Tragia L. Genus

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Tragia L. is a genus of plants belonging to the Euphorbiaceae family with worldwide intertropical distribution, composed of more than 150 species.

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1. Genus

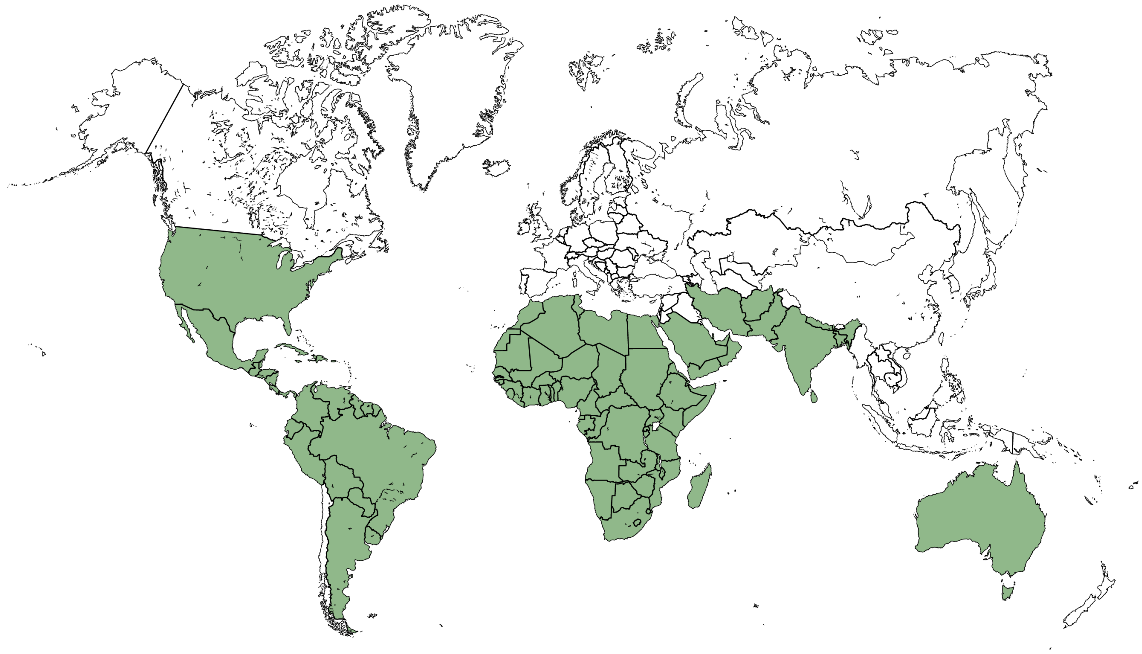
The genus *Tragia* is one of the 317 genera in the *Euphorbiaceae* family. There are 161 accepted names belonging to 154 species in the *Tragia* genus, with “pantropical and warm temperate distribution” [1][2]. The etymology for the name of this genus comes from the Greek *tragos*, meaning goat. This name may stem either from the name of the German botanist Hieronymus Bock—Bock means “ram” or “he-goat” in German, or from the hairy appearance of the plant that would resemble a male goat [3].

Tragia species exhibit very ample morphological characters: they are perennial plants with herb, shrub, subshrub and twining vine growth habits, with lanceolate leaves presenting either entire or serrated margins. Plants belonging to this genus sting when touched due to the presence of leaf hairs with a needle-shaped crystal of calcium oxalate (raphide) in the terminal cells that is expelled on contact and punctures the skin, allowing irritants to enter and cause transient stinging [4][5], presumably a defense mechanism against herbivores [6]. Several common names for Tragias, such as noseburn (*Tragia* spp.), Indian stinging nettle (*T. involucrata*), fireman (*T. volubilis*) or stinging nettle creeper (*T. durbanensis*), are due to this stinging property.

Species belonging to *Euphorbiaceae* in general and to *Tragia* in particular are still not fully settled [7], as new species are being discovered [8] and species are being reassigned to other genera [1][9], so the number of species in the genus is still subject to change.

2. Distribution and Localization

Species belonging to the *Tragia* genus are present in subtropical America, Eastern and Southern Africa, the Indian subcontinent and Northeastern Australia. Of the 154 species listed in the genus [10], 94 are found in Africa, 48 in America, 10 in Asia and 3 in Oceania, with some species such as *T. arabica* and *T. plukenetii* present both in Africa and Asia.



3. Ethnopharmacological Usage

Of the more than 150 species of the genus, few appear in the scientific literature, and even fewer are mentioned from an ethnopharmacological perspective. Notwithstanding, *Tragia* species are a part of traditional medicinal systems of East Africa and the Indian subcontinent, such as Siddha and Ayurveda [11], with documented uses of *T. involucrata* appearing as early as the 1st century CE [12] and with only a handful of mentions of *Tragia* species in the New World pharmacopoeia, concerning mostly topical applications. There is concern over an excessive use of *Tragia* species, e.g., *Tragia bicolor*, which poses a conservation hazard [13][14].

Most of the interest in this genus has been focused on four species: *Tragia involucrata*, *Tragia spathulata*, *Tragia plukenetii* and *Tragia benthamii* [15], with the bulk of the research focused on *T. involucrata*. Nevertheless, several more species and their medicinal uses appear in literature.

According to the ATC classification, the most frequent ethnopharmacological uses of *Tragia* spp. in ethnopharmacology are: genitourinary system and sex hormones, with 19% of occurrences (15 of 77); nervous system, with 12%; and alimentary tract and metabolism, anti-infective for systemic use and antineoplastic and immunomodulating agents with 10% of occurrences each. The “various” classification presents 17% of occurrences, which include non-specified and vague uses, such as “toxic” or “medicinal”.

As for the morphological structures used per species, the most common are the leaves, 38%; followed by “not specified”, 33%; whole plant, 15%; roots, 13% and a single occurrence of endophytes (3%).

4. Biological Activity

Biological activity tests of *Tragia*, both in vitro and in vivo, are performed mostly with plant extracts and to a much lesser degree with essential oils: leaf, root or the whole plant, although ethnopharmacological uses mostly employ the plant via infusions, decoctions or ashes [15][16]. Different solvents and solvent mixtures have been used for the extracts, mainly methanol and ethanol. Due to the presence of *Tragia* in ethnomedical traditions in Africa and Asia, there is a team of research about the bioactivity of Old World *Tragia* extracts that have confirmed their activity and potency in some cases. Not all the health claims or traditional uses recorded have been validated through research. Again, the bulk of the research is centered on *T. involucrata*.

4.1. In Vitro Activity

Extracts of *T. benthamii*, *T. brevipes*, *T. involucrata*, *T. pungens* and *T. spatulatha* have been tested to ascertain their in vitro activity for a variety of uses.

In vitro biological activity tests devote the most attention to leaves (36%), with whole plant and root used to a lesser extent, with both 14%. Extraction solvents are methanol (47%), DCM (5%), Ethyl acetate (10%), water (6%), chloroform

(5%), petroleum ether (5%), ethanol (5%) and acetone (5%). This solvent usage supports the assumption that most active compounds are moderately polar and are thus extracted with polar solvents.

Testing centers on antibacterial (41%) and antifungal (18%) activity of the extracts, with antiproliferative (12%) and antidiabetic, antiurolithiatic, radioprotective, immunomodulatory and cytotoxic effects (6% each) behind. This is a different profile than what was found in the ethnomedicinal claims, which centers on the genitourinary system and sex hormones. This is justified because aphrodisiacs do not have the expected properties [17].

4.2. In Vivo Activity

Besides in vitro activity testing, research has been done in animal models, mostly mice and also chicks, with at least one clinical trial performed in humans.

Most of the research (73%) centers on *T. involucrata*, with *T. plukenetii* (18%), *T. benthamii* (9%) and *T. furialis* (5%) behind. In vivo assay extracts were obtained from leaves (29%), whole plant (25%), root (21%) and aerial parts (8%). Solvents used are methanol (48%), ethanol (26%) and water (13%), which shows that most active compounds are polar and are thus extracted with polar solvents.

For both in vitro and in vivo testing, the most common effect is antibacterial and antimicrobial with 22% of the reviewed studies. This is higher than the 10% reported in the ethnopharmacological uses. Effects having to do with cancer prevention and treatment—antiproliferative, antitumor, cytotoxic immunomodulatory and radioprotective—add up to 17% of the reported effects, which makes it the second most frequent use. Analgesic and anti-inflammatory activity is equally reported in 10% of the tests.

The findings reported in literature validate several medicinal use cases for *Tragia* species and dismiss some claims, e.g., *T. meyeriana* as an antineoplastic [18].

5. Phytochemical Composition

Phytochemical studies allow for the identification, separation and isolation of compounds of interest [19]. Based on phytochemical screenings published in the literature, the main secondary metabolites found in *Tragia* species extracts are alkaloids, glycosides, flavonoids, and sterols [15][20].

Some compounds found in plants belonging to the *Tragia* genus, classified according to their chemical nature, are listed in **Table 1**. Where applicable, the biological activity of the identified compound has been mentioned.

Table 1. Compounds isolated/identified in *Tragia* extracts and oils and their biological effect.

No.	Compound	Identified	Isolated	Methodology Used	Species	Collection area	Plant Organ Used	Use	Effect	Reference
Acetal										
1	1,1-diethoxy-2- methylpropane	X		Ethanol extract GC, MS	*T. plukenetii*	NS	Whole plant	NS	NS	[21]
							Aldehydes			
2	16-heptadecenal	X		Ethanol extract GC, MS	*T. plukenetii*	NS	Whole plant	NS	NS	[21]
3	Hexanal	X		Hydrodistillation GC/GC-MS	*T. benthamii*	Ibadan, Nigeria	Leaves	NS	NS	[22]
							Alkaloid			
4	(E)-4-(1-hydroxypropyl)-7,8-dimethyl-9-(prop-1-en-1-yl)-[1,3] dioxolo [4,5-g]quinolin-6(5*H*)-one	X	X	Acidified ethanol extract GC, MS, LC	*T. plukenetii*	NS	Whole plant	NS	NS	[21]
Esters										
5	4-oxo-4*H*-pyran-2,6-dicarboxylic acid *bis*-[6-methyl-heptyl] ester	X	X	Ethanol extract IR ^{1}H, ^{13}C NMR, MS	*T. involucrata*	Salem, India	Roots	Antidiabetic	Blood glucose reduction	[23]

No.	Compound	Identified	Isolated	Methodology Used	Species	Collection area	Plant Organ Used	Use	Effect	Reference
6	Ethyl linoleate	X	X	Ethanol extract GC, MS	*T. plukenetii*	NS	Whole plant	NS	NS	[21]
7	Ethyl palmitate	X	X	Ethanol extract GC, MS	*T. plukenetii*	NS	Whole plant	NS	NS	[21]
							Ether			
8	Vinyl hexyl ether	X	X	Aqueous extract GC, MS	*T. involucrata*	Tamil Nadu, India	Leaf	Antibacterial *Escherichia coli* *Proteus vulgaris* *Staphylococcus aureus*	MBC 12.25 μg/mL	[24][25]
Flavonoids										
9	3-(2,4-dimethoxyphenyl)-6,7-dimethoxy-2,3-dihydrochromen-4-one	X	X	Ethyl acetate extract FTIR, MS, ^{1}H NMR	*T. involucrata*	Odisha, India	Root	Antibacterial Fungicidal	MIC 1.25-12.5 μg/mL	[26]
10	Iridin	X	X	Ethyl acetate extract FTIR, MS, ^{1}H NMR	*T. involucrata*	Odisha, India	Root	Toxic		[26]
11	Quercetin	X	X	Ethyl acetate extract FTIR, MS, ^{1}H NMR	*T. involucrata*	Odisha, India	Root	Antioxidant		[26]
12	Rutin	X	X	Ethyl acetate extract FTIR, MS, ^{1}H NMR	*T. involucrata*	Odisha, India	Root	Antioxidant		[26]
Heterocycle										
13	2,5-dithia-3,6-diazabicyclo[2.2.1]heptane	X	X	95% aqueous ethanol extraction ^{1}H, ^{13}C NMR	*T. benthamii*	Ibadan, Nigeria	Whole plant	NS		[27]
Hydrocarbons										
14	2,6-dimethylheptane	X	X	Aqueous extract GC, MS	*T. involucrata*	Tamil Nadu, India	Leaf	Antibacterial *Proteus vulgaris*	MBC 10 μg/mL	[24]
15	2,4-dimethylhexane	X	X	Aqueous extract GC, MS	*T. involucrata*	Tamil Nadu, India	Leaf	Antibacterial *Staphylococcus aureus*	MBC 12.25 μg/mL	[24]
16	2-methylnonane	X	X	Aqueous extract GC, MS	*T. involucrata*	Tamil Nadu, India	Leaf	Antibacterial *Escherichia coli* *Proteus vulgaris* *Staphylococcus aureus*	MIC 5.0 μg/mL	[24]
17	Shellsol (2-methyldecane)	X	X	Aqueous extract GC, MS	*T. involucrata*	Tamil Nadu, India	Leaf	Antibacterial *Proteus vulgaris* *Staphylococcus aureus*	MBC 25.0 μg/mL	[24]
18	3,5-di-*tert*-butyl-4-hydroxyanisole	X	X	95% aqueous ethanol extraction ^{1}H, ^{13}C NMR	*T. benthamii*	Ibadan, Nigeria	Whole plant	Antioxidant		[27]
19	5-hydroxy-1-methylpiperdin-2-one	X	X	Methanol extract IR, ^{1}H, ^{13}C RMN, LC	*T. involucrata*	Kerala, India	Leaf	Antihistamine	Muscle relaxant, bronchodilating and anti-allergic effects	[28]
Polyols										

Identification of the compounds relies heavily on spectroscopic and spectrometric methods [19], and chromatography retention times and comparison with the literature are also used for tentative identification.

No.	Compound	Identified	Isolated	Methodology Used	Species	Collection area	Plant Organ Used	Use	Effect	Reference
20	Erythritol	X	X	95% aqueous ethanol extraction ^{1}H, ^{13}C NMR	*T. benthamii*	Ibadan, Nigeria	Whole plant	NS	NS	[27]
21	Glycerol	X	X	95% aqueous ethanol extraction ^{1}H, ^{13}C NMR	*T. benthamii*	Ibadan, Nigeria	Whole plant	NS	NS	[27]
Terpenoids										
22	10,13-dimethoxy-17-(6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthrene	X	X	Ethyl acetate extract FTIR, MS, ^{1}H NMR	*T. involucrata*	Odisha, India	Root	NS	NS	[26]
23	Stigmasterol	X		Aqueous extract GC, MS	*T. involucrata*		Leaf	NS	NS	[24]
24	Caryophyllene	X		Hydrodistillation GC/GC-MS	*T. benthamii*	Ibadan, Nigeria	Leaves	Anti inflammatory		[22]
25	Citronellal	X	X	Ethanol extract IR, ^{1}H RMN, LC	*T. ramosa*	Maharashtra, India	Leaves	Antibacterial		[29]
26	Clerodane	X	X	Ethanol extract IR, ^{1}H RMN, LC	*T. ramosa*	Maharashtra, India	Leaves	NS	NS	[29]
27	Geranylacetone	X		Hydrodistillation GC/GC-MS	*T. benthamii*	Ibadan, Nigeria	Leaves	NS	NS	[22]
28	Neophytadiene (2-(4,8,12-Trimethyltridecyl) buta-1,3-diene)	X	X	Ethanol extract GC, MS	*T. plukenetii*	NS	Whole plant	NS	NS	[21]
29	Phytol	X	X	95% aqueous ethanol extraction ^{1}H, ^{13}C NMR	*T. benthamii*	Ibadan, Nigeria	Whole plant	NS	NS	[27]
30	Squalene (all *trans*)	X	X	Ethanol extract GC, MS	*T. plukenetii*	NS	Whole plant	NS	NS	[21]
31	α-terpinene	X	X	Ethanol extract IR, ^{1}H RMN, LC	*T. ramosa*	Maharashtra, India	Leaves	Antiinflammatory, Antimicrobial	NS	[29]

A strength of the genus is its diversity and its pantropical distribution, which makes it readily available in most tropical countries. A weakness would be that, despite the interest shown concerning *T. involucrata* and other traditionally medicinal species, there appear to be no drugs derived from plants of these species, remaining in the realm of herbal remedies and plant extracts, entailing less medicinal interest than other genera of the *Euphorbiaceae* family, notably *Euphorbia* [7]. This can be attributed to the stage of research, with most work performed in vitro or in vivo and with a single clinical trial [30]. Hopefully the current research will advance into new drugs.

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