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PHARMACOLOGICAL POTENTIAL OF *ACMELLA ULIGINOSA*: A COMPREHENSIVE REVIEW OF PHYTOCHEMISTRY, TRADITIONAL USES, AND THERAPEUTIC ACTIVITIES

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ABSTRACT

Acmella uliginosa (Sw.) Cass. (family Asteraceae): more commonly called marsh paracress or toothache plant, is a medicinal herb which is found in wet and marshy areas throughout India and in other tropical regions. It has for a long time been used in traditional medicine to treat toothache, oral ulcers, inflammation, microbial infections, pain, and metabolic disorders. The current level of scientific interest in *A. uliginosa* is due to its rich phytochemical composition and a wide range of pharmacological effects. The plant includes a number of bioactive components such as spilanthol, alkamides, flavonoids, tannins, saponins, terpenoids, coumarins, lignans, naphthoquinones, and essential oil components including limonene and caryophyllene oxide. Experimental research has shown that different extracts have considerable antioxidant, anti-inflammatory, analgesic, antimicrobial, antifungal, antidiabetic, and cytotoxic properties. These effects are mainly the result of the synergistic action of phenolic compounds, flavonoids, and alkamides, which influence oxidative stress, inflammatory mediators, microbial growth, and glucose metabolism. Although there has been some progress in assessing its pharmacological potential, the evidence regarding hepatoprotective, nephroprotective, wound-healing, and cardiovascular activities is still very limited or only indirect. This review provides a critical summary of what is currently known about the botany, traditional uses, phytochemistry, pharmacological properties, molecular mechanisms, and toxicological aspects of A. uliginosa, points out the existing research gaps, and proposes future lines of work aimed at developing standardised herbal preparations and bioactive compounds from this promising medicinal plant.

KEYWORDS: *Acmella uliginosa, Asteraceae, spilanthol, alkamides, phytochemistry, antioxidant, anti-inflammatory, analgesic, antimicrobial, antidiabetic, medicinal plants.*

1. INTRODUCTION

Medicinal plants are still important in providing healthcare and have given rise to a wide variety of bioactive substances. Since they are still used in traditional medicine, there has been a great deal of research carried out into their phytochemical composition, pharmacological activities, mechanisms of action, and safety. Yet the creation of standardised herbal products depends on having reliable evidence concerning the botanical identity, chemical composition, efficacy, and toxicity.[1]

Acmella uliginosa (Sw.) Cass. is a species which is important in traditional medicine but has been relatively little studied. It has long been used to treat toothache, mouth ulcers, sore throats, inflammation and other painful or infectious disorders, especially in South and Southeast Asia as well as in certain areas of Africa. The peculiar tingling and numbing effect of the plant is due to alkylamides, especially spilanthol, this compound being regarded as a major bioactive component of the *Acmella* genus. Experimental research has shown that extracts of *A. uliginosa* have significant antinociceptive activity, with evidence indicating that both peripheral and central analgesic mechanisms are involved, including modulation of the opioid system.[2]

Investigations into the phytochemical content have found the presence of flavonoids, phenolics, tannins, saponins, coumarins, triterpenes, lignans, naphthoquinones, and volatile compounds in *A. uliginosa*.[2,5–7] It is possible that these compounds are responsible for the antioxidant, antimicrobial, antifungal, anti-inflammatory, analgesic, and anti-arthritic properties noted in the experimental studies. Yet the phytochemical composition and biological activity are probably likely to differ depending on the part of the plant, its geographical origin, the time of harvest, the method of extraction, and the analytical technique used, which makes it difficult to compare the various studies and to standardise the preparations.[1]

Initial toxicological studies indicate that extracts of *A. uliginosa* are not acutely lethal at some of the doses tested; however, biochemical, haematological, and histopathological alterations have been observed at high doses in animal studies. As a result, further research is needed in order to determine its long-term toxicity, pharmacokinetics, reproductive safety, genotoxicity, and potential for herb–drug interactions before it can be confidently developed into standardised therapeutic agents or nutraceuticals.[1,3]

Although there is increasing interest in the Acmella species, the evidence relating to *A. uliginosa* is still fragmentary and dispersed among ethnobotanical, phytochemical, and pharmacological reports. This review thus aims to summarise and critically assess the existing knowledge regarding its botanical features, ethnomedicinal applications, phytochemical constituents, pharmacological activities, possible mechanisms of action, toxicological aspects, and therapeutic potential. It also points out the present limitations and identifies future research priorities in order to develop standardised herbal formulations and bioactive lead compounds from this promising medicinal plant.[2,3]

2. Plant Profile

The plant Acmella uliginosa (Sw.) Cass. (also known as Spilanthes uliginosa) is commonly called marsh paracress, swamp spilanthes or toothache plant and is an upright, short-lived annual herb from the Asteraceae family. It is known as Tridaksha4 in Sanskrit and as Aharkara in some of the Indian languages. The species is found in wet areas of India such as Andhra Pradesh, Kerala, Maharashtra, Odisha, West Bengal and Tamil Nadu, and also occurs in other tropical and subtropical countries.[4] It grows in moist, marshy soils, in wet fields and as a winter weed in agricultural areas and is highly valued in both Ayurvedic and folk medicine for the treatment of a variety of illnesses.[5,25]

2.1 Vernacular Names

- **English:** Marsh paracress, swamp spilanthes
- **Sanskrit:** Tridaksha
- **Bengali:** Piraj
- **Odia:** Biri biri
- **Assamese:** Bon narji
- **Nepali:** Bhuin timur
- **Sinhala:** Heen akmella
- **Mizo:** An-sa-te-chi-khat
- **Spanish:** Chimpaya, Chinapaya
- **French/Creole (West Indies):** Bouton d'or, Créosote pays, Herbe mal aux dents
- **Chinese:** Zhao sheng jin niu kou
- **Fiji:** Mbotembotekoro
- **Malay:** Sunbang nenek
- **Indonesian:** Jotang kecil, legetan
- **Sundanese:** Jotang
- **Vietnamese:** Cúc ao dam lay, cuca o thon

2.2 Taxonomy[25]

- **Domain:** Eukaryota
- **Kingdom:** Plantae
- **Phylum:** Tracheophyta (Spermatophyta)
- **Subphylum:** Angiospermae
- **Class:** Magnoliopsida (Dicotyledonae)
- **Order:** Asterales
- **Family:** Asteraceae
- **Genus:** *Acmella*
- **Species:** *Acmella uliginosa* (Sw.)

2.3 Botanical Characteristics

A. uliginosa is an annual, branched herb, typically 15–40 cm tall (sometimes taller): with a prostrate base that becomes erect. The stem is cylindrical, fleshy, light green, occasionally striated, glabrous or sparsely pubescent with short appressed hairs.[4,6,25]

- Roots: Primary root is taproot-like; secondary roots are adventitious and fasciculate.
- The stem is branched, becoming prostrate at first and then growing erect; the upper aerial parts are densely branched.
- The leaves are simple, occur in opposite pairs, and have petioles; the lamina is between 1 and 10 cm in length and 0.5 and 6 cm in width, shaped lanceolate to ovate-lanceolate; the margin is irregularly and weakly toothed; the upper surface is almost smooth while the lower surface is hairy, particularly along the veins.
- The inflorescences are conical heads (5 to 6 mm in diameter and 7 to 11 mm long): occurring singly at the ends of the stems or in the upper leaf axils; the peduncles are 1 to 12 cm long and angular, having short white hairs.
- The flower has a capitulum consisting of two kinds of florets: female, ligulate florets located at the periphery (yellow, measuring 2 to 2.5 mm) and hermaphroditic, tubular florets in the centre (1.3 to 1.5 mm, also yellow); the involucral bracts number between 5 and 10 and are arranged in a single row (rarely in two rows): having ciliate margins.
- The fruit is composed of achenes; the achenes produced by the ligulate florets are truncated and ellipsoidal with a keeled underside; those produced by the tubular florets are flattened and elliptical (~2 mm × 1 mm): black, smooth, and have a ciliate

membranous edge together with a pappus consisting of two very short, erect hairs (~0.3 mm).

- The cotyledons are petiolate, oval, slightly emarginate, fleshy, glabrous, and smooth.
- The first leaves are simple, have opposite arrangement, are light green in colour, have an oval lamina, a cuneate base, an acute apex, a margin that is weakly toothed and are attached by green petioles.

Figure No 1: *Acmella uliginosa* Plant.

Figure NO 1B: *Acmella uliginosa* Plant.

2.4 Phytochemical Constituents

A. uliginosa contains many secondary metabolites. These include alkamides, especially spilanthol, as well as flavonoids, phenolics, terpenoids, steroids, fatty acids, and essential oil components.[7,29]

Table No 1: Phytochemical Constituents.

Phytochemical Clas	Identified Compounds
Alkaloids	1. Spilanthol 2. N-(2-Phenylethyl)(2E,6Z,8E)-decartrienamide
Phenolics	3. Benzaldehyde 4. Mequinol 5. 4-vinyl-2-methoxy-phenol 6. Eugenol 7. Benzeneacetyldehyde 8. p-Vinylguaiacol
Steroids	9. Cholesterol 10. Stigmasterol 11. Ergost-5-en-3-ol,(3β)- 12. Ergost-5-en-3-ol,(3β,5α)- 13. β-Sitosterol 2.49 14. δ-8(14)-stigmastenol 15. Campesterol 16. Dihydrochondrillasterol 17. γ -Sitosterol
Terpenoids	18. Cyperene 19. Caryophyllene 20. β-Cubebene 21. Germacrene D 22. Caryophyllene oxide 23. Phytol 24. Squalene 25. α-Amyrin 26. 12-Oleanen -3-yl-acetate(3α) 27. α- Amyrenyl acetate 28. Lupenyl acetate 29. Trans-β-Caryophyllene 30. Neophytadiene 31. α-Cubebene

	32. β-Amyrin 33. Sitostenone
Fatty acids and others	34. Lauric acid 35. Myristic acid 36. Palmitic acid 37. Linoleic acid 38. Stearic acid 39. Margaric acid 40. Linolenic acid 41. Eicosanoic acid 42. Behenic acid 43. Vitamin E 44. γ-Tocopherol 45. β-Monolinolein 46. 2-Monolinolenin 47. Lauric acid, methyl ester 48. Palmitic acid, methylester 49. Linoleic acid, methylester 50. 9,12,15-Octadecatrienoic acid, methyl ester 51. Stearic acid, methylester 52. Linolenic acid 53. Eicosanoic acid, methyl ester 54. Tricosanoic acid, methyl ester 55. 2-Cyclopentene-1,4-dione 56. Butyrolactone 57. 1(3,6,6-trimethyl-1,6,7,7a-tetrahydrocyclopenta(c) pyran-1-yl ethanone 58. Looplure 59. 1-Pentadecene 60. 1,13-Tetradecadiene 61. Butan-4-olide 62. 1H-Pyrrole-2,5-dione, 3-ethyl-4-methyl 63. 1-Undecanol 64. 9,12,15-Octadecatrien-1-ol 65. Silikonfett se30 (grevels) 66. 2-Furanmethanol 67. Benzyl alcohol 68. Butanoic acid, 4-hydroxy 69. 1,2-cyclopentanedione 70. Cis-7-Dodecen-1-yl acetate 71. 1-Nonadecene 72. Spiro [2.4] heptane, 1,5-dimethyl-6-methylene 73. Tricosanoic acid, methyl ester 74. Lignoceric acid, methyl ester 75. Furfural 76. 2(3H)-Furanone, 5-methyl 77. 2-Cyclopenten-1-one, 2-hydroxy 78. 2-Furancarboxaldehyde, 5-methyl 79. 2-Furancarboxaldehyde, 5-(hydroxymethyl) 80. 1,11-Dodecadiene 81. 2-Tridecanone 82. Cyclononasiloxane, octadecamethyl 83. Nonanoic acid, 9-(3-hexenylidenecyclopropylidene)-,2-hydroxy-1-(hydroxymethyl)

2.4.1 Major Bioactive Compounds[7,29]

Alkamides/Amides

- Spilanthol [(2E,6Z,8E)-N-isobutyl-2,6,8-decatrienamide] is the main alkamide which is responsible for the local anaesthetic, analgesic, and insecticidal properties.
- N-(2-Phenylethyl)(2E,6Z,8E)-decatrienamide and related N-alkylamides.

Phenolics and Flavonoids

- Benzaldehyde, mequinol, 4-vinyl-2-methoxyphenol, eugenol, p-vinylguaiacol, and related phenolic aldehydes and phenols.

- Flavonoids have a significant contribution to antioxidant and anti-glycation activities.

Steroids
- Cholesterol, stigmasterol, beta-sitosterol, campesterol, ergost-5-en-3-ol derivatives, and related sterols.

Terpenoids
- Things like limonene, caryophyllene, caryophyllene oxide, germacrene D, α- and β-amyrin, phytol, squalene, and the like.

Fatty Acids and Derivatives
- Fatty acids such as lauric, myristic, palmitic, stearic, linoleic, linolenic, and others which are saturated or unsaturated, together with their methyl esters and monoacylglycerols.

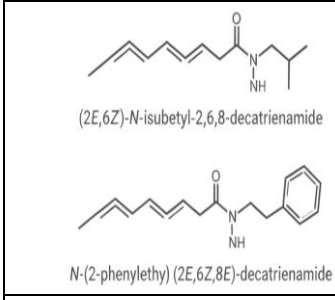
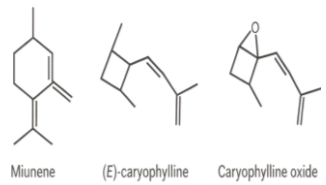
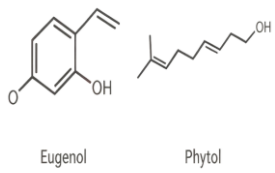
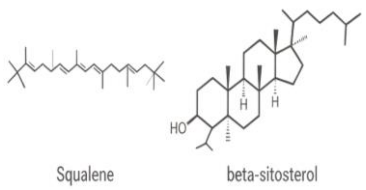
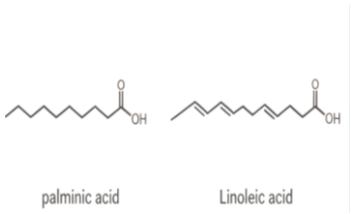
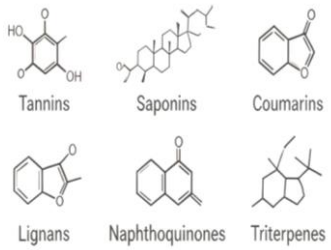
Essential Oil Constituents
- Limonene, which is a main monoterpene, caryophyllene oxide, (E)-caryophyllene, sesquisabinene isomer, myrcene, and other volatile compounds.

Other Secondary Metabolites
- Tannins, saponins, coumarins, lignans, naphthoquinones, and triterpenes.

2.4.2 Chemical structures of main phytoconstituents found in *Acmella uliginosa*[29]

A list of the compounds found in water and in organic extracts (as determined by GC–MS and other techniques) consists of alkaloid-like amides (such as spilanthol and similar compounds): phenolics, steroids, terpenoids, fatty acids, and various heterocyclic compounds. Structural diagrams of the main compounds (for example, spilanthol, limonene, caryophyllene oxide, and β-sitosterol) should be included as figures in the final manuscript.

Table No 2: Phytochemical structure of *Acmella uliginosa*.[29]

		
Alkylamide	**Monoteroenes**	**Phenolics & Diterpenes**
		
Triterpenes	**Fatty Acids**	**Polyphenols & Other Metabolites**

3. Pharmacological Activities

3.1 Antioxidant Activity

The extracts of *A. uliginosa* show antioxidant activity which is dependent on the dose as measured in various in vitro tests (DPPH radical scavenging, metal chelation, reducing power). Both the essential oil and the hexane extract from the flowers demonstrated significant DPPH scavenging, metal chelation, and reducing power, the IC_{50}/RP_{50} values showing that their activity is strong when compared with that of the standard antioxidants. Particularly, the flower extracts have a higher content of flavonoids and exert stronger antioxidant effects than the extracts from the entire plant, reducing the level of protein carbonyls and preserving the thiol groups in a dose-dependent fashion, and thus protecting the proteins from oxidative damage.[2]

It is believed that linoleic acid, limonene, alkamides, and phenolic compounds produce these effects by scavenging free radicals, boosting the body's own antioxidant enzymes, and decreasing oxidative stress.[8]

3.2 Anti-inflammatory and anti-arthritic activity

The extract of *A. uliginosa* shows strong anti-inflammatory and anti-arthritic properties in experimental studies. Both the crude extract and the components of the essential oil prevent inflammatory markers, stop protein denaturation, and reduce oedema in laboratory tests, their effectiveness being similar to that of standard NSAIDs. GC–MS investigations have detected compounds including 9-octadecenoic acid (Z)-phenylmethyl ester, astaxanthin, and other terpenoids which may be responsible for these effects. In the in vitro

assays, the essential oil displayed powerful anti-inflammatory activity with an inhibition concentration (IB_{50}) much lower than that of diclofenac sodium.

3.3 Analgesic and antinociceptive activity

A. uliginosa has traditionally been used as a "toothache plant" in order to relieve dental pain, mouth ulcers, sore throats and other kinds of painful conditions. The main alkamide, spilanthol, has a local anaesthetic and pain-relieving effect by blocking nerve impulses and causing a numbing sensation when the plant is chewed or applied topically.

In studies using mice to investigate chemical and thermal pain responses, methanolic extracts of *A. uliginosa* (MEAU) were found to have both central and peripheral analgesic effects. The fact that naloxone partially abolished the antinociceptive effect indicates that the opioid receptor system is involved in the centrally mediated analgesia, although there was no significant impairment of motor function. These results support the traditional use of *A. uliginosa* as a natural painkiller.[5]

3.4 Antimicrobial and Antifungal Activity

The extract of *A. uliginosa* has moderate to strong antimicrobial properties against various bacterial and fungal pathogens. Those obtained from the leaves by using dichloromethane or methanol show significant inhibitory effects, especially against Gram-positive bacteria such as *Enterococcus faecalis* and *Staphylococcus aureus*, and also against some Gram-negative strains like *Pseudomonas aeruginosa*, although *Escherichia coli* is generally relatively resistant.

The plant also shows considerable antifungal activity, stopping mycelial growth by as much as ~75.7% and reducing sporulation by 22 to 99.8% according to the fungal species. This effect is due to a synergistic combination of flavonoids, tannins, coumarins, naphthoquinones, and alkamides rather than being caused by a single compound.[2,28]

3.5 Antidiabetic and antiglycation activity

The antidiabetic and hypoglycaemic effects of *A. uliginosa* are promising and can mainly be attributed to its high content of flavonoids and strong antioxidant properties. In vivo studies showed that the flower extracts caused a significant reduction in blood glucose levels in diabetic mice, the levels reaching normal ones within a week and with an efficacy similar to that of glibenclamide. The extracts also inhibited the formation of advanced glycation end-products (AGE): decreased the protein carbonyl content, and provided protection against oxidative damage to proteins, indicating possible advantages in the prevention of diabetic complications.[11]

Molecular docking studies show that N-(2-phenylethyl)(2E,6Z,8E)-decatrienamide, an alkamide extracted from the leaves, could function as a ligand for human glucokinase and has a strong binding affinity, favourable intestinal absorption, and the ability to cross the blood–brain barrier, which supports its potential as an antidiabetic agent.

3.6 Cytotoxic and anticancer activity

The non-polar fractions (for example, n-hexane) of *A. uliginosa* have demonstrated in vitro cytotoxic effects upon cancer cell lines, a result attributable to the presence of steroids, alkaloid-like amides, and flavonoids. Since these extracts have effects which are both toxic and inhibitory on cell proliferation, they suggest possible anticancer properties. Nevertheless, comprehensive studies into their mechanism of action, together with selectivity indices and evaluations of their anticancer activity in vivo, are still lacking and therefore require further investigation.[13]

3.7 Other Activities

3.7.1 Anti-obesity effects and inhibition of pancreatic lipase: It has been stated that various *Spilanthes/Acmella* species are able to inhibit pancreatic lipase and show anti-obesity effects, although there is very little specific information available regarding *A. uliginosa.*

3.7.2 The antipyretic, anticonvulsant, diuretic, vasorelaxant and anti-HIV properties have been recorded in *Spilanthes acmella* (syn. *Acmella oleracea*) and in other related species, but in the case of *A. uliginosa* direct evidence is still limited and is often based on data obtained from closely related species.

Table No 3: Treditional use of different plant part.

Plant part	Traditional activity or use
Flowers	Chewed or applied for toothache and dental pain.
Flowers	Used for sore throat, gum infection, and throat discomfort.
Flowers	Used for paralysis or numbness of the tongue.
Flowers	Used as a sialagogue, meaning to stimulate saliva production.
Flowers	Used as an ingredient in cooking in northern Brazil.
Flower buds	Prepared as tea by some communities.
Leaves	Used as an analgesic for pain.
Leaves	Prepared as a beverage in some communities.
Leaves	Used traditionally for toothache, mouth ulcers, and infectious conditions.
Aerial parts	Crushed and applied as a paste dressing for external injuries in Ethiopia.

Whole plant/aerial material	Used traditionally for rheumatism or rheumatic pain.
Whole plant	Used for fever as an antipyretic remedy.
Whole plant	Used for stomachache and digestive discomfort.
Whole plant	Used traditionally for antimicrobial or "antibiotic" purposes in infectious diseases.
Whole plant	Used for antifungal and antiseptic purposes in traditional medicine.

4. Current Evidence and Gaps (Hepatoprotective, Nephroprotective, Wound-Healing, and Cardiovascular Activities)

There is at present no direct evidence to show that *Acmella uliginosa* has hepatoprotective, nephroprotective, wound-healing, or cardiovascular effects. Acute toxicity studies have shown that high doses can affect the biochemical markers of the liver and kidneys and cause mild histopathological changes, indicating a possible toxicity rather than protection. Although other Acmella species (for example, *A. oleracea*) have demonstrated renal and wound-healing activities, these results cannot be applied to *A. uliginosa* without carrying out specific studies. Therefore, well-conducted in vivo investigations are required in order to establish the organ-specific safety and therapeutic potential of the plant.

4.1 Hepatoprotective Activity

There are no direct experimental studies which specifically show that extracts of *A. uliginosa* have a hepatoprotective effect. Although some models have demonstrated liver-protective activity in related species such as *Acmella oleracea* (formerly *Spilanthes acmella*): these results cannot be directly applied to *A. uliginosa* without the conduct of specific studies. It is therefore still speculative to claim that *A. uliginosa* has a hepatoprotective effect.[19]

4.2 Nephroprotective Activity

Just as in the case of A. uliginosa, there is at present no direct scientific evidence or well-documented indigenous practice that supports its nephroprotective properties. On the other hand, with respect to *Spilanthes filicaulis*, some studies have reported changes in renal biochemical markers or histopathological parameters which indicate a protective effect on the kidneys at specific doses, although further investigation is required. This shows a clear research gap.[20]

4.3 Wound-Healing Activity

There is no direct evidence to show that A. uliginosa has a wound-healing effect. A related species, *Tamilnadina uliginosa* (not *Acmella uliginosa*): has demonstrated significant wound-healing activity in rat excision studies, the 5% w/w ethanol extract ointment stimulating fibroblast proliferation, collagen deposition, and tissue repair to a degree similar to that of povidone–iodine. Yet, it cannot be said that this effect is due to *A. uliginosa* without carrying out specific studies.[23]

Amazonian communities have for a long time used *Acmella oleracea* in the treatment of skin and mucous membrane wounds, influenza, cough, toothache, and both bacterial and fungal infections. The phytoconstituents present in it—such as alkylamides, phenolic compounds, and terpenes—might be responsible for these therapeutic effects and thus help to support its traditional medicinal uses. Nevertheless, the scientific evidence concerning the effectiveness and safety of *A. oleracea* bioactive products for the treatment of wounds is still very limited and needs further investigation.[21]

In Ethiopia, and in particular within the Gamo people's community as well as among other groups in the central and southern highlands, the plant Acmella caulirhiza—which has previously been linked with or included under *Spilanthes*—is used for medicinal purposes. The fresh leaves and the above-ground parts of the plant are crushed or crushed up into a paste and then applied directly to cuts, wounds and other external injuries. Though it is believed that this practice helps in the healing of wounds, its effectiveness has not yet been established by rigorous scientific or clinical studies.

A. uliginosa has two vasorelaxant effects. Although related species like *Acmella oleracea* have shown antiarrhythmic and vasorelaxant properties, this does not mean that those findings can be directly applied to *A. uliginosa*. Therefore, any cardiovascular claims regarding *A. uliginosa* should be regarded as hypothetical until they have been validated by experimental research.

4.4 Bioinsecticide Activity

The insecticidal properties of various Spilanthes species are promising, primarily because of the presence of spilanthol and other alkamides. Extracts of these plants have proved effective against the eggs, larvae, pupae of mosquitoes and agricultural pests such as the diamondback moth. They might also interfere with the nerve and muscle function of ticks and other arthropods. Yet the majority of the evidence is based on studies carried out in the laboratory and the degree of effectiveness depends on the species, the part of the plant, the method of extraction and the dosage used. Before Spilanthes extracts can be used commercially as pesticides24, further field tests and safety studies are still required.

4.5 Aphrodisiac Activity

Spilanthes acmella has for long been used as an aphrodisiac and its active component, spilanthol, might have an effect on sexual activity and on erections. Research carried out on animals has shown an increase in mating behaviour and erection responses. Although there is some evidence from humans indicating possible

advantages for sexual function, further clinical research is still needed before it can be considered as a replacement for Viagra.[30,31]

5. Toxicological Profile

Acute oral toxicity studies show that extracts of *A. uliginosa* are generally not lethal to rats when given at the doses tested. Extracts administered at a dose range of 200 to 1000 mg per kg of body weight were well tolerated and showed analgesic and other pharmacological effects without any obvious signs of toxicity. Nevertheless, at higher doses (for example, 2000 mg/kg): some changes were noted in the blood biochemistry and in the haematological parameters (including the counts of both red and white blood cells): as well as mild histopathological changes in the liver and kidney, even though no deaths were recorded.

A similar situation was found in some other species of A. uliginosa, for example *Spilanthes acmella* extract, which exhibited no significant lethal effects at a concentration of 20% v/v; however, at higher concentrations it caused spasms, tremors, loss of posture, seizure-like behaviour, reduced motility, and death in zebrafish, along with histopathological changes in the gills, liver, intestine, and kidney.[26]

The fact that has been found indicates that the traditional or moderate therapeutic use of *A. uliginosa* is fairly safe, but that high-dose or long-term unsupervised use might involve risks, especially concerning the liver and the kidneys. It therefore follows that care should be taken when consuming it in large amounts or over a long period, and further studies on subchronic and chronic toxicity are needed.

6. DISCUSSION

The idea that *A. uliginosa* is a "toothache plant" and a multi-purpose medicinal herb is strongly backed by recent pharmacological studies. The wide variety of phytochemicals it contains—mainly spilanthol and other alkamides, as well as flavonoids, phenolics, terpenoids and components of the essential oil—gives it a wide range of biological properties, such as antioxidant, anti-inflammatory, analgesic, antimicrobial, antifungal, antidiabetic and cytotoxic effects.

The fact that flower extracts have antioxidant and anti-glycation properties shows that *A. uliginosa* has promise in the management of disorders related to oxidative stress and diabetic complications; moreover, since opioid receptors are involved in its pain-relieving effect this gives a scientific basis for its traditional use as a pain reliever, and because of its antimicrobial and antifungal characteristics it can be used to treat infectious and inflammatory conditions of the mouth and skin.

Even though there have been these advances, considerable knowledge gaps still remain. Evidence of the hepatoprotective, nephroprotective, wound-healing, and cardiovascular effects is either missing or can only be indirectly deduced from related species.[1-5] Since A. uliginosa is widely used in traditional medicine and is becoming increasingly popular as a functional food and therapeutic agent, there is a need for rigorous in vivo studies, mechanistic investigations, and well-designed clinical trials in order to confirm these possible benefits and to determine safe dosage regimes.

It will be essential to standardise the extracts, identify the marker compounds (for example, spilanthol): and develop formulations that can be consistently reproduced if the results from preclinical studies are to be turned into therapeutic uses. Moreover, thorough toxicological evaluations, covering subchronic and chronic studies, genotoxicity studies, and reproductive toxicity studies, are necessary to guarantee safety for use over a long period.

7. CONCLUSION

Acmella uliginosa is a medicinal plant which has a considerable traditional use and contains a wide variety of bioactive compounds. The antioxidant, anti-inflammatory, analgesic, antimicrobial, antifungal, antidiabetic, and cytotoxic properties of this plant have been supported by scientific evidence, mostly due to the presence of spilanthol, alkamides, flavonoids and other phytochemicals. Nevertheless, the assertions about its hepatoprotective, nephroprotective, wound-healing and cardiovascular effects are not backed by direct experimental data. Further research should aim at identifying the molecular mechanisms involved, carrying out in vivo and clinical studies, standardising the herbal preparations and carefully assessing the long-term safety in order to fully make use of the therapeutic potential of *A. uliginosa*.

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