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Review Article

Pharmacological Potential of the Stinging Plant *Tragia* Species: A Review

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ABSTRACT

Tragia is well known in the botanical world a stinging plants. Apart from this, the genus also occupies an important constituent of alternative systems of medicine as well as ethnobotany. Among the various species of *Tragia*, the most studied and experimented species is *T. involucrata.* This genus is used for several ethnobotanical uses such as cancer, diarrhea, constipation, scorpion bite, rheumatism, whooping cough and diabetes. Apart from this the genus is also an important constituent of ayurvedic and siddha medicines. Owing to these properties several researches has been conducted to validate the traditional uses, finding out new uses and understanding the phytochemical profile. Alkaloids, phenols, terpenoids and tannin are present in the genus *Tragia.* Calcium oxalate and shellsol is responsible for the stinging property. Various species of *Tragia* has been validated for its important properties such as antibacterial, antifungal, cytotoxic, wound healing and anti-inflammatory activities. All these properties has been related to the occurrence of secondary metabolites. However the exact lead metabolite for the pharmacological properties has to be identified. Based the experimentally proved pharmacological properties, *Tragia* possesses significant potential on a medicinal species.

Key words: Alkaloids, Antibacterial, *Tragia*, Nanoparticles, Phytochemistry, Pharmacological activities.

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INTRODUCTION

In the recent scenario of emerging diseases and global pandemic, botanicals are gaining a tremendous popularity. Plants serve as a source elements and nutrients for boosting immunity as well as drug molecules. Some of these plants are attractive because of its color, aroma, habit or its ecological role. A few plants are stinging as well. Stinging plants are stinging, an adaptive strategy evolved in plants against herbivores. The reason for stinging is a chemical reaction. It possesses a trichome which act as a hypodermic syringe. Once contacted the trichome breaks and releases the toxins such as shellsol and calcium oxalate leading to itching, pain and inflammation for several days[1].Therefore stinging plants will be a treasure house of valuable secondary metabolites. *Tragia* genus is most celebrated for its stinging activity. *T. involucrata* is the most discussed species of the genus.

BOTANY

Tragia occupies natural flora in the tropical and subtropical areas[2]. The genus *Tragia* are perennial herbs. They climb on host by twining mechanism. The leaves are serrate and palmately trilobed. Leaves are arranged as alternate phyllotaxy. The common species are *T. involucrata* and *T. praetervisa*[3]. *Tragia* belongs to the family Euphorbiaceae. Stinging hairs are present in all the species of the genus. The plant is also recorded from the sacred groves of Kerala[4].

ETHNOBOTANY

The use of *Tragia* as an ethnobotanical medicine has been recorded from several parts of the world. In Ethiopia, *T. brevipes* is used for curing pain of abdomen, diarrhea, anthrax, cancer and babesiosis[5,6,7]. While the local communities of Kenya uses this species for the treatment of rheumatism[8]. In Namibia, *T. okanyua* is used to cure oedema[9]. The indigenous people of Odisha state of India uses the roots and leaves of *T. involucrata* is highly beneficial in curing whooping cough[10]. The people from Karandamalai, Tamil Nadu uses the juice of the root of *T. involucrata* to get relieved from constipation[11]. In West Bengal, the root paste of this species used for the treatment of scorpion sting[12]. The paste made from the seeds are applied on the head to prevent hair loss[12]. Paste is also used to treat alopecia[13]. The people from North East India uses the decoction of *T. involucrata* to cure diabetes[14]. It is also applied to breast tumours[15]. In Uganda, leaf extracts of *T. brevipes* is a traditional herbal remedy for the management of sexual impotence and erectile dysfunction[16,17].

GENERAL MEDICINAL USES

The whole plant as well as root, stem, leaves and fruits has got medicinal properties. In Africa, root decoction of *T. brevipes* is considered as having purgative properties. Root is also useful in reliving labour pain. Rubbing with leaves on joints are useful to treat pain from rheumatism. Leaf decoction is used to treat gonorrhoea, intestinal parasites and

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gastro-enteritis problem. Whole plant is useful in treating polio. Leaves are burnt to ash and inhaled in treating elephantiasis[18]. Roots are useful in treating asthma, fever, skin problems, epilepsy and snakebite[19]. It is also a useful medicine for wound healing[20,21]. 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[22,23]. *T. furialis* is a traditional antimalarial drug[24]. Whole plant is used in the preparation of *Gandarvahasthadi Kwatha* which is used to treat sciatica and back pain[25]. It is also a content of *Kabasura Kudineer Choornam*, a traditional siddha medicine[26].

PHYTOCHEMISTRY

The complete phytochemical profiling and the main active principles are not known from this genus. Based on the few researches available, presence of alkaloids, flavonoids, sterols, saponins essential oils and glycosides has been confirmed[27] (Table 1). Phytochemical analysis of *T. involucrata* confirmed the presence of significant phenol content and tannin content (654 μg g^{-1} dry wt), terpenoid (212 μg g^{-1} dry wt) and alkaloid (375 μg g^{-1} dry wt) [28]. Presence of essential oils like caryophyllene, ethylene glycol mono-tert-butyl ether and geranyl acetone were confirmed from GC MS analysis[29].

Ethyl acetate root extract of *T. involucrata* provided 3-(2, 4-dimethoxyphenyl) - 6,7-dimethoxy -2, 3 - dihydrochro-men - 4 - one, Rutin, Quercetin, and Stigmasterol. Presence of 10, 13-dimethoxy-17-(6-methylheptan-2-yl)-2,3, 4, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17-tetradecahydro-1H-cyclopenta[a]phenanthrene is also confirmed from sepctroscopical studies[30]. Ar- Tumerone; 9, 10 Anthracenedione 1,8-dihydroxy-3-methyl and Friedelane-3-one were identified from the methanol extract[31]. Presence of a pyaran ester derivative, 4-Oxo-4H-pyran-2,6-dicarboxylic acid bis-[6-methyl-heptyl] ester has been confirmed from the chloroform extracts of the roots of *T. cannabina*[32]. GCMS analysis from the ethanolic extract *T. plukenetii* exhibited the presence of a series of compounds such as 1,1-diethoxy-2-methylpropane, 1,1-diethoxy-2-methylbutane, (1-methyl-2- pyrrolidinyl)methanol, (2,2-diethoxyethyl)benzene, 4-(2,4,4-trimethlcyclohexa-1,5-dienyl) but-3-ene-2-one, Neophytadiene, 16-heptadecanal,Neophytadiene, Ethyl linoleolate, Alpha-tocopherol-beta-D-mannoside and Stigmast-5-en-3-ol (3-beta,24S)- Clionasterol[33]. Spectral studies also confirmed the presence of a steroid and an isoquinoline type compounds[33]. Vinyl hexylether, shellsol, 2,4-dimethyl hexane, 2-methylnonane and 2,6-dimethyl heptane were confirmed in *T. involucrata*[20]. NMR and MS studies revealed the presence of 5-hydroxy-1-methylpiperidin-2-one from the leaves of *T involucrata*[34].

Even though 152 species are available under the genus *Tragia*, phytochemical studies has been confined to *T. involucrata*[35,36,37], *T. spathulata*[38], *T. plukenetii*[33], and *T. benthamii*[39].

PHARMACOLOGICAL ACTIVITIES

The genus *Tragia* possesses a wide range of pharmacological activities (Table 2). Most of the studies has been conducted on *T. involucrata.*

Antibacterial activity

Only four species from the genus such as T. *involucrata*, *T. benthamii, T. spathulata* and *T. brevipes* has been evaluated for the ability to inhibit bacterial growth. (Table 3). All these species exhibited antibacterial properties. Petroleum ether, chloroform and acetone extracts of *T. involucrata* were effectively inhibited the growth of *E. coli*. Water extract didn't exhibited any effect on the growth of *E. coli*[27]. Alcohol extracts

Table 1: Phytochemicals extracted and identified from the genus *Tragia*.

Name	Plant species	Reference
1,1-diethoxy-2- methylpropane	*T. plukenetii*	33
1,1-diethoxy-2-methylbutane	*T. plukenetii*	33
10, 13-dimethoxy-17-(6-methylheptan-2-yl)-2,3, 4, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17-tetradeca-hydro-1H-cyclopenta[a] phenanthrene	*T. involucrata*	30
16-heptadecanal,Neophytadiene	*T. plukenetii*	33
1-methyl-2- pyrrolidinyl)methanol	*T. plukenetii*	33
2,2-diethoxyethyl)benzene	*T. plukenetii*	33
2,4-dimethyl hexane	*T involucrata*	20
2,6-dimethyl heptane	*T involucrata*	20
2-methylnonane	*T involucrata*	20
3-(2,4-dimethoxyphenyl)-6,7-dimethoxy-2,3-dihydrochro-men-4-one	*T. involucrata*	30
4-(2,4,4-trimethlcyclohexa-1,5-dienyl)but-3-ene-2-one	*T. plukenetii*	33
4-Oxo-4H-pyran-2,6-dicarboxylic acid bis-[6-methyl-heptyl] ester	*T. cannabina*	32
5-hydroxy-1-methylpiperidin-2-one	*T involucrata*	52
9, 10 Anthracenedione 1,8-dihydroxy-3-methyl	*T. involucrata*	31
Alpha-tocopherol-beta-D-mannoside	*T. plukenetii*	33
Ar-Tumerone	*T involucrata*	31
Ethyl linoleolate	*T. plukenetii*	33
Friedelane-3-one	*T. involucrata*	31
Neophytadiene	*T. plukenetii*	33
Quercetin	*T. involucrata*	30
Rutin	*T. involucrata*	30
shellsol	*T. involucrata*	20
Stigmast-5-en-3-ol (3-beta,24S)- Clionasterol	*T. plukenetii*	33
Stigmasterol	*T. involucrata*	30
Vinyl hexylether	*T. involucrata*	20

Table 2. Summary of the pharmacological activities of the genus *Tragia*.

Pharmacological properties	References
Alzheimer's disease therapy	63
Analgesic	21,33
Antarthritic and haemolytic	56
Antibacterial	20,21,27,41,42
Anticonvulsant	55
Antifungal	28,30
Antihistamine	52
Anti-inflammatory	21,33
Antioxidant	59
Antiurilithiatic	49
Covid 19 therapy	26
Cytotoxic	58
Diuretic	47
Filaricidal	48
Hepatoprotective	54
Psychopharmacological	44
Radical scavenging	51,52,53
Wound healing	30

Table 3: Antibacterial activity of various species of *Tragia* species.

Sample	Plant part	Species	Bacteria	Reference
2,4-dimethyl hexane 2-Methylnonane 2,6-dimethyl heptane Vinyl hexylether Shellsol	Leaves	*T. involucrata*	*Escherichia a coli* *Proteus vulgaris* *Staphylococcus aureus*	20
Methanol: water extract 9:1	Leaves	*T. brevipes*	*Bacillus cereus* *Enterobacter aerogenes* *Escherichia coli* *Salmonella sp* *Serratia liquefaciens* *Prpteus vulgaris*	42
Ethyl acetate extract Methanol extract Petroleum ether extract	Roots	*T. involucrata*	*Bacillus brevis* *Bacillus subtilis* *Escherichia coli* *Staphylococcus aureus* *Shigella dysenteirae Pseudomonas aeruginosa* *Staphylococcus epidermidis* *Vibrio cholera*	30
Ethanol extract Methanol extract Acetone extract	Leaves	*T. spathulata*	*Escherichia coli* *Klebsiella pneumoniae Salmonella typhi* *Proteus mirabilis* *P. aeruginosa* *Staphylococcus aureus* *Staphylococcus pneumonia*	38
Methanol extract	Whole plant	*T. benthamii*	*Pseudomonas aeruginosa* *Klebsiella pneumoniae* *Enterobacter aerogenes* *Escherichia coli* *Providencia stuartii*	41
Acetone extract Chloroform extract Ethanol extract Methanol extract Petroleum ether extract	Leaves	*T. involucrata*	*Escherichia coli* *Proteus mirabilis* *Staphylococcus aureus* *Serratia marcescens*	40
Acetone extract Chloroform extract Ethanol extract Methanol extract Petroleum ether extract	Leaf, root, stem and flower	*T. involucrata*	*Escherichia coli*	27

was effective in inhibiting the growth of *Pseudomonas aeruginosa* and *Vibrio cholera*. The compound shellsol was very effective against *in vitro* cultures of *Staphylococcus aureus*[20,21]. However other species of *Staphylococcus* such as S. *aureus*, *S. epidermidis* and *S. saprophyticus* were resistant to shellosol[40]. However methanol extracts of *T. benthamii* were not effective in multi drug resistant bacterial growth inhibition when compared to other medicinal plants such as *Canarium schweinfurthii, Dischistocalyx grandifolius, Fagara macrophylla* and *Myrianthus arboreus*[41]. *T. brevipes* also exhibited antibacterial properties.[42]

Antifungal activity

Tragia also possesses significant antifungal activity as evidenced from the experimental studies. Growth of *Alternaria solani, Aspergillus niger, Rhizopus stolonifera and Tilletia indica* were inhibited by the extracts from *T. involucrata*. However *Chaetomium globosum* and *Mucor indicus* were resistant[28]. Extracts from root also exhibited antifungal activity. *In vitro* cultures of *Malassezia furfurand* and *Trichophyton rubrum* were inhibited by root extracts prepared from *T. involucrata* [30].

Wound healing property

Shellsol obtained from the leaf extracts of *T. involucrata* exhibited ability to facilitate healing of wound. When shellsol fed to rats at a dosage of 50 μg/kg body weight complete healing was observed after 24 days[21]. This observation was further supported by histological evidences[21]. This finding justifies the use of *Tragia* as a wound healing botanical.

Analgesic and anti-inflammatory activity

T. involucrata possesses both analgesic as well as anti-inflammatory properties. The aqueous (leaves) and methanol (root) extracts were experimentally proved to have these properties in animal models [20,21,43]. Maximum effect on healing of oedema was found in aqueous extracts[20,21].

Psychopharmacological properties

Psychopharmacological experimental studies were conducted in rodents with methanol extracts from the roots obtained from *T. involucrata*[44]. This study revealed that treated rats possesses less aggressive behaviour along with conditioned avoidance response. The extracts also induced sleep. An altered behaviour coupled with reduced motility of animal was revealed. The research concluded that these properties are due to the loss of central nervous system function[44].

Toxicity

Animal studies on rats confirmed that there is no evidence of toxicity as evidenced from biochemical markers. The experimental animals treated with extracts obtained from *T. plukenetii* didn't exhibited significant change in hepatic enzyme and hematological parameters[45].

Diuretic activity

Diuretic drugs may induce complications in patients. Therefore, it is logical to use a herbal drug[46]. Hot water extract from the whole plant of *T. involucrata* exhibited significant diuretic properties. *T. involucrata* hot water extract acted as a loop diuretic as evidenced from the enhanced Na^+ and K^+ in urine samples coupled with reduced urine pH[47].

Filaricidal properties

Tragia is used in the North West Region of Cameroon for the treatment of onchocerciasis. Therefore, the species was evaluated for filaricidal property *T. benthamii* exhibited filaricidal activity. Among the various extracts tested, hexane extracts from roots were only active against the parasite *Onchocerca ochengi*. However, this activity was not significant compared to extracts from *Piper umbellatum*[48].

Anti-urilithiatic activity

Investigation on the Water extracts of *T. involucrata* confirmed the anti-urilithiatic properties[49]. The extract was rich in secondary metabolites such as phenols, flavonoids and terpenoids. In addition to the above properties discussed, extracts of *T. plukenetii* exhibited properties to inhibit steel corrosion[50].

Radical scavenging activity

Samples obtained from T. involucrata exhibited superoxide, DPPB and ABTS radical scavenging activity[51-53]. Root and leaf segments from *T. involucrata* were subjected for extraction using methanol and the DPPH and ABTS radical scavenging activity were measured. This has been correlated to the presence of secondary metabolites such as flavonoids and phenols[34,53]. Essential oils from *T. benthamii* exhibited potential of radical scavenging activities[29].

Antihistamine properties

Chromatographic fractions from the leaf extracts of *T. involucrata* were further separated and characterized by various spectroscopic techniques. Among this 5-hydroxy-1-methylpiperidin-2-one compound exhibited potential antihistamine properties[34]. Further investigations in this direction are essential for purifying the underlying mechanisms.

Hepatoprotective activity

Hepatoprotective effect of *T. involucrata* has been confirmed in experimental trails in rats. Root extract of *T involucrata* exhibited dose dependent hepatoprotective activity in rat models[54]. The ability of protecting hepatocytes by the compounds from *T. involucrata* are of interesting for further studies and identification of the lead compound as well as the mechanism of action.

Anticonvulsant activity

Extracts from leaf segments of *T. plukenetii* exhibited anticonvulsant properties as evidenced from the mice models. The results generated from the animal models are convincing towards the further research as well as the use of *T. plukenetii* as a drug for the treatment of tonic-clonic phases of muscle activity[55].

Anti-arthritic and haemolytic properties

Experimental evidence suggests a significant potential towards anti-arthritic property of *T. involucrata.* Protein denaturation assay revealed that chloroform extract and petroleum ether extract possessed significant anti-arthritic activity. The study also revealed that extracts made from the leaves of *T. involucrata* are non-hemolytic[56].

Tragia based nanoparticles

Researchers has used green chemistry method to synthesize silver as well as platinum nanoparticles from the extracts of *T. involucrata.* The results confirmed these nanoparticles exhibited a wide spectrum activity.

Silver nanoparticles[49,57,58]

Studied on Human leukaemia MOLT-4 cell lines treated with silver nanoparticles produced from the extracts of *T. involucrata* revealed a significant cytotoxic potential, antimicrobial as well as antiangiogenic activity. The silver nanoparticles were rod shaped and particle size was found to be less than 100 nm[58]. Animal models using silver nanoparticles exhibited anti-urolithiatic activity and confirmed the potential of *Tragia* in the treatment of urinary stones[49].

Platinum nanoparticles

Platinum nanoparticles prepared from the leaf extracts of *T. involucrata* exhibited antioxidant activities[54]. The nanoparticles prepared from the leaf extract of *T. involucrata* also exhibited significant antibacterial activity against gram positive and gram negative bacteria. It was also found an enhanced protein leakage in bacteria. Potential cytotoxic activity was also confirmed from these nanoparticles. These nanoparticles were spherical and possessed a particle size of 10 nm. The research study was conducted on HeLa cell lines[59].

Alzheimer's disease therapy[60]

Network-pharmacology *in silico* approach study found that *T. involucrata* can be a good medicine for Alzheimer's disease therapy. *T. involucrata* also contains 2-4-dimethylheptane which is considered as a potential natural product in the therapy of Alzheimer's disease[60].

Covid-19 therapy

T. involucrata is a constituent of the traditional Siddha drug *Kabasura Kudineer Choornam*. The phytochemicals 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 the evidences from *in silico* studies, *Tragia* containing Siddha medicine *Kabasura Kudineer Choornam* may be potential for Covid-19 therapy because of the affinity towards spike protein.

CONCLUSIONS

The genus *Tragia* occupies an important role as evidenced from the ethnobotanical knowledge in various parts of the world. The genus exhibits several medicinal properties and is used in several drug preparations. The experimental evidences are pointing to the fact of activity directed fractionation and identification of the lead compounds. Also it is interesting to raise *in vitro* cultures and characterization of the secondary metabolites from these cultures. Various species of *Tragia* has been experimentally proved that it possesses several pharmacological properties. Based on these experimental evidences discussed, it is quite interesting for further investigation and understanding the exact mechanism of action. The demand of the species for drug preparations may also lead to a threat for the natural populations. Therefore, both *ex situ* and *in situ* strategies for conservation are highly beneficial in saving the germplasm for future generation.

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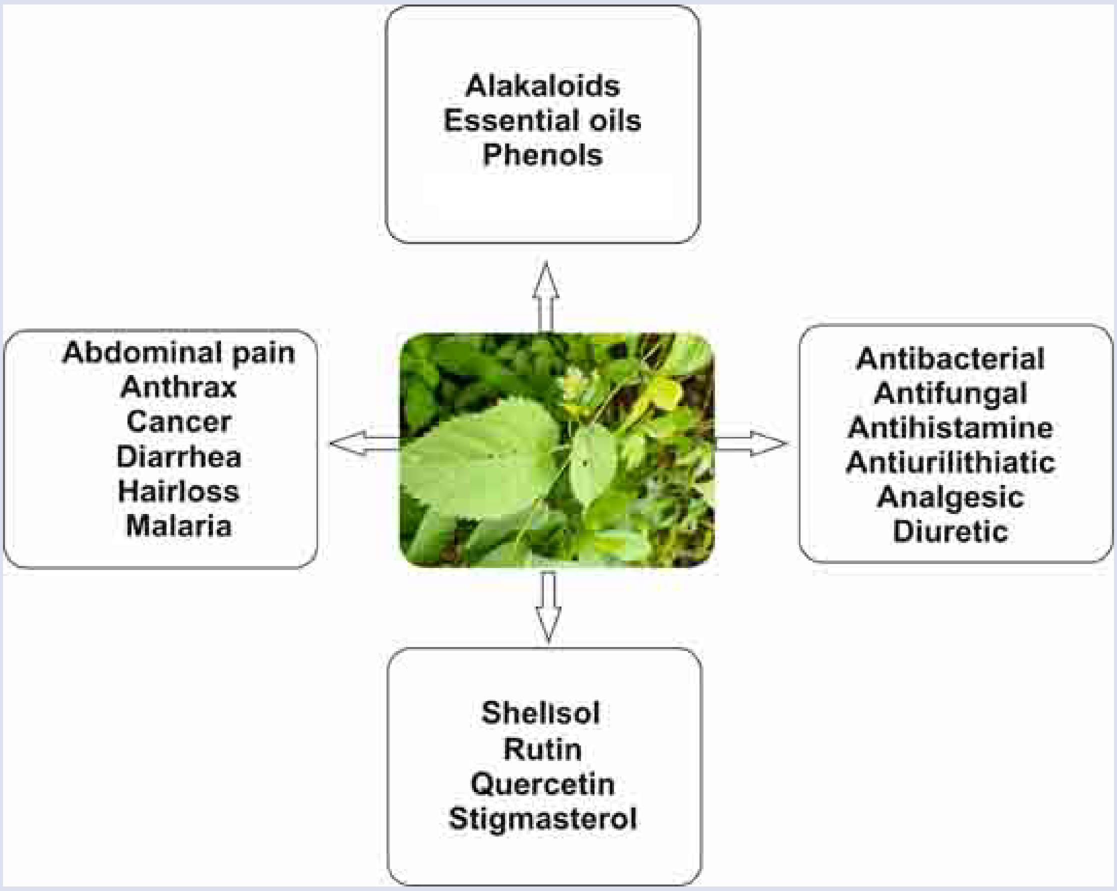
GRAPHICAL ABSTRACT



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