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COMPREHENSIVE STUDY OF FORMULATIONS AND PHARMACOLOGICAL ACTIVITIES OF SPILANTHUS ACMELLA

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ABSTRACT

Spilanthus acmella (SA) commonly referred to as the toothache plant, is a member of the Asteraceae family. This plant is known by various names in different regions. The phytochemical composition of SA includes components such as triterpenoids, α and β-amyrin esters, and alkaloids, which are particularly rich in N-isobutyl amides and alkyl amides. It also contains stigmasterol and myricyl alcohol, Spilanthol the main constituent, is involved in various biological activities such as antimicrobial, immunomodulatory, antioxidant, anti-inflammatory, hepatoprotective, diuretic, antinociceptive, and insecticidal actions. SA is utilized in medical and dental applications, as well as in beauty care cosmetics. Its pharmacological properties include anti-inflammatory, antipyretic, analgesic, local anesthetic, vasorelaxant, immunomodulatory, diuretic, antioxidant, antimicrobial, antifungal, larvicidal, bio insecticidal, convulsant, laxative, anticancer, aphrodisiac, antinociceptive, anti-obesity, and neuroprotective properties. This article provides a brief review of the pharmacological activities and toxicological studies of SA. It also discusses various formulations of SA.

KEYWORDS: Spilanthus acmella, Phytochemistry, Toxicology, Pharmacological activities, Formulations.

INTRODUCTION

SA also known as the toothache plant, Paracress, or eyeball plant, is an important member of the Asteraceae/Compositae family of medicinal plants.[1] SA grows well in both full sun and partial shade, reaching a height of 12 to 15 inches and a spread of 24 to 30 inches. It's ideal

soil is rich, moist, well-drained, and has a pH range of 6.1 to 6.5. Direct seeding in indoor pots or gardens is an easy way to get started. The ideal way to sow seeds is in flats. An additional technique for spreading SA is through stem cuttings. It thrives in soils with high humidity and good drainage, but it still needs to be watered frequently. 20–24°C (67–75°F) is the optimal temperature range for seed germination.[2] It is called the "toothache plant" because biting into the blooms or leaves numbs the gums and tongue. In the Ayurvedic medical system, flower heads and roots are used to treat a variety of conditions, including scabies, psoriasis, scurvy, toothaches, infections of the gums and throats, paralysis of the tongue, and childhood stammering.[3] This herb comes from Brazil and can be found all over the world, but it is particularly common in North Australia, America, Borneo, Malaya, Africa, India, and Sri Lanka. The whole plant is unbearably bitter, but the strongest flavor comes from the flower heads, which have an itchy, tingling, numbing, and salivary feeling.[4] The two primary ingredients, "spilanthol" and "acmellonate," are occasionally used to lessen toothache discomfort and promote salivation. Other noteworthy traditional uses of this herb include antipyretic use, stammering, treating sore throats, gum infections, paralysis of the tongue, and treating rheumatism. SA has long been known for its uses as a spice, antiseptic, antibacterial, antifungal, and antimalarial medication. Additionally, studies have demonstrated its efficacy in treating rabies infections, coughs, toothaches, the flu, and tuberculosis.[5] Figure of SA is given in **(Figure 1)**.

It has small conical yellow flowers. The whole plant is said to possess medicinal properties. In certain parts of the world, the leaves are eaten raw or cooked like vegetables. When ingested, they give the tongue tingling and numbness. The crushed leaves have stunned the fish. The local anesthetic activity of the SA aqueous extract was assessed in this study using the following methods (i) intracutaneous wheal in guinea pigs; (ii) plexus anesthesia in frogs; and (iii) antipyretic activity in albino rats induced by yeast-induced pyrexia.[6] Common names for Spilanthes acmella var oleracea include jambú, SA, and Acmella oleracea. Its bioactive compounds are mainly studied for their role in plant defense against herbivory, plant growth regulator functions, and other interspecies defenses because they have pharmacological, antibacterial, and fungicidal properties. Additionally, recent research has demonstrated that cold infusions of Jambu flower flowers can dissolve urinary system calculi and have a strong diuretic effect. By possibly inhibiting prostaglandin synthesis, the same extracts showed anti-hyperalgesic and anti-nociceptive effects against persistent inflammatory pain.[7] In order to treat toothaches and throat pain topically, this species' aerial

parts are frequently used as anesthetics.[8] Extracts from Acmella wild plants were investigated as a potential source of cutting-edge antibiotics to treat bacterial infections.[9] A variety of biological activities, including diuretic, antioxidant, gastroprotective, immunomodulatory, anti-inflammatory, enzyme inhibitory, antimicrobial, insecticidal, and larvicidal qualities, were found in extracts from several Spilanthes species, according to later research. The pharmaceutical industry was drawn to this discovery and utilized the extracts to create a variety of medical products.[10] Its root powder extract is also quite effective for treating HIV/AIDS infection.[11] Utilized as a bio-insecticide, immunostimulant, anesthetic and antipyretic, bio-anti-inflammatory, analgesic, and to treat rheumatism and gum infections.[12] The plant's roots are used as a purgative, while its decoction can be consumed as a diuretic and to treat bladder stones.[13]

SYNONYMS[12]

Synonyms of SA are given in a **(Table 1)** according to various names in different countries.

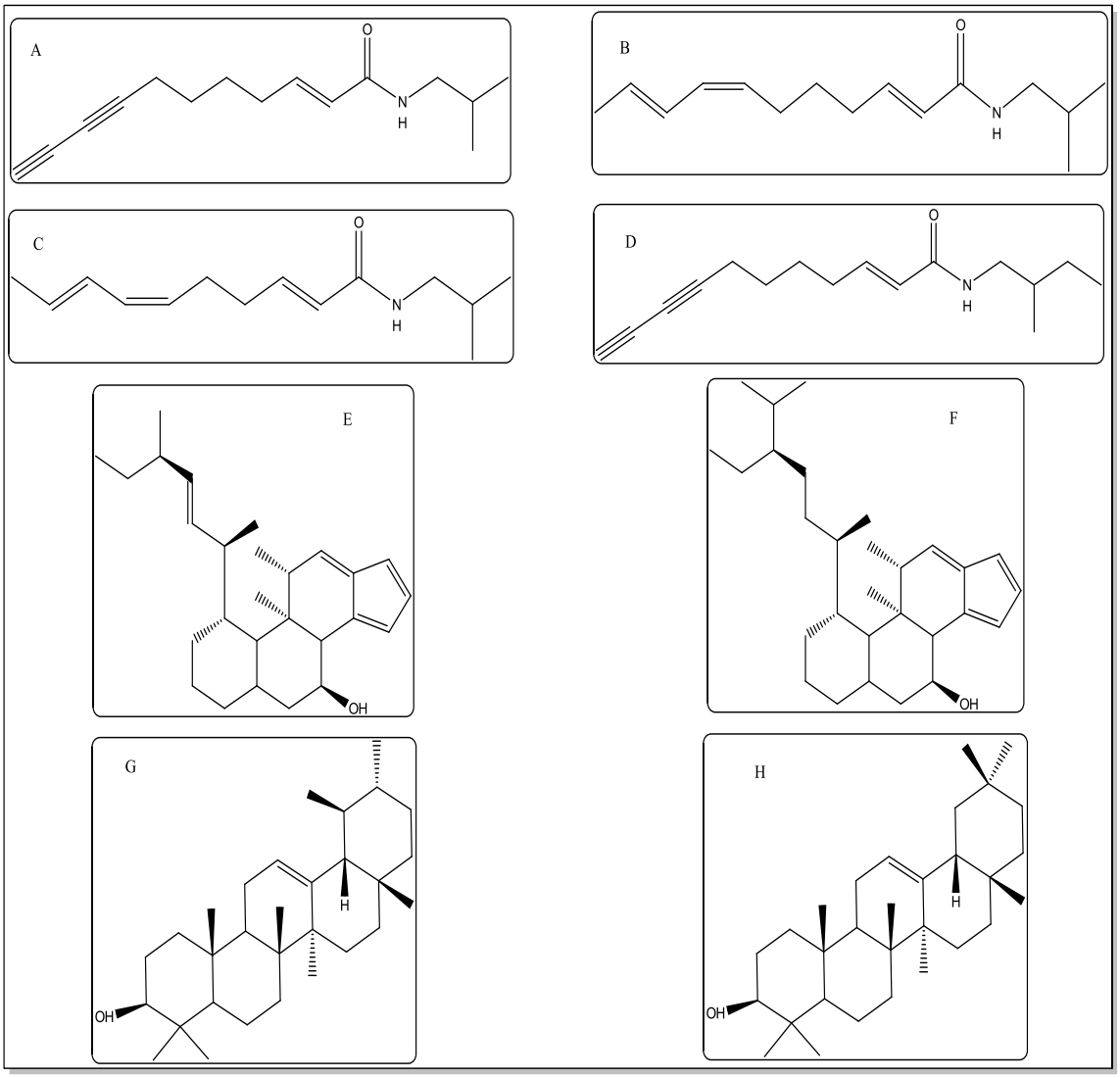
TAXONOMIC CLASSIFICATION[4]

Taxonomic classification of SA are given in a **(Table 2)**.

PHYTOCHEMISTRY

Investigating a medicinal plant's phytochemical constituents is essential to establishing a relationship between its pharmacology and chemistry. The structure and chemical analysis of the pungent alkamides derived from SA have been the subject of numerous investigations.[5] Alkamides have a strong taste that causes people to salivate and become itchy when they chew them.[14] Alkamides show high levels of activity in the central nervous system and are structurally related to endocannabinoids found in animals. Specifically, anandamide (N-arachidonoyl-ethanolamine) is an endogenous cannabinoid cerebral neurotransmitter.[15] Traditional medicine uses medicinal plants that contain a variety of bioactive compounds that may have significant physiological effects on humans. Triterpenoid, amino acids, α- and β-amyrin esters, myricyl alcohol (including sitosterol glucosides), and isobutyl amide derivatives are reported to be present in SA.[4] Eight plant families, including the Asteracea family, have been found to contain alkamides as secondary metabolites.[16] As per earlier reports, the phytochemical composition of S. acmella comprises of various components such as triterpenoids, α and β-amyrin esters, alkaloids that are particularly rich in N-isobutylamides and alkyl amides, stigmasterol and myricyl alcohol. Using LC-MS and HPLC/ESI-MS techniques, eleven N-alkylamides six N-isobutylamides, two 2-

methylbutylamides, and one 2-phenylethylamide were recently isolated and identified from ethanolic Spilanthes extracts.[7] Spilanthes acmella leaf powder ethanol extracts were subjected to a phytochemical screening process, which revealed the presence of alkaloids, polyphenol, tannins, flavonoids, and glycosides. These phytochemical components allow the extract of plant leaves to display a variety of pharmacological activities.[17] Various plant constituents and their presence are given in a **(Table 3)**. Phytochemical compounds classification based on type of nucleus used in a **(Table 4).**[12]



Structure: Chemical structures of secondary metabolites of spilanthus acmella: A) Spilanthol B) 2E-N-(2-methylbutyl)-2-undecene-8,10-diyamide C) Undeca-2E-en-8, 10-diyonic acid isobutyl amide D) Undeca-2E-7Z-9E trienoic acid isobutyl amide E) Stigmasterol F) β-Sitosterol G) α-Amyrin H) β-Amyrin.

BIOACTIVE METABOLITES

Spilanthol (N-isobutyl-2E, 6Z, 8E-decatrienamide) is an olefinic alkylamide that is widely distributed in this species and is involved in a variety of biological activities. Its isobutyl side chain is responsible for the sensorial effect that this plant exhibits.[7] SA air-dried whole plant contains myricyl alcohol, α-and β-amyrins, β-sitosterol, stigmasterol, and other compounds.[19] Spilanthol is a popular medicinal herb that contains an olefinic N-alkylamide ($C_{14}H_{23}NO$, 221.339 g/mol) and an isobutyl side chain. (2E, 6Z, 8E) Its IUPAC name is N - isobutyl-2, 6, 8-decatrienamide. It is also known as affinin.[18] Bioactive compounds called alkylammides are beneficial to the dental, agrochemical, pharmaceutical, and nutraceutical sectors.[20] Spilanthol is currently used in patented products as an anti-wrinkle and flavor enhancer. Significant antimicrobial, immunomodulatory, antioxidant, anti-inflammatory, hepatoprotective, diuretic, antinociceptive, and insecticidal properties of spilanthol have been shown to exist without any negative side effects.[7] Spilanthol has been reported to be 61% yielding when synthesized stereoselectively. Its refractive index is 1.5135 at 298 °C, it's melting and boiling points are 23 °C and 165 °C, respectively, and its maximum UV absorption is 228.5 nm (Jacobson, 1957). Its color is light yellow.[21]

TRADITIONAL USES

The whole plant, known as Spilanthes, has been used in food and medicine, including the flowers, leaves, stems, roots, and aerial parts. In particular, a number of traditional medicinal uses have been made of the well-known antitoothache plant SA/S. oleracea, also referred to as the paracress or eyeball plant.[15] It was well known for treating toothaches in Sudan, stomatitis in Java, and wound healing in India. India has long used the flower heads of S. acmella to treat and cure children's stuttering. In Cameroonia, this plant is also used as a deterrent against snakebite and as a treatment for articular rheumatism. But the entire plant was employed as a "poisonous sting".[22] According to the dictionary of Malay Peninsula plant products, the infusion of this plant's leaves is used as a purgative and as a diuretic to get rid of bladder stones.[4] In Thai, it's called Phak-Kratt Huawaen. A laxative and diuretic drug has been made from its root decoction.[23] It also promotes healthy digestion and guards against scurvy. Mouth ulcers are treated with SA inflorescence juice in India. Tribes in Bangladesh have long utilized the leaves and flowers of SA as a leucorrhea remedy. In addition to its medicinal applications, this species' flowers are used in Japan to flavor appetizers and gum and dentifrices.[4] Crushed aerial parts are applied as a paste dressing to external injuries by Ethiopian traditional healers. Sri Lanka and Nigeria both use SA as a

sialagogue.[1] Applications and traditional uses for various parts of the Spilanthes acmella plant is given in **(Table 5)**.

MEDICINAL USES

Most people refer to SA as the "toothache plant". This important medicinal herb helps relieve toothache pain by increasing saliva production. For centuries, people have been cultivating S. acmella for medicinal, horticultural, culinary and insecticidal uses. For these reasons, it is still widely used all over the world. The entire SA plant is rich in secondary metabolites, which offer a variety of medicinal uses. The plant has various parts that contain a multitude of pharmacological activities, such as.[1]

1) Diuretics

The substance known as a diuretic increases the production and excretion of urine. Rat experiments imply that SA cold water extract functions as a loop diuretic (Savant & Kareppa, 2022).

2) Scurvy and digestion

A vitamin C deficit causes the skin condition known as scurvy. The flowers of SA are used as a preventative measure against scurvy and to enhance or preserve digestion.[24]

3) Anti-malarial

In Africa, spilanthes sp. is a traditional antimicrobial. Spilanthol, a compound found in SA, exhibits Anti-Plasmodium falciparum activity.[25]

4) Rheumatism

An illness called rheumatism affects the elderly and is brought on by joint wear and tear. Gout can be cured by using the entire plant.[25]

5) Gastrointestinal diseases

For gastrointestinal tract disorders, chewing the roots of these plants is beneficial.[24]

6) Cosmetics

It immediately relaxes muscles and has an anti-wrinkle effect. The decrease in facial wrinkles leads to skin that is notably smoother.[25]

7) Other uses

It shields the person from the flu and colds. A traditional remedy for stomatitis, flu, cough, rabies, tuberculosis, throat complaints, headaches, and fever involve extracting the leaves and flowers.[25]

8) Toothache treatment

The plant SA is known as an antitoothache herb. People chewed on the fragrant flower heads of the plants to relieve tooth pain, throat issues, or tongue paralysis. Spilanthol is the component that is accountable for this.[25]

9) Local anaesthetic property

These plants have an anesthetic effect that is localized. Agents known as local anesthetics cause a particular body area to lose sensation.[24]

10) Dentifrice

Mouth rinses and toothpastes now contain spilanthol. The goal is to deliver a long-lasting, zesty mint flavor that also enhances appetite by increasing salivation. Because the spilanthol has a mild anesthetic effect, people with toothache can brush more comfortably.[25]

11) Anti-bacterial

Noor Jahan et al. demonstrated the antimicrobial activity of the ethanolic extract of SA against the following bacteria: Salmonella typhi, Enterococcus faecalis, Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae, Streptococcus pyogenes, Shigella dysenteriae, and Staphylococcus aureus. Additionally, the extracts showed efficacy against bacteria that were resistant and carried the Bla gene.[26]

12) Antifungal

SA exhibits very little antifungal activity. Research indicates that the prevalent opportunistic ailment primarily affecting people with compromised immune systems due to AIDS pathogens is caused by the fungi Microsporum gypseum and Cryptococcus neoformans.[24]

13) Hepatoprotective

The hepatoprotective effect of SA extracts against CCl4-induced liver toxicity in rats was found. The antihepatotoxic activity of Spilanthes ciliate was investigated by Suja et al. in 2003. The ethanolic plant extracts from Rhinacanthus nasuta, Ixora coccinea, and Spilanthes ciliate were administered orally to the rats as a pretreatment. When aflatoxin B1 was

discovered, Spilanthes ciliate provided a significant defense against the toxin's damage to the liver.[13]

14) Scabies and Psoriasis

One small species of mite is responsible for the rapid spread of scabies, a skin condition. One example of an autoimmune disease is psoriasis, a skin condition. Scabies, psoriasis, and scurvy are treated with A. olerecea flower heads and roots in an herbal medicine system, while skin conditions are treated topically with leaves.[13]

15) Periodontitis

Periodontitis is a result of inflammation in the gums. Chewing on the roots and flower heads is a treatment for periodontitis and has been shown to reduce gum inflammation.[25]

PHARMACOLOGICAL ACTIVITIES:

The plant SA exhibits a variety of pharmacological activities in its various parts. There is antibacterial, antiseptic, and antimalarial activity in the leaves and flower extract of SA. SA flower heads can be chewed to relieve pain and provide analgesic effects. The Ayurvedic medical system treats several illnesses, such as scabies, psoriasis, scurvy, and gum infections, with the use of flower heads and roots. Parts of the leaf have been used by various health systems.[1] Researchers have performed several in vivo and in vitro pharmacological screenings in order to confirm the traditional applications. These investigations have demonstrated that the plant has development potential based on natural resource-based medicine.[13]

1) Anti-inflammatory activities

Chen et al. investigated the anti-inflammatory effects of spilanthol derived from SA on macrophages in mice by inhibiting LPS-Induced Inflammatory Mediators. Study results indicate that spilanthol (isolated from SA) partially inhibits lipopolysaccharide-induced inflammatory responses in murine macrophages, based on the inactivation of NF-κB, which is known to negatively regulate the synthesis of proinflammatory mediators.[27] In experimental animal models, an aqueous extract of the ariel portion of SA indicated potent anti-inflammatory and analgesic properties by showing dose-dependent inhibition of paw edema and an increase in pain threshold.[6] Over the course of 120–240 minutes, a maximum inhibition of 80% on paw edema was obtained for all doses. At 60, 120, 180, and 240 minutes of treatment, AOEE-F 100 mg/kg decreased rat paw edema, producing an inhibitory effect of

60, 80, 85, and 90%, respectively, in comparison to the control. In lipopolysaccharide-activated murine macrophage model RAW 264.7.[8] Because spilanthol inhibits the production of pro-inflammatory mediators by inactivating NF-KAPPA B, it has a significant anti-inflammatory effect.[27] The two stages of the acute inflammation mechanisms take place within the first hour of serotonin, histamine and kinin release[28], and prostaglandin-like compounds that are released in the second and third hours. Therefore, through Cyclooxygenase (COX) enzyme inhibition, SA anti-inflammatory activity may later play a role.[29]

2) Anti-pyretic activities

SA is commonly used to induce pyrexia, so we studied its antipyretic activity using an approach induced by yeast. SA flavonoids, which are mainly lipo or cyclooxygenase inhibitors, account for the study's findings regarding its antipyretic activity.[6] Antipyretics increase body temperature when a patient has a fever, but they do not cause hypothermia in normothermic individuals. Fever during an infection is brought on by the growth of pyrogens, Interleukin (ILs), Tumour Necrosis Factor (TNFα), and interferons, which cause the hypothalamus to release Prostaglandin E2 (PGE2) and increase its internal temperature to 40℃. The activity of pyrogens is blocked by Non-steroidal Anti-inflammatory Drugs (NSAIDs), but they do not stop the injection of PGE2 into the hypothalamus. The COX-2 isoform is present here (possibly also COX-3). On the other hand, non-PG mediated mechanisms can also cause fever.[2]

3) Local anaesthetic activity

The potential of Spilanthes acmella as a local anesthetic has been investigated using two distinct animal models: (i) plexus anesthesia in frogs, where the onset of anesthesia is measured using cocaine as a standard; (ii) intracutaneous application in guinea pigs, where the standard use of nupercaine (suitable for determining degree of anesthesia). The mean onset of the local anesthetic action was very potent because alkylamides were present.[6] The majority of local anesthetics, such as xylocaine or lidocaine, are composed of amide compounds. Its mechanism of action involves blocking voltage-gated Na+ channels. Similarly, Local anesthesia was produced by the alkamides of S. acmella extracts, most likely by blocking Na+ channels. It has been reported that Piper piscatorum, another plant known to relieve toothaches, works similarly to isobutylamide in its mechanism of action to produce local anesthetic effects.[15]

4) Analgesic activities

Spilanthes acmella's analgesic properties, they employed tail flick method and acetic acid-induced abdominal constriction. Higher outcomes when the aqueous extract was compared to the tail flick method indicate that the plant may have some use as a peripherally acting diuretic and analgesic.[2] Using tail flick and hot plate tests at various post-treatment intervals, male rats were given an aqueous extract of fresh Spilanthes acmella flowers orally at varying dosages to assess their analgesic potential. The supra-spinally mediated effects are sedative and analgesic.[13]

5) Vasorelaxant activity

The effects of extracts from SA. (hexane, chloroform, ethyl acetate, and methanol) on vascular function were investigated in rat thoracic aortas precontracted with phenylephrine (PE) under a range of conditions, including the presence or absence of inhibitors like NG-nitro-L-arginine methyl ester (L-NAME) and indomethacin (INDO), as well as the removal of functional endothelial cells. Additionally, the effects of a vehicle like polyethylene glycol (PEG), a positive control like acetylcholine (ACh), and a negative control like sodium nitroprusside (SNP) were studied. The findings confirmed the connection between nitric oxide (NO) and the vasorelaxation of Ach.[23] SA extract in chloroform and ethylacetate causes a dose-dependent maximal vasorelaxation in response to phenylephrine, though not as much as acetylcholine-induced nitric oxide (NO) vasorelaxation. Chloroform extract showed the strongest vasorelaxant and antioxidant properties.[13]

6) Antimicrobial activity

Strong antimicrobial activity against common pathogens like Escherichia coli, Proteus vulgaris, Pseudomonas aeruginosa, Bacillus subtilis, E. faecalis, Staphylococcus aureus, Streptococcus mutans, C. albicans, Klebsiella pneumoniae, and Staphylococcus albus has been demonstrated in studies using the flower head of SA.[30] The crude extracts of the leaves and flowers were made using a variety of solvents, including petroleum ether, ethanol, and double-distilled water. Each extract's antimicrobial activity was examined against Aspergillus Niger, gram positive (Bacillus subtilis), gram negative (E. coli and K. pneumonia), and gram positive (Bacillus subtilis) bacteria.[31] Methanol (MeOH) and Ethyl acetate (EtOAc) extracts from SA leaves showed the strongest antimicrobial activity when tested using the well diffusion method against Klebsiella pneumonia.[3]

7) Antifungal activity

SA had been actively combating four different fungal species: Fusarium moniliformi, Aspergillus parasiticus, Aspergillus niger, and Fusarium oxysporum. Different concentrations of flower head extracts were used to demonstrate this. It was found that the fungal species were inhibited to varying degrees of sensitivity by each concentration of the test solution. At every concentration, the fungal species was inhibited by the test solution to differing degrees of sensitivity.[22] The highest concentration and a direct proportion to the dose were found to be the maximum zones of inhibition. The test organisms with the highest inhibition zones were A. niger and A. paraiticus, followed by F. oxysporium and F. moniliformis.[5] Research investigating the antifungal characteristics of various SA constituents showed that SA leaf extracts (EtOAc and aqueous) exhibited greater efficacy against Rhizopus arrhigus and Rhizopus stolonifera than the conventional drug, fluconazole. Furthermore, the leaf extract's effectiveness against Aspergillus niger and Penicillium chrysogenum was only mediocre.[3] Spilanthol and alkamides may be responsible for the antifungal activity of SA extracts.[32] Saponins and sesquiterpenoids that are not volatile.[15]

8) Antioxidant activity

By preventing the oxidative chain reaction, antioxidant activity limits or inhibits the oxidation of nutrients (especially lipid and protein oxidation). Recent studies on SA leaves' antioxidant potential have shown that flavanoids, tannins, and phenolic compounds are responsible for the plant's strong antioxidant activity in the crude ethanol extract of the leaf blades.[2] To assess the antioxidant activity of methanol extracts from SA stem and leaves, tests for 2, 2-Diphenyl-1-picryl hydrazyl (DPPH) and superoxide radical scavenging were performed. The stem of SA exhibited the highest scavenging activity of superoxide radicals in the methanol extract, while the leaves showed the highest scavenging activity of DPPH. The resulting superoxide radical scavenging assay showed that the stem and callus exhibited the highest levels of radical scavenging activity, while the roots displayed the lowest levels. It was discovered that leaves had the highest radical scavenging activity in DPPH, while roots had the lowest. Callus showed significant DPPH radical scavenging activity.[33]

9) Immunomodulatory activity

Macrophage morphometric and functional changes in mice treated with an ethanolic extract of SA revealed a time-dependent increase in the number of macrophage cells on the fifteenth day following drug administration. The herb in question appears to possess potential as a

natural immunostimulant medication due to its significant ability to stimulate macrophages and enhance their function when compared to the control group.[33] The ethanol extract from the leaves of the herb strongly activated macrophages and enhanced their function in comparison to the control group, suggesting that the herb may have applications as a natural immunostimulant medication.[13] Researchers found that at 80 mcg/mL, SA extracts in hexane and chloroform decreased the amount of nitric oxide produced by stimulated macrophages by 72% and 85%, respectively. Isolated spilanthol demonstrated dose-dependent prevention of macrophage activation, producing 60% and 20% of nitric oxide at 90 and 360 5ÔßM concentrations, respectively. These inhibitory features were linked to decreased nF-kB activation in the nucleus, decreased cytokine production from macrophages, and decreased mRNA and protein content of nitric oxide synthetase and COX-2.[1]

10) Diuretic activity

When taken orally in a single dosage, the entire plant SA and fresh flowers extracted using the cold-water extract method demonstrated strong diuretic activity.[2] Urine Na+ and K+ levels were found to significantly increase in response to the strong diuresis that SA flowers produced, which was comparable in intensity to furosemide. It was thought by researchers that the urine might be acting as a loop diuretic due to its slight acidity. The aqueous extract quickly showed signs of a diuretic effect. Due to the potential to lower dosage frequency, this diuretic profile is appealing.[5] An aqueous extract of Spilanthus Paniculata (SpE) flowers also diureses rats, as evidenced by the diuretic response of rats to SA flowers. There is a notable increase in urine Na+ and K+ levels, which is the cause of SpE flowers' diuretic action. SpE at a dosage of 500 mg/kg demonstrated the strongest diuretic effect among the three aqueous SpE doses tested (100 mg/kg, 300 mg/kg, and 500 mg/kg).[34] The use of SA extracts as a diuretic in ethnopharmacology is substantiated by their diuretic effect. The effects of extracts at 500 mg/kg body weight on urinary electrolyte excretion are significant, supporting the claims of diuretic efficacy. Further evidence for the traditional use of SA in the management of hypertension is provided by the current study.[35]

11) Antimalarial activity and larvicidal activity

The SA 95% ethanol extract decreased parasitemia by 36% at 50 mg/kg, albeit less successfully. These findings provide the first indication of SA potential as a malaria treatment and show that the plant contains active ingredients capable of combating P. falciparum. The results showed that the separated alkylamides from SA, undeca-2E-ene-8, 10-diynoic acid

isobutylamide and spilanthol, exhibited IC50 values of 16.5 µg/mL and 41.4 µg/mL on Plasmodium falciparum strain PFB, and IC50 values of 5.8 µg/mL and 16.3 µg/mL for the P. falciparum K1 strain, which is resistant to chloroquine.[36] Herbal extracts of three Spilanthes species—Spilanthes paniculata, S. calva L., and SA L.var oleraceae Clarke—have been used to develop a system for the biocontrol of filarial mosquito vectors and malaria. SA extract was the most effective of these in inducing total lethality at low dosages, with LC50 and LC90 values of 4.57, respectively.[37] Additionally, a number of studies have shown how effective spilanthol is as a larvicidal agent.[2] Spilanthol is more effective against eggs and pupae, even at low dosages.[1] Significantly present in the ethanolic extract of SA flower heads, spilanthol possesses potent larvicidal, ovicidal, and pupicidal effects.[38]

12) Bioinsecticidal activity

The extract of SA demonstrated efficacious insecticidal activity against the seeds of Plutella xylostella. Spilanthol's anti-P. xylostella activity was discovered. This is the first report of a substance from S. acmella flower heads showing insecticidal action against P. xylostella.[39] It was discovered that the Aedes, Culex, and Anopheles mosquito species were the targets of the most toxic extracts from spilanthes. Both spilanthol and alkamides were implicated in the insecticidal peculiarity. Additionally, saponins—non-volatile sesquiterpenoids were reported. Additionally, it was discovered that the SA flower head extract was an effective way to control the dangerous, polyphagous agricultural pest Spodoptera litura.[2] Experiments show that spilanthol is toxic to adult P. americana. Its efficacy was determined to be 1.3, 3.8, and 2.6 times greater than that of common insecticides like bioresmethrin, lindane, and carbaryl. It is therefore among the most powerful substances.[5] It was found that the active ingredient was spilanthol, which, when applied topically, was more acutely toxic to cockroaches than common pesticides such as carbaryl, lindane, and bioresmethrin (Kadir et al). Electrophysiological tests revealed that the cockroaches exhibited tremors immediately following application, and that there was a hyper-excitation of the cereal nerve followed by a complete inhibition of nervous activity.[40]

13) Convulsant activity and laxative activity

When rats' electroencephalograms displayed the usual electrographic seizures, the hexanic extract of SA resulted in epilepsy.[22] It appears that SA contains a substance or substances with strong laxative effects. A common stimulant laxative used to treat constipation, bisacodyl successfully counteracted the effects of atropine-induced constipation.[12]

14) Anticancer activity

As a member of the Asteraceae family, among other bioactive substances, SA is abundant in proteins, alkaloids, phenolics, and flavonoids. The plant extract was assessed for its in-vitro anticancer activity against liver cancer (HEP-2) and colon cancer (HT-29) cell lines using the Sulforhodamine B (SRB) assay. The results showed growth inhibition of 77±1.90% and 74±1.03%, respectively. A statistical analysis showed significant results against certain cancer cell lines. One possible mechanism could be lowering the generation of free radicals and triggering apoptosis, which includes growth regulators.[41] Extract from SA shows promise as a preventative measure for breast cancer. When used topically to treat breast cancer, the extract-containing cream exhibits promise.[42]

15) Aphrodisiac Activity: (Interaction with Testosterone and Sexuality)

Sharma et al. (2011) investigated the plant extract's aphrodisiac effects in male rats.[43] After the extract was taken orally, it was discovered that mount latency, ejaculation frequency, intromission latency and postejaculatory interval increased in a dose-dependent manner. The improvements in intromission latency, mount latency and post-ejaculatory latency were estimated using graphs, although the exact measurement of these improvements wasn't given. When 150 mg/kg of medication was taken for 28 days, the improvements decreased. One possible sign of a build-up effect is the fact that the benefits were noticed 28 days after supplementation, compared to 14 days later. Apart from its proerectile properties, the plant performed better than Viagra in every research area.[5]

16) Antinociceptive Activity

It is activity against nociception termed as "antinociception," also known as "nocioception" or "nociperception," describes how the sensory nervous system responds to potentially toxic stimuli such as dangerous chemicals (like capsaicin, formalin), mechanical injuries (like cutting, crushing), or extreme temperatures (heat, cold).[2] The antinociceptive effect of the crude ethanol extract of SA is investigated further in a mouse model of acetic acid-induced writhing. The animals in the test groups received doses of 250 and 500 mg/kg body weight of the test material. The positive control group was given the usual medication Diclofenac sodium at a dose of 25 mg/kg body weight, while the vehicle control group was treated with 1% Tween 80 in water at a dose of 10 mL/kg body weight. The control vehicle, standard medication, and test samples were all given orally 30 minutes before 0.7% acetic acid was injected intraperitoneally. The mice were observed to be writhing for five minutes after a

fifteen-minute break (absconstriction of the abdomen, trunk turning, and extension of the hind legs). Strong antinociceptive effects were observed in the SA leaf crude ethanol extract.[5]

17) Antiobesity activity

Fat metabolism is mediated by the enzyme pancreatic lipase. A. meleguetta and SA extracts significantly ($p < 0.001$) decreased the in vitro activity of human pancreatic lipase. Using these extracts, the lipase activity was found to be significantly dose-dependently reduced ($p < 0.001$), with A. meleguetta showing higher lipase inhibition activity than SA. Our findings demonstrate that lipase inhibitors are present in extracts from A. meleguetta and SA.[44] Empirical studies reveal that ethanolic extracts of SA flowers can inhibit pancreatic lipase activity by 40% at a concentration of 2 mg/mL. The 0.75 mg/mL extract of Spilanthes was found to inhibit pancreatic lipase more than Aframomum meleguetta, which was found to have lower activity (90% inhibition).[5]

18) Neuroprotective activity

The aerial part of SA may contribute to neuroprotection by minimizing cell degeneration in pirimicarb-induced neurotoxicity by maintaining calcium homeostasis-mediated calpain and calpastatin regulation.[45]

TOXICOLOGY

1) Acute oral toxicity

Albino mice of both sexes, weighing 25–30g, and maintained under controlled conditions of temperature (20–25°C) and humidity (55%) were used for toxicity studies using the up-and-down or staircase method. The ethanolic extract of SA was found to be effective at an oral dosage of 500 mg/kg of body weight.[46] The fact that the rats survived the entire study period after being given an aqueous extract of SpE flower orally at doses of 100 mg/kg, 300 mg/kg, or 500 mg/kg indicates that there was no acute toxicity in these animals.[34] It was discovered that diplandinhol effectively killed mosquitoes, exhibiting a 50% mortality rate at 6.25 µg/mL and an LD100 (at 24 hours) at 12.5 µg/mL. The combination of spilanthol isomers, at a concentration of 250 µg/mL, decreased the weight of H. Zea neonate larvae by 66% after six days.[47]

2) Insecticidal toxicity of spilanthol

Spilanthol, an extract from SA flower heads, was an active ingredient in the fight against Plutellaxylostella.[22] Aedes, Culex, and Anopheles are the mosquito species that the SA extracts may inhibit. Usually, Spilanthol and alkylamides were blamed for their insecticidal properties.[48] An ethanol extract of Spilanthes flower heads has shown strong insecticidal, ovicidal, and pupacidal activity against Culex, Anopheles and Aedes mosquitoes at a dosage of 7.5 ppm concentration.[1] Spilanthol and alkamides were identified as the sources of the insecticidal effect. Additionally, non-volatile saponins and sesquiterpenoids were also reported.[5] As mentioned previously, it was discovered that the hexane extract of dried SA flower buds were particularly effective against Aedesaegypti larvae. Spilanthol extract is a potent toxin that works well against adult Periplaneta americana. It is among the most effective substances when measured against common insecticides like bioresmethrin, lindane, and carbaryl; the potencies have been found to be 2.6, 3.8, and 1.3 times, respectively.[22] It was also discovered that the SA flower head extract was an effective way to control the dangerous and polyphagous agricultural pest Spodoptera litura.[2]

3) Neurotoxicity

According to Herdy et al., spilanthol depolarized heart atrial nerve cells by interfering with the fast component of the action potential. When 100 mg/kg of SA var. oleracea extracts were administered intraperitoneally (IP), Moreira et al. caused fast clonic-tonic seizures in rats that were comparable to epileptic seizures. After the dose, the animals trembled and within two minutes started convulsing. By this point, Electroencephalography (EEG) recordings also exhibit spiking activity. In numerous pharmacological tests on motor activity, peripheral nervous system function, and EEG recordings, the extract of S. americana flowers was tested. Within an hour, treated animals that did not die resumed normal behavior and EEG recordings, suggesting the existence of an acute toxicity threshold. The extract was shown to have both the typical CNS stimulatory effect of anesthetics and a cholinergic action on the central nervous system.[13]

4) Genotoxicity

In the Ames/Salmonella test, tobacco extracts were supplemented with extracts of S. calvus and eugenol.[49] Both substances considerably lessened the tobacco extract's mutagenic potential. Additionally, they greatly prevented methylurea from being nitrosated by nitrite to create mutagenic nitrosourea.[13]

FORMULTIONS

Various formulations of SA are available in a **(Table 6)**.

Table 1: Synonyms.

Country	Synonyms
India	Akarkara
Indonesia	Dung getang and Jotang, jocong
Chinese	San lu cao, Tian wen cao, Xiao tong chui, Bian di hong
Japanese	Supirentesu panikurata
Malaysai	Subhang nenek
Thai	Raan

Table 2: Taxonomic classification.

Kingdom	Plantae
Subkingdom	Tracheobiont
Phylum	Tracheophyta
Division	Magnoliophyta
Superdivision	Spermatophyte
Class	Magnoliopsida
Sub Class	Asteridae
Order	Asterales
Family	Asteraceae
Subfamily	Mimosoideae
Genus	Spilanthes
Species	Acmella

Table 3: Presence of plant constituents in ethanolic extracts.

Plant constituents	Ethanolic extract
Alkaloids	+
Polyphenol	+
Carbohydrates	+
Saponin	-
Flavanoids	+
Tannins	+
Glycoside	+
Triterpenes	-
Steroids	-

Table 4: Phytochemical compounds in plant spilanthus.

Sr. no.	Type of nucleus	Name of compound	Part used	Solvents
1	Alkamide	Spilanthol and Undeca-2E-7Z-9E-trienoic acid isobutylamide	Flower buds	Hexane
2	Alkamide	8E-trienamide Q α and β-amyrin esters stitosterol-O-D-glucoside.	Whole plant	Hexane
3	Aliphatic compound	Lauric, myristic, almitic and linolenic acid.	Whole plant	Ethylacetate

4	Sterols coumarin	B-sitosterone and mixture of stigmasteryl and β-sitosteryl-3-O- β-Dglucopyranoside	Aerial parts	Hexane and petroleum ether
5	Triterpenoid saponins	Olean-12-en-3-O-beta-D-galactopyranosyl-(1-4)-O-alpha-1- rhamo pyranoside	Root	Hexane
6	Long chain 2-keto ester	AcmellonateN-isobutyl-dedeca-2E,4E,8Z,10,E-tetraen amide	whole plant	Chloroform

Table 5: Applications and traditional uses for various parts of the Spilanthes acmella plant.

Health Care	Treatment	Plant part Used
Medical	Rheumatism, cough, rabies diseases, antimalarials, fever Diuretics Flu, Tuberculosis, Antibacterial.	Leaves, flowers
	Antifungal, skin diseases Immunomodulatory, Antiscorbutic, Obesity control (lipase inhibitor), Local anesthetics Digestive.	Leaves
	Snakebite	Whole plant
Dental	Toothpaste	Leaves
	Toothache	Leaves, Flower
	Periodontal disease	Flower heads, Roots
Beauty care cosmetics	Anti-wrinkle, Fast acting muscle relaxant	Whole plant

Table 6: Formulations.

Formulations	Descriptions	References
Mucoadhesive oral gel	Natural herbal extract was used to successfully prepare mucoadhesive oral gel. This extract can be used to treat oral cavity diseases such as toothaches, tooth decay, and mouth ulcers. It also increases the bioavailability of the herbal extract, which will improve patient compliance and minimize side effects while treating anti-inflammatory and anti-microbial conditions.	[50]
Nano formulation	Traditional Amazonian medicine uses a common plant species called Acmella oleracea (L.) R. K. Jansen (Asteraceae) to treat sexual dysfunction. The tingling sensation and other sensory qualities of this plant have led to an increasing amount of its use. We assessed a nano-formulation containing an ethanolic extract of A. oleracea inflorescences for therapeutic efficacy in patients with premature ejaculation.	[51]
Anti-wrinkle cream	Using an Acmella oleracea extract, Spilanthol is an anti-wrinkle product that works by preventing the contraction of subcutaneous muscles, particularly those of the face.One way to treat wrinkles cosmetically is to apply a sufficient amount of a composition based on pure spilanthol or Acmella oleracea extract subcutaneously or locally.	[52]
Makeup foundation	Use of Dry Acmella oleracea extract	[52]

O/W emulsion	Use of Dry Acmella oleracea extract	[52]
W/O emulsion	Use of Dry Acmella oleracea extract	[52]
Microemulsion	Use of Dry Acmella oleracea extract	[52]
W/O/W multiple emulsion	Use of Dry Acmella oleracea extract	[52]
Lozenges	Lozenges containing SA extract and Cinnamomum Tamala were created after research to treat sore throats and toothaches. The combined extracts of C. Tamala and SA exhibit antimicrobial activity against the selected test microorganisms (S. Aureus, S. Mutans, and E. coli).	[53]
Herbal tooth gel	SA stimulates salivation and eases toothache. Green tea's polyphenolic catechins combat plaque and germs. The goal of this project is to create an herbal tooth gel that will relieve toothaches and gingivitis. This herbal gel contains clove oil, green tea, and SA.	[54]
Mucoadhesive film	A potential substitute for oral topical use is a mucoadhesive film containing activated carbon-treated crude extract of jambu, which could stimulate further clinical research. Utilizing an extract from Acmella oleracea, popularly known as jambu, to create a topical anesthetic mucoadhesive film for oral mucosa.	[55]
Tablets	Zingiber officinale and Acmella oleracea standardized extracts in a novel food-grade lecithin formulation demonstrated statistically significant reduction in knee OA symptoms (pain and knee function) because of the anti-inflammatory activity demonstrated by a decrease in inflammatory markers (CRP and ESR). Indena S.p.A. prepared a lecithin-based formulation of standardized extracts of Acmella oleracea and Zingiber officinale for 350 mg of film-coated tablets. This formulation is equivalent to 37.5 mg of Zingiber officinale and 7.5 mg of Acmella oleracea.	[56]
Polyherbal formulation	The ayurvedic medical system uses a variety of poly-herbal formulations to treat pain and inflammation brought on by osteoarthritis, rheumatoid arthritis, frozen shoulder, ankylosing spondylitis, and chronic backaches.A polyherbal formulation shows anti-inflammatory and good analgesic properties in animal models used in experiments.	[57]
Nanoparticles	According to this study, SA leaf extract derived biosynthesized AgNPs provide exceptional defenses against hepatotoxicity and cardiotoxicity. Production of silver nanoparticles (AgNPs) with leaf extract from SA and its protective properties against doxorubicin-induced toxicity.	[58]
Emulgel	One of SA main ingredients, spilanthol, has potent antibacterial qualities. This study aimed to create an herbal emulgel to treat bacterial infections on the skin because microorganisms have developed strong resistance to antimicrobials.	[59]

FIGURE LEGENDS

Figure 1: Spilanthus Acmella.

CONCLUSION

SA is shown to be a botanical treasure that blends traditional wisdom with cutting-edge scientific research thanks to its rich pharmacological profile. Its diverse properties, demonstrated by a broad spectrum of pharmacological activities, make it a priceless resource in many fields, including drug development, cosmetic science, and conventional medicine. The bioactive components of the plant, especially spilanthol, show promise in treating a range of ailments, from inflammation and pain to cardiovascular disease and immune system support. Its documented uses, which include analgesic, antibacterial, and antimalarial qualities, demonstrate its adaptability in therapeutic domains. SA's adaptability is further evidenced by the development of numerous formulations that address conditions such as sore throats, erectile dysfunction, and diseases of the oral cavity. These formulations include oral gels and creams as well as lozenges and creams. It is a vital tool in both modern medicine and traditional because it can be used to address a wide range of health and wellness needs. Despite the plant's potential, more investigation and clinical testing are required to completely grasp its mechanisms of action, determine the best dosages, and guarantee human safety. The significance of careful dosage calculations is highlighted by toxicity-related factors, especially when considering genotoxicity and neurotoxicity. In essence, SA is a special and priceless natural resource that has significantly advanced the disciplines of medicine and cosmetic science. Its transition from conventional applications to a range of formulations demonstrates its adaptability and suggests more study and use in various therapeutic and wellness contexts.

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AUTHORS CONTRIBUTION

Shahabaz Pathan: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Writing – original draft.

Moizul Hasan: Conceptualization, Investigation, Methodology, Supervision, Validation, Writing – review & editing.

DECLARATIONS

Competing interests

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