Comprehensive review of Clerodendrum phlomidis: a traditionally used bitter

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Abstract: Clerodendrum phlomidis Linn. f. (syn. Clerodendrum multilorum (Burm. f.) O. Kuntze, Volkanaria multilorum (Burm. f.) (Lamiaceae) is an important and well-known medicinal plant extensively used in Ayurveda and Siddha system of medicine for treatment of various ailments. The popular therapies include on inflammation, diabetes, nervous disorder, asthma, rheumatism, digestive disorders, and urinary disorders as well as a bitter tonic. It was reported that pectinolaringenin, scutellarein, cierodin, cierodendrin, clerosterol, 24β-ethylcholesta-5,22E,25-triene-3β-ol, lup-20(29)-en-3-triacetanatoate, 4,2′,4′-tri-hydroxy-6′-methoxyxalchone-4, 4′α-D-diglicoside, 7-hydroxyflavone, 7-hydroxyflavanone-7-O-glucoside and α-L-rhamnopyranosyl-(1→2) α-D-glucopyranosyl-7-O-naringin-4′-O-α-D-glucopyranoside-5-methyl ether had been isolated from this plant. The alcoholic and aqueous extracts were reported active as analgesic, antidiarrhoeal, antiplasmodial, hypoglycemic, minor tranquilizers, anti-asthmatic, antifungal, nematocidal, anti-ammestic and anti-arthritis. There are coincidences between some of the traditional usages of this plant and experimentally observed effects of the extracts but very few biological studies available on bioactive fractions and/or pure compounds. This review is an attempt to compile the exhaustive literature on Clerodendrum phlomidis, to highlight, analyze and critically assess the pharmaceutical potential of this underestimated plant in a systematic way.

Keywords: Clerodendrum phlomidis; bitters; review literature; medicine, Ayurvedic


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传统苦味药用植物苦郎树

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摘要：苦郎树是一种广泛用于印度阿育吠陀医学和悉达医学中的药用植物，常被用来治疗多种不同的疾病，如炎症性疾病、糖尿病、精神疾病、哮喘、风湿病、消化系统疾病、泌尿系统疾病等。此外，它也是一种常用的苦味补药。目前已报道从该种植物中提取出多种化合物，这些水溶性或醇溶性化合物具有止疼、止泻、抗炎、降血糖、镇静、平喘、抗真菌、抗寄生虫及抗关节炎等多种作用和疗效。这些经研究证实的药理作用与苦郎树的药用用途相吻合，然而针对苦郎树中所提取的生物活性成分及提纯化合物的生物学研究较少。本文将有关苦郎树的各类文献进行了详尽的整理与综述，系统分析和评价了这种药用植物的功效及应用前景。

关键词：苦郎树；苦味；综述文献；医学，印度传统
Ethnopharmacological knowledge, with its holistic systems approach supported by experiential base, can serve as an innovative and powerful discovery engine for newer, safer and affordable medicines\(^{[3, 4]}. In the last few decades there has been an increasing interest in the ethnopharmacological studies on medicinal plants, which is evident by numerous publications and reports. However, these reports on medicinal plants are widely scattered in journals and books pertaining to different disciplines, such as botany, chemistry, pharmacology, pharmacy and medicine. This review is an attempt to compile the exhaustive literature on *Clerodendrum phlomidis*, to highlight, analyze and critically assess the pharmaceutical potential of this plant that has been underestimated in a systematic way.

The genus *Clerodendrum* of the family Lamiaceae is a diverse genus with about 560\(^{[5]}\) to 580\(^{[5]}\) species of small trees, shrubs, lianas, or occasionally perennial herbs, mostly in the tropics and subtropics of the old world\(^{[4]}\). This genus was first described by Linnaeus in 1753 based on the type species *Clerodendrum infortunatum* from India, and later Adanson changed the Latinized form “*Clerodendrum*” to its Greek form “*Clerodendron*” in 1763. After almost two centuries Moldenke readopted the Latinized word “*Clerodendrum*” in 1942, which is now commonly used by taxonomists for classification and description of the genus\(^{[5]}\). *Clerodendrum* displays a high degree of morphological and cytological variations, of which many species have been described by more than one author\(^{[6]}\). Throughout its taxonomic history *Clerodendrum* has been delimited in many ways, some delimitations being more inclusive than others. *Clerodendrum* has been divided between as many as a dozen different genera; sometimes these smaller genera were divided among different families\(^{[7, 8]}\). The 19th and 20th century taxonomic and phylogenetic studies did much to rectify these. Even now, especially with the development of molecular systematic methods, the delimitation of *Clerodendrum* continues to be modified\(^{[9]}\). Phenetic and cladistic studies have led to a suggestion that *Clerodendrum* is paraphyletic\(^{[10]}\) or polyphyletic\(^{[11, 12]}\). Parsimony analyses of 456 potentially informative characters identified four large discrete clades (Clades I – IV) within *Clerodendrum*\(^{[13]}\). The sequence analyses of internal transcribed spacers of the nuclear ribosomal DNA concluded the genus to be polyphyletic\(^{[4]}\).

*Clerodendrum* is also a chemically diversified genus. Terpenoids are the major secondary metabolite, i.e., steroids\(^{[14,16]}\), neo-clerodane diterpenes\(^{[17, 18]}\), triterpenes\(^{[19, 50]}\) and iridoids\(^{[21, 22]}\). Phenolic compounds have frequently been reported among which phenyl propanoids\(^{[23, 24]}\) and flavonoids predominates\(^{[25, 26]}\). A few of species have been reported to have macrocyclic alkaloids\(^{[27, 28]}\) and cyanogenetic glycosides\(^{[29, 30]}\). *Clerodendrum* has been found to have a number of biological activities mainly including anti-inflammatory\(^{[31, 32]}\), hepatoprotective\(^{[33, 34]}\) antihypertension\(^{[35, 36]}\), antioxidant\(^{[37, 38]}\), cytotoxicity\(^{[39]}\), antitumour\(^{[40]}\) and antifeeding activities\(^{[41]}\), and effects on central nervous system\(^{[41]}\).

Bitters are a group of botanicals predominantly bitter in taste, due to the presence of chemical constituents like alkaloids, monoterpenes (iridoid and secoiridoids), sesquiterpene lactones, diterpenes, triterpenes and rarely flavonanes, acyl phloroglucides and steroids (pregnane type)\(^{[42]}\). In Ayurveda, for the high heat, fever and Pitta conditions, fire purging and heat dispelling herbs, i.e., bitters, are used\(^{[43]}\). *Clerodendrum phlomidis* Linn. f. (Lamiaceae) is one such traditionally recommended bitter for various ailments in India.

1 *Clerodendrum phlomidis*

1.1 Taxonomical hierarchy The taxonomical hierarchy of *C. phlomidis* is listed in Table 1.

<table>
<thead>
<tr>
<th>Taxonomical hierarchy</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Domain</td>
<td>Eukaryota</td>
</tr>
<tr>
<td>Kingdom</td>
<td>Plantae</td>
</tr>
<tr>
<td>Subkingdom</td>
<td>Viridae-plantae</td>
</tr>
<tr>
<td>Phylum</td>
<td>Tracheophyta</td>
</tr>
<tr>
<td>Subphylum</td>
<td>Euphyllophyta</td>
</tr>
<tr>
<td>Infra-phylum</td>
<td>Radistopae</td>
</tr>
<tr>
<td>Class</td>
<td>Magnoliosida</td>
</tr>
<tr>
<td>Subclass</td>
<td>Lamiidae</td>
</tr>
<tr>
<td>Superorder</td>
<td>Lamiaceae</td>
</tr>
<tr>
<td>Order</td>
<td>Lamiales</td>
</tr>
<tr>
<td>Family</td>
<td>Lamiaceae</td>
</tr>
<tr>
<td>Subfamily</td>
<td>Ajugoideae</td>
</tr>
<tr>
<td>Genus</td>
<td>Clerodendrum</td>
</tr>
<tr>
<td>Species</td>
<td>Phlomidis</td>
</tr>
</tbody>
</table>

1.2 Botanical and geographical sources *Clerodendrum phlomidis* Linn. f. (syn. *Clerodendrum multiflorum* (Burm. f) O. Kuntze, *Volkameria multiflorum* Burm. f.) belongs to the family Lamiaceae. It is commonly known as *Clerodendrum* or wind-killer in English and has different vernacular names in India (Table 2)\(^{[44-48]}\).
C. phlomidis is a common shrub of arid plains, low hills and tropical regions. They are distributed throughout the drier parts of India (Andhra Pradesh, Uttar Pradesh, Diu Island, Delhi, Gujarat, Haryana, Karnataka, Madhya Pradesh, Maharashtra, Bihar, Orissa, Punjab, Rajasthan, Tamil Nadu, Uttar Pradesh and West Bengal), Pakistan (Sindh, Baluchistan and north-western provinces), Sri Lanka, Myanmar and south-east Asia.

### Table 2 Different vernacular names of C. phlomidis in India

<table>
<thead>
<tr>
<th>Language</th>
<th>Vernacular name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sanskrit</td>
<td>Agnimanta, Agnimanthini, Arani, Gandhapatra, Gandhapushpa, Ganakarika, Jatha, Jaya, Jayanti, Jayarini, Krishanuga, Kshudra-Agnimanta, Laghumanta, Nadeyi, Parmako, Prasarin, Tanuvaccha, Tapuna, Tarkari, Tejovriksha, Vajjayanti, Vataghn, Vijaya</td>
</tr>
<tr>
<td>Tamil</td>
<td>Takkari, Thalanji, Thalludhalai, Tirugudalai, Sayandhi, Vadamadakki</td>
</tr>
<tr>
<td>Marathi</td>
<td>Airanamula, Arani, Arni, Iran, Takalimula, Tekar</td>
</tr>
<tr>
<td>Hindi</td>
<td>Arni, Piran, Pirun, Urni</td>
</tr>
<tr>
<td>Telugu</td>
<td>Nelli, Taluki, Takkolamu, Tekkali</td>
</tr>
<tr>
<td>Malayalam</td>
<td>Munja, Peruvaelum, Tirutalai</td>
</tr>
<tr>
<td>Bengali</td>
<td>Arani, Ganiyari, Goniari</td>
</tr>
<tr>
<td>Gujarati</td>
<td>Aranimula, Arni, Irun</td>
</tr>
<tr>
<td>Kannada</td>
<td>Taggi, Taggi-Beru</td>
</tr>
<tr>
<td>Oriya</td>
<td>Hontari, Ganiary</td>
</tr>
</tbody>
</table>

1.3 Controversy regarding its synonym in Ayurveda

Agnimanta or Arani is an important drug of Ayurvedic system of medicine. In some Nighantas (materia medica) of Ayurveda, only one type of Agnimanta is described but in some cases, two types of Agnimanta have been mentioned, i.e. Laghu or Kshudra (Small) and Brihad (Large) which have minor differences in their medicinal properties.[53-55] Some texts refer to the source of Kshudra Agnimanta or Laghu Agnimanta as dried mature roots of *C. phlomidis/C. inerme/C. nereifolium* and *Premma integrifolia/P. serratifolia/P. longifolia* as Brihad Agnimanta.[56, 57, 58] Some consider the smaller type as *P. integrifolia* and the larger ones as *C. phlomidis*.[56] Nair[56] quotes that *P. integrifolia* is used as Agnimanta in Kerala, India and both *C. phlomidis* and *P. integrifolia* may be used as Agnimanta according to availability. Some refer to Agnimanta as *P. integrifolia* and Arani as *C. phlomidis*.[56] Others quote both as Agnimanta and/or Arni[56, 59-61]. Nadkarni et al.[64] clearly mentions *C. phlomidis* as Agnimanta and also quotes Haines in addition who recognized two varieties, the white (Safed Tekar) and the black (Kala Tekar), the former alone being useful. In “Ayurvedic Formulary of India” the Latin name for Agnimanta is *C. phlomidis* and it also states that *Premma* sp. can be used as a substitute.[62-64] Though Tarkari is regarded as a synonym of Agnimanta, Susruta has enumerated both Agnimanta and Tarkari side by side in one group,[65] while Dravyagunavigyan (Science of treatment - Science of medicines) considers Agnimanta to be Valiya munna (*P. mucronata*) and Tarkari to be Ceriya munna (*C. phlomidis*). However throughout Kerala, India *Premma* sp. is used for both Agnimanta and Tarkari,[66] but Tarkari also refers to *P. integrifolia*, *Sesbania aegyptiaca* Pers. and *Cassia tora* Linn[66].

1.4 Commerce and trade

*C. phlomidis* is one of the highly traded medicinal plants from tropical forests, as the leaves and roots are used in folklore, Ayurveda, Siddha and Unnani medicines. The estimated consumption/trade of *C. phlomidis* was 306 metric tonnes for the year 2005 — 2006 and the estimated annual trade is 200 to 500 metric tonnes. It is sold under the trade name of “Arnimul” (leaf and root), the price range being 0.32 to 0.5 $ per kilogram.[67]

1.5 Anatomy, histology, microscopy and proximate analysis

Anatomical, histological and powder characteristics of different parts of *C. phlomidis* are shown in Table 3.[68, 69-70] The leaf constant values vary from those reported by Chunekar et al.[70] and Krishnamurthy et al.[69]. The Ayurvedic Pharmacopoeia of India has specified the thin-layer chromatography (TLC) pattern and some parameters, viz., foreign matter (not more than 2%), total ash (not more than 6%), acid insoluble ash (not more than 1%), alcohol soluble extractive (not less than 2%) and water soluble extractive (not less than 5%) values for recognizing the identity, purity and strength of roots of *C. phlomidis*.[47]
### Table 3 Anatomical, histological and powder characteristics of different parts of *C. phomoidis*

<table>
<thead>
<tr>
<th>Part</th>
<th>Anatomical characteristics</th>
<th>Histological characteristics</th>
<th>Powder characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Root</td>
<td>7 to 15 cm long and 0.2 to 3.0 cm in diameter; occasionally branched; cylindrical; tough; yellowish-brown externally; thin bark; rough outer surface; light-yellow wood; hard fracture</td>
<td>Exfoliating cork; rhomboidal crystal of calcium oxalate packed in xylem parenchyma and xylem rays; usual elements all being lignified; abundant round starch grains measuring 6 to 17 μm in diameter</td>
<td>Dull yellow; slightly astringent in taste; small, pointed, aseptate, lignified fibres; lignified cells packed with rhomboidal crystals of calcium oxalate; numerous simple, round to oval starch grains</td>
</tr>
<tr>
<td>Leaf</td>
<td>Simple; opposite; exstipulate; deltoid ovate to rhomboid ovate; 1.5 to 5 cm in length and 1 to 4 cm in breadth; entire to sinuate-crenate; sub-acute to obtuse; petiole 3.5 cm long; both surfaces of leaf are puberulous; reticulate; unicostate; 4 to 7 pairs of secondary nerves</td>
<td>Lamina is dorsiventral; non-glandular trichomes are slightly warty; glandular trichomes with one celled stalk and 4 to 8 celled head; cruciferous type of stomata; large number of open collateral vascular bundles; few pericyclic fibres only in the central meristele of petiole</td>
<td>Pale green; taste is bitter and astringent; cruciferous type of stomata; amoeboid intercostals cells in the upper epidermis; sunken glandular trichomes</td>
</tr>
<tr>
<td>Stem</td>
<td>Straight; unbranched; cylindrical; 9 cm long and 2.5 cm in diameter; uneven surface; irregularly interconnected axially elongated ridges; no lenticels marked</td>
<td>Tracheidal fibres, end walls sometimes present; oblique; the number of tracheidal fibres intervening two adjacent medullary structures is 3 to 4; pitting usually not seen; 3 celled, less elongated medullary rays mostly in 2 regions</td>
<td>Ash grey; indistinct odour; insipid in taste; tracheidal fibres; less elongated medullary rays</td>
</tr>
</tbody>
</table>

## 2 Ethnomedical uses

Indian system of medicines particularly Ayurveda and Siddha uses *C. phomoidis* as a single drug or in combination with other drugs. It was found that, a village nearby Pondicherry, India is called after the Tamil name, Thalludhalai. The Ayurvedic properties of *C. phomoidis* are: *Rasa* (taste) — Tikta (bitter), Katu (pungent/acrid), Kashaya (astringent), and Madhura (sweet); *Guna* (quality) — Rooksha (non-unctuous), and Laghu (light); *Veerya* (potency) — Ushna (heat); *Vipaka* (transformation with digestion) — Katu (pungent). Due to its bitter and pungent nature *C. phomoidis* is considered to normalize the vitiating Vata and Kapha *dosa*. It is constituted as a number of Ayurvedic formulations indicated for digestive disorders, acidity, gas, diarrhoea, laxative, liver tonic and general health tonic. The roots are used in different Ayurvedic formulations such as Ayushyavardhaaka tel, Bhachtanchamula, Chandraprabha vati, Lavanbhasker churna, Abhayarisht, Chavanprasha, Dasamularista, Ashwagandharishta, Mritisanjivini, Dasamula Kvatha Churna, Haritakiyleh, Indukanta Ghrita, Dhanvantara Ghrita, Gorocanadi Vati, Narayana Taila, Ras pitari, Vrahat Panchamul, and Muthu Marunthu (a Siddha polyherbal formulation). *C. phomoidis* is also an ingredient of many stress/pain relief massage oil blends and many polyherbal formulations that are used as rejuvenation tonic. Though root is considered to be the authentic drug it is the leaf that finds application in folkloremedicines. The ethnomedical uses of different parts of *C. phomoidis* are given in Table 4.

## 3 Veterinary uses

*C. phomoidis* finds a lot of applications in Indian traditional veterinary practices. The tribals Santals feed *C. phomoidis* to their cattle for diarrhoea and worms or when the stomach swells. Extracts of leaves are applied on body of domestic animals to kill lice. Leaves are good fodder especially for goats. Leaf paste is applied to infected hooves to give a relief for the animals and reportedly cures foot and mouth diseases and secondary infections. Fresh leaf extracts are pasted on animals with skin problems and used for hypothermia or shivering in cattle. In Chittoor, Ananthapur districts of Andhra Pradesh and Southern India *C. phomoidis* is used for alleviating diseases of livestock by the local traditional herbal practitioners. Leaves are given orally twice daily to cure convulsive seizures and trypanosomiasis infection until cured.

## 4 Utilization in agriculture

In *Surapala’s Vrshayurveda* (a 1 000 AD text), root of *C. phomoidis* is mentioned in the application of various tree disorders. *C. multiflorum* is used as a herbal pesticide particularly for insect pest like aphids and red hairy caterpillar. Leaf extracts are also used for preserving grains and to control green worms (*Heliotis sp.*). Jowar (sorghum) seeds are treated at the spike forming stage with leaf juice of *C. multiflorum* to protect from fungal infections (*Sporisorium sp.*).

## 5 Chemistry

A crystalline non-glucoside bitter principle (*C₉H₁₅O₂*₂, melting point (m.p.) 213°C), ceryl alcohol, β-sitosterol, γ-sitosterol, palmitic acid, erucic acid and an unidentified sterol (*C₉H₁₅O₂*, m.p. 155°C) have been isolated from the leaf and identified as pectolinaringenin as well by Subramanian et al., and was earlier reported.
by Bhakuni et al. The water extracts were found to contain glucose, arabinose and potassium nitrate. Two compounds (C₃₀H₄₆O₂₉, m.p. 67 °C and C₃₀H₄₄O₁₈, m.p. 93 °C) and a bitter resinous substance reported are yet to be characterized. D-mannitol, β-D-glucoside of β-sitosterol, β-sitosterol and ceryl alcohol were also isolated from the stem. Scutellarein (5, 6, 7, 4′-tetrahydroxy flavones), pectolinarinigenin (6, 4′-dimethoxy scutellarein) and a flavanone have been isolated from the leaf. A chemotaxonomic marker of the genus, (24S)-ethylcholesta-5, 22, 25-triene-3β-ol (C₃₈H₅₈O) m.p. 151 – 153 °C was isolated from the leaf.

β-sitosterol, γ-sitosterol, ceryl alcohol, clerodin (C₃₀H₄₆O₂), clerosterol (C₃₀H₄₆O) and clerodendrin-A (C₃₀H₄₆O₂) were also isolated from the root. Seth et al. reported 6, 4′-dimethyl-7-acetoxyscutellarein, pectolinarinigenin, hispidulin, apigenin and luteolin isolated from the flower. Chalcone glycoside (4, 2′, 4′-trihydroxy-6′-methoxychalcone-4, 4′-α-D-glucoside, m.p. 186 – 188 °C, C₃₀H₃₄O₁₂), pectolinarinigenin, 7-hydroxy flavone and 7-hydroxy flavanone 7-O-glucoside were reported isolated from the flower and the leaf. α-L-rhamnopyranosyl-(1→2)-α-D-glucopyranosyl-7-O-glucopyranoside-5-methyl ether (C₃₄H₅₀O₁₉) was reported isolated from the root by Anam.

### Table 4 Ethnomedical uses of different parts of C. phlomidis

<table>
<thead>
<tr>
<th>Part</th>
<th>Ethnomedical uses</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Root</td>
<td>12 to 24 g as decoction is used in Sthaha (inflammation, swelling), Pandu (jaundice), Arna (haemorrhoids, piles), Vibanda (constipation), Agnimantha (slowness of digestion, dyspepsia), Adhmana (swelling of the body), Gulma (a chronic enlargement of the spleen or any glandular enlargement in the abdomen), Mutrakroccha (painful discharge of urine, a class of urinary affections) and Mutraghatra (urinary disease). Used as bitter tonic, antidiote, analgesic, anti-asthmatic; for inflammatory diseases and in rheumatism. Used as bitter tonic, for nervous disorder and in debility.</td>
<td>46, 74, 75</td>
</tr>
<tr>
<td>Root bark</td>
<td>Used in cough, asthma, cold, anaemia, oedema and nervous disorders.</td>
<td>76</td>
</tr>
<tr>
<td>Root and root bark</td>
<td>Used as alternative, better tonic, and is given in the convalescence of measles by natives of Western India.</td>
<td>44, 50, 77</td>
</tr>
<tr>
<td>Root decoction</td>
<td>Used as aromatic, astringent and as demulcent in gonorrhea.</td>
<td>44, 74</td>
</tr>
<tr>
<td>Root juice</td>
<td>Used to reduce over-corpulence.</td>
<td>78</td>
</tr>
<tr>
<td>Whole plant</td>
<td>Used as hypoglycemic.</td>
<td>71, 79</td>
</tr>
<tr>
<td>Whole plant decoction</td>
<td>Used for ailments involving swellings, joint pains and inflammation. The properties are quoted same as those of P. integrifolia but C. phlomidis is considered better in inflammation. The tribes “Santals” rub the plant over their bodies in dropsey. The tribes “Sahariya” use the plant in fever, postnatal complaints, dyspepsia, colic and anthrax.</td>
<td>46, 50, 81</td>
</tr>
<tr>
<td>Whole plant and root</td>
<td>Used in colic, body-ache, diarrhoea, cholera, dysentery, dyspepsia, fever, headache, postnatal fever, stomachache, during convalescence from measles and specially used for mental diseases.</td>
<td>72, 75, 83–85</td>
</tr>
<tr>
<td>Whole plant and root</td>
<td>Used to treat diabetes.</td>
<td>86</td>
</tr>
<tr>
<td>Leaf</td>
<td>Used as a remedy to treat diabetes in southern parts of India especially tribes of Nilgiris. Used in fever due to sunstroke and malaria as febrifuge; ground leaves are given in stomach pain, dyspepsia, digestive disorders, eye complaints, lung diseases, rheumatism, asthma, inflammatory diseases, swellings. Locally tied for the treatment of guinea worms.</td>
<td>46, 74, 87</td>
</tr>
<tr>
<td>Leaf juice</td>
<td>Used to treat mental tension and mental disturbance in Tamilnadu.</td>
<td>90</td>
</tr>
<tr>
<td>Leaf and leaf juice</td>
<td>Used as bitter tonic, alternative and prescribed in neglected syphilitic complaints in doses of half an ounce or more twice daily in Southern India.</td>
<td>44, 46, 48, 50, 81</td>
</tr>
<tr>
<td>Leaf decoction</td>
<td>Used for inflammation, and is effective in treating bronchitis, headache, weakness, drowsiness and digestive problems.</td>
<td>44</td>
</tr>
<tr>
<td>Leaf and root</td>
<td>Used for body-ache, headache and unconsciousness.</td>
<td>85</td>
</tr>
<tr>
<td>Aerial parts</td>
<td>The tribes “Sahariya” apply the paste on body joints for about a month to reduce pain or stiffness of joints.</td>
<td>82</td>
</tr>
</tbody>
</table>
Lup-20 (29)-en-3-triacontanooate (C_{30}H_{108}O_{2}), tetratriacontanol and 24β-ethylcholesta-5,22E,25-triene-3β-ol were reported isolated from aerial parts^{[14]}]. Shanker et al^{[15]} reported a new validated TLC method for the quantification of a marker sterol, 24β-ethylcholesta-5,22E,25-triene-3β-ol with chloroform-methanol (98.5 : 1.5) (R_{f} 0.54±0.05) and densitometric evaluation at 650 nm after anisaldehyde-sulphuric acid derivatization. The amounts quantified in different solvent extracts were hexane 0.055 2, chloroform 0.054 7, ethanol (95%) 0.033 8, methanol 0.092 7 and ethyl acetate 0.104 7% w/w. Figure 1 and 2 show the chemical structures of some isolated compounds from C. phlomidis.

Figure 1  Chemical structures of some isolated compounds from C. phlomidis (1)
Figure 2  Chemical structures of some isolated compounds from C. phlomidis (II)
6 Non-clinical investigations

Many studies have reported the diversified biological activities of *C. phlomidis* which are described in details as followed.

6.1 Analgesic activity An ethanolic extract of leaves (150 and 300 mg/kg, i. p.) was evaluated for analgesic activity in albino mice (either sex, 20 to 25 g) by Eddy’s hot plate method. The extract at 300 mg/kg showed significant activity, supporting the folklore claim as analgesic\(^{[114]}\).

6.2 Anti-amnesic activity An aqueous extract of bark (yield 2% w/w) at 100 and 200 mg/kg, p.o. was evaluated for anti-amnesic activity in young Swiss mice (8 weeks, either sex) and old Swiss mice (28 weeks, either sex). Acute toxicity studies showed hypersensitivity, grooming, convulsions, sedation, hypothermia, ptosis and mortality at dose of above 1 000 mg/kg. The dose at 200 mg/kg more significantly enhanced the learning and memory of aged animals rather than the young ones. The extract profoundly increased step-down latency (SDL) indicating improvement in the memory of younger mice and significantly inhibited the acetylcholinesterase (AchE) activity indicating its potential in the attenuation of learning and memory deficits especially in aged mice\(^{[115]}\). The study concluded *C. phlomidis* as a potential nootropic and anti-cholinesterase agent\(^{[115]}\).

6.3 Anti-asthmatic activity An aqueous extract (yield 7.9% w/w) of leaves was studied for anti-asthmatic activity in male albino mice (Swiss strain, 22 to 25 g). The effect of extract (2, 4, 10 mg/mL) on goat tracheal chain was also studied, indicating a significant activity at 4 and 10 mg/mL with the relaxant effect (depression of histamine receptor 1). The extract at dose levels of 25, 50 and 100 mg/kg, i.p. in milk-induced eosinophilia showed significantly at 100 mg/kg the antagonizing effect. In three-day treatment by the aqueous extract (25, 50 and 100 mg/kg, i. p.), the 100 mg/kg dose showed 73.25% protection of mast cell degranulation. The aqueous extract, when studied for capillary permeability (25, 50 and 100 mg/kg, i. p.), at 100 mg/kg dose level significantly decreased transmittance, indicating its effect on optical density of the eye. The overall study lends credence to the beneficial use of aqueous extract in the treatment of asthma and related conditions\(^{[116]}\). The authors have quoted a back reference regarding the anti-ulcerogenic activity of *C. phlomidis*, which is misleading. In fact, *C. splendens* was screened for anti-ulcerogenic activity in the mentioned reference\(^{[117]}\).

6.4 Antidiarrhoeal activity A successive methanolic extract (yield 7.5% w/w) of leaves showed no mortality till an oral dose of 1 g/kg. The methanolic extract at doses of 200, 400, 600 and 800 mg/kg was evaluated for castor oil-induced diarrhea, gastrointestinal motility and prostaglandin E\(_2\)-induced enteropooling in albino rats (Wistar strain, 180 to 200 g, either sex). The methanolic extract at 600 and 800 mg/kg showed significant inhibition of defecation frequency and decrease in propulsion of the charcoal meal through gastrointestinal tract. The extract also significantly inhibited prostaglandin E\(_2\)-induced enteropooling in almost all the dose levels. The mechanism appears to be spasmyolytic and anti-enteropooling\(^{[118]}\). Although the extract has shown only the presence of steroids, alkaloids and flavonoids, the authors concluded that the activities of the extract might be due to tannins, which is controversial.

6.5 Anti-inflammatory activity The aqueous and alcoholic leaf extract-treated group showed general decrease in the size of the swelling following certain initial fluctuations and reduction in suppuration especially in speed of general drying up of the pus\(^{[64]}\). No details were found regarding the dose of the extract administered.

6.6 Antimicrobial studies Twenty microliters of defatted methanolic (yield 4. 4% w/w) and acetone (yield 1.7% w/w) extracts of stems and leaves (combined) were screened for five Gram-positive bacteria, seven Gram-negative bacteria and three fungi species by an agar diffusion method, respectively. Acetone extract was not active while the methanolic extract showed inhibition against *Citrobacter freundii* and *Staphylococcus epidermidis*\(^{[119]}\). The preliminary phytochemical analysis of *C. phlomidis* extracts was not clear whether it is for methanolic or acetone extract. Furthermore, it was astonishing to note that although the data indicated the absence of alkaloids, tannins, cardiac glycosides, steroids, flavonoids and saponins, the authors concluded that the antimicrobial activity might be attributed to various active constituents present in either mono or combined way of them.

Ethyl acetate and hexane extracts of leaves (yield 8.4% and 1.1% w/w) and stems (yield 3.21% and 0.52% w/w) at concentration of 1 mg/ml were screened for human pathogens and plant pathogens by poison plate technique, respectively. The leaf extract (particularly hexane extract) was more active than stem extract on both pathogens. However, the stem extract was only inhibitory to plant pathogens. The study revealed that both extracts were more effective in controlling plant pathogens than human pathogens and could be utilized in pesticide formulations\(^{[120]}\). Antifungal activity of two flavones, flavonone glucoside and one chalcone glucoside isolated from *C. phlomidis* were studied. Chalcone glucoside was highly promising followed by pectolinaringenin, flavonone glucoside and flavones\(^{[116]}\).

6.7 Antiplasmodial activity An ethanolic leaf extract showed 96% inhibition at 100 µg/mL and a 50% inhibitory concentration (IC\(_{50}\)) value of
25 μg/mL against *Plasmodium falciparum*. The study concluded that the activity might be due to the presence of iridoids[121] but no iridoids have been reported yet from *C. phlomidis*.

6.8 Antiviral studies An ethanolic extract of leaves was evaluated for antiviral activity against sunnhemp rosette virus (SRV) on *Cyamopsis tetragonoloba*. The virus inhibitory activity was 29% with no significant antiviral response[122].

6.9 Brine shrimp lethality study Both biological activity and toxicity of a root aqueous extract using *Artemia salina* (Brine shrimp test) were studied. The extract with a median lethal concentration (LC₅₀) value of 3,750 μg/mL showed no brine shrimp lethality[123].

6.10 Hypoglycemic activity Chaturvedi et al[55] studied the effect of decoction and alcoholic extract of *C. phlomidis* on adrenaline-induced hyperglycemia and alloxan-induced diabetics in rats, in which the alcoholic extract had a more significant inhibitory effect. Both decoction and alcoholic extract brought down the blood sugar levels effectively and exhibited the same degree of action in alloxan-induced diabetic rats. In a comparative study between the immediate effect (hourly basis) and long term effect (30 days) of decoction in normal rats, *C. phlomidis* produced comparable fall in blood sugar both on immediate as well as on long term use.

A defatted ethanol extract of leaves was screened for hypoglycemic activity in alloxan-induced diabetic rats at two dose levels, 100 and 200 mg/kg. The extract at 200 mg/kg exhibited significant hypoglycemic activity and also correction of altered cholesterol and triglycerides levels. In the histopathological studies more prominent islet cells were seen in both metformin and ethanol extract (200 mg/kg) treated groups[147].

6.11 Immunomodulatory activity A methanolic extract of roots was evaluated for specific immune response (antihyauronidase titer, plaque forming cell assay and delayed-type hypersensitivity test) and non-specific immune response (carbon clearance and *E. coli*-induced abdominal sepsis). The specific immune response was studied in BLAB/c albino mice (either sex, 22 to 25 g) for 7 days. The extract at 300 mg/kg showed significant antihyauronidase titer, plaque forming cell assay and delayed-type hypersensitivity test. In carbon clearance test (5-day treatment) and *E. coli*-induced abdominal sepsis (15-day treatment) the extract showed increased phagocytic index, significant clearance of carbon particles and only 20% mortality in 24 h particularly without any symptoms of peritonitis in surviving animals. The study concluded that the methanolic extract exhibited a high response in most of the studied models and the chemical constituents diterpenoids and flavonoids might contribute to the immunomodulatory activity[125].

6.12 Nematicidal activity An aqueous leaf extract showed a moderate nematicidal activity against larvae of root-knot nematode *Meloidogyne incognita* and antifungal effect (43.5% inhibition) against *Fusarium oxysporum* f. sp. *Cuminii*[126].

6.13 Psychopharmacological activity A successive methanolic leaf extract (yield, 7.5% w/w) was studied in Swiss albino mice (either sex, 20 to 25 g) for phenobarbitone sodium-induced sleep, general behavior test, muscle relaxant activity and exploratory behavior (rat model) at doses of 200, 400 and 600 mg/kg, respectively. The dose at 400 and 600 mg/kg, i. p. significantly lengthened the phenobarbitone sodium-induced sleep time in mice. The same dose levels produced slight/moderate spontaneous, sound, pain and touch responses. The studies at all dose levels showed significant losses of motor coordination and tone of muscles. A significant decrease was shown by all three dose levels in the exploratory behavior of rats in Y-maze test and in head dips responses in mice. The study concluded that the extract possessed most of the pharmacological activities of minor tranquilizers[69]. The authors have quoted that the extract is non-toxic and causes no death even up to an oral dose of 3.2 mg/kg while the doses selected for the study was 200, 400 and 600 mg/kg, i. p. which is contradictory.

6.14 Pharmacological effects of pure compounds The isolated compound 7-hydroxy flavone acts on targets like aromatase, alcohol dehydrogenase, 17β hydroxyl steroid oxydoreductase, multidrug resistance transporter (MDR-TR)-P-glycoprotein transporter (PGP-TR) and 3, 5- cyclic nucleotide phosphodiesterase. This flavone also exerts in vivo antinoiceptive activity[137] and is active towards fatty acid amide hydrolase (FAAH) with an IC₅₀ value of 0.5 to 1 μmol/L. Furthermore, it was reported that it also reduced the FAAH-dependent uptake of anandamide and its metabolism in intact RBL2H3 basophilic leukaemia cells[138].

6.15 Studies on formulation containing *C. phlomidis* A 50% ethanolic extract of Chyavanaprasha showed a nitric oxide scavenging activity[129]. A defatted 50% ethanolic extract of Chyavanaprasha showed a radioprotective effect in mice exposed to lethal dose of γ-radiation[130]. Muthu Manuruthu showed a very good controlling capacity on the biochemical events during tumor progression without producing any toxic effects[131]. The aqueous and alcoholic extracts of Amrit nectar tablets and the herbal Ayurvedic food supplement M-4 (Maharishi-i) reduced toxicities induced by Adriamycin and Cisplatin[132], showing antineoplastic activities[133-137]. The studies with formulations containing *C. phlomidis* were not emphasized much as it would be unscientific to attribute the overall activities of the formulation to a single plant.
7 Clinical investigations

In a clinical study, a 22% reduction of blood sugar was observed when 8 pills with an alcoholic extract were administered to 10 normal and 33 maturity-onset diabetic patients. Effects of age, sex and complications on the results were not considered in this study.

A case report stated that a 70 year male patient with complaints of polyuria, polydipsia, constipation, loss of vision, tingling, and numbness in extremities for the duration of 10 years and complicated with pulmonary tuberculosis responded well without any adverse effect, when administered with *C. phlomidis* decoction daily in 4 divided doses for three weeks along with antitubercular treatment simultaneously. Significant lowering of fasting blood sugar and improvement of polydipsia and polyuria were reported. In another clinical claim reported of 23 patients, 46% treated with *C. phlomidis* (a 1:4 decoction prepared from 15 to 30 g in daily divided doses for 5 weeks) showed 7.1% mean fall of blood sugar and 18.2% fall in urine sugar with no side effects. But the report did not contain sufficient data for re-analysis as well as statistical analysis, e.g., no means, no standard deviations. The small number of patients in the multiple arms of the study made generalization difficult. However the authors still assumes that *C. phlomidis* might be a good oral hypoglycemic agent.

Namboodari *et al.* reported that the combination of Dasmularista, Pippalyasava and Vettumaran Gutika was effective in the 90-day treatment of acute rheumatoid arthritis. Park *et al.* have evaluated the methodological quality of all randomized controlled trials (RCTs) on the effectiveness of Ayurvedic medicine for rheumatoid arthritis (RA). The Jadad score assigned for the study by Namboodari *et al.* was 2 due to poor study design and the inability to draw any meaningful conclusions.

8 Concluding remarks and future potential

Regarding the controversy if Agnimantha/Arani is *C. phlomidis* or *P. integrifolia*, it is difficult to judge as neither the Nighanthas nor any classical texts has referred to a morphological character. It is quite likely that both plants might have been actually used for the same purposes, since they were well known for their ethnomedical values. There is a discrepancy in pharmacognostical parameters reported by different authors. However the anatomical and histological studies will provide with evidence for establishing the identity and the degree of purity.

Currently, sterols, flavones, flavonones, chalcone, triterpene and neo-clerodane diterpenoids have been reported from different parts of *C. phlomidis*. The compounds C_{16}H_{28}O_{2} and C_{35}H_{49}O_{2} reported by Bhakuni *et al.* are still unidentified. Pectolinarigenin along with resinous substances might be responsible for the bitterness of the herbal agent. Only a few of bitter flavonoid glycosides have been reported earlier, e.g., naringin and neo-hesperidin. Pectolinarigenin is considered as a bitter principle of rare non-glucosidal flavone. Different extracts have shown the presence of tannins, flavonoids, terpenoids, steroids, phenolics, saponins and alkaloids. But there is difference of opinions by studies regarding the presence and absence of some secondary metabolites, such as saponins and tannins. Many authors have mentioned the presence of alkaloids in *C. phlomidis* but none of them have reported about their chemical group. A question would then be if this is apparent mutual exclusiveness between classes of secondary metabolites just a delusion resultant of insufficient studies or a reality. Relationships among the occurrences of classes of secondary metabolites would be a point deserving consideration, because it may end up useful in future prospects of pharmacological substances. Phenyl propanoids, abietane diterpenoids and lectins isolated from other *Clerodendrum* species are reported for HIV-1 integrase inhibition, angiotensin converting enzyme (ACE) inhibition, histamine and arachidonic acid release inhibition, cytotoxicity and immunosuppressive activity. The future phytochemical investigation should be focused on identification of these bio-active moiesties from *C. phlomidis*.

The ethnomedical uses give a clue that how people treat different health problems with *C. phlomidis* parts. In the view of the magnitude of its use, the more studies to be conducted seem essential. The overall pharmacological studies indicated that the alcoholic leaf extract was analgesic, antiarrhoeal, antiproliferative, hypoglycemic and minor tranquilizers, while the aqueous extract was anti-asthmatic, hypoglycemic, antifungal, nematocidal, anti-aneuritic and anti-arithmetic. The hexane soluble constituents of leaves were potent antimicrobials. The root aqueous extract was anti-inflammatory while the root methanolic extract exhibited an immunomodulatory activity. The bitter constituents might be responsible for hypoglycemic, immunomodulatory and psychopharmacological activities, since these bitter principles were found to have effects in blood sugar regulation, reducing anxiety and regenerating nervous system. Conversely, many of the pharmacological studies were experimentally poor. Very high (non-physiological) concentrations were used in both in vivo and in vitro studies before a biological response was seen. For example, in the psychopharmacological activity, the administered dose of 600 mg/kg i. p would be toxic. However there is a good coincidence of the traditional uses with
analgesic, anti-asthmatic, anti-inflammatory, anti-diarrhoeal, and hypoglycemic effects experimentally observed, which was in harmony with Farnsworth’s observation\[10\]. It is evident from the reference list of the present works that extracts have been objectives of most investigations whilst fractions of extract/pure compounds tracked to their bioactivities have been paid little attentions by phytochemists and pharmacologists. It is suggested that the future pharmacological investigations should focus on unexplored traditional uses of *C. phlomidis*. In a sense, the experimental works should explore potential uses of *C. phlomidis* with no records in the list of popular uses. A few of examples are the antimicrobial, anti-oxidant, and nematocidal effects. In the light of two clinical observations with no convincible data conducted at extract level in 1975 and 1983, it is evident to have a well-designed clinical study to confirm the hypoglycemic effectiveness of the species. It is believable that many novelties about *C. phlomidis* may disclose the relationships of their constituents to the corresponding pharmacological effects.

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