REVIEW ON MEDICINAL HERB GENUS SPILANTHES AND ITS
APPLICATIONS IN ORAL HYGIENE

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Received 15-12-2013; Revised 20-12-2013; Accepted 24-12-2013

ABSTRACT

The therapeutic use of medicinal plant has gained considerable momentum in the world during the past decade. The overuse of synthetic drugs resulting in higher incidence of adverse reaction has motivated mankind to search for an alternative bioactive product for oral cavity. In recent years, many new compounds of genus Spilanthes herb have been established. Spilanthol is known to possess analgesic, antibacterial and anti-inflammatory activity. The present review aims to compile an up-to-date and comprehensive information on genus Spilanthes with special emphasis on ethno medical uses, phytochemical, scientific documents of pharmacological activities with respect to oral care diseases. This review explores extracts, phytochemicals & formulations of Spilanthes evaluated for possible analgesic, anti-inflammatory, antioxidant activity. However there are many gaps which need to be filled by concurrent researchers in different disciplines. One must make the best use of the naturally available resources which provide valuable raw material for advanced oral care research.

Keywords: Bioactive, Spilanthes, Analgesic, Oral Hygiene, Toothache.

INTRODUCTION

Pain is the most important symptom that brings the patient to physician. Analgesics relieve pain as a symptom, without affecting its cause. Excessive generation of reactive oxygen species (ROS) and other radicals can damage proteins, carbohydrates, polyunsaturated fatty acids, and DNA, and may thus lead to oxidative stress and to a variety of degenerative processes and diseases such as aging, immune deficiencies, neurologic disorders, inflammation, arthritis, ischemia, arteriosclerosis, coronary heart disease, stroke, diabetes mellitus, Parkinson's disease, Alzheimer's disease and certain cancers. ROS are continuously produced during normal physiologic events and removed by antioxidant defense mechanisms. Therefore, the great interest has been recently focused on the natural foods, medicinal plants and phytoconstituents due to their well known abilities to scavenge free radicals (i.e. antioxidant power). Now-a-days attention is being focused on the investigation of the efficacy of plant-based drugs used in the traditional medicine because they are cheap, have little side effects. According to WHO, about 80% of the world population still rely mainly on herbal remedies.

Among the reported plants, leaves were the dominant part in oral care uses (25.44%), followed by root (20.17%), as represented in Pie chart of Figure 1.

Figure 1: Useful Plant Parts (%)

Use of plant based products in various types of oral care problems is as depicted in below graph of Figure 2.
One of very interesting herbal ingredient that can reduce the toothache caused due to tooth sensitivity is flowers of naturally occurring plant: Spilanthes Acmella (Botanical Name)

Spilanthes Acmella is popularly known in the world as toothache-plant because by chewing the leaves or flowers, it produces a numbing effect on the tongue and gums. Acmella oleracea also known by Spilanthes acmella and Spilanthus oleraceae is an important medicinal plant with rich source of therapeutic constituents. The flower heads of S. acmella can be used to relieve toothache and also as anti-inflammatory and analgesic.

Spilanthes acmella L. (tooth-ache plant) is an annual herb belonging to the family Compositae. The genus is widely distributed throughout the tropics and subtropics and can be found in damp pastures, at swamp margins, on rocks near the sea and as a weed of roadside and cultivations. The flower heads were chewed to relieve the toothache and other mouth related complications. Leaves are used externally in treatment of skin diseases. Root decoction is used as purgative. Leaf decoction is used as diuretic and lithotriptic. Whole plant is used in treatment of dysentery\(^8\). Preliminary studies have reported as diuretic\(^14\), anti-inflammatory and analgesic\(^7\), vasorelaxant and antioxidant\(^9\). The Spilanthus acmella is one of the active ingredients in compositions for acute- or long-term treatment of microbial infections, particularly, oral pathogenic microorganisms, dental caries, periodontosis, gum disease, gum bleeding and/or plaque reduction\(^10\). Around 60 species of genus Spilanthes have been reported from different regions of the world\(^11\). Out of these, five species occur in India namely S. acmella Mull, S. acmella L. var. oleraceae Clarke, S. calva L., S. paniculata L., and S. mauritiana L\(^12\).

**ETHNO MEDICINAL USES:**

In India, the traditional uses of Spilanthes according to the parts of the plant used\(^13\) are presented in Table 1.

<table>
<thead>
<tr>
<th>Part used</th>
<th>Traditional uses</th>
<th>Reference No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flowers</td>
<td>Relieve toothache, Cure paralysis of tongue, Remedy for stammering, in treatment of scabies, psoriasis, scurvy, infections of gums, periodontosis, paralysis of tongue and remedy for stammering in children and in mouthwashes.</td>
<td>43, 44, 25,</td>
</tr>
<tr>
<td>Leaves</td>
<td>Stimulant, Sialagogue, Local anaesthetic, immunomodulatory, adaptogenic, toothpaste, lithotriptic, antiscorbutic, Sialagogue, antibacterial and digestive</td>
<td>26, 45, 46</td>
</tr>
<tr>
<td>Roots</td>
<td>In headache, Asthma, Rheumatism, treatment of scabies, psoriasis, scurvy, infections of gums, periodontosis, paralysis of tongue and remedy for stammering in children and in mouthwashes.</td>
<td>43, 44, 25</td>
</tr>
<tr>
<td>Whole plant</td>
<td>In treatment of dysentery and rheumatism</td>
<td>54</td>
</tr>
</tbody>
</table>

**PHYTOCHEMISTRY:**

The active constituent spilanthol chiefly present in leaves and flower heads produce analgesic activity to numb toothache. The analgesic activity of spilanthol has been attributed to an increased Gama amino butyric acid (GABA) release in the temporal cerebral cortex\(^14\). Interestingly, spilanthol has been demonstrated to inhibit nitric oxide (NO) production in a murine macrophage cell line, to efficiently down-regulate the production of inflammatory mediators Interleukin-1 beta (IL-1β), Interleukin (IL-6) and Tumor necrosis factor (TNF-α) and to attenuate the expression of Cyclooxygenase (COX-2) and inducible nitric oxide synthase (iNOS)\(^15\).
Several secondary volatile metabolites like sesquiterpenes, alkamides and oxygenated compounds have been isolated and identified in S. Americana. However, the most abundant alkamide found was spilanthol. The formula of spilanthol was determined as (2E, 6Z, 8E)-N-isobutylamide-2, 6, 8-decatrienamide. It is present in the roots, flower heads and whole aerial parts of genus spilanthes. The flower heads and root part of the plant genus have been reported to be especially rich in this active principle content. Spilanthol has a strong pungent taste; it may produce local stringency and anesthetic effects.

Several secondary volatile metabolites like sesquiterpenes, alkamides and oxygenated compounds have been isolated from the flower head of S. acmella Var. oleraceae has been determined by spectroscopic methods. In another study, structures of the pungent alkamides of S. acmella L. were determined by using nuclear magnetic resonance spectroscopy and high-performance liquid chromatography-mass spectrometry (HPLC-MS) with atmospheric-pressure chemical ionization and electron-impact ionization. The structures of some alkamides are given below.

(2E, 4Z)-N-isobutyl-2,4-undecadiene-8,10-dynamide

(2Z)-N-isobutyl-2-nonene-6,8-dynamide

(2E,6Z,8E)-N-(2-methylbutyl)-2,6,8-decatrienamide (Spilanthol)

The potential of the extract of S. paniculata as acute anti-inflammatory agent may be due to the presence of phytoconstituents like flavonoids (high amount), tannins etc. Again, no mortality was recorded in the acute toxicity test; it showed that the plant might be safe for use. Therefore, it can be revealed that the ethanolic extract of S. paniculata leaves possess acute anti-inflammatory activity and justify its use as a traditional folk remedy for toothache, pain etc. However, a more extensive study is necessary to determine the exact mechanism(s) of action of the extract and its active compound(s). The leaves contain alkaloids, carbohydrates, pungent amide tannins, steroids, carotenoids, provitamin A, α-carotene and β-carotene, essential oils, sesquiterpenes, and amino acids etc. Chemical analysis shows that Spilanthes acmella contain major pungent compound, spilanthol (N-isobutyl-2E, 6Z, 8E-decatrienamide) which is naturally occurring insecticide, and Butylated Hydroxytoluene. Antioxidant, butylated hydroxytoluene (BHT) and fatty acids (n-Hexadecanoic acid and tetradecanoic acid) could be obtained from extracts of mother plant of flower heads. The leaves contain alkaloids, carbohydrates, pungent amide tannins, steroids, carotenoids, essential oil, amino acid etc.

The pungent flavour of Spilanthes acmella is due to an unsaturated alkamid, spilanthol which present in its highest concentration (1%) in the flowers. Essential oil was isolated from the flower of S. acmella, whose main constituents were limonene, B-caryophyllene, Z-β-ocimene, γ-cadinene, thymol, germacrene D and myrcene. The different fractions were isolated from crude ethyl acetate extract of S. acmella and were studied against 27 strains of microorganisms. The results showed that fraction E3 completely inhibited the growth of Corynebacterium diphtheria with minimum inhibitory concentration (MIC) value of 128µg/mL.

**PATENTS ON SPILANTHES HERB:**

**US patent application 2009/0155445 A1** reveals a compositions capable of providing stimulation of the trigeminal nerve to induce sensations of the cooling, warming, tingling and salivating type in the animal and human mouth and claimed to achieve a synergistic effect between mixtures of well-known acidulants with a tingling ingredient of Jambu oleoresin or spilanthol. **EP 1454 533 A1** discloses products that promote saliva generation in the mouth, through the use of various food grade acceptable acids, in foods such as chewing gums, breath films, toothpaste and lozenges. It discloses in particular food grade compositions comprising a flavoring component, the flavoring component containing at least eight weight percent acid or acid salts selected from the group consisting of citric, malic, adipic, tartaric, Glutaric and fumaric acids; wherein the food grade composition spends at least one minute in the mouth.

**US patent application 20030118628 A1** addresses the issues related to the xerostomia conditions and the need to provide products capable of alleviating them, discloses confectionery in the confectionery product. The confectionery base may be a carbohydrate or carbohydrate derivative, namely a sugar and the salivation agents include acidulants, cooling compounds, salts, salt enhancers, monosodium glutamate (MSG), MSG enhancers, flavors and mixtures thereof. Mixtures of acidulants include citric acid, malic acid, succinic acid and adipic acid.

**US patent 3720762** comprises compositions containing at least one of the materials, spilanthol or the isomers thereof formed in the plants of Spilanthes oleracea Jacquin or Spilanthes acmella Var, oleraceae or the...
Phenylephrine-induced contraction of rat thoracic aorta as well as their antioxidant activity. Results show that the extracts exert maximal vasorelaxation in a dose-dependent manner, but their effects are less than acetylcholine-induced nitric oxide (NO) vasorelaxation. Significant reduction of vasorelaxation is observed in both NG-nitro-L-arginine methyl ester (L-NAME) and indomethacin (INDO). In the presence of L-NAME plus INDO, synergistic effects are observed, leading to loss of vasorelaxation of both acetylcholine and the extracts. Similarly, the vasorelaxation of the extracts are completely abolished upon the removal of endothelial cells. This demonstrates that the extracts exhibit vasorelaxation via partially endothelium-induced NO and prostacyclin in a dose-dependent manner. Significantly, the ethyl acetate extract exerts immediate vasorelaxation (ED50 76.1 ng/mL) and is the most potent antioxidant (DPPH assay). The chloroform extract shows the highest vasorelaxation and antioxidation (SOD assay). These reveal a potential source of vasodilators and antioxidants in Spilanthes acmella Murr. showed interesting bioactivities, e.g. strong local anesthetic, analgesic.

Spilanthes acmella Murr. (Compositae) has been used as a traditional medicine for toothache, rheumatism and fever. Its extracts had been shown to exhibit vasorelaxant and antioxidant activities. Herein, its antimicrobial, antioxidant and cytotoxic activities were evaluated. Agar dilution method assays against 27 strains of microorganisms were performed. Results showed that fractions from the chloroform and methanol extracts inhibited the growth of many tested organisms, e.g. Corynebacterium diphtheriae NCTC 10356 with minimum inhibitory concentration (MIC) of 64-256 μg/mL and Bacillus subtilis ATCC 6633 with MIC of 128-256 μg/mL. The tested fractions all exhibit antioxidant properties in both DPPH and SOD assays. Potent radical scavenging activity was observed in the DPPH assay. No cytotoxic effects of the extracts against KB and HuC1 cell lines were evident. Bioassay-guided isolation resulted in a diverse group of bioactive compounds such as phenolics [vanillic acid (2), trans-ferulic acid (5) and transisoferulic acid (6)], coumarins (scopeatin, 4) and triterpenoids like 3-acetylaureuritolic acid (1), α-sitostenone (3), stigmasterol and stigmasteryl-3-O-B-D-glucopyranosides, in addition to a mixture of stigmasterol-α and -sitosteryl-3-O-B-D-glucopyranosides. The compounds 1-6 represent bioactive metabolites of S. acmella Murr. that were never previously reported. Our findings demonstrate for the first time the potential benefits of this medicinal plant as a rich source of high therapeutic value compounds for medicines, cosmetics, supplements and as a health food.

S. acmella was evaluated for anti-inflammatory action by Carrageenan-induced rat paw edema. The analgesic activity was tested by acetic acid-induced writhing response in albino mice and tail flick method in albino

**PRECLINICAL STUDIES ON SPILANTHES HERB:**

The effect of Spilanthes acmella Murr. extracts on Phenylephrine-induced contraction of rat thoracic
The aqueous extract of S. Acmella in doses of 100, 200 and 400mg/kg showed 52.6, 54.5 and 56.1% inhibition of paw edema respectively at the end of three hours and the percentage of protection from writhing was 46.9, 51.0 and 65.6 respectively. In the tail flick model, the aqueous extract of S. acmella in the above doses increased the pain threshold significantly after 30 min. 1, 2 and 4 h of administration. S. acmella showed dose-dependent action in all the experimental models. The antioxidant activity of methanol extract of stem and leaves of S. acmella were measured using DPPH and superoxide radical scavenging assays. The result showed the methanol extract of stem of S. acmella to have the highest superoxide radical scavenging activity while leaves showed maximum DPPH scavenging activity. In superoxide radical scavenging assay, highest radical scavenging activity was observed in stem and callus, while minimum superoxide radical scavenging activity was found in roots. In DPPH radical scavenging activity was found maximum in leaf and minimum in root. Callus showed significant DPPH radical scavenging activity.

Different doses of aqueous extract of fresh flowers were orally administered to male rats and their analgesic potential was determined at different post treatment periods by using hot plate and tail flick tests. The analgesic activity is mediated supra-spinally accompanied with sedation.

Aqueous extract of aerial part of S. acmella, in experimental animal models showed dose-dependent inhibition of paw edema and increased pain threshold indicating significant anti-inflammatory and analgesic properties. Spilanthes shows significant anti-inflammatory activity on lipopolysaccharide-activated murine macrophage model RAW 264.7, partly from inactivation of NF-KAPPA B which negatively regulates production of pro-inflammatory mediators.

Drug loaded ethosomes prepared using phospholipid and ethanol, were optimized and characterized for entrapment efficiency, vesicular size, shape, in vitro skin permeation, and stability. The ethosomal vesicles were incorporated in carbopol gel base and its anti-inflammatory efficiency was compared with the marketed diclofenac gel. Mucoadhesive oral gels containing extract were formulated using different concentrations of polymers and extracts and tested for parameters like viscosity and mucoadhesive behavior. The optimized formulation was evaluated for antimicrobial activity against different microorganisms responsible for causing tooth decay using well diffusion method. The results fully validate the claims of the traditional medicine about the use of Akkalkara for local anti-inflammatory and anti-microbial properties and confirm the suitability of ethosomes for transdermal delivery of active constituents of this herbal formulation. Both formulations show results comparable to that of standard allopathic formulations. The investigation is evaluated for the potential of novel vesicular carrier, ethosomes, containing the methanolic extract of Spilanthes acmella, for anti inflammatory action via transdermal route and to test the potential of the herbal extract for antimicrobial property when formulated as an oral mucoadhesive gel.

The local anesthetic action of ethanol extract of Spilanthes acmella was studied in guinea pigs and frog’s sciatic nerves, subcutaneous injection of 0.1ml of 10% test solution in to guinea pig’s back revealed that the onset of action occurred immediately after injection and lasted for 21 minutes. The Duration of action was significantly shorter than that of 2% lidocaine (p<0.001). The action potential of isolated frog’s sciatic nerve was completely abolished within 5 minutes after application of the test solution. The tissue specimen obtained from guinea pig’s back muscle showed mild congestion of small blood vessels and mild intercellular edema. There was no significant difference as comparing to lidocaine injection. Results indicated that Spilanthes acmella possessed local anesthetic activity and further clinical trial should be investigated.

Sedative potential of the extract was evaluated by using rat hole board technique. The extract was well tolerated. A dose dependent analgesic activity with an EC50 =313 mg kg−1 was evident when evaluated in hot plate but not in tail flick test. This analgesic activity had a rapid onset and short duration of action and was not blocked by naloxone, an opioid receptor antagonist. The mid dose of the extract also induced significant sedation. It is concluded that the analgesic activity is mediated supra-spinally accompanied with sedation. In this study, the analgesic potential of fresh flowers of Spilanthes acmella Murr. Family (Compositae) used by some Sri Lankan traditional medical practitioners to suppress toothache. The Different doses of water extracts of fresh flowers (111, 335 and 671 mg kg−1) were orally administered to male rats and their analgesic potential was determined at different post treatment periods by using hot plate and tail flick tests.

The total phenolics and alkaloid contents were quantified by using gallic acid and atropine as standards and antioxidant activity was evaluated by using three free radicals (Superoxide, Hydroxyl and DPPH). Spilanthes acmella extracts revealed the presence of different phytochemical constituents like steroids, terpenoids, flavonoids, alkaloids, glycosides, tannins, carbohydrates, oils and amino acids. The methanol extract have more phenolics and alkaloid contents i.e. 38.83±0.68 (mg/gm) and 26.37±0.16 (mg/gm) than other extracts. The extracts were produced concentration dependent percentage inhibition on free radicals and produced maximum activity at concentrations of 320 and 640μg. Among all
extracts, methanolic extract showed better activity compared to other extracts with mean IC₅₀ values on superoxide, hydroxyl and DPPH radicals were 189g, 153g and 313g. The above results suggest that Spilanthes acmella extracts have antioxidant activity. Phytochemical analysis, quantification of total phenolics, alkaloid contents and antioxidant activity of Spilanthes acmella extracts (70% Ethanol, Methanol, Ethyl Acetate and Hexane) were evaluated.

The genus Spilanthes includes many plant species that are being used for the treatment of various disorders. Researchers have done different in-vivo and in-vitro pharmacological screenings to authenticate the traditional uses. These studies have revealed the potential of the plant to be developed as a curative agent from natural resources. Reported pharmacological activities of different Spilanthes species are reported in Table 2.

### Table 2: Pharmacological activities of different Spilanthes species

<table>
<thead>
<tr>
<th>Pharmacological activity</th>
<th>Species</th>
<th>Part used</th>
<th>Type of extract</th>
<th>Models used</th>
<th>Reference No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antioxidant</td>
<td>S. acmella Murr.</td>
<td>Aerial parts</td>
<td>Chloroform, hexane, ethyl acetate, Methanol</td>
<td>2,2-diphenyl-1-picrylhydrazyl (DPPH) and superoxide dismutase (SOD) assay</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>S. acmella Murr.</td>
<td>Leaves, stems</td>
<td>Methanol</td>
<td>DPPH, SOD assay</td>
<td>47</td>
</tr>
<tr>
<td>Anti-inflammatory</td>
<td>S. acmella</td>
<td>Aerial parts</td>
<td>Aqueous</td>
<td>Carrageenan-induced paw edema in rats</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>S. acmella</td>
<td>Aerial parts</td>
<td>Ethanol</td>
<td>Lippopolysaccharide-activated murine macrophage model</td>
<td>53</td>
</tr>
<tr>
<td>Local anesthetic</td>
<td>S. acmella</td>
<td>NA</td>
<td>Aqueous</td>
<td>Xylocaine-induced guinea pig and frog</td>
<td>37</td>
</tr>
<tr>
<td>Analgesic</td>
<td>S. acmella</td>
<td>Aerial parts</td>
<td>Aqueous</td>
<td>Acetic acid-induced writhing response in albino mice</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>S. paniculata</td>
<td>leaves</td>
<td>NA</td>
<td>Bacillus subtilis, Staphylococcus aureus, Enterococcus faecalis, Escherichia coli, Pseudomonas aeruginosa, Candida albicans and Microsporum gypseum</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>S. americana</td>
<td>Whole plant</td>
<td>Aqueous, ethanol and hexane</td>
<td>Staphylococcus aureus, Streptococcus hemolytic, Bacillus cereus, Pseudomonas aeruginosa and Escherichia coli</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>S. mauritiana</td>
<td>Roots and flowers</td>
<td>NA</td>
<td>Staphylococcus, Enterococcus, Pseudomonas, Escherichia and Klebsiella, Salmonella Fusarium oxysporium, F. moniliformis, Aspergillus niger and A. paraciticus</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>S. acmella Linn.</td>
<td>Flower heads</td>
<td>Petroleum ether</td>
<td>Candida species and Aspergillus species</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>S. mauritiana</td>
<td>Roots and flowers</td>
<td>NA</td>
<td>Candida species and Aspergillus species</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>S. calva</td>
<td>Roots</td>
<td>Methanol</td>
<td>Oral microflora: Streptococcus mutans, Lactobacillus acidophilus and Candida albicans</td>
<td>52</td>
</tr>
</tbody>
</table>

### CONCLUSION

Literature research afforded several plants (single or poly-herbal), extracts and active constituents with significant anti-inflammatory activity. Majority of the active constituents, were identified as alkaloids, flavonoids and rarely xanthenones and sterols. Experts are of the view that there is no acute shortage of leads for developing anti-inflammatory drugs. We need to initiate pending work on these phyto-constituents with emphasis on side-effect profile. Spilnthes plant holds great promise as a commonly available medicinal plant and it is indeed no surprise that the plant is referred to in the Indian traditional
circles. From the available literature on various aspects of the plant - traditional to biochemical and ethno
tobotanical to pharmacological - there are many gaps
which need to be filled by concurrent researchers in
different disciplines. One must make the best use of
the naturally available resources which provide
valuable raw material for advanced research.
After the study of chemical based oral products and
plant based products it is obvious that use of plant
based or herbal products is safer than & as effective as
chemical based products. Due to adverse effects of
chemical based remedies and high cost search for
alternative products still continues and the
phytochemicals isolated from the plants proves to be a
good alternative. The present review is an attempt to
create an interest among people regarding the
potential of natural plants in treating the infections
and disorders of oral cavity.
In conclusion it can be revealed that the crude
ethanolic extract of Spilanthes leaves possess
significant antinociceptive as well as antioxidant
activities. The potential of the extract of Spilanthes as
antinociceptive and antioxidant agents may be due to
the presence of phytoconstituents like tannins,
flavonoids, phenolics etc that might be responsible for
these activities. To add, clinical trials are warranted to
justify the ancient and pre-clinical findings about
medicinal applications of Spilanthes herbal agents in
oral hygiene.

ACKNOWLEDGEMENT

Authors are thankful to Kemwell Biopharma Pvt Ltd.,
Bangalore for their encouragement for this study.

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Source of support: Nil, Conflict of interest: None Declared