WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 14, Issue 18, 97-110. Review Article ISSN 2277–7105

SPILANTHOL GEL IN PERIODONTITIS: BRIDGING TRADITIONAL WISDOM WITH MODERN DENTISTRY

Mrs. Ansira P.[1*], Prof. Dr. K. Premaletha[2], Mrs. Baby Nishma[3], Ms. Arya P. V.[4], Ms. Twinkle N. U.[5]

[1*,3,4,5]B Pharm Graduate, M Pharm Student CPS GMC Kannur, Kerala, India, Pin code: 670503.

[2]M Pharm, Ph.D., Associate Professor College of Pharmaceutical Sciences, Govt. Medical College, Kannur, Pariyaram-670503.

Article Received on
23 July 2025,

Revised on 12 August 2025,
Accepted on 01 Sept. 2025

DOI: 10.20959/wjpr202518-38241

***Corresponding Author**
Mrs. Ansira P.
B Pharm Graduate, M Pharm Student CPS GMC Kannur, Kerala, India, Pin code: 670503.

ABSTRACT

Periodontitis is a chronic inflammatory disease characterized by destruction of tooth-supporting tissues due to microbial dysbiosis and host immune response, remains challenging to treat effectively with conventional therapies alone. Spilanthol, the bioactive alkylamide extracted from *Spilanthes acmella* and *Acmella oleracea*, (commonly known as the toothache plant), exhibits significant pharmacological properties such as local anesthetic, anti-inflammatory, analgesic, antimicrobial, and immunomodulatory effects, making it a promising therapeutic agent in oral healthcare. Spilanthol is primarily extracted from the flower heads of *Spilanthes acmella* using methods like Natural Deep Eutectic Solvents (NADES), Supercritical CO_2 extraction, Ethanol extraction, and Solid-Phase Extraction (SPE). These methods aim to optimize yield and purity while being eco-friendly. Various studies have developed spilanthol-based gels for different applications. These gels demonstrate robust antimicrobial, antioxidant, and anti-inflammatory activities suitable for treating periodontal conditions. Spilanthol offers a unique combination of therapeutic properties beneficial for treating periodontitis. Incorporating spilanthol into gels presents a promising localized treatment strategy that combines sustained release, targeted action, and reduced systemic side effects. Although no standardized commercial spilanthol gel for periodontitis exists yet, the evidence supports its potential for future development.

KEYWORDS: Periodontitis, spilanthol, *spilanthes acmella*, periodontal gel.

INTRODUCTION

Periodontitis is a prevalent and serious inflammatory condition affecting the tissues surrounding the teeth, leading to the destruction of the periodontium and potentially resulting in tooth loss.[1] The World Health Organization (WHO) estimates that periodontal diseases affect around 19% of adults around the world. It is primarily caused by the accumulation of bacteria in dental plaque, leading to chronic inflammation, tissue damage, and bone resorption.[1] The main goal of periodontal therapy is to eliminate or control the microbial biofilm and the restoration of the periodontium's health and function.

Effective management of periodontitis typically involves deep cleaning procedures such as scaling and root planing, anti-inflammatory drugs and antibiotics to control bacterial infection, and sometimes in severe cases, surgical interventions like flap surgery, bone grafts, or tissue grafts may be necessary.[2] These treatments can be invasive and uncomfortable, often requiring multiple visits and longer recovery times. Various antimicrobial and anti-inflammatory drugs have been used along with mechanical debridement (professional removal of microbial biofilm) for the treatment of periodontitis.[3] Orally administered drugs for periodontal treatment can be less effective due to variable absorption influenced by factors like food and gastric pH, leading to inconsistent drug levels in the bloodstream. Additionally, these drugs undergo first-pass metabolism in the liver, reducing their bioavailability. They can also cause gastrointestinal side effects such as nausea and vomiting, and may not be suitable for patients with swallowing difficulties or those who are unconscious.[4]

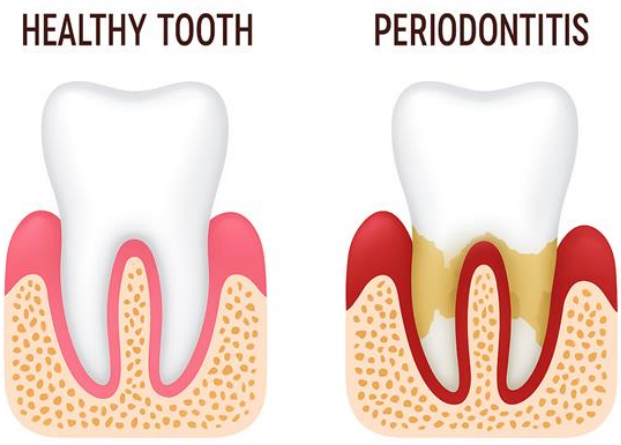

Figure i: Healthy v/s periodontal teeth.

To circumvent these issues, clinicians prefer localized drug delivery to inflamed periodontal sites. Delivering drugs locally into the pocket region provides the best efficiency in terms of drug concentration at the site while eliminating systemic side effects in patients. The different local drug delivery systems include films, gels, microspheres, nanoparticles etc, which can release drugs over an extended period.[5] Among the various types of local drug delivery systems, gels have received considerable attention for periodontal applications. Gels are semi-solid systems that consist of a liquid phase entrapped within a three-dimensional network of cross-linked polymers or solid particles. Gels represent a versatile and patient-friendly local drug delivery system for periodontal treatment, capable of delivering antimicrobial and anti-inflammatory drugs directly to periodontal pockets with controlled release profiles.[6] Hydrogels, oleogels, and bigels each provide complementary benefits, and ongoing research is enhancing their clinical applicability and overcoming existing limitations. Their superiority in biocompatibility, ease of use, and sustained drug delivery is why gels have gained considerable attention in the management of periodontitis.[7]

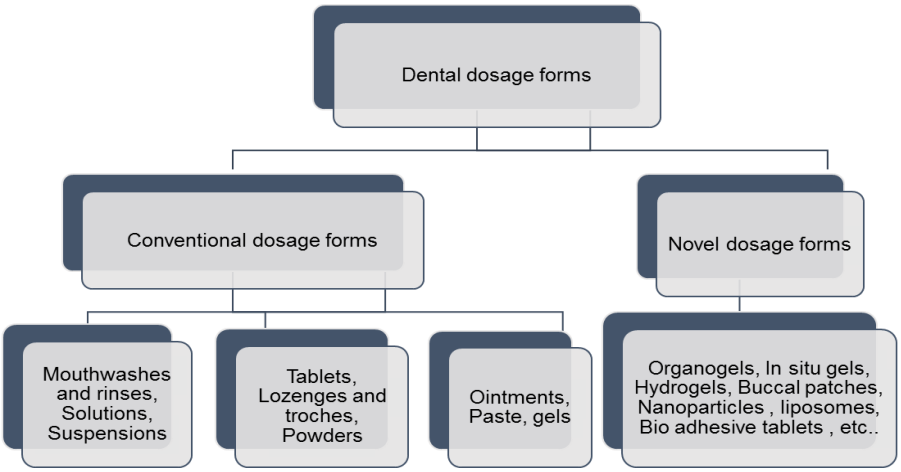

Figure ii: various types of dental dosage forms.

Spilanthol is a potent alkylamide found as a primary bioactive compound in *Spilanthes acmella* (a.k.a. toothache plant).[8] *Spilanthes acmella* has been a staple in traditional medicine for treating oral diseases.[9] Spilanthol possesses multiple biological activities like analgesic,[10] anti-inflammatory,[11] anesthetic[12] and antimicrobial activity[13] that make it effective for treating periodontal conditions. Spilanthol works by interacting with sensory nerve endings, especially those responsible for pain and temperature perception. It modulates ion channels on nerve cells, leading to a tingling and numbing sensation and

temporary desensitization to pain stimuli.[14] Antimicrobial activity against periodontal pathogens, and modulation of immune responses, collectively reducing periodontal tissue inflammation, bacterial load and pain.[15]

EXTRACTION OF SPILANTHOL

Spilanthol concentration is highest in flower heads compared to leaves and stems of *Spilanthes acmella*. Extraction yield and purity can be optimized by controlling temperature, solvent composition, and extraction duration. Purified spilanthol can be quantified by HPLC-DAD or NMR methods. Green extraction methods (NADES, SFE) offer eco-friendly and efficient routes with minimal toxicity and environmental impact.

Figure iii: *Acmella* flower extract powder.

i. Natural Deep Eutectic Solvents (NADES) Extraction

Choline chloride-based NADES mixed with various hydrogen bond donors (especially 1,2-propanediol at 1:2 molar ratio with 20% water) can efficiently extract spilanthol from *Spilanthes acmella* flower heads at 50–80 °C for 1 hour with a 1:10 (plant material to solvent) ratio. NADES are non-toxic, green solvents, and offer an eco-friendly alternative to organic solvents.[16]

ii. Supercritical CO_2 Extraction

Extracted from flowers with CO_2 at supercritical conditions (~35–40 MPa, 40–50 °C). Uses ethanol/water as cosolvents to increase spilanthol yield and Collects solvent-free extract containing enriched spilanthol.[17]

iii. Extraction with Ethanol

Plant material is macerated with 96% ethanol at room temperature for 24 hours with stirring, then filtered and evaporated to yield a dry resinous extract.[18]

iv. Solid-Phase Extraction (SPE)

SPE on C18 phases with isocratic elution (e.g., 52% ethanol) is an efficient, scalable, and simple purification step compatible with both NADES and ethanolic extracts, achieving up to ~94% purity post-fractionation(19).

THERAPEUTIC ACTIVITY OF SPILANTHOIL

i. Anti-Inflammatory and Neuroprotective Activity

Spilanthol significantly inhibits pro-inflammatory cytokines Interleukin-8 (IL-8) and Tumor Necrosis Factor-alpha (TNF-α) release from lipopolysaccharide-activated human neutrophils, demonstrating potent anti-inflammatory properties. In macrophage models (RAW 264.7 cells), spilanthol reduces iNOS expression and nitric oxide production, contributing to anti-inflammatory effects at cellular signaling levels.[20]

Spilanthol attenuates neuroinflammation, a pathological hallmark in several neurodegenerative diseases (NDDs) such as Alzheimer's and Parkinson's. It suppresses proinflammatory cytokines (e.g., TNF-α, IL-6, IL-1β), nitric oxide (NO) production, and key enzymes inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2). Mechanistically, spilanthol modulates toll-like receptor 4 (TLR4) and nuclear factor κB (NF-κB) pathways, inhibiting downstream signaling and expression of neuroinflammatory mediators. Studies combining in silico ADMET (absorption, distribution, metabolism, excretion, toxicity) and network pharmacology reveal spilanthol's favorable blood–brain barrier permeability and molecular docking affinity with TLR4-related targets.[21]

ii. Analgesic and Local Anesthetic activity

Traditional use for toothache and oral mucosa analgesia is attributed to spilanthol's ability to inhibit nerve conduction and stimulate gamma-aminobutyric acid (GABA) release in the cerebral cortex. It produces localized tingling, numbing, and mouth-watering sensations. Spilanthol-containing preparations are used in dental care products for pain relief and in topical anesthetic gels.[22,23]

iii. Antimicrobial and Antibacterial activity

Exhibits broad-spectrum antibacterial activity against pathogens responsible for dental caries and periodontal disease, including *Streptococcus mutans*[24] *Staphylococcus aureus*,[25] *Porphyromonas gingivalis*, and *Aggregatibacter actinomycetemcomitans*.[26] Demonstrated antifungal activity against *Aspergillus* and *Fusarium* species.[27]

iv. Antioxidant activity

Contains significant phenolic and flavonoid contents, contributing to strong antioxidant effects. Protects cells from oxidative stress by scavenging free radicals and enhancing activity of endogenous antioxidant enzymes.[25]

v. Immunomodulatory activity

Enhances both humoral and cellular immune responses and modulates oxidative stress and inflammatory cytokines in models of chronic fatigue syndrome. Flavonoids and polyphenols in spilanthol-containing extracts contribute to immune modulation.[28]

vi. Antimalarial and Larvicidal activity

Spilanthol is active against mosquito vectors and parasitic eggs/pupae; lethal to insect vectors but safe for vertebrates. Extracts containing spilanthol are effective against malaria parasites (Plasmodium species) and various mosquito vectors (Anopheles, Culex, Aedes), which are responsible for transmitting malaria, filariasis, and dengue fever.[29]

vii. Vasorelaxant and Diuretic activity

Spilanthol shown to induce vasodilation and increase urine output in animal studies. *Spilanthes acmella* extracts exhibited dose-dependent vasorelaxant effects mediated by endothelial nitric oxide and prostacyclin.[30]

viii. Anti-cancer and Aphrodisiac activity

Preliminary evidence suggests anticancer activity(31) and stimulation of sexual function(32).

PERIODONTAL GELS

Periodontal gels have emerged as promising local drug delivery systems for the treatment of periodontitis. These gels upon administration in the periodontal pocket, allowing for sustained and controlled release of therapeutic agents directly at the infection site.

Common Types of Periodontal Gels

1. Antibiotic-loaded gels

Metronidazole, satranidazole, doxycycline, and minocycline gels have demonstrated effective antimicrobial action against anaerobic pathogens such as *Porphyromonas gingivalis* and *Tannerella forsythia* and *Satranidazole* may provide superior clinical effects compared to metronidazole in chronic periodontitis with less side effects.[33-36]

2. Herbal and natural product gels

Curcumin in situ gels show anti-inflammatory, antioxidant, antimicrobial properties enhancing wound healing and reducing inflammation locally.[37] Clove oil gels, often formulated with carbopol 934 as gelling agent, exert broad-spectrum antibacterial and analgesic effects beneficial in periodontal therapy.[38]

3. Novel oxygen-releasing and other adjunct gels

Formulations like Blue M gel (oxygen releasing) aid healing by elevating oxygen levels in pockets and reduce infection risk.[39]

PREPERATION OF SPILANTHOL-CONTAINING GEL

Afzal et. al (2022) developed and evaluated an herbal emulgel formulation based on *Spilanthes acmella* extract for treatment of bacterial skin infections, addressing antibiotic resistance issues. Methanolic extract of S. acmella incorporated into emulgel bases with natural oils and polymers to enhance gel consistency, bioadhesive strength, spreadability, and skin permeation.[40] The *Spilanthes acmella*-based emulgel shows robust antimicrobial, antioxidant, and anti-inflammatory activities suitable for topical treatment of bacterial and fungal skin infections including eczema, cellulitis, and dermatitis caused by common bacterial pathogens. Emulgel formulation improves drug delivery via dual emulsion-gel properties, provides sustained release, better skin adherence, and enhanced penetration while maintaining a non-greasy, cosmetically acceptable texture.[41]

Kiełbratowski et. al, demonstrated that a mouthwash containing cannabidiol and spilanthol significantly improves oral health indicators in patients with gingivitis compared to a tea tree oil rinse. This suggests the potential for these natural ingredients to be effective in maintaining oral microbiota balance and reducing inflammation.[42] Kashyap P et. al, focused on the development of an herbal tooth gel aimed at managing gingival bleeding and toothache. The gel incorporated *Spilanthes acmella*, Green Tea, and clove oil as its primary ingredients. The combination of *Spilanthes acmella* and Green Tea extracts provided synergistic benefits for managing toothaches and gingival bleeding. Clove oil and menthol oil served as effective natural preservatives, enhancing the shelf life of the gel. The study concludes that this herbal tooth gel has significant potential for treating gingival issues.[43]

Verma K et. al, evaluated the efficacy of locally delivered *Acmella oleracea* and *Acacia catechu* gels in managing generalized chronic periodontitis, focusing on clinical parameters

and subgingival microflora and shown an improvement in periodontal healing compared to scaling and root planning.[44] Daundkar S, developed a herbal tooth gel utilizing spilanthol and evaluated against marketed preparations and found formulation's effectiveness and its potential application in maintaining oral hygiene and managing mouth ulcers.[45]

CONCLUSIONS

Spilanthol-containing gels represent a promising advancement in the management of periodontitis. By leveraging the bioactive properties of spilanthol extracted from *Spilanthes acmella* and *Acmella oleracea* these gels deliver targeted anti-inflammatory and antimicrobial effects directly within periodontal pockets. This localized drug delivery approach enhances treatment efficacy while minimizing systemic side effects, addressing limitations associated with conventional oral or systemic therapies. Spilanthol exhibits unique combination of analgesic, anti-inflammatory, antimicrobial, and immunomodulatory properties makes it highly beneficial for treating periodontitis. Its incorporation into gels provides a promising localized treatment strategy for periodontitis, combining sustained release and targeted action. The use of spilanthol gel bridges traditional herbal wisdom with modern dental practices, offering a novel therapeutic option for the effective control of periodontal disease.

However, further research particularly large-scale clinical trials and comprehensive safety assessments is necessary to fully establish the clinical effectiveness and optimize the use of spilanthol-containing gels in routine periodontal therapy.

FUTURE PERSPECTIVES

Spilanthol-containing gel formulations are suitable and have been studied for oral applications such as reducing inflammation and microbial infection in periodontal tissues. While no widely commercialized specific "spilanthol gel" for periodontitis is standardized yet and research supports the potential of spilanthol-based gels for periodontitis management due to its anti-inflammatory, analgesic, antimicrobial, and local anesthetic properties.

ACKNOWLEDGEMENT

I would like to express my sincere gratitude to everyone who helped me during the completion of this work. My deepest appreciation goes to my husband for his unwavering support, patience, and motivation that were crucial in overcoming difficult moments. I am profoundly thankful to my family for their love and encouragement throughout my life. I

extend my heartfelt thanks to my teachers for their expert guidance and valuable insights, which enriched my learning experience. I also appreciate my friends for their constant support and understanding. Without all of you, this accomplishment would not have been possible.

REFERENCES

4. Łasica A, Golec P, Laskus A, Zalewska M, Gędaj M, Popowska M. Periodontitis: etiology, conventional treatments, and emerging bacteriophage and predatory bacteria therapies. Front Microbiol., 2024 Sep 26; 15: 1469414.
5. Garg S. Local Drug Delivery Systems as an Adjunct to Cure Periodontitis-The Novel Dental Applicant. October 2025 Pharmaceutical Methods, 6(1): 01-08.
6. Mehta A, Kangowkar Vijayapremakumar V, Shivanand P, Prakash S. Nature's Anti-inflammatory agent and its use as a Local drug delivery agent for treatment of chronic periodontitis: A clinical, microbiological and biochemical study. Journal of Ayurvedic and Herbal Medicine, 2021 [cited 2025 Aug 12]; 7(1): 30–5. Available from: www.ayurvedjournal.com
7. Maurya R, Vikal A, Patel P, Narang RK, Kurmi B Das. "Enhancing Oral Drug Absorption: Overcoming Physiological and Pharmaceutical Barriers for Improved Bioavailability." AAPS PharmSciTech, 2024 Oct 1 [cited 2025 Aug 12]; 25(7): 1–20. Available from: https://link.springer.com/article/10.1208/s12249-024-02940-5
8. Ruth Gethsie K, Fathima Zinneerah S, Sudhakar U, Priyanka H. Local drug delivery drugs and systems. International Journal of Applied Dental Sciences, 2020 [cited 2025 Aug 12]; 70(4): 70–3. Available from: https://doi.org/10.22271/oral.2020.v6.i4b.1047 Baghwan RR, Ambekar AW, Tamboli SS. Formulation, Development and Evaluation of in-situ Periodontal Gel Containing Ofloxacin. Res J Pharm Technol, 2021 Sep 14 [cited 2025 Aug 12]; 14(9): 4609–14.
9. Chao E, Li J, Duan Z, Fan L. Bigels as emerging biphasic systems: Properties, applications, and prospects in the food industry. Food Hydrocoll, 2024 Sep 1 [cited 2025 Aug 12]; 154: 110089. Available from: https://www.sciencedirect.com/science/article/abs/pii/S0268005X24003631
10. Peretti P, Rodrigues ET, de Souza Junior BM, Bezerra RM, Guitián Fernández E, Sousa FFO de, et al. Spilanthol content of Acmella oleracea subtypes and their bactericide and antibiofilm activities against Streptococcus mutans. South African Journal of Botany, 2021 Dec 1; 143: 17–24.

11. De B, Goswami TK. Spilanthol (affinin). A Centum of Valuable Plant Bioactives, 2021 Jan 1; 733–43.
12. Rondanelli M, Fossari F, Vecchio V, Braschi V, Riva A, Allegrini P, et al. Acmella oleracea for pain management. Fitoterapia, 2020 Jan 1; 140: 104419.
13. Freitas Blanco VS de, Michalak B, Zelioli ÍAM, Oliveira A da SS de, Rodrigues MVN, Ferreira AG, et al. Isolation of spilanthol from Acmella oleracea based on Green Chemistry and evaluation of its in vitro anti-inflammatory activity. J Supercrit Fluids, 2018 Oct 1; 140: 372–9.
14. Alonso IG, Yamane LT, de Freitas-Blanco VS, Novaes LFT, Franz-Montan M, de Paula E, et al. A new approach for the total synthesis of spilanthol and analogue with improved anesthetic activity. Tetrahedron, 2018 Sep 20; 74(38): 5192–9.
15. Afzal A, Shah NH, Hussain I, Munawar SH, Mumtaz A, Qureshi N. Preparation of Spilanthes acmella based emulgel: Antimicrobial study and evaluation. Pak J Pharm Sci., 2022 Jan 1 [cited 2025 Aug 7]; 35(1): 287–95. Available from: https://www.researchgate.net/publication/357604768_Preparation_of_Spilanthes_acmella_based_emulgel_Antimicrobial_study_and_evaluation
16. Spelman K, Depoix D, McCray M, Mouray E, Grellier P. The Traditional Medicine Spilanthes acmella, and the Alkylamides Spilanthol and Undeca-2E-ene-8,10-diynoic Acid Isobutylamide, Demonstrate in Vitro and in Vivo Antimalarial Activity. Phytotherapy Research, 2011 Jul [cited 2025 Aug 7]; 25(7): 1098–101. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles /PMC3374932#id-name=PMC
17. Jayashan SS, Darai N, Rungrotmongkol T, Dasuni Wasana PW, Nwe SY, Thongphichai W, et al. Exploring the Therapeutic Potential of Spilanthol from Acmella paniculata (Wall ex DC.) R. K. Jansen in Attenuating Neurodegenerative Diseases: A Multi-Faceted Approach Integrating In Silico and In Vitro Methodologies. Applied Sciences (Switzerland), 2024 May 1 [cited 2025 Aug 7]; 14(9): 3755. Available from: https://www.mdpi.com/2076-3417/14/9/3755/htm
18. Alperth F, Feistritzer T, Huber M, Kunert O, Bucar F. Natural Deep Eutectic Solvents for the Extraction of Spilanthol from Acmella oleracea (L.) R.K.Jansen. Molecules, 2024 Feb 1 [cited 2025 Aug 13]; 29(3): 612. Available from: https://www.mdpi.com/1420-3049/29/3/612/htm
19. Dias AMA, Santos P, Seabra IJ, Júnior RNC, Braga MEM, De Sousa HC. Spilanthol from Spilanthes acmella flowers, leaves and stems obtained by selective supercritical

carbon dioxide extraction. J Supercrit Fluids, 2012 Jan 1 [cited 2025 Aug 13]; 61: 62–70. Available from: https://www.academia.edu/24528890/Spilanthol_from_Spilanthes_acmella_flowers_leaves_and_stems_obtained_by_selective_supercritical_carbon_dioxide_extraction

20. Alperth F, Erhart S, Kunert O, Bucar F. Simple Green Purification of Spilanthol from Natural Deep Eutectic Solvent and Ethanolic Acmella oleracea (L.) R.K. Jansen Extracts Using Solid-Phase Extraction. Separations, 2024 Aug 1 [cited 2025 Aug 19]; 11(8): 251. Available from: https://www.mdpi.com/2297-8739/11/8/251/htm
21. Freitas Blanco VS de, Michalak B, Zelioli ÍAM, Oliveira A da SS de, Rodrigues MVN, Ferreira AG, et al. Isolation of spilanthol from Acmella oleracea based on Green Chemistry and evaluation of its in vitro anti-inflammatory activity. J Supercrit Fluids, 2018 Oct 1 [cited 2025 Aug 19]; 140: 372–9. Available from: https://www.sciencedirect.com/science/article/abs/pii/S0896844618302158
22. Freitas Blanco VS de, Michalak B, Zelioli ÍAM, Oliveira A da SS de, Rodrigues MVN, Ferreira AG, et al. Isolation of spilanthol from Acmella oleracea based on Green Chemistry and evaluation of its in vitro anti-inflammatory activity. J Supercrit Fluids, 2018 Oct 1 [cited 2025 Aug 19]; 140: 372–9. Available from: https://www.sciencedirect.com/science/article/abs/pii/S0896844618302158
23. Jayashan SS, Darai N, Rungrotmongkol T, Dasuni Wasana PW, Nwe SY, Thongphichai W, et al. Exploring the Therapeutic Potential of Spilanthol from Acmella paniculata (Wall ex DC.) R. K. Jansen in Attenuating Neurodegenerative Diseases: A Multi-Faceted Approach Integrating In Silico and In Vitro Methodologies. Applied Sciences (Switzerland), 2024 May 1 [cited 2025 Aug 19]; 14(9): 3755. Available from: https://www.mdpi.com/2076-3417/14/9/3755/htm
24. Alonso IG, Yamane LT, de Freitas-Blanco VS, Novaes LFT, Franz-Montan M, de Paula E, et al. A new approach for the total synthesis of spilanthol and analogue with improved anesthetic activity. Tetrahedron, 2018 Sep 20; 74(38): 5192–9.
25. Rani AS, Sana H, Sulakshana G, Shravya Puri E, Keerti M. Spilanthes acmella-an important medicinal plant. IJMFM & AP, 2019; 5(2).
26. Peretti P, Rodrigues ET, de Souza Junior BM, Bezerra RM, Guitián Fernández E, Sousa FFO de, et al. Spilanthol content of Acmella oleracea subtypes and their bactericide and antibiofilm activities against Streptococcus mutans. South African Journal of Botany, 2021 Dec 1 [cited 2025 Aug 19]; 143: 17–24. Available from: https://www.sciencedirect.com/science/article /pii/S0254629921003069

27. Lima TM de FG, Silva LMR da, de Sousa PHM, Magalhaes FE, Ricardo NMPS, Vieira IGP, et al. Bioactive jambu extract (Acmella ciliata) as source of spilanthol for the development of a functional vegetable gelatin. Food Biosci., 2024 Oct 1 [cited 2025 Aug 19]; 61: 104706. Available from: https://www.sciencedirect.com/science/article/abs/pii/S2212429224011362
28. Shivananda S, Doddawad VG, Bhuyan L, Shetty A, Pushpa VH. Assessment of the Antibacterial Activity of Spilanthes acmella Against Bacteria Associated with Dental Caries and Periodontal Disease: An In-vitro Microbiological Study. J Pure Appl Microbiol., 2024 Mar 1; 18(1): 476–82.
29. Rani S, Murty S. Antifungal potential of flower head extract of Spilanthes acmella Linn. African Journal of Biomedical Research, 2009 Dec 8; 9(1).
30. Nipate SS, Tiwari AH. Antioxidant and immunomodulatory properties of Spilanthes oleracea with potential effect in chronic fatigue syndrome infirmity. J Ayurveda Integr Med., 2018 Apr 1; 11(2): 124–30.
31. Saraf DK, Dixit VK. Spilanthes acmella Murr. : Study on Its Extract Spilanthol as Larvicidal Compound. Asian J Exp Sci., 2002; 16(1) & (2): 9-19.
32. Wongsawatkul O, Prachayasittikul S, Isarankura-Na-Ayudhya C, Satayavivad J, Ruchirawat S, Prachayasittikul V. Vasorelaxant and Antioxidant Activities of Spilanthes acmella Murr. Int J Mol Sci., 2008 Dec [cited 2025 Aug 19]; 9(12): 2724. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC2635640/
33. Pinheiro MS da S, Moysés DA, Galucio NCR, Santos WO, Pina JRS, Oliveira LC, et al. Cytotoxic and molecular evaluation of spilanthol obtained from Acmella oleracea (L.) R. K. Jansen (jambu) in human gastric cancer cells. Nat Prod Res., 2024; 38(10): 1806–11.
34. Pradhan NR, Mishra KG, Patnaik N, Nayak R. Evaluation of effects of Spilanthes acmella extract on muscle mass and sexual potency in males: A population-based study. J Family Med Prim Care, 2021 Nov [cited 2025 Aug 19]; 10(11): 4242–6. Available from: https://pubmed.ncbi.nlm.nih.gov/35136796/
35. Mehravani M, Houshyar E, Jamalnia S, Gharaaghaji R. Effects of Local and Systemic Metronidazole as Adjunctive Treatment in Chronic Periodontitis Patients. Clin Exp Dent Res., 2024 Dec 1 [cited 2025 Aug 20]; 10(6): e70050. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC11608504/
36. Adha N, Ervina I, Agusnar H. The effectiveness of metronidazole gel based chitosan inhibits the growth of bacteria Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Fusobacterium nucleatum (In vitro). 30 ~ International Journal of Applied

Dental Sciences, 2017 [cited 2025 Aug 20]; 3(2): 30–7. Available from: www.oraljournal.com

37. Sato S, Fonseca MJV, Del Ciampo JO, Jabor JR, Pedrazzi V. Metronidazole-containing gel for the treatment of periodontitis: an in vivo evaluation. Braz Oral Res., 2008 [cited 2025 Aug 20]; 22(2): 145–50. Available from: https://www.scielo.br/j/bor/a/HVKCz5DH89vnP9zhy94jyFv/ ?format=html&lang=en
38. Kesarwani S, Parihar S, Singh S, Gautam A, Pandey A, Anjum M. A new era of Nano!!! Comparative evaluation of ganglioside polymeric nanoparticle coated satranidazole gel and 1% metronidazole gel for the treatment of periodontitis. J Indian Soc Periodontol., 2022 Jul 1 [cited 2025 Aug 20]; 26(4): 378–83. Available from: https://journals.lww.com/jisp/fulltext/2022/26040/a_new_era_of_nano____comparative_evaluation_of.12.aspx
39. A Nasra MM, Khiri HM, Hazzah HA, Abdallah OY. Formulation, in-vitro characterization and clinical evaluation of curcumin in-situ gel for treatment of periodontitis. Drug Deliv., 2017 [cited 2025 Aug 20]; 24(1): 133–42. Available from: https://www.tandfonline.com/action/journalInformation?journalCode=idrd20http://informahealthcare.com/
40. Tyagi A, Rana M, Agarwal K. To Develop And Evaluate Dental Gel Containing Clove As The Chief Constituent For The Treatment Of Periodontitis. International Journal of Creative Research Thoughts, 2025 [cited 2025 Aug 20]; 13: 2320–882. Available from: www.ijcrt.org
41. Alayadi H, Talakey A, Aldulaijan H, Shaheen MY. The Impact of a Topical Oxygen-Releasing Gel (blue®m) on Deep Periodontal Pockets: A Case Report. Medicina (Lithuania), 2024 Sep 1 [cited 2025 Aug 20]; 60(9): Available from: https://pubmed.ncbi.nlm.nih.gov/39336568/
42. Afzal A, Shah NH, Hussain I, Munawar SH, Mumtaz A, Qureshi N. Preparation of Spilanthes acmella based emulgel: Antimicrobial study and evaluation. Pak J Pharm Sci., 2022 Jan 1 [cited 2025 Aug 19]; 35(1): 287–95. Available from: https://www.researchgate.net/publication/357604768_Preparation_of_Spilanthes_acmella_based_emulgel_Antimicrobial_study_and_evaluation
43. Afzal A, Shah SNH, Javed H, Mumtaz A, Saeed J, Rasheed HM, et al. Spilanthes acmella Extract-Based Natural Oils Loaded Emulgel for Anti-Microbial Action against

Dermatitis. Gels, 2023, 9: Page 832-2023 Oct 20 [cited 2025 Aug 19]; 9(10): 832. Available from: https://www.mdpi.com/2310-2861/9/10/832/htm

44. Kiełbratowski M, Kuśka-Kiełbratowska A, Mertas A, Bobela E, Wiench R, Kępa M, et al. Evaluation of the Effectiveness of a Mouthwash Containing Spilanthol and Cannabidiol on Improving Oral Health in Patients with Gingivitis—Clinical Trial. J Clin Med., 2025 Mar 1 [cited 2025 Aug 21]; 14(5): 1641. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC11899771/
45. Kashyap P, Shamim MZ, Plawan B, Kakoti D, Suantak G, Nath P, et al. HERBAL TOOTH GEL FOR THE MANAGEMENT OF GINGIVAL BLEEDING AND TOOTHACHE. Journal of Pharmaceutical Negative Results ¦. 14.
46. Verma K, Dhruvakumar D, Pande M. A clinical and microbiological study to assess the efficacy of Acmella oleracea and Acacia catechu herbs as local drug delivery in treatment of chronic generalized periodontitis patients. J Indian Soc Periodontol., 2022 May 1 [cited 2025 Aug 21]; 26(3): 254. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC9118937/
47. Daundkar S. Formulation and Evaluation of Herbal Oral Mouth Ulcer Gel. SSRN Electronic Journal, 2025 May 1 [cited 2025 Aug 21]; Available from: https://papers.ssrn.com/abstract=5363346