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PHYTOCHEMICAL, PHARMACOLOGICAL AND BIOLOGICAL PROFILES OF TRAGIA SPECIES (FAMILY: EUPHORBIACEAE)

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Abstract

Background: Tragia belongs to the family Euphorbiaceae which contains about 152 species. Interestingly, most of the earlier investigations have been done using only five Tragia species, namely, *Tragia involucrata, Tragia cannabina, Tragia spathulata, Tragia plukenetii,* and *Tragia benthamii*. The objective of the present review is to compile the phytochemical, pharmacological and biological studies of the selected five Tragia species reported in the literature.
Methods: The reported data/information was retrieved mainly from the online databases of PubMed (MEDLINE), EMBASE and Botanical Survey of India.
Results: The present review elaborated the phytochemical, pharmacological and biological properties of the selected five Tragia species obtained from recent literature.
Conclusion: This review provides a basis for future investigation of Tragia species and, especially for those species that have not been explored for biological and pharmacological activities.

Key words: Euphorbiaceae; *Tragia involucrata; Tragia cannabina; Tragia spathulata; Tragia plukenetii; Tragia benthamii*

Introduction

Herbs having medicinal properties are commonly used as herbal tonics which mostly contain peppermint, ginger, garlic, nettles, lemon, balm etc. (Winston and Nvwoti, 1992). According to the Dietary Supplement Health and Education Act, 1994 of the US, herbal medicines are classified as food supplements (Klepser and Klepser, 1999). Herbal medicines are used in daily life to treat a simple common ailment to life threatening diseases. The Indian subcontinent and Africa have long been recognized as an herbal hub and a variety of herbal medicines in different formulations have been used for several years. Furthermore, ancient India had given divine Vedas (Rigveda, Yajurveda, and Atharvaveda) and Samhitas (Charak Samhita and Sushrut Samhita) which describes the medicinal properties and uses of many herbal species. Kushagara et al., (2011) conducted a study about different health care systems practiced in India on 492 people. The outcome of this study revealed that Ayurveda, allopathy and homeopathy were practiced in 41, 31 and 28% of the studied population respectively. Increasing population size, drugs insufficiency, higher cost, severe adverse effects and ineffectiveness of many allopathic drugs, escort to the significance of herbal medicines to combat many diseases (Panda et al., 2012). Most of the drugs available in the market are mainly isolated from the herb source. For example, vincristine, vinblastine from *Catharanthus roseus*, podophyllotoxin from rhizomes of Phodophyllum species, palcitaxol from *Taxus brevifolia* used in cancer chemotherapy, digitoxin from the *Digitalis purpurea* in cardio protective therapy, caffeine from *Camellia sinensis*, codeine and morphine from the *Papaver somniferum* for central nervous system activities (Moss et al., 2006).

India and Africa are enriched with a variety of different species of medicinal plants, however, many plant species are not fully explored. Tragia, one among the plant species has to be further explored by the scientific community. People from the folklore have been using Tragia species to treat variety of ailments since many years ago Recently, an increasing attention has been drawn to Tragia species because of the identification of multiple bioactive phytoconstituents and their numerous biological and pharmacological activities. The focus of this short review is to elaborate the total phytochemical constituents and pharmacological activities reported for the selected species of Tragia. The reported data were retrieved up to November 2016 mainly from online databases PubMed (Medline) and EMBASE by using the key word, 'Tragia' which resulted in 21 and 58 results respectively. For additional information, Botanical survey of India database was referred.

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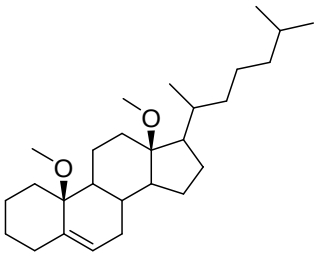
Taxonomy

Kingdom: Plantae
Phylum: Mangoleophyta
Class: Mangoliopsida
Order: Malpighiales
Family: Euphorbiaceae
Genus: Tragia
Species: *T. involucrata, T. cannabina, T. spathulata, T. plukenetii, and T. benthamii*

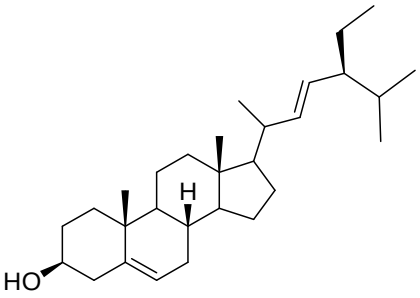
Worldwide distribution of Tragia species: Somalia, Ehiopia, Kenya, India, and Tanzania

Tragia involucrata

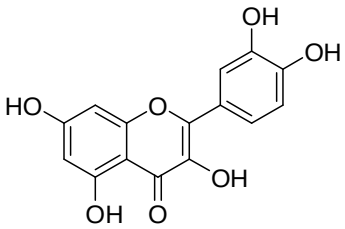
T. involucrata is a shrub, widely distributed in the Indian subcontinent and grows in dry land weed. It is found to have enormous medicinal properties and have been used by the Malaiyali tribes of Western Ghats of India. The preliminary phytochemical screening results revealed the presence of alkaloids, carbohydrates, protein, tannins, flavonoids, sterols and saponins in the different extracts of *T. involucrata* (Table 1) (Dash et al., 2000). Several colorless phytocompounds have been isolated and characterized from *T. involucrata* such as vinyl hexylether, shellsol, 2,4-dimethyl hexane, 2-methylnanone, and 2,6-dimethyl heptane. In addition, five other different compounds, namely; TIR-01, TIR-02, TIR-03, TIR-04 and TIR-05 has been identified in the ethyl acetate extract of *T. involucrata* as shown in figure 1 (Panda et al., 2012).



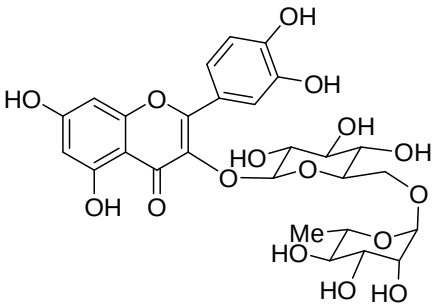
10, 13-dimethoxy-17-(6-methylheptan-2-yl)-2, 3, 4, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17-tetradecahydro-1H-cyclopenta[a]phenanthrene (TIR-01)



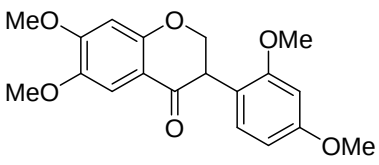
Stigmasterol (TIR-02)



Quercetin (TIR-03)



Rutin (TIR-04)



3-(2,4-dimethoxyphenyl)-6,7-dimethoxy-2,3-dihydrochro-men-4-one (TIR-05)

Figure 1: Structures resulted from the ethyl acetate extract of *Tragia. involucrata* (Panda et al., 2012).

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Table 1: List of phytochemical constituents of Tragia species

Tragia Species	Parts of plants used	Extract	Phytochemical constituents								Reference
			Alkaloid	Glycoside	Reducing sugar	Tannin	Protein	Flavonoid	Sterols	Saponin	
T. involucrata	Leaf	Ethanol	+	+	-	-	-	+	+	-	Sathish, 2013
	Root	Petroleum ether	-	-	-	-	-	-	+	-	Dash et al., 2000
		Chloroform	+	-	-	-	-	-	+	-	
		Ethyl acetate	+	-	-	-	-	-	-	-	
		Methanol	-	-	+	+	-	+	-	+	
		Water	-	-	+	+	+	+	-	+	
T. cannabina	Whole plant	Chloroform	-	-	-	+	-	+	+	-	Raju, 2012
		Methanol	+	-	-	+	-	-	-	-	
T. spathulata	Leaf	Ethanol	+	+	-	-	-	-	-	-	Ogundare and Olorunfemi, 2007
		Methanol	+	+	-	-	-	-	-	-	
		Acetone	+	+	-	-	-	-	-	-	
T. plukenetii	Leaf	Ethanol	+	+	-	+	-	+	+	+	Daniel, 1991
T. benthamii	Whole plant	Ethanol	+	-	+	+	-	-	-	+	Oladosu et al., 2013

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T. involucrata leaf has been traditionally used to treat inflammation, wounds, eczema, scabies and skin infections. It has also been found to be effective in treating pain and bronchitis (Kirtikar and Basu, 1987). The *T. involucrata* root has been traditionally used for the treatment of high fever. It reduces the elevated body temperature to normal by its diaphoretic action. Besides, the antimicrobial activity of *T. involucrata* root/leaf extracts have been reported against *P. vulga*ris, *E. coli*, (Gram-negative bacteria) and *S. aureus* (Gram-positive bacteria) with disc diffusion techniques (Gopalakrishnan et al., 2006, Sathish et al., 2013). Recently, the methanolic extract *T. involucrata* has been found to be very effective in treating foot ulcer pathogens obtained from diabetic patients *(*Subbu Lakshmi et al., 2016).

Acute oral toxicity studies in mice revealed that the methanolic extract of root/leaf was found to be safe with doses up to 2000 mg/kg (Dhara et al., 2000). The methanolic extract of root/leaf of *T. involucrata* has also been reported for anti-inflammatory activity in carrageenan-induced rat paw edema model. Similarly, the anti-inflammatory activity of the methanolic extract of root/leaf of *T. involucrata* was further confirmed by cotton pellet granuloma technique. In addition, the same author reported the analgesic activity of root/leaf of *T. involucrata* and postulated that the analgesic activity of *T. involucrata* was mediated by the inhibition of prostaglandins sensitized pain receptors at the inflammatory site (Dhara et al., 2000). Recently, root extracts of *T. involucrata* have been reported for hepatoprotective activity against CCl_4 –induced hepatotoxicity in rats (Alanazi et al., 2015). Moreover, ethanolic leaf extract of *T. involucrata* exhibited a significant antibacterial activity against opportunistic pathogens namely *E. coli*, *S. aureus*, *P. mirabilis and S. marcescens* isolated from clinical cases of suspected symptomatic HIV/AIDS patients. (Xavier et al., 2015). Recently, Sulaiman and Balachandran (2016) evaluated for antioxidant potential of butanolic fractions (Fr B1, Fr B2, Fr B3, Fr B4 and Fr B5) of *T. involucrata* aqueous-methanolic extract using *in vitro* DPPH radical scavenging assay. Their findings revealed that the fractions (Fr B3 and Fr B4) exhibited significant free radical scavenging activity with EC50 of 4.58 and 4.26 µg/ml respectively. It has been further confirmed the presence of flavonoids such as iridin, dihexosyl quercetin, quercetin-3-O-rutinoside, rhamnosyl hexosyl methyl quercetin, gentenstein 7-glucoside for FrB3 and orientin, C-(O-caffeoyl-hexosyl)-O-hexoside and tricin 7-O-hexosyl-O-hexoside for FrB4 (Sulaiman and Balachandran, 2016). The isolated compounds from *T. involucrata* root has also been reported for antimicrobial and wound healing activities. The isolated compounds from the methanolic extract of *T. involucrata* root or leaf, shellsol and vinyl hexyl ether have been reported for their antimicrobial activity against *S. aureus* with effective MIC (minimum inhibitory concentrations) of 0.182, 0.198 µg/ml, respectively (Gopalakrishnan et al., 2013). Furthermore, the shellsol purified from *T. involucrata* leaf has been studied topically for wound healing activity in rats. The percentage of wound healing effect was gradually increased by the shellsol (10g/kg) from 4th to 16th day, but the higher wound healing effect was observed on the 20th day (83.2%) and 24th day (88.18%) when compared to the vehicle treated control group (only 50% healing). The other compounds isolated from *T. involucrata,* namely 2-methylnonane, 2,4-dimethyl hexane and 2,6- dimethyl heptane exerted only a weak activity against the *S. aureus and P. vulgaris* (Gopalakrishnakone et al., 2006b, 2006c) . In another study, the hydrocarbon esters such as shellsol, vinyl hexylether, and 2, 4-dimethyl hexane isolated from *T. involucrata* showed a potent antimicrobial and anti-inflammatory activities and suggested that it could be effective to control the growth of certain food-borne and food-spoilage pathogens (Samy et al., 2013). Recently, antihistaminic activity of 5-hydroxy-1-methylpiperidin-2-one, an isolated phytocompound from the leaf of *T. involucrata* has been established using *in vivo*, *ex vivo* and *in silico* studies and demonstrated the therapeutic potential in treatment of asthma (Alagar Yadav et al., 2015). Farook and Atlee (2011a) demonstrated the antidiabetic activity of the alcoholic extract of *T. involucrata* root/leaf in rats and showed a significant decrease in the rate of intestinal glucose absorption thereby resulting in improved glucose tolerance. Administration of a single oral dose of 500 mg/kg of aqueous extract of *T. involucrata* root/leaf (AETI) showed a significant reduction in blood glucose level. It has been proposed that the reduced glucose transport, extra pancreatic action or decreased activity of glycolytic enzymes could be the possible mechanisms of action of *T. invalucrata* (Farook and Atlee, 2011a). This was further confirmed by a series of enzymatic assays to detect the free radical scavenging property of AETI. Lipid peroxidation is commonly observed in streptozotocin *(*STZ*)* and nicotinamide (*NA*) - induced diabetic rats. The diabetic animals significantly decreased the antioxidant enzyme levels, such as SOD, CAT, GPx and GSH in liver and kidneys (Farook and Atlee, 2011b). The extracts of *T. involucrata* leaf significantly enhanced these natural antioxidant enzymes in diabetic animals and demonstrated the therapeutic potential against diabetes and its associated complications (Farook and Atlee, 2011b). Recently, an *in vitro* study revealed that aqueous, ethyl acetate, and chloroform extracts of *T. involucrata* leaf dose-dependently inhibited α-amylase activity using dinitrosalicylic acid (DNS) method and demonstrated for its antidiabetic effect (Vinodhini et al., 2015). In another study, hexane and ethyl acetate extracts of aerial parts of the *T. involucrata* was reported for anticancer activity. This study revealed the optimum anticancer activity of these extracts on Ehrlich's Ascites Carcinoma (EAC) model and demonstrated the involvement of antioxidant property of *T. involucrata* in the anticancer activity (Jayaprasad et al., 2012). A recent study by Bhattacharya and Chandra (2014) demonstrated the mosquitocidal activity of *T. involucrata* root extracts against Culex quinquefasciatus (female mosquito) in Phagodeterrence test. In that study, they used different extracts of *T. involucrata* root like chloroform: methanol (1:1 v/v), petroleum ether: ethyl acetate (1:1 v/v), benzene: ethyl acetate (1:1 v/v), acetone: absolute alcohol (1:1 v/v). It was found that chloroform: methanol (1:1 v/v) extract showed a significant mosquitocidal activity (Bhattacharya and Chandra, 2014). Furthermore, CNS depressant activity of methanolic extract of *T. involucrata* (MTI) leaf was reported using a battery of neuropharmacological studies in rodents which demonstrated a significant reduction in spontaneous locomotor activity, a significant potentiation of

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pentobarbitone-induced sleep, a significant depression of body temperature and suppression of the aggressive behavior pattern (Chaudhuri et al., 2002). It has been hypothesized that the CNS depressant activity of MTI could be mediated through a $GABA_A$-cascade signalling mechanism similar to mechanism of actions of benzodiazepines like diazepam. Similarly, the antiepileptic activity of methanolic leaf extract of *T. involucrata* Linn. in mouse models of maximal electroshock-induced convulsions (MES), pentylenetetrazole (PTZ) and picrotoxin (PTX) -induced convulsions was reported (Ganapathi et al., 2014). These authors also hypothesized that the GABAergic mediated mechanism of the methanolic leaf extract of *T. involucrata* Linn. could be responsible for the antiepileptic activity. Taken together, it has been suggested that MTI produced CNS activities mediated through GABAergic mechanism (that is opening of chloride channels associated with $GABA_A$ receptors).

Tragia cannabina

The vernacular name of *T. cannabina*, in Tamil is cherukanjuru or Karunchenthatti. Preliminary phytochemical analysis revealed the presence of tannins, flavonoids, sterols, and alkaloids in different extracts of *T. cannabina* leaf/root (Table 1). Methanol and chloroform extracts of whole plant of *T. cannabina* showed anti-inflammatory activity in Sprague-Dawley rats using carrageenan-induced paw edema model (Raju et al., 2012). This study revealed that the percentage inhibition of carrageenan-induced paw edema by methanolic extract (300 mg/kg, p.o.) and chloroform extract (300 mg/kg, p.o.) of *T. cannabina* was found to be 37.5% and 17.05%, respectively, which were comparable to the reference drug, ibuprofen (55.69%) (Raju et al., 2012). The sub-acute toxicity studies of alcoholic extract of *T. cannabina* leaf revealed that a dose of 125, 250, and 500 mg/kg body weight every 24 h for 28 days respectively, did not show any signs of toxicity and mortality in the experimental animals. Surprisingly, it was observed that the overall well-being of treated animals was improved by evidence of increasing body weight and higher food intake (Patel et al., 2012). Ethanolic extract of *T. cannabina* leaf at an oral dose of 250 mg/kg, showed remarkable antihyperglycemic and antioxidant effects in STZ-induced diabetic rats. This study also confirmed the nontoxic properties of the ethanolic extract of *T. cannabina* leaf (Sivajothi et al., 2007). Moreover, the antidiabetic effect of an isolated phytocompound, 4-oxo-4H-pyran-2,6-dicarboxylic acid-bis-[6-methyl-heptyl] ester from *T. cannabina* have been demonstrated using *in vitro* streptozotocin (STZ) -treated chick embryo and *in silico* docking studies targeting active sites of AMPK (Sivajothi and Dakappa, 2014).

Tragia spathulata

T. spathulata is slender turner, armed with stinging hair. Its leaf relieves symptoms of stomachache, backache and also prevents measles in infants (Sofowora, 1982). Phytochemical screening of ethanolic, methanolic and acetone leaf extracts of *T. spathulata* resulted in the presence of alkaloids and glycosides (Table 1). *T. spathulata* showed antibacterial effect against *S. aureus, P. mirabilis, K. pneumonia, S. typhi, S. pneumonia, E. coli, C. albicans, A. flavus* and *A. fusarium.* It has been postulated that the antimicrobial activity of *T. spathulata* could be due to the presence of alkaloids and glycosides (Ogundare and Olorunfemi, 2007).

Tragia plukenetii

The vernacular names of *T. plukenetii* R. Smith in Telugu and Marathi are duradagondi and churchuri respectively. It is widely distributed in India, Somalia, Ethiopia, Kenya and Tanzania**.** It has unisexual flowers with hairy racemes and 3-lobed-capsules with globose seeds. The leaf is palmately 3-partite, pinnatifid. Traditionally, this plant has been used to treat sore throat (Yoganarasimhan, 2000). The medicinal properties of ethanolic extract of *T. plukenetii* leaf is due to the presence of phytoconstituents like alkaloids, carbohydrates, flavonoids, glycosides, sterols, saponins and tannins reported in the literature as shown in Table 1. Flavonoids are widely distributed in *T. plukenetii* in the form of glycosides. Leo Stanley et al. (2012) reported the presence of about 16 miscellaneous compounds in *T. plukenetii* and extracted the steroid (TP-I) and isoquinoline (TP-II) as shown in figure 2. Minor flavonoids aurones (sulpheretin), chalcones (butein) and flavanones (naringin), and major flavonoids include quercetin, kaempferol and myricetin have also been reported (Leo Stanley et al., 2012). Quercetin helps in reducing aggregation of erythrocytes (Daniel, 1991) and in the treatment of capillary fragility. It has been demonstrated for antioxidant and antiulcer activities (Parmar and Shikha, 1998). The antitumor activity of *T. plukenetii* leaf extracts using Ehrlich ascites carcinoma (EAC) tumor model have been reported. It has been proposed that antioxidant property of *T. plukenetii* could be involved in its antitumor activity (Meenakshi et al., 2008). Similarly, the contribution of antioxidant property of *T. plukenetii* in its antihyperglycemic effect has been demonstrated by Venkatesh et al. (2014).

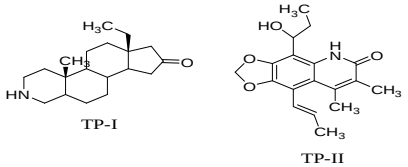

Figure 2: Structures resulted from the ethanolic extract of *Tragia plukenetii* (Leo Stanley et al., 2012).

A review by Gupta and Jain (2010) revealed the wound healing effect of the ethanolic extract of *T. plukenetii* in albino rats. In the same review, it has also been described about the wound healing and antimicrobial activities of the methanolic extracts of root and leaf of *T. plukenetii* (Gupta and Jain, 2010). It has been proposed that the presence of higher amount of phenols and flavonoids in *T. plukenetii* could be responsible for its wound healing activity (Gopalakrishnakone et al., 2006a; 2006b). Kalaivanan and Jesudass (2012) reported for antipyretic and diuretic activities of *T. plukenetii* leaf extracts. *In vivo* study using Guinea pig revealed the antiasthmatic effect of *T. plukenetii* leaf extracts. Similarly, an *ex vivo* study using rabbit jejunum demonstrated antispasmodic activity of *T. plukenetii*. These studies explained that the presence of saponins in the extract could be responsible for its antiasthmatic activity (Kalaivanan and Jesudass, 2012).

The oral administration of *T. plukenetii* leaf extract was found to be effective in treating gonorrhea and tapeworm infestation and other pathogens, thereby treating gastroenteritis and stomachache (Meenakshi et al., 2005). A review by Chavre et al. (2010) reported that the seed powder of *T. plukenetii* with milk is recommended to control the blood glucose in diabetic patients. Similarly, the other parts such as root, twigs and leaf are used to treat polio. The root has helped out in male impotency (Chavre et al., 2010). On the inhalation of the burnt leaf, elephantiasis can be controlled (Chavre et al., 2010). The leaf of *T. plukenetii* plays a key role in treating uterine complaints and also in relieving skin irritation (Leo Stanley et al., 2012, Kirtikar and Basu, 1987, Chandra Kumar et al., 2011). Venkatesh and Fatima (2013) evaluated the antinociceptive effect of ethanolic, petroleum ether, chloroform, ethyl acetate and butanolic extracts of *T. plukenetii* leaf. Interestingly, chloroform extract (68.83%) alone produced a significant antinociceptive effect which was comparable to the reference drug, aspirin (72.09%). Based on a naloxone interaction study, it has been proposed that the possible mechanism of action of *T. plukenetii* was not mediated through opioid receptors, but it could be due to the activation of peripheral receptors (Venkatesh and Fatima, 2013).

Tragia benthamii

Tragia benthamii Baker is widely available in West, Central and Southern Africa. Its root extract is used as an abortifacient and to ease the delivery of the child and also used to treat gonorrhoea (Schmelzer and Gurib-Fakim, 2008). The antimalarial activity of ethanolic extract of *T. benthamii* against *P. berghei* (NK-65) was reported and the results were comparable to the reference drug, chloroquine (Oladosu et al., 2013). At a recent conference proceeding, it has been reported for the therapeutic potential of *T. benthamii*, one of the Nigerian medicinal plants for the treatment of migraine and common headache and suggested that it could be utilized for the development of novel drug discovery in the treatment of migraine (Saganuwan, 2014). Currently, there is only very limited information of *T.benthamii* about its biological and pharmacological actions available. Phytochemical analysis using GC/GC-MS of volatile oil from hydro distilled leaf of *T. benthamii* revealed the presence of caryophyllene, caryophyllene oxide, ethylene glycol mono-tert-butyl ether and hexahydrofarnesyl acetone. It has been found that the volatile oil from *T. benthamii* leaf exhibited higher free radical scavenging activity (42.4%) than the reference standard, ascorbic acid (13.8%) in the DPPH scavenging assay (Olaoye et al., 2016). Therefore, further studies focusing on isolation and characterization of bioactive compounds and establishing their biological and pharmacological actions are warranted.

Conclusion

This review provides a basis for the future investigation using Tragia species, especially for those species that have not been much explored for isolation and standardization of bioactive compounds, and pharmacological activities. Further studies on Tragia species are warranted to identify the active phytoconstituents responsible for various biological and pharmacological activities.

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