurement of Mechanical Hind Paw Withdrawal Threshold

Mechanical hyperalgesia was assessed by determining the PWT using a Semmes–Weinstein set of monofilaments (von Frey hairs, #37450-275, Ugo Basile, Comerio, Italy). Six filaments ranging from 1 to 15 g were employed. Rats were placed individually in Plexiglas cubicles (8 × 12 × 14 cm) positioned on a wire mesh platform and allowed to habituate for at least 5 minutes prior to testing. The mechanical PWT was measured as the withdrawal response of the hind paw to von Frey filament stimulation. Filaments were applied to the central plantar surface of the left hind paw in ascending order of force. Each filament was applied until buckling occurred and held for 2 s. A trial consisted of five applications at 5 s intervals. A valid response was defined as complete lifting of the hind paw from the platform. The 50% paw withdrawal threshold was calculated using the Dixon up–down method.[21,22]

Assessment of Weight-Bearing Asymmetry

Functional pain deficits were evaluated by measuring static weight-bearing using an incapacitance meter (#600MR, IITC Life Science, Los Angeles, CA, USA). Before testing, rats were acclimatized to the testing room in their home cages for 10 min. Subsequently, each animal was placed in a Plexiglass restrainer for 15–30 min to ensure comfortable positioning, with both hind

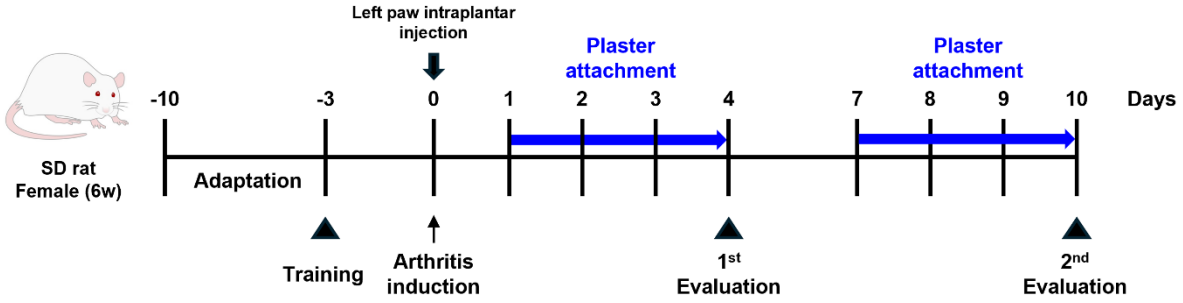

Fig. 1. Schematic representation of experimental design. The experimental timeline consists of initial handling and training, followed by Complete Freund's Adjuvant (CFA) induction. The treatment involves plaster application with an E-collar for 5 h, with subsequent evaluations conducted on day 4 and day 10.

paws resting on separate force plates. The weight distribution ratio between the contralateral (non-injured) and ipsilateral (injured) hindlimbs was recorded over a 2–3 s interval. Three replicate readings were obtained for each animal; any trials interrupted by movement or attempts to turn around were excluded and repeated.[23] Baseline measurements were established prior to CFA injection, followed by subsequent assessments on days 4 and 10 post-injection.

Statistical Analysis

All data are expressed as Mean ± Standard Error of the Mean (SEM). Statistical significance between groups was determined using a one-way analysis of variance (ANOVA) followed by Tukey's post-hoc test. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Flucoxfen reduces CFA-induced mechanical hyperalgesia

To verify pain induction, the development of mechanical allodynia was assessed. The von Frey test was performed to investigate whether Flucoxfen and J Plaster could alleviate CFA-induced pain. Prior to the induction of Adjuvant-Induced Arthritis (AIA) with CFA, no response to von Frey filament stimulation was observed; however, reactivity increased following induction and persisted until day 10, the final day of evaluation. On days 4 and 10 post-induction, the PWT in the Control group was significantly lower compared to the Normal group, confirming the successful establishment of the pain model.

Four days after pain induction, the Flucoxfen group showed a statistically significant improvement in pain of approximately 122% compared to the Control group, whereas the J Plaster group exhibited levels similar to the Control group (Fig. 2A). On day 10, pain persisted in the Control group compared to the Normal group. The Flucoxfen group demonstrated a statistically significant improvement of approximately 193% compared to the Control group. Although the J Plaster group showed a slight improvement compared to the Control group, no statistical significance was observed (Fig. 2B). The Control group showed a significant decrease in PWT following CFA injection. At the 1st (Day 4) and 2nd (Day 10) assessments, the Flucoxfen group exhibited a significantly higher withdrawal threshold compared to the J Plaster group, indicating superior mechanical pain relief.

Flucoxfen ameliorates percent ipsilateral static weight-bearing

The application of nociceptive stimuli or the quantification of nociceptive outcomes can be considered subjective analyses. Therefore, a more objective method with minimal researcher intervention is required. One potential alternative to address this issue is the use of a weight-bearing device. CFA induction had no inhibitory effect on body weight. However, unlike Flucoxfen, which facilitated a return to normal weight, J Plaster resulted in a sustained, slightly lower body weight relative to the Normal and Control groups (Fig. 3A).

A severe shift in weight-bearing toward the right limb occurred after CFA injection and persisted through day 10. Consistent with the von Frey data, the Control group's weight-bearing on the affected left limb remained significantly lower than that of the Normal group during this period. In contrast to the von Frey test results, weight-bearing in both the Flucoxfen and J Plaster groups remained reduced on day 4, similar to the Control group. However, upon evaluation on day 10, the Flucoxfen group showed a statistically significant improvement of 44%, recovering to a level comparable to the Normal group. Conversely, the J Plaster group continued to exhibit reduced weight-bearing on the left limb, similar to the Control group (Fig. 3B). The Flucoxfen group demonstrated a more rapid and substantial recovery of weight distribution on the affected left paw compared to the J Plaster group, suggesting a reduction in spontaneous pain during standing.

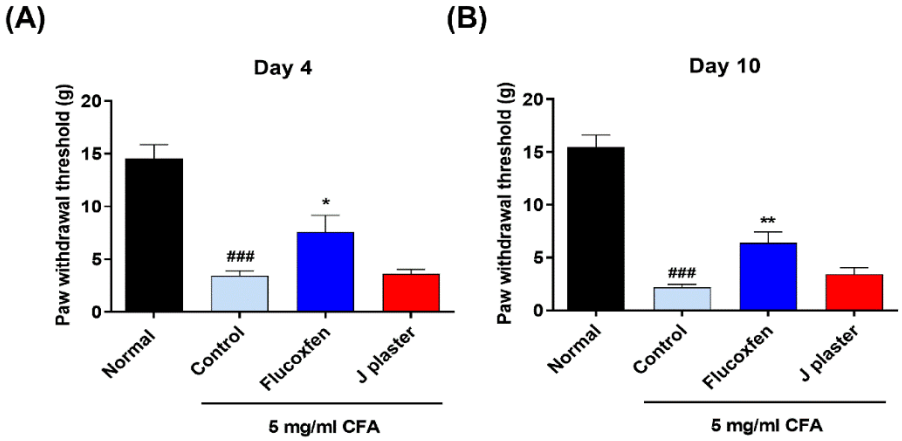

Fig. 2. Effect of Flucoxfen on mechanical hyperalgesia. PWT was measured on (A) day 4 and (B) day 10 post-CFA induction. The Flucoxfen-treated group exhibited a significant increase in PWT compared to the CFA control group. Data are presented as mean ± standard error of the mean (SEM). *p < 0.05 and **p < 0.01 vs. CFA control group; ###p < 0.001 vs. Normal group.

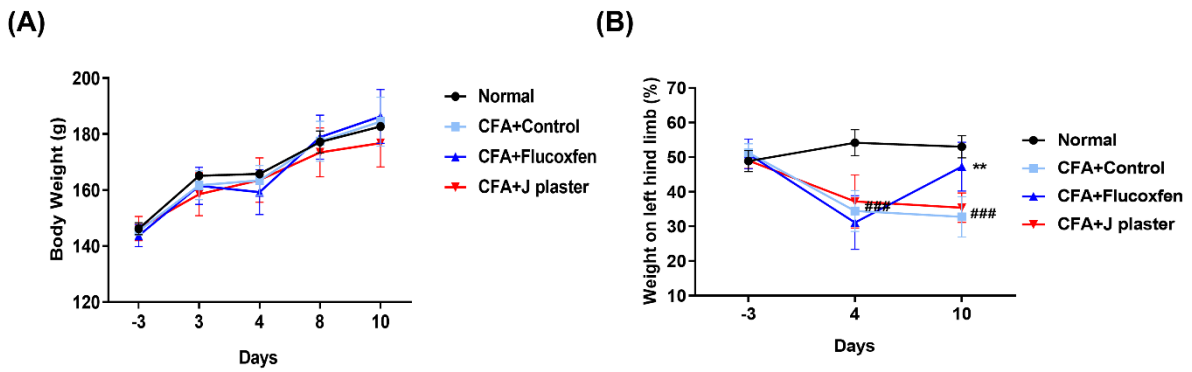

Fig. 3. Effects of Flucoxfen on body weight and weight-bearing distribution. (A) Changes in body weight across the experimental groups during the study period. (B) Percentage of weight distribution on the left (affected) hind limb. Data are expressed as mean ± SEM. *p < 0.05 and **p < 0.01 vs. CFA control group; ###p < 0.001 vs. Normal group.

Flucoxfen alleviates or attenuates paw swelling effect

In the CFA-induced paw edema model, intraplantar injection of CFA resulted in a time-dependent increase in paw thickness and the degree of edema. Swelling reached its peak at approximately day 4 and remained elevated throughout the 10-day period. Visual inspection and photographic records confirmed that the Flucoxfen group had reduced swelling compared to the Control and J Plaster groups (Fig. 4). The addition of natural berry herb oil appeared to accelerate the subsidence of inflammatory edema.

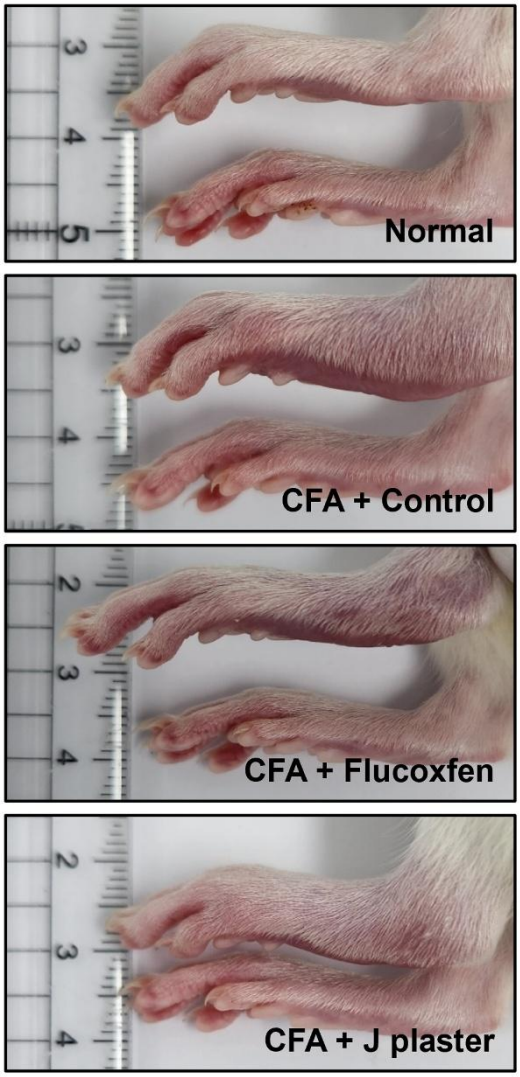

Fig. 4. Comparative analysis of paw edema across experimental groups. Representative photographs of the left hind paws from the Normal, CFA + Control, CFA + Flucoxfen, and CFA + J plaster groups. The Flucoxfen-treated group (C) shows a marked reduction in swelling and erythema compared to the CFA control and J plaster groups.

DISCUSSION

This study evaluated the clinical analgesic efficacy of a modified flurbiprofen plaster, "Flucoxfen," enriched with natural berry-herb oil. Our findings demonstrate that this novel formulation significantly enhances both analgesic and anti-inflammatory outcomes compared to the conventional J Plaster. This improvement is likely attributable to a synergistic interaction where the berry-herb oil facilitates flurbiprofen absorption, thereby increasing its bioavailability at the site of inflammation.

The induction of arthritis was achieved using the AIA model.[24] While AIA has long been utilized in Rheumatoid Arthritis (RA) research, it remains crucial to recognize that the histological and immunological profiles of AIA align more closely with reactive arthritis.[25,26] By employing this robust model, we observed Flucoxfen's ability to modulate the intense inflammatory response triggered by Mycobacterium tuberculosis.[24] The superior recovery in mechanical hyperalgesia and weight-bearing symmetry suggests that the berry-herb oil provides a distinct advantage in managing pain pathways associated with acute reactive-type inflammation. Notably, the use of an E-collar[20] confirmed that these therapeutic benefits resulted from localized transdermal delivery rather than systemic ingestion, reinforcing the formulation's safety profile.

A critical and unexpected observation was the negligible efficacy of the conventional J Plaster. Despite flurbiprofen being

a well-established NSAID, its failure in this specific setting warrants analysis. We hypothesize that the inflammatory severity induced even at a 5 mg/mL CFA dose may surpass the therapeutic threshold of standard formulations. In such severe models, physiological barriers and tissue edema may impede the drug's penetration from a standard plaster. In stark contrast, Flucoxfen's robust performance suggests that the natural berry-herb oil acts as a potent permeation enhancer. EOs and terpene-rich herb oils are known to perturb the stratum corneum lipid bilayer,[27,28] facilitating the deep penetration of active compounds into inflamed synovial tissues. This mechanism is consistent with previous reports where EOs, such as Eucalyptus globulus and galangal, enhanced the anti-inflammatory efficacy and bioavailability of flurbiprofen.[29] Furthermore, it has been demonstrated that the integration of peppermint and rosemary EOs into nano delivery systems results in improved bioavailability and superior analgesic efficacy in osteoarthritis management, reinforcing their pharmacological potential.[30] Beyond their role as penetration enhancers, the aromatic components of berry herb oils may offer intrinsic bioactive benefits, further modulating complex pain signaling pathways.

While this study did not delve into specific molecular signaling pathways—a limitation to be addressed in future research—the clinical superiority of Flucoxfen is evident. These results indicate that in severe arthritis models, the presence of an active pharmaceutical ingredient alone is insufficient. Rather, the formulation's capacity to bypass physiological barriers through synergistic additives is the key determinant of therapeutic success.

CONCLUSION

Flucoxfen plaster demonstrated superior efficacy in increasing mechanical pain thresholds, restoring weight-bearing balance, and reducing edema compared to conventional formulations in an AIA model. The addition of berry-herb oil significantly enhances the transdermal delivery and therapeutic potential of flurbiprofen, positioning Flucoxfen as a promising topical intervention for severe inflammatory pain.

ACKNOWLEDGEMENT

None

RESEARCH FUNDING

This research was conducted without external financial support.

CONFLICT OF INTEREST

The authors state that there is no conflict of interest.

REFERENCES

1. Herrero-Beaumont G, Castro-Dominguez F, Migliore A, Naredo E, Largo R, Reginster JY. Systemic osteoarthritis: the difficulty of categorically naming a continuous condition. Aging Clin Exp Res. 2024;36(1):45.
2. Culbreth GT, Haile LM, Rafferty Q, Lo J, Fukutaki KG, et al. Global, regional, and national burden of osteoarthritis, 1990–2020 and projections to 2050: a systematic analysis for the Global Burden of Disease Study 2021. Lancet Rheumatol. 2023;5(9):e508-22.
3. Hussain S, Neilly D, Baliga S, Patil S, Meek R. Knee osteoarthritis: a review of management options. Scott Med J. 2016;61(1):7-16.
4. Richard MJ, Driban JB, McAlindon TE. Pharmaceutical treatment of osteoarthritis. Osteoarthritis Cartilage. 2023;31(4):458-466.
5. Sasaki S, Sasaki E, Kimura Y, Naraoka T, Yamamoto Y, Tsuda E, et al. Treatment efficacy of single topical NSAID (S-flurbiprofen plaster) for knee symptoms and locomotive dysfunction in knee osteoarthritis patients. Prog Rehabil Med. 2021;6:20210008.
6. Evans A, Roy D, Dhanda S, Lane S, Coutinho G, Kulasekaran A, et al. A systematic review of flurbiprofen 8.75 mg dose and risk of adverse events (excluding haemorrhagic) resulting from drug-drug interactions. Front Pharmacol. 2024;15:1107185.
7. Yang C, Guo Q, Cheng Y, Liu F, Zhang H, Wang H. In-depth summary of adverse events associated with flurbiprofen: a real-world pharmacovigilance study from 2004 to 2024 using the FAERS database. PLoS One. 2025;20(8):e0329636.
8. Sharif A, E-Rabbani M, Akhtar MF, Akhtar B, Saleem A, Farzana K, et al. Design and evaluation of modified release bilayer tablets of flurbiprofen. Adv Clin Exp Med. 2011;20(3):343-9.
9. Morimoto Y, Hatanaka T, Sugibayashi K, Omiya H. Prediction of skin permeability of drugs: comparison of human and hairless rat skin. J Pharm Pharmacol. 1992;44(8):634-9
10. Farooqui H, Upadhyay S, Upadhyay P. Transdermal patches approach towards self-nano-emulsifying drug delivery system (SNEDDS) using essential oil as penetration enhancer. Micro Nanosystems. 2022;14(4):314-40.
11. Miguel MG. Antioxidant and anti-inflammatory activities of essential oils: a short review. Molecules. 2010;15(12):9252-87.

12. Lenardão EJ, Savegnago L, Jacob RG, Victoria FN, Martinez DM. Antinociceptive effect of essential oils and their constituents: an update review. J Braz Chem Soc. 2016;27(3):435-474.

13. Silva LL, Garlet QI, Benovit SC, Dolci G, Mallmann CA, Bürger ME, et al. Sedative and anesthetic activities of the essential oils of Hyptis mutabilis (Rich.) Briq. and their isolated components in silver catfish (Rhamdia quelen). Braz J Med Biol Res. 2013 Sep;46(9):771-9.

14. Lopes Campêlo LM, Gonçalves e Sá C, de Almeida AA, Pereira da Costa J, Costa Marques TH, Mendes Feitosa C, et al. Sedative, anxiolytic and antidepressant activities of Citrus limon (Burn) essential oil in mice. Pharmazie. 2011;66(8):623-7.

15. Kowalczyk T, Merecz-Sadowska A, Ghorbanpour M, Szemraj J, Piekarski J, Bijak M, et al. Enhanced natural strength: Lamiaceae essential oils and nanotechnology in in vitro and in vivo medical research. Int J Mol Sci. 2023 Oct 17;24(20):15279

16. Abena AA, Diatewa M, Gakosso G, Gbeassor M, Hondi-Assah Th, Ouamba JM. Analgesic, antipyretic and anti-inflammatory effects of essential oil of Lippia multiflora. Fitoterapia. 2003;74(3):231-6.

17. Dong J, Zhu XM, Wu FY, Yang BQ, Feng H, Dong YF, et al. Development of galangal essential oil-based microemulsion gel for transdermal delivery of flurbiprofen: simultaneous permeability evaluation of flurbiprofen and 1,8-cineole. Drug Dev Ind Pharm. 2020 Jan;46(1):91-100.

18. Shuang F, Zhu J, Song K, Hou S, Liu Y, Zhang C, Tang J. Establishment of a rat model of adjuvant-induced osteoarthritis of the lumbar facet joint. Cell Biochem Biophys. 2014;70(3):1545-51.

19. Sekiguchi M, Shirasaka M, Konno SI, Kikuchi SI. Analgesic effect of percutaneously absorbed non-steroidal anti-inflammatory drugs: an experimental study in a rat acute inflammation model. BMC Musculoskelet Disord. 2008;9:15.

20. Jang Y, Park YE, Yun CW, Kim DH, Chung H. The vest-collar as a rodent collar to prevent licking and scratching during experiments. Lab Anim. 2016;50(4):296-304.

21. Dixon WJ. Efficient analysis of experimental observations. Annu Rev Pharmacol Toxicol. 1980;20:441-462.

22. Chaplan SR, Bach FW, Pogrel JW, Chung JM, Yaksh TL. Quantitative assessment of tactile allodynia in the rat paw. J Neurosci Methods. 1994;53(1):55-63.

23. Bove SE, Calcaterra SL, Brooker RM, Huber CM, Guzman RE, Juneau PL, et al. Weight bearing as a measure of disease progression and efficacy of anti-inflammatory compounds in a model of monosodium iodoacetate-induced osteoarthritis. Osteoarthritis Cartilage. 2003;11(11):821-30.

24. Cannon GW, Openshaw S, Clayton F, Sawitzke AD, Griffiths MM. Adjuvant arthritis in rats: susceptibility to arthritis induced by Mycobacterium butyricum and Mycobacterium tuberculosis. Transplant Proc. 1999;31(3):1590-1.

25. Berke MS, Hansen CP, Kromann S, Colding-Jørgensen P, Kalliokoski O, Jensen HE, Sørensen DB, Hau J, Abelson KSP, Hestehave S. Refining the adjuvant-induced rat model of monoarthritis by optimizing the induction volume and injection site. Sci Rep. 2025;15:40281.

26. Kim HO, Lee SI. Experimental animal models for rheumatoid arthritis: methods and applications. J Rheum Dis. 2012;19(4):189-95.

27. Saha S, Verma RJ. Molecular interactions of active constituents of essential oils in zwitterionic lipid bilayers. Chem Phys Lipids. 2018;213:76-87.

28. Herman A, Herman AP. Essential oils and their constituents as skin penetration enhancer for transdermal drug delivery: a review. J Pharm Pharmacol. 2015;67(4):473-85.

29. Arooj B, Asghar S, Saleem M, Khalid SH, Asif M, Chohan T, et al. Anti-inflammatory mechanisms of eucalyptol rich Eucalyptus globulus essential oil alone and in combination with flurbiprofen. Inflammopharmacology. 2023;31(4):1849-62.

30. Mohammadifar M, Aarabi MH, Aghighi F, Kazemi M, Vakili Z, Memarzadeh MR, Talaei SA. Anti-osteoarthritis potential of peppermint and rosemary essential oils in a nanoemulsion form: behavioral, biochemical, and histopathological evidence. BMC Complement Med Ther. 2021;21:57.