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Pharmacology, Phytochemistry, Toxicology and Micropropagation of *Spilanthes Acmella* (L.) Murr.: A Comprehensive Review

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Abstract- ***Spilanthes acmella (L.) Murr., commonly known as the toothache plant or eyeball plant, is an important medicinal herb belonging to the family Asteraceae. The plant is widely distributed in tropical and subtropical regions and has been extensively used in traditional medicine for the treatment of toothache, oral infections, inflammation, rheumatism, fever, and skin diseases. The therapeutic potential of S. acmella is mainly attributed to the presence of bioactive alkamides, particularly spilanthol, along with flavonoids, phenolics, triterpenoids, phytosterols, coumarins, and essential oils. Numerous pharmacological investigations have demonstrated its antimicrobial, anti-inflammatory, analgesic, antioxidant, antimalarial, hepatoprotective, anti-obesity, vasorelaxant, and insecticidal activities. Recent toxicological studies suggest that the plant exhibits relatively low toxicity at therapeutic doses. However, increasing commercial demand and habitat depletion have raised concerns regarding its conservation. Consequently, in vitro micropropagation techniques have been developed to facilitate large-scale cultivation and sustainable utilization. This review summarizes the ethnomedicinal uses, phytochemical constituents, pharmacological activities, toxicological profile, and advances in micropropagation of S. acmella, highlighting its significance as a promising medicinal and industrial plant.***

Keywords: Spilanthes Acmella, Spilanthol, Alkamides, Medicinal Plant, Pharmacology, Toxicology, Micropropagation

I. INTRODUCTION

Medicinal plants continue to serve as valuable sources of therapeutic agents for pharmaceutical, cosmetic, nutraceutical, and agricultural applications. Increasing concerns regarding environmental contamination, pesticide resistance, and adverse effects associated with synthetic chemicals have renewed interest in plant-derived bioactive compounds1,2. Among medicinal plants, Spilanthes acmella (L.) Murr. [syn. Acmella oleracea (L.)]3 has gained considerable attention due to its diverse pharmacological properties and rich phytochemical composition4,5.

Spilanthes acmella, popularly known as the toothache plant, eyeball plant, or paracress, is a short-lived herbaceous species belonging to the family Asteraceae. Native to tropical South America, particularly Brazil, it is now cultivated throughout tropical and subtropical regions worldwide4,5. The plant is characterized by its distinctive flower heads, which produce a tingling sensation and temporary numbness when chewed. These sensory properties are primarily attributed to spilanthol, the major bioactive alkamide present in the plant6,7.

Traditionally, S. acmella has been employed for the treatment of toothache, oral infections, sore throat, rheumatism, dysentery, fever, and skin disorders. Modern pharmacological investigations have validated many of these traditional uses and revealed additional biological activities, including antimicrobial, antioxidant, anti-inflammatory, hepatoprotective, insecticidal, antimalarial, and immunomodulatory effects1,2,5. Owing to its growing commercial demand in pharmaceutical, cosmetic, and oral healthcare industries, the species is increasingly subjected to overexploitation, necessitating sustainable cultivation and propagation strategies2,5.

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II. TRADITIONAL AND ETHNOMEDICINAL USES

The medicinal use of Spilanthes acmella (syn. Acmella oleracea) has been documented across various traditional healthcare systems. The flower heads are widely chewed to alleviate toothache and oral discomfort due to their analgesic and local anesthetic effects1,4. Indigenous communities in India, Bangladesh, and Southeast Asia utilize the plant for the treatment of gum infections, throat disorders, rheumatism, tuberculosis, snake bites, scabies, psoriasis, and fungal infections2,7.

In Ayurvedic medicine, the flower heads and roots are used to manage periodontitis, tongue paralysis, stammering in children, and inflammatory conditions1. The plant has also been employed as a sialagogue to stimulate salivation and improve oral health owing to the sensory action of spilanthol5,7. Additionally, extracts of S. acmella have found applications in cosmetic formulations because of their wrinkle-reducing, skin-firming, and anti-aging properties2,5.

III. PHYTOCHEMICAL CONSTITUENTS

The phytochemical profile of S. acmella is dominated by alkamides, particularly spilanthol [(2E,6Z,8E)-N-isobutyl-2,6,8-decatrienamide], which is responsible for the characteristic pungent taste, tingling sensation, and local anesthetic properties of the plant6,7,8,9. Recent phytochemical investigations have identified more than 120 secondary metabolites from A. oleracea, including alkylamides, terpenoids, flavonoids, phenolic acids, coumarins, phytosterols, and triterpenoids2,5.

3.1 Alkamides

- Spilanthol6
- Undeca-2E-en-8,10-diynoic acid isobutylamide7
- Undeca-2E,7Z,9E-trienoic acid isobutylamide7
- N-isobutyl tridecadienediynamides7

3.2 Terpenoids and Essential Oils

- β-Caryophyllene
- Germacrene D
- Limonene
- Myrcene
- β-Ocimene

These volatile constituents have been identified in the essential oil and contribute to the plant's antimicrobial and insecticidal activities1,10.

3.3 Phytosterols and Triterpenoids

- β-Sitosterol
- Stigmasterol
- β-Amyrin
- α-Amyrin
- β-Sitostenone
- 3-Acetylaleuritolic acid

These compounds have been isolated from various extracts of S. acmella and are associated with anti-inflammatory and antioxidant activities2,7.

3.4 Phenolic and Coumarin Compounds

- Vanillic acid
- Trans-ferulic acid
- Trans-isoferulic acid
- Scopoletin

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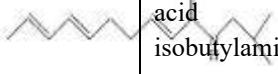
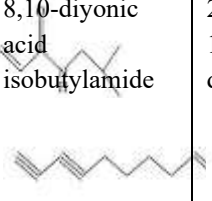
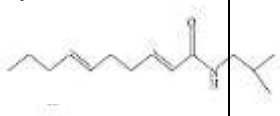
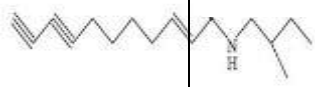
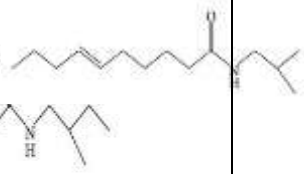
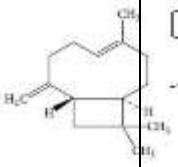
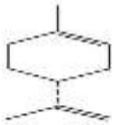
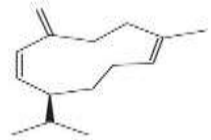
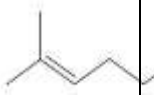
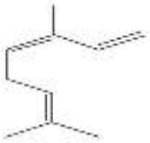
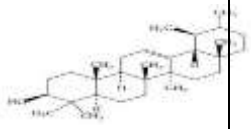
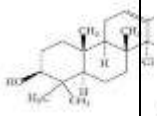
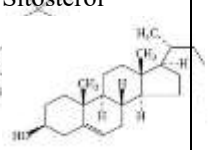
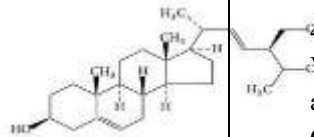
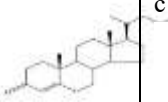
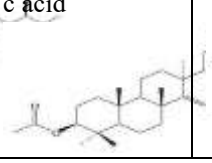
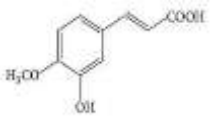
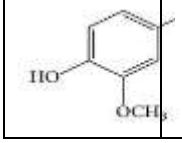
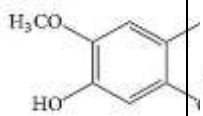
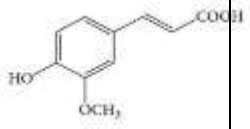
Phenolic acids and coumarins contribute significantly to the antioxidant, antimicrobial, and pharmacological properties of the plant5,7.

Phytochemical Constituents		
Spilanthol 	Undeca-2E-en-8,10-diyonic acid isobutylamide 	2E,7Z-N-Isobutyl-2,7-tridecadiene-10,12-diynamide 
Undeca-2E,7Z,9E-trienoic acid isobutylamide 	2E-N-(2-Methylbutyl)-2-undecene-8,10-diynamide 	7Z-N-Isobutyl-7-tridecene-10,12-diynamide 
β-Caryophyllene 	Limonene 	Germacrene 
Myrecene 	(Z)-*β*-Ocimene 	*α*-Amyrin 
β-Amyrin 	*β*-Sitosterol 	Stigmasterol 
β-Sitostenone 	3-Acetylaleuritolic acid 	*trans*-Isoferulic acid 

Vanillic acid	Scopoletin	*trans*-Ferulic acid
		

The diversity of these phytoconstituents contributes significantly to the broad spectrum of biological activities exhibited by the plant.

IV. PHARMACOLOGICAL ACTIVITIES

4.1 Local Anaesthetic Activity

The local anesthetic property of S. acmella is primarily attributed to spilanthol. Animal studies have demonstrated significant anesthetic effects comparable to standard anesthetic agents. This activity validates the traditional use of the plant in managing toothache and oral pain1,4,6.

4.2 Anti-inflammatory and Analgesic Activities

Extracts of S. acmella have shown substantial anti-inflammatory effects in carrageenan-induced paw edema models. The presence of flavonoids and alkamides contributes to inhibition of inflammatory mediators such as prostaglandins. Analgesic activity has been confirmed through tail-flick and acetic acid-induced writhing tests1,2,11.

4.3 Antipyretic Activity

Studies employing yeast-induced pyrexia models demonstrated significant reduction of elevated body temperature following administration of S. acmella extracts. The activity is associated with suppression of cyclooxygenase and lipoxygenase pathways1,11.

4.4 Antimicrobial Activity

Various extracts of S. acmella exhibit broad-spectrum antibacterial activity against Gram-positive and Gram-negative bacteria. Significant inhibition has been reported against Corynebacterium diphtheriae and several oral pathogens1,2,7.

4.5 Antifungal Activity

The plant demonstrates antifungal activity against several pathogenic fungi including Aspergillus niger, Aspergillus parasiticus, Fusarium moniliforme, and

Fusarium oxysporum. These findings support its traditional application in fungal skin infections1,4.

4.6 Antioxidant and Vasorelaxant Activities

Ethanolic extracts of S. acmella possess potent antioxidant activity owing to their phenolic and flavonoid contents. Vasorelaxant effects have been linked to nitric oxide-mediated endothelial responses and prostacyclin release2,7,12.

4.7 Hepatoprotective Activity

Ethanolic extracts of the whole plant have demonstrated protective effects against paracetamol-induced hepatotoxicity and aflatoxin-induced liver damage in experimental animal models1,4.

4.8 Anti-ulcer and Diuretic Activities

The plant exhibits significant gastroprotective effects in experimental ulcer models. Furthermore, aqueous and ethanolic extracts increase urine volume and electrolyte excretion, suggesting a loop diuretic-like mechanism1,2.

4.9 Antimalarial and Larvicidal Activities

Spilanthol exhibits potent activity against malaria parasites and mosquito vectors. The compound has demonstrated ovicidal, larvicidal, and pupicidal activities against Anopheles, Aedes, and Culex species2,13,14.

4.10 Anti-obesity Activity

Extracts of S. acmella have been shown to inhibit pancreatic lipase activity, thereby reducing lipid absorption and contributing to weight management2,5,15.

4.11 Diuretic Activity

Acmella oleracea (syn. Spilanthes acmella) has demonstrated significant diuretic activity in experimental studies. Oral administration of a cold aqueous extract (1500 mg kg^{-1}) to hydrated rats resulted in a marked increase in urine output, confirming its diuretic potential.

The extract exhibited a mechanism comparable to that of loop diuretics, characterized by increased urinary excretion of sodium (Na^+) and potassium (K^+) ions along with a reduction in urine osmolarity.

Similarly, ethanolic leaf extracts significantly enhanced total urine volume and promoted the excretion of electrolytes, including sodium, potassium, and chloride ions. These findings suggest that A. oleracea may possess therapeutic potential in the management of conditions associated with fluid retention and electrolyte imbalance1,2.

4.12 Bioinsecticidal and Convulsant Activity

Several species of the genus Spilanthes/Acmella, including Spilanthes alba, S. mauritiana, Acmella oleracea (syn. Spilanthes acmella), and related taxa, are known to contain bioactive insecticidal compounds, particularly alkylamides such as spilanthol. These compounds exhibit potent insecticidal, larvicidal, ovicidal, and pupicidal activities against a wide range of agricultural pests and disease-vector mosquitoes. Owing to their effectiveness and relatively low mammalian toxicity, spilanthol-rich extracts have attracted considerable interest as environmentally friendly biopesticides2,16.

In addition to its insecticidal properties, neuropharmacological studies have reported that hexane extracts of S. acmella can induce convulsive responses in experimental animals at high doses. Electroencephalographic (EEG) analyses revealed abnormal neuronal activity consistent with seizure-like episodes in rats, suggesting that certain lipophilic constituents may influence central nervous system function. Although these findings indicate potential neurotoxicity at elevated concentrations, further investigations are required to identify the specific compounds involved and to establish their safety profile1,17.

Recent studies continue to emphasize the potential of A. oleracea as a source of botanical insecticides for sustainable pest management. However, comprehensive toxicological and mechanistic studies remain necessary to ensure safe agricultural and pharmaceutical applications2,5.

V. TOXICOLOGICAL STUDIES

Toxicological investigations suggest that Spilanthes acmella (syn. Acmella oleracea) possesses a favorable safety profile when used within therapeutic

limits. Zebrafish embryo toxicity studies demonstrated that aqueous extracts of the plant produced no significant lethal effects at concentrations up to 20% (v/v), although mild sublethal developmental abnormalities were observed at higher concentrations18. Acute and subacute toxicity studies have generally indicated low toxicity of plant extracts at pharmacologically effective doses, supporting their traditional medicinal use1.

The insecticidal activity of spilanthol has been extensively documented against agricultural pests and mosquito vectors. Despite its pronounced toxicity toward insects, spilanthol exhibits comparatively low toxicity in mammals, making it an attractive candidate for the development of environmentally friendly botanical insecticides and biopesticides19,20. Recent reviews have emphasized that although current evidence supports the safety of A. oleracea extracts, further long-term toxicological, pharmacokinetic, and clinical studies are required to establish standardized safety profiles for pharmaceutical and agricultural applications2,5.

VI. IN VITRO MICROPROPAGATION

The increasing commercial demand for Spilanthes acmella (syn. Acmella oleracea) and the depletion of its natural populations have necessitated the development of efficient propagation techniques. In vitro micropropagation provides a reliable strategy for the rapid multiplication, conservation, and sustainable utilization of elite germplasm1,2.

6.1 Axillary Bud Culture

Axillary bud explants cultured on Murashige and Skoog (MS) medium supplemented with benzyladenine (BA) have been shown to induce multiple shoot formation efficiently. This method is considered one of the most effective approaches for rapid clonal propagation of S. acmella21.

6.2 Nodal Segment Culture

Nodal segment cultures have demonstrated high regeneration efficiency on MS medium supplemented with 3.0 mg L^{-1} 6-benzylaminopurine (BAP) and 1.0 mg L^{-1} indole-3-acetic acid (IAA), resulting in prolific shoot multiplication and successful rooting22.

6.3 Leaf Explant Culture

Leaf-derived callus cultures can be established using auxins such as 2,4-dichlorophenoxyacetic acid (2,4-D). Subsequent transfer to regeneration media containing appropriate cytokinin–auxin combinations promote shoot organogenesis and plant regeneration2,23.

6.4 Apical Meristem Culture

Apical and axillary meristems cultured on MS medium supplemented with BAP and naphthaleneacetic acid (NAA) exhibit efficient shoot proliferation and regeneration. These techniques are particularly valuable for the production of disease-free planting material and germplasm conservation1,21.

Several studies have reported that micropropagated plants exhibit enhanced accumulation of spilanthol and improved biological activities, including larvicidal and antimicrobial effects, when compared with conventionally propagated plants. Consequently, micropropagation represents an important biotechnological tool for the large-scale production of high-quality planting material and bioactive metabolites2,5,24.

VII. FUTURE PERSPECTIVES

Despite extensive studies on S. acmella, several aspects require further investigation. Standardization of extracts, elucidation of molecular mechanisms, pharmacokinetic studies, and clinical evaluations are necessary to establish its therapeutic efficacy and safety. Additionally, sustainable cultivation and conservation strategies should be prioritized to ensure long-term availability of this valuable medicinal resource.

VIII. CONCLUSION

Spilanthes acmella is an important medicinal plant possessing remarkable ethnopharmacological significance and diverse biological activities. The plant is particularly rich in spilanthol and other bioactive metabolites that contribute to its anesthetic, anti-inflammatory, antimicrobial, antioxidant, hepatoprotective, antimalarial, and insecticidal properties. Toxicological studies indicate a favorable

safety profile, while advances in micropropagation provide effective approaches for conservation and large-scale cultivation. Continued research on the phytochemistry, pharmacology, and clinical potential of S. acmella may facilitate the development of novel therapeutic agents and value-added products for pharmaceutical, cosmetic, and agricultural applications.

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