CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.1214982

Available online at: http://www.iajps.com Review Article

PHARMACOLOGICAL AND TOXICOLOGICAL EFFECTS OF *HELIOTROPIUM UNDULATUM* [*H. BACCIFERUM*] AND *HELIOTROPIUM EUROPAEUM*- A REVIEW

Ali Esmail Al-Snafi

Department of Pharmacology, College of Medicine, University of Thi qar, Iraq.
Cell: +9647801397994. E mail: aboahmad61@yahoo.com

Abstract:

The phytochemical analysis of Heliotropium undulatum [Heliotropium bacciferum] revealed the presence of alkaloids, saponins, tannins, steroids, terpenoids, flavonoids, glycosides, and phenols. While, Heliotropium europaeum was shown to contain three major alkaloids: heliotrine N-oxide 0.08%, lasiocarpine 0.09% and lasiocarpine N-oxide 0.05%; and four minor alkaloids: heliotrine 0.02%, europine 0.02%, acetyllasiocarpine 0.03% and a novel alkaloid acetyllasiocarpine N-oxide 0.05%. Twenty six compounds were identified in the essential oil of Heliotropium europaeum. The previous pharmacological studies showed that these species possessed antioxidant, antimicrobial, anti-inflammatory and hapatoprotective effects. However, pyrrolizidine alkaloids were toxic for animals and human. This review was designed to highlight the chemical constituents, pharmacological and toxic effects of Heliotropium undulatum [Heliotropium bacciferum] and Heliotropium europaeum.

Keywords: *chemical constituents, pharmacology, toxicology,Heliotropium undulatum, Heliotropium bacciferum, Heliotropium europaeum*

Corresponding author:

Ali Esmail Al-Snafi

Department of Pharmacology,
College of Medicine,
University of Thi qar, Iraq
Cell: +9647801397994.
E mail: aboahmad61@yahoo.com

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Please cite this article in press Ali Esmail Al-Snafi., ***Pharmacological and Toxicological Effects of Heliotropium Undulatum [H. Bacciferum] and Heliotropium Europaeum- A Review,*** *Indo Am. J. P. Sci, 2018; 05(04).*

INTRODUCTION:

Plants are a valuable source of a wide range of secondary metabolites, which are used as pharmaceuticals, agrochemicals, flavours, fragrances, colours, biopesticides and food additives [1-20]. The phytochemical analysis of *Heliotropium undulatum* [*Heliotropium bacciferum*] revealed the presence of alkaloids, saponins, tannins, steroids, terpenoids, flavonoids, glycosides, and phenols. While, *Heliotropium europaeum* was shown to contain three major alkaloids: heliotrine N-oxide 0.08%, lasiocarpine 0.09% and lasiocarpine N-oxide 0.05%; and four minor alkaloids: heliotrine 0.02%, europine 0.02%, acetyllasiocarpine 0.03% and a novel alkaloid acetyllasiocarpine N-oxide 0.05%. Twenty six compounds were identified in the essential oil of *Heliotropium europaeum*. The previous pharmacological studies showed that these species possessed antioxidant, antimicrobial, anti-inflammatory and **hapatoprotective** effects. However, pyrrolizidine alkaloids were toxic for animals and human. This review was designed to highlight the chemical constituents, pharmacological and toxic effects of *Heliotropium undulatum* [*Heliotropium bacciferum*] and *Heliotropium europaeum*.

Plant profiles:

Synonyms:

***Heliotropium undulatum*:**

H. bacciferum Forssk., *H. affghanum* Boiss, *H. arenarium* F. Muell., *H. eriocarpum* Delile ex Lehm., *H. nubicum* Bunge, *Sericostoma arenarium* [Vatke] IM Johnst and *Dialion undulatum*[21].

***Heliotropium europaeum*:**

H. album St.-Lag., *H. commutatum* Schult., *H. dioscoridis* Bubani, *H. glandulosum* R. Br., *H. gymnocarpum* Borbás, *H. lacunarium* F. Muell., *H. subcanescens* Steven and *H. vulgare* Gaterau [21].

Taxonomic classification:

Kingdom: Plantae, **Subkingdom**: Viridiplantae, **Infrakingdom**: Streptophyta, **Superdivision**: Embryophyta, **Division**: Tracheophyta, **Subdivision**: Spermatophytina, **Class**: Magnoliopsida, **Superorder**: Asteranae, **Order**: Boraginales, **Family**: Heliotropiaceae, **Genus**: *Heliotropium*, **Species**: *Heliotropium undulatum* and *Heliotropium europaeum*[22-23].

Common names:

***Heliotropium undulatum*:**

Arabic: Ramram Zerraij, Thanb Al Agrab, Hâbaliya, Hbaïlia[24].

***Heliotropium europaeum*:**

Arabic: Tanoom, Karee, Tafeen, Aqrabana, I'jairbeh, Hashishat Al Agrab; **English**: Barooga-weed, Caterpillar-weed, Common heliotrope, European heliotrope, European turnsole, Heliotrope, Hemp-agrimony, Wandarrie-curse, Wild heliotrope; **French**: Héliotrope d'Europe; **German**: Europäische Sonnenwende, Sonnenwende; **Iran**: Aftab parast, Akreer**; Italy**: Eliotropio, Commune, Erba porraja**; Portuguese**: Heliotrópio-europeu; **Spanish**: Verrucaria; **Swedish:** Ogräsheliotrop; **Turkey**: Akrep out, Bambul out[25-26].

Distribution:

***Heliotropium undulatum*:**

Heliotropium undulatum was distributed in Bahrain, Egypt, Iran, Iraq Palestine, Jordania, Kuwait, Oman, Saudi Arabia, United Arab Emirates, Yemen, Afghanistan, Pakistan, Libya, Morocco, Algeria, Tunisia, Mauritania, Mali, Chad, Burkina Faso, Cameroon, Somalia, Sudan, Senegal, Comoros, Madagascar, India and Australia[27].

***Heliotropium europaeum*:**

Heliotropium europaeum was reported to be native to southern and central Europe, northern Africa, and western Asia. Now, it presents in Africa [Algeria, Egypt, Libya, Morocco, Tunisia]; Asia: [Afghanistan, China, India, Pakistan , Indonesia, Iran, Iraq, Palestine, Jordan, Lebanon, Oman, Saudi Arabia, Syria, Turkey, Turkmenistan, Uzbekistan, Armenia, Georgia, Russian Federation]; Europe [Moldova, Russian Federation-European part, Ukraine, Austria, Czech Republic, Germany, Hungary, Slovakia, Switzerland, Albania, Bulgaria, Croatia, Greece, Italy, Romania, Serbia, Slovenia]; Australasia [Australia] and Northern America [United States][25-26].

Description:

***Heliotropium undulatum*:**

Perennial, decumbent or procumbent with a woody base, short and stout up to 15 mm thick at base. Leaves lanceolate to linear-lanceolate, 5-55 x 2-16 mm, flat or t terete, hairy on both surfaces, margin revolute, longer hairs stiff, up to 2 mm long, arising from bulbous base. Inflorescence reduced, up to 20 mm long, bearing close set uniseriate flowers. Calyx persistent, 2-2.5 mm long, 5-partite into lanceolate lobes, hairy to the outside; hairs often stiff and arising from a bulbous base. Corolla white, c. 2.5-3 mm long; tube shortly cylindrical, hairy outside, glabrous within; lobes imbricate, 0.7-0.8 mm long, oblong to suborbicular, crenulate to t undulate. Anthers 1-1.2

mm long, elongate, broader at base, attached c. 1.1 mm from the corolla base, slightly furrowed and sometimes 2-fid at apex. Style shorter than stigma. Fruit globose, usually hairy when young; nutlets 4, brown, margin winged, back rugulose, sometimes with a membranous inflated back[28-29].

***Heliotropium europaeum*:**
Herbs annual, 20-50 cm tall. Stems erect or ascending, branched from base, strigose or hirtellous. Petiole 1-4 cm; leaf blade elliptic to elliptic-ovate, 1.5-4 × 1-2.5 cm, abaxially gray-green and densely hirtellous, adaxially green and sparsely hirtellous, base widely cuneate to rounded, apex obtuse to acute. Cymes terminal and axillary, scorpioid, simple or dichotomously branched, 2-4 cm. Flowers sessile. Calyx lobes ovate to ovate-lanceolate, 2-3 × 1-1.5 mm, not enlarged in fruit, strigose. Corolla white, 4-5 mm, base 1.5-2 mm wide; throat slightly contracted; limb [2-]3-4 mm wide; lobes rounded, ca. 1.5 mm wide, short strigose outside, glabrous inside. Anthers ovate-oblong, ca. 1 mm, without filaments, attached ca. 1 mm above base of corolla tube. Ovary globose, 0.5-0.7 mm in diam. Style short; stigma long conical, deeply 2-cleft, 1.2-1.5 mm, ringlike portion glabrous, apex short strigose. Fruit 2.5-3 mm in diam.; mericarps ovate, ca. 2 mm, ± distinctly tuberculate, glabrous[30]

Traditional uses:

***Heliotropium undulatum* [*H. bacciferum*]:**
Heliotropium bacciferum was used for hypotension, fever and stomach ulcers in traditional medicine[31]. It was used in Cape Verde as a cardiotonic. It was also used as a repellent for storage insects in Egypt and Pakistan[32].

***Heliotropium europaeum*:**
It was used as purifier. Flowers were used to give relief from constipation and piles. Powder of leaves was used to treat skin problems[33].
The juice of the crushed *Heliotropium europaeum* was used topically to treat dermatophytosis of hair, nails and skin in domestic animals, while boiled leaves were applied on skin to treat pimples and eruption[34-36]

Part used:
Flowers and leaves[33].

Physicochemical characteristics:
***Heliotropium undulatum*:**

Extractive value of the leaves in methanol, n-hexan, ethyl acetate, *n*-Butanol and aqueous were 32.64 ± 0.02, 14.76 ± 0.03, 15.83 ± 0.02, 16.43 ± 0.04 and 23.79 ± 0.05%, extractive value of the stems were 18.13 ± 0.05, 12.46 ± 0.01, 13.89 ± 0.03, 14.13 ± 0.10 and 20.10 ± 0.03% and that of roots were 13.10 ± 0.08, 10.32 ± 0.03, 12.70 ± 0.06, 11.34 ± 0.12 and 17.16 ± 0.08% respectively. Moisture value of the leaves was 11.36 ± 0.04% and Ash value of the whole plant was 8.67 ± 0.06 %[37].

Chemical constituents:

***Heliotropium undulatum* [*H. bacciferum*]:**
Phytochemical analysis of crude and fractions of the plant revealed the presence of alkaloids, saponins, tannins, steroids, terpenoids, flavonoids, glycosides, and phenols[37].
Alkanes, alkenes, alkyl halides, amines, carboxylic acids, amides, esters, alcohols, phenols, nitrocompounds, and aromatic compounds were identified from the extracts of *Heliotropium bacciferum*[38].

Four pyrrolizidine alkaloids [heleurine, heliotrine, supinine, and europine] were isolated from *Heliotropium bacciferum*[39].

Quantitative analysis of fatty acids of *Heliotropium bacciferum* by GC-MS analysis revealed the presence of linoleic acid 65.70%, eicosadienoic acid 15.12%, oleic acid8.72%, palmitic acid 8.14%, stearic acid 1.74%, elaidic acid 0.58% and myristic acid 0.20%[37].

***Heliotropium europaeum*:**
Twenty six compounds were identified in the essential oil of *Heliotropium europaeum* represented 91.4% of the total essential oil. The identified compounds and their percent were: *trans*-linalool oxide 1.6%, *cis*- linalool oxide 1.8%, eugenol 1.6%, β- longipinene 1%, geranyl acetone 6.3%, [*E*]- β-ionone 4.8%, *n*-tridecanol 1.9%, silphiperfol-6-en-5-one 7.1%, alloaromadendiene epoxide 3.8%, β-eudesmol 0.7%, *n*-tetradecanol 2.4%, eudesma-7[11]-en-4-ol 0.6%, *E*-coniferyl alcohol 1.1%, α-oxobisabolene 0.3%, *n*-pentadecanol 2.6%, β-eudesmol acetate 1.2%, *n*-hexadecanol 1.8%, phytol 28.7%, *n*-octadecanol 3.2%, *Cis*- linoleic acid methyl ester *7.3%*, *n*-heneicosane 3.2%, phytol acetate 4.3%, n- pentacosane 0.9%, n- hexacosane0.8%, n-heptacosan 1.3%e and n- octacosane 1.1%[40].

The pyrrolizidine alkaloids isolated from the aerial plant parts of *Heliotropium europaeum* were included: supinine-type 2.3 ± 0.4 µg/g dry [included: supinine, supinine-N-oxide, heleurine, heleurine-N-oxide]; Heliotrine-type 80.0 ± 7.9 µg/g dry weight [included: heliotrine, europine, heliotrine-*N*-oxide, europine-*N*-oxide, rinderine, 5'-hydroxyrinderine, 3'-acetylrinderine, rinderine-N-oxide, 5'-hydroxyrinderine-N-oxide, 3'-

acetylrinderine-N-oxide, 5'-acetyleuropine, 5'-acetyleuropine-*N*-oxide , echinatine-*N*-oxide]; and Lasiocarpine-type 28.7 ± 2.2 µg/g dry weight [included: 7-angeloylheliotrine-*N*-oxide, lasiocarpine**,** lasiocarpine-*N*-oxide**,** *iso*-lasiocarpine, *iso*-lasiocarpine-*N*-oxide, 5'-acetyllasiocarpine, 5'-acetyllasiocarpine-*N*-oxide, *iso*-acetyllasiocarpine, *iso*-acetyllasiocarpine-*N*-oxide, heliosupine, 3'-acetylheliosupine, heliosupine-*N*-oxide and 3'-acetylheliosupine-*N*-oxide][41].

The total pyrrolizidine alkaloid and tertiary base content of the seeds of *Heliotropium europaeum* were found to be 0.28 % and 0.02 % respectively. Higher percentage of alkaloids were present as N-oxides [92.86 % of the alkaloids]. Alkaloids found in the tertiary base fraction and total alkaloid fraction were identified as europine 14.27%, heliotrine 2.44%, supinine 9.09%, heleurine 2.65%, lasiocarpine 8.69% and 7-angelylheliotrine 2.86%[42-43].
Heliotropium europaeum population Garmsar was shown to contain three major alkaloids: heliotrine N-oxide 0.08%, lasiocarpine 0.09% and lasiocarpine N-oxide 0.05%; and four minor alkaloids: heliotrine 0.02%, europine 0.02%, acetyllasiocarpine 0.03% and a novel alkaloid acetyllasiocarpine N-oxide 0.05%[44].
Alkaloid, heliotridine esterified on the methylol hydroxyl with lasiocarpic acid [2,3-dihydroxy-4-methoxy-2-methylpentane-3-carboxylic acid], supinine [supinidine esterified with trachelanthic acid], supinidine esterified with heliotric acid [3-hydroxy-4-methoxy-2-methylpentane-3-carboxylic acid], N-oxides of heliotrine and lasiocarpine were isolated from *Heliotropium europaeum*[43]

Pharmacological effects:
Antioxidant effect:
The leaves, stem, and roots extracts of *Heliotropium bacciferum* exhibited significant DPPH radical scavenging activities. The plant leaves extracts revealed excellent DPPH radical scavenging activities ranging from 52.59 ± 0.84 to 90.74 ± 1.00 at concentrations of 50, 100, 150, 200, and 250 mg/ml[37].

The antioxidant effect of *Heliotropium bacciferum* flower extracts was investigated against 2, 2-diphenyl-1-picryl hydrazyl radical. Extracts displayed noteworthy radical scavenging activities at all concentrations [25–225 μg/ml]. Notable activities were recorded by crude, chloroform and ethyl acetate extracts up to 88.27% at 225 μg/ml concentration[38].

Antimicrobial effect:
The antimicrobial activity of *Heliotropium europaeum* oil [250, 500, 1000, 2000, 4000 and 8000 µg/ disk] was investigated against *Bacillus subtilis* PTCC 1023, *Staphylococcus aureus* PTCC 1112, *Escherichia coli* PTCC 1330, *Salmonella typhi* PTCC 1639, *Aspergillus niger* PTCC 5011 and *Candida albicans* PTCC 5027. The diameter of zone of growth inhibition was 12, 12.5 and 15.75mm against *Bacillus subtilis* and 11.75, 12.5 12mm against *Salmonella typhi* at concentration of 2000, 4000 and 8000 µg/ disk respectively. However it showed weak activity against *Escherichia coli* and *Aspergillus niger*, and no activity against *Staphylococcus aureus* and *Candida albicans*[40].

The antimicrobial effects of leaves, flowers, and stem extracts of *Heliotropium bacciferum* were against seven bacterial species *[Escherichia coli* [ATCC 25922], *Staphylococcus aureus* [ATCC 6538], *Bacillus cereus* [ATCC 7722], *Pseudomonas aeruginosa* [ATCC 9721], *Klebsiella pneumoniae* [ATCC 6824], *Proteus mirabilis* [ATCC 7103], and *Erwinia carotovora* [ATCC 8452]] and five fungal strains *[Aspergillus niger, Aspergillus flavus, Aspergillus parasiticus, Aspergillus oryzae,* and *Aspergillus fumigates*]. All extracts exhibit a range antibacterial effects. Methanol, *n*-hexane, and ethyl acetate extracts of plant leaves [15 μg] revealed significant activities [18 ± 0.46 mm, 20 ± 0.71 mm, and 21 ± 0.69 mm] against *Klebsiella pneumoniae*, *Staphylococcus aureus* [16 ± 0.51 mm, 17 ± 0.34 mm, and 19 ± 0.53 mm], *Pseudomonas aeruginosa* [16 ± 0.44 mm, 17 ± 0.58 mm, and 15 ± 0.53 mm], and *Escherichia coli* [13 ± 0.32 mm, 19 ± 0.46 mm, and 18 ± 0.65 mm], respectively. Plant leaves chloroform and *n*-butanol extracts [15 μg] were active against *Pseudomonas aeruginosa* [16 ± 0.37 mm and 14 ± 0.75 mm] and *Klebsiella pneumoniae* [17 ± 0.73 mm and 10 ± 0.28 mm]. Plant flowers *n*-hexane, ethyl acetate, and *n*-butanol extracts [15 μg] showed prominent activities against *Escherichia coli* [17 ± 0.46 mm, 16 ± 0.64 mm, and 14 ± 0.34 mm], *Staphylococcus aureus* [19 ± 0.76 mm, 20 ± 0.74 mm, and 11 ± 0.54 mm], and *Klebsiella pneumoniae* [19 ± 0.75 mm, 19 ± 0.48 mm, and 13 ± 0.46 mm], respectively. Chloroform and *n*-butanol extracts [15 μg] of plant stem showed noteworthy activities [15 ± 0.53 mm and 11 ± 0.43 mm] against *Escherichia coli* and *Klebsiella pneumonia* [17 ± 0.56 mm and 15 ± 0.64 mm], respectively. Aqueous extracts [15 μg] of plant stem were active against *Klebsiella pneumoniae*

[13 ± 0.42 mm], *Proteus mirabilis* [10 ± 0.29 mm], and *Erwinia carotovora* [11 ± 0.26 mm]. Ethyl acetate and *n*-hexane extracts [15 μg] of plant stem were active against all bacterial microorganisms. Methanol, *n*-hexane, chloroform, ethyl acetate, and *n*-butanol extracts [15 μg] of leaves showed prominent activities against *Aspergillus niger* [17 ± 0.44 mm, 14 ± 0.52 mm, 12 ± 0.28 mm, 15 ± 0.43 mm, and 11 ± 0.43 mm], *Aspergillus flavus* [15 ± 0.38 mm, 17 ± 0.67 mm, 13 ± 0.53 mm, 17 ± 0.32 mm, and 14 ± 0.51 mm], and *Aspergillus oryzae* [11 ± 0.54 mm, 16 ± 0.68 mm, 16 ± 0.45 mm, 17 ± 0.83 mm, and 15 ± 0.57 mm], respectively. Methanol, chloroform, and *n*-butanol extracts [15 μg] of flowers revealed noteworthy activities against *Aspergillus niger* [14 ± 0.25 mm, 11 ± 0.26 mm, and 13 ± 0.47 mm] and *Aspergillus flavus* [17 ± 0.63 mm, 14 ± 0.46 mm, and 11 ± 0.23 mm], respectively. Significant activities were recorded by *n*-hexane and ethyl acetate extracts of plant flowers against *Aspergillus niger* [17 ± 0.63 mm and 16 ± 0.59 mm], *Aspergillus flavus* [15 ± 0.48 mm, 15 ± 0.59 mm], and *Aspergillus oryzae* [12 ± 0.27 mm and 15 ± 0.44 mm], respectively. Methanol and chloroform extracts [15 μg] of plant stem were active against *Aspergillus niger* [16 ± 0.54 mm and 15 ± 0.54 mm] and *Aspergillus fumigatus* [15 ± 0.51 mm and 14 ± 0.37 mm], respectively. Excellent activities were shown by *n*-hexane and ethyl acetate extracts [15 μg] against *Aspergillus flavus* [11 ± 0.31 mm and 18 ± 0.50 mm], *Aspergillus oryzae* [17 ± 0.54 mm and 15 ± 0.55 mm], and *Aspergillus fumigatus* [12 ± 0.33 mm and 16 ± 0.54 mm], respectively[38].

The crude [methanol fraction] and n-hexane, ethyl acetate, butanol and aqueous fractions of *Heliotropium bacciferum* were subjected to antibacterial and antifungal activities against bacterial isolates: *Salmonella typhi, Escherichia coli, Pseudomonas Aeroginosa, Staphylococcus aureus, Erwinia carotovora, Klebsiella pneumoniae, Bacillus subtilis, Bacillus atrophaeus*, and fungal isolates: *Trichoderma longibrachiantum, Aspergillus flavus, Aspergillus niger, Fusarium solani* and *Candida albican*. All the fractions were active against different bacterial strains but n-hexane and ethyl acetate showed [zone of inhibition ranged from 18-30 mm] highest activity. Excellent inhibitory effect was observed against all fungal strains. The minimum inhibitory concentrations [MICs] of the investigated plant fractions ranged from 0.5- 2.00 mg/ml[45].

The antibacterial effects of *Heliotropium bacciferum* aerial parts extracts and chloroform, ethyl acetate and aqueous fractions, were evaluated against five bacterial strains. *H. bacciferum* extracts exhibited a significant activity against *Staphylococcus aureus, Bacillus cereus, Pseudomonas aeruginosa, E.coli* and *Salmonella enteritidis*. MICs were ranged between 7.6 and125 µg/ml. Among the extracts, the aqueous extract showed the most antibacterial[31, 46].

Hepatoprotective effect:

The hapatoprotective effect of n-butanol extract of *Heliotrpium undulatum* [HUBE] was evaluated in acetylhydrazide [ACHD] induced hepatotoxicity in rats. Hepatic damage was induced by administration of ACHD [300 mg/Kg op]. HUBE [200 mg/Kg, op] administered for 14 days before ACHD administration, caused a decrease in LPO levels and in the transaminase and ALP levels and restored the GSH and its related enzymes [GPx, GST, GR] [50-62 %]. Simultaneous administration of HUBE afforded a partial protection in hepatic GSH[47]

Antiinflammatory effect:

The anti-inflammatory effect of extracts of 17 plant genera were studied using the carrageenan induced inflammation in rats' paws. The plant extracts were obtained using methanol and dichloromethane as solvent and administered intraperitoneally at the concentration of 2g/kg bw. Dichloromethane extract of the aerial parts of *Heliotropium bacciferum* caused 28.2±3.1% inhibition of oedema volume, 2 hours after injection of carrageenan[48].

Pyrrolizidine alkaloids poisoning:

Pyrrolizidine alkaloids poisoning of livestock caused by the accidental ingestion of feed contaminated with *Heliotropium* spp, was common worldwide. The most common toxic pyrrolizidine alkaloids found in *Heliotropium* were mono- or di- esters of C1-C2 unsaturated necine bases [1,2-dehydro PAs] of the supinidine-type, heliotridine-type, and retronecine-type[49-51].

Cattle were more susceptible than sheep, while horses were the most susceptible. Pyrrolizidine alkaloids - poisoning in livestock was clinically characterized by staggering, tremor, tenesmus and sudden death, the latter usually occurs several weeks up to several months from the time of exposure. Macroscopically, the livers were pale and firm, histopathological feature characterized by proliferation of bile-duct epithelial cells, megalocytosis, veno-occlusive lesions, nodular regeneration and fibrosis[52-54]

A herd of 15-18 months old mixed breed beef cattle [n=73] from the Galilee region in Palestine, was accidently fed hay contaminated with 12% *Heliotropium europaeum* [average total PA intake was 33 mg PA/kg BW/d]. After 42 day of feed, sudden death occurred over a time period of 63 day

with a mortality rate of 33%. Necropsy and histopathological examination revealed fibrotic livers, moderate ascites, as well as various degrees of bile duct epithelial cells hyperplasia and fibrosis. Elevated ɤ-glutamyl-transferase and alkaline phosphatase levels were indicative of severe liver damage[41, 55].

Most sheep fed for prolonged periods on a ration containing 50% dried *Heliotropium europaeum* developed some of the clinical manifestations seen in field cases of pyrrolizidine alkaloidosis. Histologically demonstrated liver damage was comparatively mild, but the marked decline in their bromosulphophthalein [BSP] clearance rates indicated severe depletion of liver functional capacity. In sheep fed on *Heliotropium europaeum* for 13 wk periods separated by 18 weeks rests, simultaneous oral administration of iodoform [16 mg twice daily] led to an increase from 33-55 weeks in the time required for death of half the susceptible sheep. All susceptible sheep not given iodoform died following 2 periods of *Heliotropium europaeum* feeding, while 3 such periods were needed for iodoform-treated animals. Iodoform prophylaxis may be a useful protective measure in the field for sheep exposed to *Heliotropium europaeum* grazing during a single season. Up to 20% of the sheep used survived ingestion of *Heliotropium europaeum* for the full experimental term and some sustained little or no decline in BSP clearance rate[56-59].

In a field experiment, ewes and wethers grazed *Heliotropium europaeum* over periods of 3 to 4 months in 4 successive years. 12% [14 of 120] of the sheep had died by the end of the second year; after 4 years the loss attributable to *Heliotropium europaeum* was between 18% and 35%. Mortality was not affected by intraruminal treatment with cobalt or antimethanogen. At the end of the experiment the highest concentration of copper in the liver was 1.95 mmol/kg wet weight [approximately 413 micrograms/g dry weight][60].

The disease produced by feeding chickens and ducks a commercial poultry feed containing heliotrine and lasiocarpine [pyrrolizidine alkaloids of *Heliotropium europaeum*], was studied. Ascites, ill thrif and degenerative lesions in the liver were the major findings. Similar lesions were occurred in chickens fed a diet containing *Heliotropium europaeum* [61].

Human poisoning with pyrrolizidine alkaloids was usually accidental, caused most commonly by the ingestion of grain contaminated with pyrrolizidine containing weeds and using of herbs for medicinal purposes. Pyrrolizidine alkaloid poisoning in humans were recorded in South Africa, Jamaica, USSR and Tadjikistan. To date the largest reported outbreak of human intoxication by pyrrolizidine alkaloid was in Afghanistan in 1974 when an estimated 35000 people were affected after grain was contaminated with *Heliotropium* plant material. Among 7200 cases examined, 1600 were affected and many died 3-9 months after the onset of clinical signs[62-67].

In acute cases there were sudden attacks of abdominal pain, vomiting, ascites occured in 96%, hepatomegaly in 85%, with marked increase in liver enzymes in 92% of patients. Liver biopsies during the acute stage showed collagenous occlusion of the small branches of the hepatic venous tree with dilated sinusoids forming collaterals in the parenchyma, massive centrilobular congestion and centrilobular necrosis [veno-occlusive liver disease]. Subacute cases characterized by ascites, persistent hepatomegaly, small vein occlusion, and surrounding fibrosis. Symptoms include abdominal pain, diarrhea, vomiting, and abdominal swelling with the development of collateral venous channels over the abdomen. Chronic cases characterized by progressive ascites and signs of portal hypertension. Histologically there were fibrosis and inflammatory infiltration of the portal tracts, giving rise to a picture of cirrhosis. Complete recovery may occurred in limited lesions, but extensive lesions may caused hepatic failure leading to death[68-73].

Side effects:

The possible toxic effects of water extract of *H. bacciferum* on the reproductive system was investigated in rats. Histological examinations revealed no changes in the tissues of the testes, although, some changes were detected in the cauda epididymis, the most important of which was the development of small lesions of spermatic granulomas[74].

The effect of ethanol extracts of *Heliotropium europaeum* [orally at 3 dose levels; 100, 200 and 400 mg/kg for a period of 7 weeks] on reproductive organs and fertility was studied in male rats. Sperm motility, count, viability and morphology and serum levels of testosterone, follicle stimulating hormone [FSH], leutinizing hormone [LH] and prolactin were

assessed. Percentage of mating and fertility success and fertility index were also calculated. The testes, liver and kidney were processed for histological examination. The effect on biochemical parameters

like aspartate aminotransferase [AST], alanine aminotransferase [ALT], urea, and creatinine were estimated. Hematological profiles such as red blood cell [RBC] count, total leucocyte count [TLC], hemoglobin [Hb] concentration and packed cell volume [PCV] were quantified. The results showed that the ethanol extract of *Heliotropium europaeum* possesses potential fertility lowering effects without altering general body metabolism[34].

CONCLUSION:

This review discussed the chemical constituents, pharmacological and toxic effects of *Heliotropium undulatum* [*Heliotropium bacciferum*] and *Heliotropium europaeum*.

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