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Exploring the healing powers of *Spilanthes acmella murr.*: An in-depth examination review

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Abstract
Spilanthes acmella Murr., popularly known as the toothache plant or "Akarkara," highlights its traditional usage, phytochemistry, pharmacological properties, and possible applications in modern medicine. *Spilanthes acmella* Murr. has a rich history in traditional medicine, employed throughout cultures for ages to manage many maladies, including toothaches and oral health difficulties. Phytochemical investigations suggest that it includes several bioactive chemicals, including as alkamides, flavonoids, and terpenoids. These substances contribute to the plant's various medicinal advantages, including pain alleviation, anti-inflammatory, antibacterial, antioxidant, immunomodulatory, and aphrodisiac characteristics. The considerable analgesic effects, particularly those related to spilanthol, as well as its anti-inflammatory and antibacterial characteristics, suggest prospective uses in treating pain, inflammatory disorders, and infectious infections. Additionally, its immunomodulatory and antioxidant activities, combined with its aphrodisiac characteristics, hint at larger therapeutic potential in dentistry, dermatology, gastrointestinal, urology, and sexual health. The review underlines the need for future study to clarify its mechanisms of action, optimize formulations, and confirm its usefulness in clinical settings, exploiting its promise for human health and well-being.

Keywords: Aphrodisiac, biotechnological advancements, clinical applications, pharmacological properties, phytochemistry, *Spilanthes acmella Murr.*, therapeutic potential, etc

Introduction

In the realm of botanical medicine, few plants rival the remarkable therapeutic potential of *Spilanthes acmella*, colloquially known as the toothache plant or "Akarkara." *Spilanthes acmella Murr*., with a rich history deeply rooted in traditional healing practices, has captured the attention of researchers and practitioners alike, revealing a treasure trove of healing properties waiting to be explored. This review embarks on a journey through the intricate labyrinth of *Spilanthes acmella*'s pharmacological landscape, shedding light on its multifaceted role as nature's formidable ally in the pursuit of health and well-being. Historically revered for its analgesic properties, *Spilanthes acmella* has been a staple in traditional medicine systems across diverse cultures. From ancient Ayurvedic texts to indigenous healing traditions, this botanical gem has been employed to alleviate toothaches, oral ailments, and a myriad of other afflictions. However, as modern science delves deeper into its intricate biochemistry, a plethora of bioactive compounds have been unearthed, catapulting *Spilanthes acmella* into the spotlight as a potent therapeutic agent with far-reaching implications.

At the heart of *Spilanthes acmella*'s healing prowess lies its rich phytochemical profile, comprising a symphony of N-alkylamides, flavonoids, triterpenoids, and other secondary metabolites. These compounds orchestrate a diverse array of pharmacological activities, ranging from analgesic and anti-inflammatory effects to antimicrobial, antioxidant, and immunomodulatory properties. Chief among these bioactive constituents are the N-alkylamides, with spilanthol emerging as a star player in the plant's pharmacological repertoire. The antioxidant potential of *Spilanthes acmella* stands as a testament to its ability to combat oxidative stress, scavenge free radicals, and safeguard cellular integrity. Studies have elucidated its efficacy in mitigating oxidative damage, thereby mitigating the risk of chronic diseases such as cancer and cardiovascular disorders. Meanwhile, its anti-inflammatory properties offer relief from inflammatory conditions, ranging from arthritis to colitis, by modulating key inflammatory pathways and cytokines.

Furthermore, Spilanthes acmella's antimicrobial activity aids in the fight against infectious agents, particularly oral pathogens linked to dental caries and periodontal disease. Its ability to inhibit bacterial growth and biofilm formation underscores its potential as a natural alternative for maintaining oral hygiene and preventing dental ailments. Moreover, research into its antimalarial and antiparasitic effects reveals promising avenues for combating malaria and other parasitic infections, offering hope in the battle against infectious diseases.

As an immunomodulatory agent, *Spilanthes acmella* emerges as a stalwart guardian of immune health, bolstering immune responses and fortifying defenses against infections. Its capacity to modulate immune cell activity holds promise for addressing immunodeficiency disorders and enhancing overall resilience against pathogens. Its analgesic and antibacterial properties find practical application in dentistry, offering relief from toothaches and promoting oral health through various dental formulations. In light of its multifaceted pharmacological properties and rich historical legacy, *Spilanthes acmella* emerges as nature's treasure trove of healing properties, awaiting further exploration and validation in the realms of modern medicine. By unraveling the intricate mechanisms underpinning its therapeutic effects and optimizing its clinical applications, we stand poised to unlock the full potential of this botanical marvel, harnessing its benefits for enhanced human health and well-being.

Spilanthes acmella is a medicinal herb with a rich history of traditional use and a growing body of scientific evidence supporting its pharmacological potential. This paper reviews

the antioxidant, anti-inflammatory, antibacterial, antimalarial, and immunomodulatory properties of *Spilanthes acmella,* highlighting its potential therapeutic applications. The paper synthesizes findings from recent research, focusing on the bioactive compounds responsible for these effects and their mechanisms of action.

Phytochemistry, Pharmacology, and Toxicology of *Spilanthes acmella*

Dubey *et al.,* (2013) [3] conclude that *Spilanthes acmella*, a well-known plant in Indian traditional medicine, exhibits multiple pharmacological actions with minor side effects. They include a summary of the pharmacological and phytochemical effects as well as a descriptive examination of ethnobotany, phytochemistry, pharmacology, and toxicity. Extracts and phytoconstituents from this plant have demonstrated various pharmacological responses, including anticonvulsant, analgesic, anti-inflammatory, vasodilatory, diuretic, and antimalarial effects. Its traditional use in reducing toothache is widespread in India and South America, while other traditional applications include treating stomach ailments and stimulating and relieving diarrhea, with rare use against tuberculosis. Researchers have suggested that the whole plant possesses local anesthetic, anti-inflammatory, antioxidant, aphrodisiac, analgesic, immunomodulatory, and insecticidal properties. Flower parts have shown diuretic, vasorelaxant, pancreatic lipase inhibition, and antifungal properties. Given its diverse traditional uses and pharmacological responses, this review provides valuable scientific information in a concise manner for the scientific community.

An extensive analysis of Spilanthes acmella's phytochemistry, pharmacology, and toxicity in order to provide a full knowledge of the plant's health benefits. The paper synthesizes data from a variety of sources to elucidate the bioactive compounds present in *Spilanthes acmella* and their pharmacological activities. Furthermore, the authors discuss the safety profile and potential toxic effects of the plant, offering valuable insights for future research and clinical applications. This review serves as a valuable resource for researchers and healthcare professionals interested in harnessing the therapeutic potential of *Spilanthes acmella* for various health conditions while ensuring its safety for human consumption (Dubey *et al.*, 2013) [3].

Therapeutic Potential

Antioxidant and Anti-Inflammatory effects

Rahim *et al*., (2021) have demonstrated through *in vitro* and *in vivo* studies that the metabolites of *S. acmella* exhibit significant anti-inflammatory and antioxidant activities. *S. acmella* reduces the production of nitric oxide (NO), IL-1β, IL-6, and TNF-α, which are inflammatory cytokines, as well as COX-2 and iNOS. Furthermore, it suppresses NF-κB and inhibits MAPK signaling pathways. The plant and its active substances have a lot of total phenolic content (TPC) and total flavonoid content (TFC). These chemicals help the plant have a lot of antioxidant activity, as shown by tests using DPPH, TBARS, and SOD in cell-free systems. There haven't been many studies on *S. acmella's* antioxidant activity in cells, but the phenolic compounds have shown strong protective effects in SH-SY5Y cells exposed to H_2O_2 by increasing the expression of SIRT1 and FoxO3a and increasing the activity of superoxide dismutase and catalase.

Thakur *et al.,* (2019) [13] highlight the significant antibacterial and antioxidant properties of *Spilanthes acmella* at various concentrations. The methanol extracts from different plant parts (leaf, flower, stem) demonstrated superior efficacy against all tested bacteria compared to acetone extracts, with *Salmonella typhi* being the most susceptible. Notably, the water extracts from any plant sections showed no antimicrobial activity. The investigation also revealed strong antioxidant activity in plant extracts, with methanol extracts dominating both acetone and water extracts in terms of antioxidant potential. These findings support the traditional medicinal use of *S. acmella* in treating infectious diseases caused by microbes, affirming its role in alternative medicine. However, the study is preliminary, indicating a need for further research to identify and characterize the specific bioactive compounds responsible for these activities. These compounds' identification may lead to a better understanding of their modes of action and therapeutic uses, which could encourage the discovery of intriguing antioxidant and antibacterial drugs.

Sharma *et al.,* (2020) [12] conduct a systematic review that evaluates the anti-inflammatory action of *Spilanthes acmella*, providing a comprehensive analysis of its efficacy and mechanisms of action. Through a meticulous examination of preclinical and clinical studies, the authors offer compelling evidence supporting the plant's anti-inflammatory properties. They explain the molecular pathways that Spilanthes acmella uses to fight inflammation, which gives us important information about how it could be used to treat inflammatory conditions. This systematic review serves as a comprehensive resource for researchers and clinicians seeking to explore the anti-inflammatory properties of *Spilanthes acmella* and their feasible applications in the management of inflammatory diseases.

Antibacterial activity

Based on the findings of Shivananda *et al.,* (2024) [14], it can be concluded that *S. acmella* ethanol extract exhibits significant antimicrobial activity against bacteria responsible for dental caries and periodontal infections. The study demonstrated that the extract's antibacterial efficacy is concentration-dependent, with higher concentrations (up to 100 mg/ml) showing the most substantial inhibition of bacterial growth. *Streptococcus mutans, Lactobacillus fermentum, Porphyromonas gingivalis, and Capnocytophaga gingivalis* all showed susceptibility to the extract, with inhibition zones measuring between 13-16 mm in diameter. Notably, erythromycin was used as a positive control and distilled water as a negative control. The broth dilution method was used to determine Minimum Inhibitory Concentration (MIC) and Minimum Bactericidal Concentration (MBC), which further validated these results. These results suggest that an ethanol extract of S. acmella could be a good alternative to common antibiotics for treating cavities and gum infections.

It has a strong antibacterial effect on Porphyromonas gingivalis (Pg) and Aggregatibacter actinomycetemcomitans (Aa), two major periodontal pathogens. This means that it could be used as a natural alternative to stop the growth of these bacteria. The range of phytochemicals that exist in *S. acmella* likely contributes to its antibacterial properties. Overall, the genus Spilanthes presents numerous research

opportunities. However, to fully understand its therapeutic effectiveness and suitability for incorporation into regular at-home oral hygiene products, additional *in vivo* research studies are needed. These studies will provide valuable insights into the safety, efficacy, and dosage considerations of utilizing *S. acmella* for oral health purposes (Gaur R, Gazala M P and Prabhuji M L V 2024).

In the study conducted by Afzal *et al.,* (2023) [1], herbal emulgels containing *Spilanthes acmella*, due to the emergence of medication resistance, showed strong antibacterial activity against a variety of deep skin tissue diseases that are resistant to antibiotics in bacteria such as *Staphylococcus aureus, Pseudomonas sp., and E. coli*. Among the formulations tested, F4 exhibited the highest efficacy against all bacterial strains. Notably, F4 contained olive oil, known for its strong permeation-enhancing properties, which likely contributed to the formulation's success in both *in vitro* and *ex vivo* studies. These results suggest that emulgels made from Spilanthes acmella extract and enhanced with spilanthol could be a good alternative way to apply medicine to the skin to treat bacterial skin infections. This research underscores the potential of natural herbal remedies in combating drug-resistant bacterial infections and highlights the importance of exploring alternative treatment modalities in addressing emerging health challenges.

Immunomodulatory activity

Spilanthes acmella also shows promise as an immunomodulatory agent. In the study by Nipate and Tiwari (2020), the results from biochemical and behavioral tests show that Spilanthes paniculata extract (SPE) has important anti-inflammatory and antioxidant properties. The extract was very good at getting rid of free radicals and changing the immune system, which made both the humoral and cellular immune systems stronger. This effect is likely attributed to the presence of flavonoids or polyphenols in the extract. As a result, SPE demonstrates the potential to restore antioxidant levels during fatigue and alleviate immune dysfunction associated with Chronic Fatigue Syndrome (CFS), offering a promising therapeutic approach to this condition. However, further investigation is warranted to elucidate the precise immunological mechanisms through which SPE operates. Determining whether it targets specific cytokine levels, such as TNF-a, or modulates IL-6 to mitigate CFS symptoms would provide valuable insights into its therapeutic efficacy. This research highlights the promising role of SPE as a natural remedy for combating CFS and underscores the importance of understanding its underlying mechanisms to optimize its clinical application.

Clinical applications, the analgesic and antimicrobial Properties

Jayashan *et al.,* (2024) [5] conclude that their study offers a comprehensive exploration of the potential of spilanthol extracted from *A. paniculata* and used in a mixture of *in vitro* and *in silico* research to mitigate neurodegenerative diseases (NDDs). Based on in silico ADMET prediction, spilanthol has advantageous pharmacokinetic qualities and drug-like traits, according to the study. The network pharmacology analysis revealed complex interactions between spilanthol and significant target proteins in the receptor 4 signaling pathway that trigger NDDs. Furthermore, simulations using molecular docking and dynamics show that spilanthol and critical TLR4 pathway proteins have substantial binding affinities. The capacity of spilanthol to decrease proinflammatory cytokines and mediators, such as NO, IL-6, and TNF-α, without causing appreciable cytotoxicity has been validated experimentally using LPS-induced BV-2 microglial cells. Nonetheless, the authors emphasize the need for more thorough research to assess spilanthol's effectiveness in *in vivo* models. Additionally, they emphasize the importance of conducting extensive toxicological studies to open the door for its use in clinical contexts.

The analgesic and antimicrobial properties of *Spilanthes acmella* make it particularly valuable in dentistry. Shivananda *et al.,* (2021) evaluated its efficacy against the microorganisms linked to periodontal disease and tooth cavities, highlighting its potential for oral health maintenance. Moreover, Shefali Arora, Saurabh Vijay, and Deepak Kumar (2011) reviewed various extracts of *Spilanthes acmella* and found them to be rich in phytoconstituents. Specifically, the methanol and ethyl acetate extracts exhibited notable antimicrobial activity against the bacterial strain *Klebsiella pneumoniae*, surpassing the inhibitory zone size of the conventional medication Doxycycline. Similarly, in fungal strains, the ethyl acetate and water extracts demonstrated significant inhibition zones against *Rhizopus arrhigus* and *Rhizopus stolonifer*, outperforming the standard drug fluconazole. These extracts are known for their antimicrobial properties because they contain phytoconstituents such as flavonoids, tannins, and other compounds. The various antimicrobial compounds present and their distinct mechanisms of action may be the cause of the variance in sensitivity of the test microorganisms to the extracts. These findings underscore the potential of *Spilanthes acmella* extracts as effective antimicrobial agents and warrant further investigation into their mechanisms of action and therapeutic applications.

Muscle mass and sexual potency in males (Aphrodisiac Effects)

In their study, Pradhan *et al.,* (2021) [8] shed light on the multifaceted health benefits of *Spilanthes acmella*, highlighting its potential as a potent muscle gainer and aphrodisiac. Beyond these primary benefits, spilanthes also have the capability of healing some other health-related issues. These benefits include acting as a toothache reliever, anti-inflammatory, diuretic, antioxidant, antibacterial, antinociceptive, vasorelaxant, and anti-human immunodeficiency virus agent. Despite its long-standing use in traditional folk medicine, the full extent of its implications for the health of mankind remains to be thoroughly investigated. The current study provides a stepping stone for future research endeavors, highlighting the necessity of cohort studies and randomized clinical trials to thoroughly assess these variables. Determining how long the association between *Spilanthes acmella* consumption and its claimed benefits exists is crucial for understanding its therapeutic potential. To confirm the results and clarify the processes behind *Spilanthes acmella's* apparent implications, further research on people is necessary. This research contributes to expanding our knowledge of the herb's medicinal properties and underscores the importance of rigorous scientific inquiry in validating its traditional uses.

In the study conducted by Prachayasittikul *et al.*, (2013) [7], the multifunctional roles of *S. acmella*, from a simple antitoothache cure to an extremely important annual plant, were investigated. Because of its high concentration of antioxidants, the plant has a wide range of uses in traditional medicine, including treatments, health care, beauty care, cosmetics, and health food or supplements. The plant species' most prevalent isolates were found to be lipid alkamides, specifically spilanthol, as well as phenolic, flavonoid, coumarin, and triterpenoid chemicals. Pharmacological studies revealed the inhibitory activity of *S. acmella* extracts and their constituents, like spilanthol and flavonoids, on prostaglandin (PG) synthesis, suggesting potential anti-inflammatory, antipyretic, and analgesic effects. Additionally, spilanthol exhibited immunostimulant activity by reducing nitric oxide (NO) release and inhibiting inflammatory mediators. The plant also demonstrated vasorelaxant and antioxidant activities, beneficial for anti-wrinkle and anti-aging applications, as well as aphrodisiac effects attributed to its propensity to enhance men's sexual performance. The structure-activity connection of derivatives of nicotinic acid in vasorelaxant and antioxidant properties was clarified by molecular modeling, which offered guidance for the synthesis and design of bioactive molecules. All things considered, *S. acmella* shows promise as a medicinal plant that is rich in chemicals with significant therapeutic potential. These compounds might be further developed to make medications, cosmetics, health care items, supplements, and health foods.

Biotechnological Advancements

In the study conducted by Sharma *et al.*, (2022) [11], HPLC analysis of sample extracts revealed that spilanthol content was highest in flowers (18.44 mg/g), surpassing levels found in other parts of the plant and several other Acmella (syn: Spilanthes) species. Phenolic and flavonoid content estimation via spectrophotometry, expressed as the equivalence of gallic acid (GAE) and quercetin (QE), respectively, showed that phenolics were most abundant in flower extracts (5.58 mg GAE/g), while flavonoids peaked in leaf extracts (31.65 mg QE/g). The extract's antioxidant activity was linked to its phenolic content, with flower extracts demonstrating an outstanding ability to scavenge free radicals in DPPH and ABTS assays compared to other plant parts. Pearson’s correlation analysis revealed a positive relationship between antioxidant activity and phenolic and flavonoid content. This study represents the first report on the quantification of these three secondary metabolites and their antioxidant activity in methanol extracts from different parts of *A. cilitata*, providing valuable insights into the plant's chemical composition and potential health benefits.

Conclusion

Spilanthes acmella Murr emerges as a promising therapeutic plant with a wide range of pharmacological properties. Its antioxidant, anti-inflammatory, antibacterial, and immunomodulatory effects, supported by scientific evidence, underscore its potential in modern healthcare. Furthermore, biotechnological advancements facilitate its cultivation and preservation, ensuring its availability for future research and clinical applications. Continued research efforts are warranted to further elucidate the mechanisms of action and optimize the therapeutic use of *Spilanthes acmella* Murr. in various medical fields.

Declaration: The authors declare that they do not have any conflicts of interest.

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