An updated review on medicinal herb genus Spilanthes

Kishan Lal Tiwari, Shailesh Kumar Jadhav, Veenu Joshi
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Abstract: Herbal medicine has been used in medical practice for thousands of years and recognized especially as a valuable and readily available resource for healthcare in Asian nations. India is a vast repository of medicinal plants that can be developed as a safe and economical system of medicine for the treatment of various ailments. Unfortunately, most of the traditionally used medicinal plants are yet unexplored or have not been fully examined by modern medical science. Therefore, exploring traditionally reported medicinal plants to leverage their potential for the betterment of human health is of great importance. The present review examines a promising medicinal plant genus Spilanthes. In recent years, many new compounds and activities of this plant genus have been established. The present review, therefore, aims to compile up-to-date and comprehensive information of genus Spilanthes with special emphasis on phytochemical and ethnomedical uses, scientifically documented pharmacological activities and tissue culture methods for conservation.

Keywords: Spilanthes; plant extracts; spilanthen; medicine; traditional; herbal drugs; review

The World Health Organization has estimated that 80% of the population of developing countries relies on plant-based traditional medicines to maintain their primary health care needs. High treatment costs and side effects along with drug resistance are major problems associated with synthetic drugs. Since traditional medicine is not only easily accessible but also affordable, there is an increased emphasis on the use of plants to treat human diseases. Therefore, the global markets are turning to plants as a potential and realistic source of ingredients for healthcare products.

Secondary metabolites are found to be the source of various phytochemicals that could be used directly or as intermediates for the production of pharmaceuticals, as additives in cosmetic, food or drink supplements. In recent years, the aim of searching for novel treatments against a variety of illnesses has lead to the discovery of many new compounds from plants. Nowadays, researchers and academicians focus on the active principle responsible for the pharmacological activity of traditionally used medicinal plants. One such medicinal plant genus is Spilanthes, which has great market potential due to its numerous medicinal uses[11]. The present review highlights

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the up-to-date phytochemistry and medicinal uses and in vitro conservation method of this medicinally useful plant.

1 General introduction

Genus *Spilanthes* belongs to the Asteraceae family and is widely distributed in tropical and sub-tropical regions of the world[1]. In India, plants of this genus are reported from some of the regions of South India, Chhattisgarh and Jharkhand[3]. There are recent reports of their presence in Jhalawar district of state Rajasthan[3, 4]. The plant genus grows naturally in damp areas, near lakes or ponds and near sewage discharge areas. It is commonly known as the toothache plant, aracress, eyeball plant and spot plant.

Around 60 species of genus *Spilanthes* have been reported from different regions of the world[5]. Out of these, five species occur in India namely *S. acmella* Murr., *S. acmella* L. var. *oleracea* Clarke, *S. calva* L., *S. paniculata* L., and *S. mauritiana* L.[5], *S. calva*, *S. paniculata*, and *S. mauritiana* grow wildly. *S. oleracea* is rare in occurrence whereas *S. acmella* is an acutely threatened species[6]. The genus *Spilanthes* is also mentioned as *Acmella* in some of the literature. *S. americana*, *S. ocmifolia*, *S. alba*, *S. uliginosa*, *S. nervosa*, *S. urens*, *S. paraguayensis*, *S. oppositifolia*, *S. macraei*, *S. ciliata*, *S. costata*, *S. repens* and *S. beccabunga* are examples of the known important species of genus *Spilanthes* which grow in different parts of the world.

Plants of genus *Spilanthes* are generally around 40 to 60 cm tall. The stems are prostrate in some of the species and erect in others, with opposite, triangular or lanceolate leaves and dentate or almost entire margins. The flower heads are yellow, cone-like or ovoid, long-peduncled and solitary. The roots are long and tapering and also emerge from the nodal regions in prostrate plants. In some of the species, the heads have a dark red spot in the center. The seeds are small and grey, black in color. This plant genus grows throughout the year in tropical regions with rich soil and organic compost. Regular watering and shady conditions are essential for the proper growth of the plant genus. Genus *Spilanthes* has no serious disease problems although it may occasionally suffer from spider mite damage. It has poor vegetative propagation and a low rate of germination[7]. However, stem cuttings are often used for its propagation.

2 Phytochemistry of *Spilanthes*

Phytochemicals are the chemical compounds that occur naturally in plants and have protective or disease-preventive properties, but are not essential nutrients. However, an analysis of phytochemicals is vital to make proper use of any medicinal plant.

Different phytochemicals like alkaloids, glycosides, flavonoids, tannins, anthraquinones, saponins and cardiac glycosides have been reported in *Acmella calva*[8]. Alkamides are the most abundant phytochemicals present in genus *Spilanthes* which account for most of its biological activity. Alkamides have been identified in several species of *Spilanthes* including *S. acmella*, *S. americana*, *S. oppositifolia*, *S. ocmifolia*, *S. ciliata*, *S. calva* and *S. mauritiana*. Alkamides are bitter in taste and could stimulate salivation.

Several secondary volatile metabolites like sesquiterpenes, alkamides and oxygenated compounds have been isolated and identified in *S. americana*[9]. However, the most abundant alkamide found was spilanhol. The molecular formula of spilanol was determined as (2E, 6Z, 8E)-N-isobutylamide-2, 6, 8-decanienamide[10]. It is present in the roots, flower heads and whole aerial parts of species *Spilanthes*[11], and the flower heads and root part of the plant genus have been reported to be especially rich in this active principle content[12]. Spilanhol has a strong pungent taste; it may produce local astringency and anaesthetic effects[13].

The structure of spilanhol and three other alkamides isolated from the flower head of *S. acmella* var. *oleracea* has been determined by spectroscopic methods[14]. 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\cite{15}. The structure of some alkaloids are given in Figure 1.

Recently, the LC-electrospray ionisation-MS method has been developed for the identification and quantification of spilanthol in \textit{S. acmella} (L.) Murr.\cite{16}.

Different compounds reported in genus \textit{Spilanthes} along with their nature are shown in Table 1.

![Image of alkaloids](image)

\textbf{Figure 1} Structure of some alkaloids present in \textit{Spilanthes}

\begin{table}[!h]
\centering
\begin{tabular}{|c|l|}
\hline
\textbf{Spilanthes species} & \textbf{Reported secondary metabolites and their chemical nature} \\
\hline
\textit{S. acmella} & N-isobutyramide: spilanthol\cite{17}, undeca-2E, 7Z, 9E-trienoic acid isobutylamide\cite{17}, undeca-2E-en-8, 10-diyionic acid isobutylamide\cite{17}, 2E-N-(2-methylbutyl)-2-undecene-8, 10-diynamide\cite{17}, 2E, 7Z-N-isobuty-2, 7-tridecadiene-10, 12-diynamide\cite{17}, 7Z-N-isobuty-7-tridecene-10, 12-diynamide\cite{17}, 7Z-N-isobuty-7-tridecene-10, 12-diynamide\cite{17}
Phytosterol: \(\beta\)-sitosterol\cite{17}, \(\alpha\)-amyrins\cite{17}\nEssential oil: limonene\cite{17}, \(\beta\)-caryophyllene\cite{17}, (Z)-\(\beta\)-ocimene\cite{17}, germacrene D\cite{17}, myrcene\cite{17}\nHydrocarbon: mixture of C22 to C35 normal hydrocarbons\cite{17}\nAlcohol: myrcyl alcohol\cite{17, 17}\n
\textit{S. alba} & N-isobutyramide: spilanthol\cite{17}, undeca-2E, 7Z, 9E-trienoic acid isobutylamide\cite{17}, acetylenic amides, acetylenes\cite{17}\n
\textit{S. oleracea} & N-isobutyramide: spilanthol\cite{17}, 2-methyl-butylamide\cite{17}, 2-(Z)-non-2-en-6, 8-diynoic acid isobutylamide\cite{17}, (Z)-dec-2-en-6, 8-diynoic acid isobutylamide\cite{17}\n
\textit{S. ovata} & Phenylethylamide: N-2-phenylethylamnamamide\cite{17}\n
\textit{S. calca} & Flavonoid glucoside: tetrahydroxidihydrochalcone 3\'-0-glucoside\cite{17}\n
\textit{S. leucocarpa} & Eudesmanolide\cite{17}\n
\textit{S. americanus} & Sesquiterpene: \(\alpha\) and \(\beta\)-bisabolens\cite{17}, caryophyllene\cite{17}, cadinens\cite{17}\nN-isobutyramide: N-(isobuty)-2E, 6Z, 8E-decatrienamide\cite{17}, N-(isobuty)-6Z, 8, 8-decadienamide\cite{17}\nPhenylethylamide: N-(2-phenylethyl)2E, 6Z, 8E-decatrienamide\cite{17}\n
\hline
\end{tabular}
\caption{Secondary metabolites in \textit{Spilanthes}}
\end{table}

3 Ethnomedical uses

Various medical beliefs and practices of indigenous cultures are associated with the genus \textit{Spilanthes}. Traditionally, the whole \textit{Spilanthes} plant is used in the treatment of dysentery. In Cameroon, the plant is used as a snakeweed remedy and in the treatment of articular rheumatism\cite{17}. It is supposed to be useful in cases of tuberculosis\cite{17}. In Germany, the plant extract is used for the treatment of soreness or bruising\cite{17}. In India, \textit{S. acmella} flower heads are used to treat stammering in children. Other traditional uses of \textit{Spilanthes} according to the parts of the plant used are presented in Table 2.

\begin{table}[!h]
\centering
\begin{tabular}{|c|l|}
\hline
\textbf{Part used} & \textbf{Traditional uses} \\
\hline
Flowers & Relieve toothache\cite{17}, in stomatitis and throat complaints\cite{17}, cure paralysis of tongue\cite{17}, remedy for stammering\cite{17}, as spice\cite{17}\n
Leaves & Stimulant\cite{17}, sialagogue\cite{17}, local anaesthetic\cite{17}, in bacterial and fungal skin diseases\cite{17}, as diuretic and lithotriptic\cite{17}, as salad\cite{17}\n
Roots & Purgative and laxative\cite{17}, in cold and flu\cite{17}, in headache, asthma and rheumatism\cite{17}\n
\hline
\end{tabular}
\caption{Traditional uses of different parts of \textit{Spilanthes}}
\end{table}
### 4 Pharmacological activities

The genus *Spilanthes* includes many plant species that are being used for the treatment of various disorders including life-threatening diseases. 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. Table 3 shows a detailed description of reported pharmacological activities on different *Spilanthes* species.

#### Table 3 (to be continued) Different pharmacological activities reported on various *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 number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretic</td>
<td><em>S. acmella</em></td>
<td>Flowers</td>
<td>CWE</td>
<td>Hydrated rats</td>
<td>36</td>
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<tr>
<td></td>
<td><em>S. acmella</em></td>
<td>Leaves</td>
<td>Petroleum ether, chloroform and ethanol</td>
<td>Hydrated Wistar albino rats</td>
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</tr>
<tr>
<td>Antimalarial, larvicidal</td>
<td><em>S. acmella</em></td>
<td>Flowers</td>
<td>Ethanol</td>
<td><em>Anopheles, Aedes, Culex larvae</em></td>
<td>38</td>
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<td></td>
<td><em>Murr.</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>S. acmella, S. calvus, S. paniculata</em></td>
<td>Flowers</td>
<td>Hexane</td>
<td><em>A. stephensi, A. culicifacies, C. quinquefasciatus larvae</em></td>
<td>39</td>
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<tr>
<td></td>
<td><em>S. mauritiana</em></td>
<td>Aerial parts</td>
<td>Methanol extract</td>
<td><em>Aedes aegypti larvae</em></td>
<td>40</td>
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<tr>
<td></td>
<td><em>S. mauritiana</em></td>
<td>Leaves</td>
<td>Crude powder</td>
<td><em>A. gambiae, Culex larvae</em></td>
<td>41</td>
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<tr>
<td>Insecticidal</td>
<td><em>S. calvus</em></td>
<td>Leaves and flowers</td>
<td>Petroleum ether, ethyl acetate and methanol</td>
<td><em>Helopeltis theivora</em></td>
<td>42</td>
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<tr>
<td></td>
<td><em>Murr.</em></td>
<td>Leaves and flowers</td>
<td>Aqueous</td>
<td><em>Chilo partellus</em></td>
<td>43</td>
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<td></td>
<td><em>S. acmella</em></td>
<td>NA</td>
<td>NA</td>
<td><em>Periplaneta Americana</em></td>
<td>44</td>
</tr>
<tr>
<td></td>
<td><em>Murr.</em></td>
<td>Aerial parts</td>
<td>Chloroform, hexane, ethyl acetate, methanol</td>
<td>Phenylephrine-induced rat</td>
<td>45</td>
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<tr>
<td>Antioxidant</td>
<td><em>S. acmella</em></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>45</td>
</tr>
<tr>
<td></td>
<td><em>Murr.</em></td>
<td>Aerial parts</td>
<td>Ethyl acetate, methanol</td>
<td>DPPH, SOD assay</td>
<td>46</td>
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<tr>
<td></td>
<td><em>S. acmella</em></td>
<td>Leaves, stems</td>
<td>Methanol</td>
<td></td>
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<tr>
<td>Antinoception, antihyperalgesic</td>
<td><em>S. acmella</em></td>
<td>Flowers</td>
<td>CWE</td>
<td>Formalin test of noiception and carragenan-induced thermal hyperalgesia in rats</td>
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<td></td>
<td><em>Acmella uliginosa</em> (Sw.) Cass</td>
<td>Flowers</td>
<td>Methanol</td>
<td>Chemicals (acetic acid-induced abdominal constriction and formalin-, capsaicin-, glutamate-induced paw-licking test) and thermal models (hot-plate test) of noiception in mice</td>
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<tr>
<td>Anti-inflammatory</td>
<td><em>S. acmella</em></td>
<td>Aerial parts</td>
<td>Aqueous</td>
<td>Carragenain-induced paw edema in rats</td>
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<tr>
<td></td>
<td><em>S. acmella</em></td>
<td>Aerial parts</td>
<td>Ethanol</td>
<td>Lipopolysaccharide-activated murine macrophage model</td>
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<tr>
<td>Antimicrobial</td>
<td><em>S. paniculata</em></td>
<td>Leaves</td>
<td>NA</td>
<td><em>Bacillus subtilis, Staphylococcus aureus, Enterococcus faecalis, Escherichia coli, Pseudomonas aeruginosa, Candida albicans and Microsporum gypseum</em></td>
<td>51</td>
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<tr>
<td></td>
<td><em>S. americana</em></td>
<td>Whole plant</td>
<td>Aqueous, ethanol and hexane</td>
<td><em>Staphylococcus aureus, Streptococcus hemolytic, Bacillus cereus, Pseudomonas aeruginosa and Escherichia coli</em></td>
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<tr>
<td></td>
<td><em>S. mauritiana</em></td>
<td>Roots and flowers</td>
<td>NA</td>
<td><em>Staphylococcus, Enterococcus, Pseudomonas, Escherichia and Kloeckera, Salmonella</em></td>
<td>53</td>
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<td></td>
<td><em>S. acmella</em></td>
<td>Flowerheads</td>
<td>Petroleum ether</td>
<td><em>Fusarium oxysporum, F. moniliiformis, Aspergillus niger and A. paraciticus</em></td>
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<td><em>Linn.</em></td>
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<td></td>
<td><em>S. maurntiana</em></td>
<td>Roots and flowers</td>
<td>NA</td>
<td><em>Candida species and Aspergillus species</em></td>
<td>55</td>
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<td></td>
<td><em>S. calvus</em></td>
<td>Roots</td>
<td>Methanol</td>
<td>Oral microflora: <em>Streptococcos mutans, Lactobacillus acidophilus and Candida albicans</em></td>
<td>56</td>
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Table 3 (continuation) Different pharmacological activities reported on various *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 number</th>
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</thead>
<tbody>
<tr>
<td>Immunomodulatory</td>
<td><em>S. acmella</em> Murr.</td>
<td>Leaves</td>
<td>Ethanol</td>
<td>Macrophage function in mice</td>
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<td>Chloroform, methanol and water</td>
<td><em>In vitro</em> HIV-1 protease solution assay method</td>
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<td>Convulsant</td>
<td><em>S. acmella</em></td>
<td>Whole plant</td>
<td>Hexane</td>
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<td>60</td>
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<td>Antiviral</td>
<td><em>S. americana</em></td>
<td>Flowers</td>
<td>NA</td>
<td>NA</td>
<td>32</td>
</tr>
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<td>Antimutagenic</td>
<td><em>S. calva</em></td>
<td>NA</td>
<td>Chloroform</td>
<td>Ames <em>Salmonella/microsome assay</em></td>
<td>61</td>
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<tr>
<td>Pancreatic lipase-inhibitory</td>
<td><em>S. acmella</em></td>
<td>Flowers</td>
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<td><em>In vitro</em> test</td>
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<td>Antihepatotoxic</td>
<td><em>S. ciliata</em></td>
<td>Whole plant</td>
<td>Ethanol</td>
<td>Paracetamol-induced hepatic damage in rats</td>
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<tr>
<td>Antipyretic</td>
<td><em>S. acmella</em> Murr.</td>
<td>NA</td>
<td>Aqueous</td>
<td>Aspirin-treated rats</td>
<td>64</td>
</tr>
<tr>
<td>Local anaesthetic</td>
<td><em>S. acmella</em> Murr.</td>
<td>NA</td>
<td>Aqueous</td>
<td>Xylocaine-induced guinea pig and frog</td>
<td>64</td>
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<tr>
<td>Aphrodisiac</td>
<td><em>S. acmella</em> L. Murr.</td>
<td>Flowers</td>
<td>Ethanol</td>
<td>Nitric oxide release in human corpus cavernosum cell line and penile erection in rats</td>
<td>65</td>
</tr>
<tr>
<td>Analgesic</td>
<td><em>S. acmella</em></td>
<td>Aerial parts</td>
<td>Aqueous</td>
<td>Acetic acid-induced writhing response in albino mice</td>
<td>49</td>
</tr>
</tbody>
</table>

CWE: cold water extract; NA: data not available.

5 Marketed preparations

Genus *Spilanthes* is well known for its “folklore remedy”. It is a potential medicinal plant which is also used for culinary purposes by tribes in various parts of the world. However, apart from its use by tribes, it is commercially cultivated and marketed in different parts of the world that indicates the increasing economic potential of this herb. Application of genus *Spilanthes* contributing to its economic potential includes its use in pharmaceuticals, as a nutritional supplement and beauty care cosmetics, etc. A recent cosmetic product “Galutine” claims that topical application of the extract of genus *Spilanthes* (*Acmella oleracea*) could reduce muscle tension and decrease facial wrinkles. Galutine is being used as a non-injectable, cheap and easy-to-apply herbal Botox replacement (a popular cosmetic injectable preparation used to prevent the development of wrinkles).

6 Tissue culture studies

With the increasing worldwide demand for plant-derived medicines, there has been a simultaneous increase in the demand for raw materials. However, the increasing human and livestock populations have affected the status of wild plants, particularly those used for making herbal medicines. Due to the multifold uses, genus *Spilanthes* is being overexploited by local populations as well as pharmaceutical companies. In addition, until now, little information is available on the biosynthetic pathway of alkaloides. It has therefore become imperative to develop methods for large-scale propagation, conservation, and optimizing production of secondary metabolites. In this context, plant tissue culture is a useful tool for the conservation and rapid propagation of medicinally important and endangered plants.

An efficient micropropagation protocol has been developed for *S. acmella* L. using seedling leaf explants through callus organogenesis. The best green and compact callus was obtained on 1 μmol/L naphthyl acetic acid and 10 μmol/L benzyladenine (BA) on the 15th day. The callus differentiated an average of 12.90 ± 0.32 shoot buds in 50% cultures.

*S. acmella* has been micropropagated using leaf explants which gave 20.00 ± 0.47 shoots per explant with 3.0 mg/L BA and 1.0 mg/L indoleacetic acid.

*S. mauritiana* DC. was successfully grown *in vitro* through auxillary bud culture; 1.0 μmol/L BA and 0.1 μmol/L naphthaleneacetic acid resulted in maximum shooting response with minimal callusing.

The aseptic auxillary buds of *S. acmella* L. formed multiple shoots within five weeks when cultured on Murashige and Skoog medium supplemented with 2.0 mg/L NAA-BA.

The nodal explants of *S. acmella* when placed vertically in a Erlenmeyer flask (250, 500, or 1 000 mL) produced more multiple shoots than those cultured in 350 mL jam bottles and 500 mL text-Z flask. It has been also observed that temperatures above 28 °C caused abnormalities of *in vitro* plantlets.

An efficient plant regeneration protocol was developed for *S. calva* using nodal segments.
grown on Murashige and Skoog medium containing 4.54 μmol/L thidiazuron which showed a better growth response and produced 22.3 ± 0.3 shoots per explant after 35 d.

*S. acmella* (L.) Murr. can be conserved at low temperature (4 °C) up to 60 d by encapsulating shoot tips using 3% sodium alginate and 100 mmol/L calcium chloride and maximum percent response for the conversion of encapsulated shoot tips into plantlets was obtained on growth regulator-free full-strength liquid MS medium.

In a gas chromatography-MS analysis, spilanthon was detected in the mother plant, flower heads and *in vitro* plantlets with similar retention time. Thus *in vitro* culture technique can become an alternative way to extract this valuable compound rather than from plants in the field.

7 Conclusion

Genus *Spilanthes* is a plant of choice for many health-related disorders. Its traditional uses have been proved pharmacologically. The active ingredient spilanthon is proposed to be responsible for most of its biological activities. There are many other alkaloids and secondary compounds reported from the plant, which can be investigated for the similar effects. Despite the fact that similar alkaloids are reported from many other species of *Spilanthes*, *S. acmella* has been more extensively explored and found more potent pharmacologically. However, there is a paradox as some of the workers reported the convulsant activity of hexane extract of *S. acmella*. Thus there is a need for optimisation and demarcation of dose, responsible for its convulsant activity and other pharmacological activities which will be a step towards a safe and effective use of the plant.

8 Acknowledgements

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9 Competing interests

The authors declare that they have no competing interests.

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药用金钮扣属植物研究综述

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摘要：植物药在人类的医学实践中已有上千年的应用历史，特别是在亚洲的一些国家，植物药资源被认为是一种可以随时随地取用的宝贵的医疗保健资源。印度拥有众多种类的药用植物，然而，其中很大一部分传统药用植物并没有被开发使用或未被现代医学科学研究证明其功效。因此，目前有必要开发传统药用植物并使其最大限度地造福人类。本文综述总结报道了一种很有潜力的药用植物即金钮扣属植物。过去几年中，很多从这类植物中提取的新化合物及其功效已经得到证实，因此本文旨在总结最新的有关金钮扣属植物的植物化学及药理学作用及物种保护方法的科学研究报道。

关键词：金钮扣属；植物提取物；千日菊素；医学；传统；植物药；综述