Ethnomedicinal uses and biological applications of *Tragia involucrata L.* -A critical review

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Abstract

Ethnomedicinal plants have been used as medicine for different ailments since ancient times. Formulation made from plant materials are used in traditional, complementary and alternative medicine and are widespread in both developing and developed countries. *Tragia involucrata L.* (Family: Euphorbiaceae) is a medicinal plant widely used in Sri Lankan and Indian traditional medicine. As this plant is a weed, it is being destroyed on a large scale due to lack of knowledge about its medicinal properties. Therefore, the objective of this study is to collect data on the medicinal value of this plant, biological and pharmacological activities with its ethnomedicinal uses. An effort was made to collect information on the ethnopharmacological uses and scientifically verified biological activities of *Tragia involucrata*. The review provides an insight into the potential of *Tragia involucrata* as a monoherbal formulation for diseases associated with multiple systems of the body. With all the scientifically verified biological activities and ethnopharmacological uses, *Tragia involucrata* can be qualified as a potent candidate to be developed as a phytomedicine and used as a preventive and therapeutic agent. Hence, the objective of this study was to collect data on the medicinal value of this plant by correlating its scientifically validated biological activities with its ethnopharmacological uses. With all the scientifically validated biological activities and the ethnopharmacological uses, *Tragia involucrata* may qualify as a potent candidate to be developed into a phytomedicine to be utilized as both a preventive and as a therapeutic agent.

Key words: Ethnomedicine, Antidiabetic, Anticancer, Antibacterial, Antioxidant, *T. involucrata*

Introduction

Traditional medicinal plants have been used medicinally since ancient times to treat various ailments. Even today, medicinal plants play an important role in global health. The use of traditional, complementary and alternative medicine, mainly using plant materials for their formulations, is widespread in both developing and developed countries. According to the World Health Organization (WHO), about 65–80% of the world's population living in developing countries depend on medicinal plants for their primary healthcare [1]. Because of this widespread use of medicinal plants, WHO has recommended initiation of research to identify and classify new herbal products from traditionally known plants and develop new effective therapeutic agents, especially in areas lacking modern medicine, such as chronic diseases [2].

Tragia involucrata L. (Family: Euphorbiaceae) is a herbal medicinal plant that has been used for centuries in Sri Lankan traditional medicine and Ayurvedic medicine [3– 4]. This plant is chiefly found and used in South Asian countries like Sri Lanka, India and Bangladesh. Ethnopharmacological uses of TI illustrate that it has been used in the treatment of disorders in various body systems. TI has a great market potential owing to its numerous medicinal values and thus has been scientifically studied for various biological activities. TI is a weed, so spreads easily and survives harsh weather conditions. Even though this plant has been used for thousands of years, currently the public is not aware of its medicinal properties and it is being destroyed on a large scale, especially in Sri Lanka,

because it causes severe stinging when touched [5-6]. Owing to the destruction of the plant, it is limited to some districts of the country. Thus, the aim of this study is to collect data on the medicinal value of this plant in order to elucidate its importance, correlate its biological activities with its ethnomedicinal uses. This review provides an insight into the potential of *Tragia involucrata* as a monoherbal formulation for non-infectious diseases owing to its many scientifically validated biological activities and its many ethnopharmacological uses which date backs to thousands of years.

Scientific classification

Kingdom	**:Plantae**
Sub Kingdom	**:Tracheobionta**
Division	**:Eudicots**
Class	**: Rosids**
Order	**:Malpighiales**
Family	**: Euphorbiaceae**
Genus	**:*Tragia***
Species	**:*T.involucrata L.***

Tragia involucrate (TI), commonly known as senthatti and Indian sting nettle, is a species of plant in the Euphorbiaceae family. It is a Tragia species that is widely used in ethnomedicinal and ethnopharmacological applications. *Tragia involvucrata* is a slender, twining herb with stinging hairs. It is a perennial, densely hispid-pubescent herb with scattered, stinging hairs throughout. The stem is elongate, slender, and twining. Leaves simple, alternate, serrate, stipulate, 2.5–12.5 cm long, 2–4.5 cm broad, densely hispid-pubescent. Regular, unisexual, and apetalous flowers are borne in the terminal axillary. Flowering period is February, March and June. Fruit a capsule 8 mm in diameter, 3-lobed, more or less hispid. The seeds are subglobose, grayish brown, smooth and lightly mottled. TI is geographically distributed in India, Sri Lanka, Burma and China. In Sri Lanka, it is common in cultivated and waste lands in Jaffna, Anuradhapuram, Minneriya, Galle and Matara. Tragia invades natural vegetation in tropical and subtropical regions [7]. The genus Tragia is a perennial herb. They mount onto the host through a twinning mechanism. Leaves are lanceolate and palmately triangular in shape. The leaves are arranged in alternate phyllotaxy. Common species are *T. involucrata* and *T. praetervisa* [8]. Tragia belongs to the Euphorbiaceae family. All species of this genus have stinging hairs. This plant is recorded from the sacred groves of Kerala [9].

Botany

Tragia involucrata L. belonging to Euphorbiaceae family is commonly known as Wel Kahambilia, Helgahambilia [10], Kahambilia or Kasambilia [11] in Sinhala and Indian Stinging Nettle or Climbing Nettle in English. In Tamil it is known as Ambu or Cherukanjuru [10] and in Sanskrit Duralaba, Dusparcha, Grahini, Kachura [10]. It is a well-known fact that this perennial herb with hispid stem and leaves causes injurious itching and stinging which limit the tangibility. The Sinhalese name Kahambilia is derived from the vesicant effect of TI, which causes stinging and itching on the skin. The book A revised handbook to the Flora of Ceylon [12], mentions four species of plants under the genus Tragia. They include *Tragia hispida Willd*., *Tragia involucrata L., Tragia bluekenettii* Radcliffe-Smith, *Tragia mulleriana Pax* and Hoffm. The vernacular name given for *Tragia hispida* Willd., Tragia involucrata L., and Tragia plukenetti Radcliffe-Smith is Well Kahambiliya. *Tragia Mulleriana* Pax and Hoffm have not been given a vernacular name in Dassanayake and Clayton [12].

Ethnobotany

The use of Tragia as an ethnobotanical medicine has been recorded from various parts of the world. In Ethiopia, *T. brevipes* is used to treat abdominal pain, anthrax, cancer, diarrhea, and babesiosis [11–13]. Local communities in Kenya use this species to treat rheumatism. In Namibia, *T.* okanyua is used to treat oedema [14]. Tribal people of Odisha state of India roots and leaves of *T.*

involucrata are used which are very effective in curing whooping cough [15]. The people from Karandamalai, Tamil Nadu uses root extract of *T. involucrata* to relieve constipation [16]. In West Bengal, root paste of this species is used to treat scorpion stings [15]. A paste made from the seeds can be applied on the scalp to prevent hair loss [15]. The paste is also used in the treatment of alopecia13. People from Northeast India use *T. involucrata* to cure diabetes. It is also used for breast tumors [20]. In Uganda, leaf extracts of *T. brevipes* are a traditional herbal medicine for the management of impotence and erectile dysfunction [21-22].

The earliest documentation of the ethnopharmacological use of *Tragia involucrata* dates back to the 1st century AD. Three major treatises of Ayurveda, Charaka Samhita, Sushruta Samhita, and Vagphata Samhita, refer to TI by its vernacular name, Vrishchakali. In the Charaka Samhita [4] documented in the 1st century AD, TI is mentioned under Apasmara chikitsa (treatment of epilepsy). In the Sushruta Samhita [23-24] documented in the 4th century AD, TI is mentioned under Jwara Chikitsa (cure for fever), and in the Vakbhata/Ashtangahrida Samhita [25] documented in the 5th century AD, TI is mentioned as an Chikitsa Sthana as an ingredient of Vidaryadi Gritha, a preparation made from cow's ghee, internally used for disorders of the respiratory tract symptoms.

In Sri Lanka, the earliest documentation of TI dates back to the reign of King Buddhadasa (341-370). The physician king of Sri Lanka compiled a comprehensive medical treatise in Sanskrit called "Sarartha Samgraha". In Sarartha Samgraha [25], TI comes under a group of drugs called "velpasmul" (roots of five climbers), which includes Ipomoea mauritiana, Hemides musindicus, Tragia involucrata, Tinospora cordifolia and Pergularia daemia. A decoction is prepared from the root of these five plants mainly for urinary tract disorders. However, the use of TI in ethnomedicine was not for the treatment of a specific disease, but for a range of unrelated disorders. The ethnomedical use of TI spans across disorders associated with various body systems.

General medicinal uses

The whole plant, like as leaves, stem, root, and fruits have medicinal properties. In Africa, *T. brevipes* root decoction is considered to have purgative properties. The root is also used to relieve labour pains. Rubbing with leaves on the joints is effective in curing pain from rheumatism. A leaf decoction is used for gonorrhea, intestinal parasites and gastro-enteritis. The whole plant is useful in the treatment of Polio. Burn the leaves to ashes and inhale for elephantiasis [26]. Roots are useful in treating asthma, fever, skin problems, epilepsy and snake bite [27]. It is an effective remedy for wound healing [28–29]. In India, Tragia is used for the treatment of a multitude of diseases such as skin itching and other diseases, venereal eruptions, cephalalgia, fever and guinea worms. The fruit is useful in the treatment of baldness. In some parts, the drug prepared from Tragia is used to treat scorpion sting [30–31]. *T. furialis* is a traditional antimalarial drug [32]. Whole plant is used in the preparation of Gandarvahasthadi Kwatha which is used to treat sciatica and back pain [33]. It is also a content of Kabasura Kudineer Choornam, a traditional siddha medicine [34].

Biological activity

Several controlled studies have been carried out in vitro and in vivo to scientifically verify the ethnopharmacological properties of TI. Due to the widespread use of TI as an ethnomedicine in traditional medical practice, a large number of studies have been devoted to scientifically evaluate its biological activities. These studies have supported the value of TI in treating diseases related to many vital systems of the body and have further shown that it has many biological activities such as antibacterial/antimicrobial activity, antidiabetic/hypoglycemic activity, antioxidant activity and anti-inflammatory activity. Since phytochemicals are responsible for these biological activities, concurrent research on phytochemical analysis of whole or parts of TI has shown that it is rich in phytochemicals consistent with its broad biological activities.

Pharmacological Activities

The genus Tragia has a wide range of pharmacological activities (Figure.1). Most studies have been conducted on *T. involucrata*.

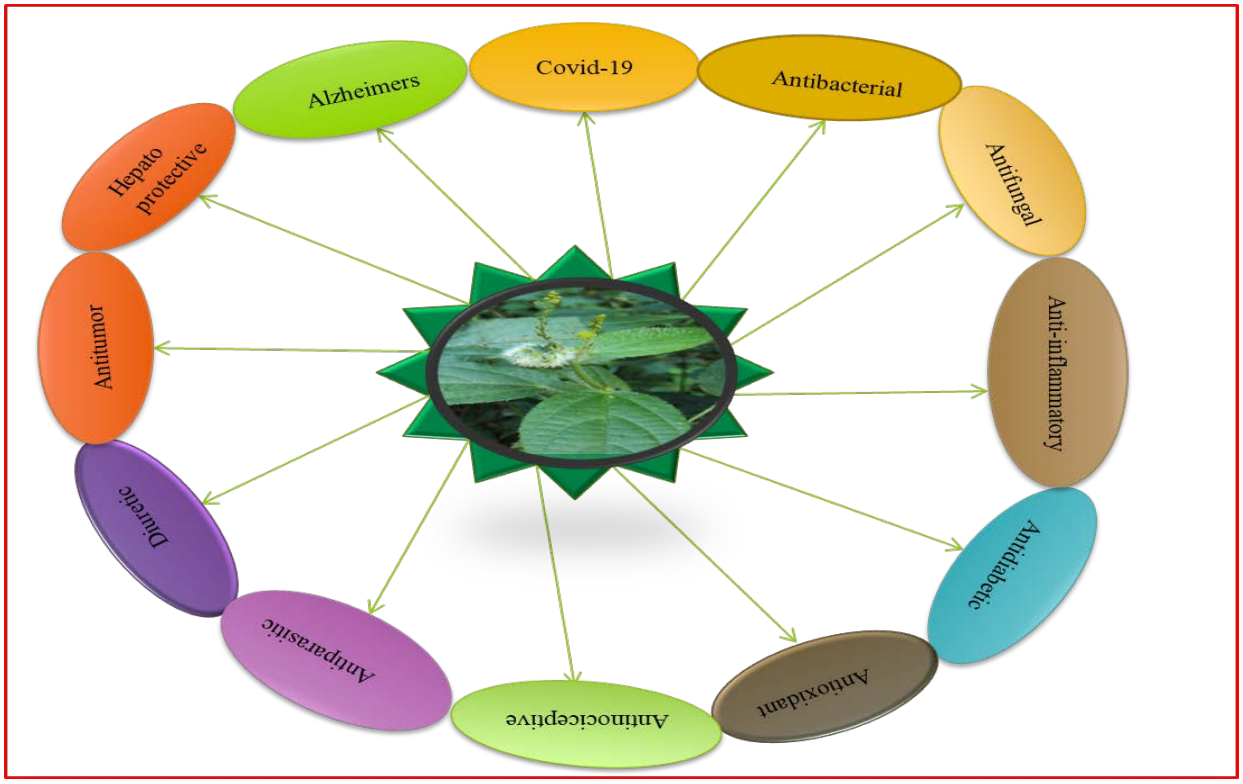

Figure.1. Schematic overview of effect of the pharmacological activities of *Tragia involucrata L.*

Antibacterial activity

T. involucrata, have been evaluated for their ability to inhibit bacterial growth and antibacterial properties. Petroleum ether, chloroform and d. Acetone extracts of *T. involucrata* effectively inhibited the growth of E. coli. The water extract did not exhibit any effect on the growth of E. coli [35– 47]. Alcoholic extracts were effective in inhibiting the growth of *Pseudomonas aeruginosa* and *Vibrio cholerae*. The Shellsol compound was highly effective against in vitro cultures of Staphylococcus aureus. However other species of *Staphylococcus* such as *S. aureus, S. epidermidis and S. saprophyticus* are resistant to Shellosol [48]. However, methanol extracts of *T. benthamii* were not effective in inhibiting the growth of multi-drug resistant bacteria when compared to other medicinal plants such as *Canarium schweinfurthii, Dischistocalyx grandifolius, Fagara macrophylla* and *Myrianthus arboreus* [49]. *T. brevipes* also exhibited antibacterial properties [50].

Antifungal activity

As evidenced from experimental studies, Tragia also has significant antifungal activity. The growth of *Alternaria solani, Rhizopus stolonifera, Aspergillus niger,* and *Tilletia indica* inhibited by extracts of *T. involucrata*. However *Chaetomium globosum* and *Mucor indicus* are resistant [51]. Extracts from the root also exhibited antifungal activity. In vitro cultures of *Malassezia furfurand* and *Trichophyton rubrum* inhibited by root extracts prepared from *T. Involucrata* [52].

Anti-Inflammatory Activity

Extracts from the roots, leaves and whole plant of TI were tested to investigate the anti-inflammatory effect. Experiments were performed on healthy Wistar rats in vivo using carrageenan-induced pawoedema and cotton pellet granuloma methods. Various solvent extracts such as aqueous, methanolic, petroleum ether and chloroform were used. All extracts at tested doses showed positive results both orally and intraperitoneally [53-55]. The active component of shellsol has shown positive results for anti-inflammatory activity [53], and indicates that TI mediates its antibacterial and anti-inflammatory activity via Shellsol.

Antidiabetic Activity

Tragia involucrata (TI) has been used for diabetes in traditional medicine practiced for centuries in South Asian countries. In Sri Lankan traditional medicine, a decoction prepared from the whole plant of TI is used for diabetes mellitus [56]. Traditional medicine rarely uses a plant to make a decoction; hence, it depicts the effectiveness of TI in treating diabetes mellitus. Several studies have been performed to investigate the antidiabetic activity of TI, both in vitro and in vivo and are discussed. In vivo studies have been carried out using diabetic induced rats. The mice were stimulated with alloxan [57], which mimic type I diabetes mellitus, and streptozotocinicotinamide [58], and a high-fat diet and low-dose streptozotocin were used to mimic type II diabetes mellitus. TI extracts showed potent antidiabetic activity in both types, because the effect of insulin on triglyceride metabolism secondarily causes hyperlipidemia, the hypolipidemic activity was also investigated during the same antidiabetic study. TI extracts normalized the values of lipid profile, which shows that TI has insulin-replicating action. An invitro antidiabetic study [59-65] was carried out with leaf extract of TI using α-amylase inhibition assay. The study showed that the extract exerted effective α-amylase enzyme inhibitory activity. α-Amylase is a protein enzyme that hydrolyzes the alpha bonds of large, alpha-linked polysaccharides such as starch and glycogen to yield glucose and maltose. By inhibiting the α-amylase enzyme, the breakdown of polysaccharides is inhibited, thereby inhibiting the digestion of starch and glycogen, and inhibiting the release of glucose into the blood [66]. It is a popular strategy for treating disorders of carbohydrate intake such as diabetes and obesity. To add to the benefits of TI in diabetes, due to its antibacterial activities, TI has shown potent activity against pathogens that cause diabetic foot ulcers and urinary tract infections [67], which are common complications of diabetes mellitus (**Figure.2**).

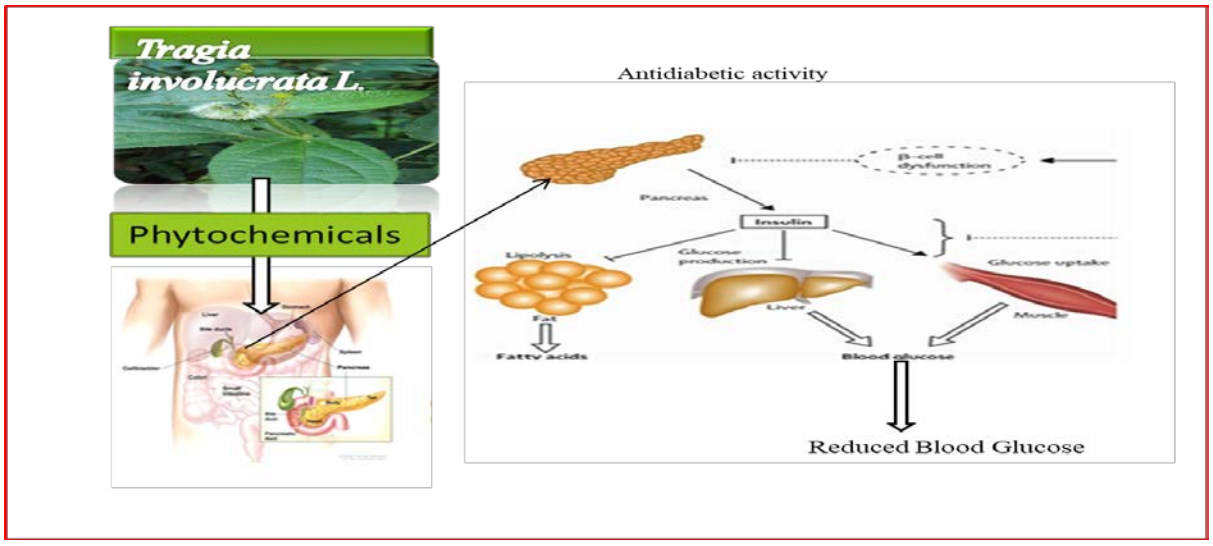

Figure.2. Schematic diagram of effect of the antidiabetic activity of *Tragia involucrata L.* can be inhibit alpha amylase, beta glucosidase activity and stimulate pancreatic cell activity, insulin secrication activity.

Antioxidant Activity

A few antioxidant experiments have been carried out using whole plant and aerial parts of TI. Alcoholic and ethyl acetate extracts were used for the experiments. Most of the research works were performed in vitro studies using methods such as free radical scavenging activity (IC_{50}), ABTS and DPPH radical scavenging methods, Griess reagent method, phosphomolybdenum method, and superoxide dismutase by nitroblue tetrazolium and superoxide radical scavenging method. Alcoholic and ethyl acetate extracts of TI showed potent antioxidant activities [68-81].

Antinociceptive Activity

The analgesic activity of TI was investigated in vivo using acetic acid-induced writing and radian thermal analgesiometer methods. Various solvent extracts of the root and whole plant have been used both orally and intraperitoneally to investigated the activity, which has been proved positively at tested doses [82-84].

Antiparasitic Activity

Various types of parasites have been used to study the antiparasitic activity of TI. Anthelmintic activity was investigated using earthworms and fish worms, and the extracts caused paralysis and death of the worms at tested doses [85,86]. Larvicidal activity of root and leaf extracts of TI using mosquito larvae showed positive results [87,85,89]. Furthermore, phagodeterrence, oviposition inhibition and mosquito repellent activities were also tested on adult female mosquitos and gravid female mosquitoe, which showed positive results [89].

Diuretic Activity

In Ayurveda and traditional Sri Lankan medicine, TI is used in dysuria and other conditions related to the urinary tract. Therefore, the diuretic activity has been evaluated using various extracts from the root and a decoction prepared from the whole plant. Experiments were performed using healthy Wistar rats. The results showed that the activity of aqueous root extract and whole plant decoction was very potent as a diuretic, and other extracts such as petroleum ether and chloroform extracts had mild activities [90].

Antitumor Activity

Hexane and ethyl acetate extracts of aerial parts of TI were used to investigate the antitumor effect in Ehrlich's ascites carcinoma (EAC) bearing mice. The extract was demonstrated to have antitumor activity at tested doses [91]. The cytotoxic activity of aerial parts of TI was investigated in an in vitro test using MTTassay, which showed potent antitumor activity [92]. Also, an in vitro study conducted on Ehrlich's ascites carcinoma-induced albino mice showed anticancer activity of TI ethyl acetate extract [92].

Hepatoprotective activity

The hepatoprotective efficacy of *T. involucreta* has been confirmed in experimental trails in rats. The root extract of *T. involucrata* exhibited dose-dependent hepatoprotective activity in rat models [93]. The capability of compounds from *T. involucrata* to protect hepatocytes is interesting for further studies and the identification and mechanism of action of the lead compound.

Alzheimer’s disease therapy

A network-pharmacology in silico approach to the study of that *T. involucrata* can be a good medicine for Alzheimer's disease theraphy. *T. Involucrata* contains 2-4-dimethylheptane, which is considered a potential natural substance in the treatment of Alzheimer's disease [94].

Covid-19 therapy

T. involucrata is a component of the traditional Siddha medicine Kabhasura Kudineer Chooranam. The phytoconstituents present in Tragia such as Stigmasterol and 3-(2,4-dimethoxyphenyl)-6,7-dimethoxy-2,3-dihydrochromen-4-one, exhibited a moderate activity 26. Based on evidence from in silico studies, Tragia containing Siddha medicince Kabasura Kudineer Choornam may be a potential treatment for covid-19 due to its activity on the spike protein[95].

Conclusion

In conclusion, this review as evidenced from ethnobotanical, traditional medicinal knowledge in various parts of the world, and also the genus of Tragia plays an important role. This review was presented in the hope of finding a medicinal herb that can act on multiple systems of the body and has diverse biological activities. This genus exhibits many medicinal properties and is used in many pharmaceutical preparations. It is critical to understand whether stimulating or inhibiting a common biochemical pathway in all body systems stimulates those functions. Therefore, it would be interesting to explore the mechanism of action of TI in depth to clearly understand its broad therapeutic indications. Since most of the activities are preliminary experiments, it is necessary to conduct randomized controlled human trials to determine whether TI can be used as an ethnomedicine, phytocompounds as a preventive and therapeutic agent.

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