ETHNOPHARMACOLOGICAL, PHYTOCHEMICAL AND PHARMACOGNOSTIC POTENTIAL OF GENUS *HELIOTROPIUM* L.

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Dedication: Dedicated to my respectable teachers Prof. Dr. Bashir Ahmed Chaudhry and Prof. Dr. Khalid Hussain Janbaz whose efforts and hard work gave me the determination to write this artifact.

ABSTRACT

In the whole world, a large number of plants have therapeutic potential and used in the treatment of various diseases in different populations. Heliotropium (Boraginaceae) is a widely spread genus of plants found in the temperate and the tropical regions of both hemispheres and used for the treatment of diseases from ancient times. In folk medicine history, the plants of genus Heliotropium include treatments of inflammations, gout, rheumatism, skin diseases, menstrual disorder, and poisonous bites. Phytochemical reports on genus Heliotropium revealed the presence of many bioactive components especially pyrrolizidine alkaloids, terpenoids and flavonoids. A large number of extracts and bioactive constituents of different species of genus Heliotropium revealed significant biological activities such as antimicrobial, antitumor, antiviral, anti-inflammatory, wound healing, cytotoxicity and phytotoxicity. Different parts of plants of genus Heliotropium are examined for valuable pharmacognostic properties. Although it's medicinal importance is recognized worldwide, this review artifact will thus, comprehensively describes the various medicinal effects of the plants, isolation of a large number of secondary metabolites and important pharmacognostic characteristics of genus Heliotropium of Boraginaceae family.

Key words: Genus Heliotropium, Biological activities, Secondary metabolites, Pharmacognostic characters, Boraginaceae.

Heliotropium L. Cinsinin Etnofarmakolojik, Fitokimyasal ve Farmakognostik Potansiyeli

Tüm dünyada terapötik potansiyeli olan çok sayıda bitki, değişik toplumlar tarafından çeşitli hastalıkların tedavisinde kullanılmaktadır. Heliotropium (Boraginaceae) her iki yarım kürenin tropic ve ılıman bölgelerinde geniş bir yayılış gösteren ve antic çağlardan beri hastalıkların tedavisinde kullanılan bitkilerin yer aldığı bir cinstir. Halk hekimliğinde Heliotropium cinsine ait bitkiler, enflamasyon, gut, romatizma, cilt hastalıkları, menstrual bozukluklar ve zehirli hayvan ısırıklarının tedavisinde kullanılır. Heliotropium cinsi üzerinde yapılan fitokimyasal çalışmalar,

özellikle pirolizidin alkaloitleri, terpenoitler ve flavonoitler gibi pekçok biyoaktif bileşiğin varlığını ortaya koymuştur.Yapılan çalışmalarla bu bitkilerin belirgin bir şekilde, antimikrobiyal, antitümör, antiviral, anti-enflamatuvar, yara iyileştirici, sitotoksik ve fitotoksik etkilere sahip olduğu gösterilmiştir. Heliotropium cinsi bitkilerinin değişik kısımları önemli farmakognostik özellikleri nedeniyle ele alınır. Bu derleme makalesi, önemi dünya çapında bilinse de, Boraginaceae familyasına ait Heliotropium cinsi bitkilerinin tıbbi etkilerini, çok sayıdaki sekonder metabolitlerinin izolasyonunu ve önemli farmakognostik karakteristiklerini kapsamlı bir şekilde ele alacaktır.

Anahtar kelimeler: Heliotropium cinsi, Biyolojik aktiviteler, Sekondermetabolitler, Farmakognostik karakterler, Boraginaceae .

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INTRODUCTION AND HISTORICAL REVIEW

Natural products are the substances which originate from plants, animal, microbial and marine sources. The constituents which are identified and isolated from plants have been used as a lead for a variety of drugs from many decades. About 40% of pharmaceutical products which are used in the present time are mainly derived from natural sources. Natural products also play a significant role in the discovery of new therapeutic agents because of their vast availability in nature, lead to the identification of bioactive molecules which allow the development of new pharmaceutical agents, as well as a tool which is involved in the clarification of complex cellular and molecular mechanisms of action involved in many biological and pathological processes. In the recent years, because of increasing interest in the use of pharmaceuticals, natural substances are the major source of complementary or alternative medicines, which are used in the treatment of many diseases (1). Western system of medicine usually limit itself to the identification, isolation and preparation of single active ingredient to cure specific ailments. From ancient times, plants are available to humans as a source of therapy. In the 19^{th} century, due to the advancements in the field of pharmaceutical chemistry especially the medicinal chemistry more than 25% of drugs used in well developed countries are of plant origin and about 120 plant derived substances are used in modern system of medicines worldwide (2).

At the present time, the plants having significant medicinal effects are used to cure the specific diseases of gastrointestinal tract and skin in countries which have poor living conditions (3). Ajwain (*Trachyspermum copticum*L.) is used to treat the discomfort of gastrointestinal tract (4) and it also demonstrated antioxidant activity (5). Nariman et al. (6) have reported anti-helicobacter pyloripotential of ajwain. Vincristine and vinblastine are potent anti-cancer agents obtained from *Catharanthus* roseus(L.) G.(7, 8). The whole plant mixture of *Cressa cretica* L. prepared in water by using black pepper and candy

(Misri) is effective in the treatment of chronic fever and jaundice problems. Also its paste of leaves is applied on sores (9). The juice of dried flowers and leaves of *Spilanthes acmella* Murr. are used in the treatment of toothache, insecticidal, colic and gastrointestinal disorders (10). In China, *Spilanthes callimorpha* A. is used as a fertility regulating agent and for amenorrhea (11). For the treatment of bleeding piles, diarrhea, toothache and inflammations, the dried leaves and flowers of*Abutilon indicum* L. (Peelibooti) are used (12). The paste of leaves of *Aervajavanica*Juss.(Booh) is externally applied for wound healing and inflammation of human being as well as livestock (9).

The family Boraginaceae comprised of 100 genera and about 2000 species. The plants of this family are widely distributed in temperate, especially mediterranean and tropical regions. In Pakistan, this family is represented by 32 genera and 135 species. Moreover, some species namely *Cordia*, *Echium*and *Anchusa*are cultivated (13). *Heliotropium*, *Cordia*, *Arnebia*, *Martensia* and *Trichodesma* are the important genera of the Boraginaceae family. Fruits of the *Cordia* are used as diaphoretic and sometimes as astringent (14). The leaves and roots of *Trichodesmaindicum*Lehm. are effective against snake bites, urinary diseases and used as diuretic. The roots of this plant is also applied as a paste on swellings, joints and is used in dysentery in children (15). Today, *Alkanna*(*Alkannatinctoria*L.) root is used almost exclusively as a cosmetic dye. Orally, it has been used for diarrhea and gastric ulcers. Traditionally, *Alkanna* root has been used topically to treat skin wounds and diseases (16).

*Heliotropium*is a large genus of family Boraginaceae which consists of about 250-300 species in the whole world. These species are widely distributed in temperate and tropical regions of both hemispheres (13). The name "heliotrope" derives from the fact that these plants turn their leaves to the sun (17). In Pakistan, it is the largest genera of family Boraginaceae with 23 species. Some of the taxa of this genus are *H. bacciferum*Forssk.,*H. europium* L.,*H. baluchistanicum* K.,*H. gillianum* R.,*H. biannulatum* B.,*H. ovalifolium*Forssk.,*H. strigosum*Willd.,*H. eichwaldi*Steud.,*H. indicum* L.,*H.glutinosum* Phil.,*H. sclerocarpum* Phil., *H. sinuatum*Miers., *H. subulatum*Hochst., *H. foertherianum* D. and *H. ovalifolium*Forssk.

Traditional medicinal uses

In the modern time, more than 80% world's population depends on the traditional system of medicines. The knowledge of traditional system of health care is widely threatened in the whole world due to revolutions in traditional philosophy (18). The native people of the area in which the plants occur, used 90% of natural products (19). Traditional and native knowledge of medicinal plants, still remain exist world widely (20). Due to the broad range importance of ethno-pharmacological flora, this review was arranged to collect ethno-medicinal knowledge about the different plants of genus *Heliotropium* (see Table 1).

Table 1. Reported uses of genus *Heliotropium* in ethnopharmacological surveys

Name of the plant	Folk medicinal uses	Population or geographic zone	Part used	Preparation and administration	Referen-ces
*H. aegyptiacum*L.	Snake bites and scorpion stings	Somalia	Roots	Pulp (E)	(21)
	Dandruff	Ethiopia	Leaves	Paste (E)	(22)
*H. indicum*L.	Eye lotion, cleaning of ulcers	Nigeria	Whole plant	Infusion (E)	(23)
	Infected gums	Gabon	Leaves	Powder (I)	
	Yaws	Tanzania	Roots	Extract (I)	
	Diuretic	Madagascar	Whole plant	Infusion (I)	
	Intractable fever, ulcers, venereal diseases and sore throat	Jamaica	Whole plant	Decoction (I)	(24)
	Head lice	West Indies	Whole plant	Paste (E)	(25)
	Rheumatism	India	Leaves	Paste (E)	(26)
	Insect bites, stings and skin rashes	India	Leaves	Decoction (E)	(27, 28)
	Whooping cough in children	Eastern Nicaragua	Leaves, roots	Decoction (I)	(29)
	Scorpion stings and bug bites	Amazon	Leaves, roots	Paste (E)	(30)
	Putrefaction, pyoderma and ringworm infection	Malaysia	Whole plant	Paste (I)	(31)
	Gonorrhea	Burma	Whole plant	Decoction (I)	
*H. amplexicaule*L.	Cough and fever	Mauritius	Whole plant	Decoction (I)	(23)
*H. supinum*L.	Tumors	Namibia	Whole plant	Mixture of pulped plant with water(E)	
*H. strigosum*Willd.	Abscesses of the breast	Tanzania and Congo	Whole plant	Plant mixture with butter (E)	(32)
	Laxative, diuretic, sore eyes and gum boils	India	Leaves	Juice (I)	(33)
*H. europaeum*L.	Acne and cattle wounds	Nara desert, Pakistan	Whole plant	Paste with sesame oil (E)	(34)
*H. curassavicum*L.	Boils		Roots	Paste (E)	
*H. crispum*Desf.	Cooling agent and lactagogue in cattle		Whole plant	Crushed in water (I)	
*H. eichwaldi*Steud.	Ear ache	Cholistan desert, Pakistan	Leaves	Raw (I)	(35)
H.	Eye diseases	Kalat, Nimargh and	Leaves	Extract (E)	(36)

*dasycarpum*Ledeb.		Zehri, Pakistan			
*H. steudneri*Verdc.	Cuts to stop bleeding and to prevent infection	Tanzania	Leaves	Juice (E)	(23)
	Squeezed over bruises	Namibia	Whole Plant	Plants are dipped in boiling water(E)	
	Eyes of cattles to cure conjunctivitis	Kenya and Tanzania	Leaves	Juice (I)	
*H. ramosissimum*Lehm.	Burns	Mauritania	Leaves	Sap (E)	

(E) = Externally; (I) = Internally

PHARMACOLOGICAL ACTIVITIES OF GENUS *HELIOTROPIUM*

Plants of the genus *Heliotropium*display a wide range of pharmacological activities.Different biological activities of extracts and their bioactive constituents provide a basis for better understanding of the underlying mechanisms involved(37).A brief overview of their activities have been presented here (also see Table 2 & 3).

Antibacterial activity

Antibacterial activity of the methanolic extract of whole plant of *H. strigosum* showed different zones of inhibition which are formed by crude extract, ethyl acetate fraction, chloroform fraction, aqueous fraction, n-hexane fraction and standard doxycycline (30µg). All these fractions are active against *Staphylococcusepidermidis* with the minimum inhibitory concentrations (MICs) of 8, 6, 8, 8, 6 mg/mlbut no fraction showed any activity against *Escherichiacoli.* The activity against methicillin resistant *Staphylococcusaureus* was only shown by ethyl acetate fraction with the zone of inhibition recorded is 8mm. Other fractions and crude extract did not demonstrate any antibacterial activity against methicillin resistant *S. aureus.* The standard doxycycline fraction showed activity against all bacteria used in the bioassay (14). From the ethanolic extraction of aerial parts of *H. subulatum* two fractions such as petroleum ether and chloroform experienced the significant activity against bacteria such as *E. coli*,*Streptococcuspneumoniae*,*Bacillussubtilis*, *B. anthracis*and*S. aureus*. Among these two fractions, the chloroform fraction retains maximum activity against *E. coli* with the zone of inhibition logged is 12.61±0.361 (38). The methaolic extract of aerial parts of *H. indicum* has broad spectrum of antibacterial activity against *S. aureus*,*Streptococcuspyogenes*, *S. pneumonia*,*Salmonella typhi*,*Corynebacterium ulcerans*, *E. coli* and*Klebsiellapneumonia* withthe zones of inhibition 32, 35, 30, 0, 0, 28, 27 mm verified for these bacteria (39).Methanol extract of the leaf of *H. indicum* was evaluated for its antibacterial activity against five bacterial isolates comprising of four gram-negative bacteria including *E.*

coli,*Pseudomonasaeruginosa*,*Klebsiella species* and *Proteusmirabilis* and one gram positive, *S. aureus* at the concentrations of 6.25, 12.5, 25, 50, 100 and 200 mg/ml of plant extract respectively. Both *S. aureus* and *Klebsiella spp*. were inhibited at 50, 100 and 200 mg/ml with MIC of 3 mg/ml while *P. aeruginosa* and *P. mirabilis* with MIC of 10 mg/ml were inhibited at 100 mg/ml and 200 mg/ml and *E. coli* with MIC of 20 mg/ml was inhibited only at 200 mg/ml concentration of the extract respectively (40). The essential oil of *H. europaeum* obtained from the process of hydrodistillationwere tested on *B. subtilis*,*S. aureus*, *E. coli* and *S. typhi*. The consequences showed the majorantibacterial activity against *B. subtilis* and *S. typhi*respectively(41). Different fractions of methanolic extract such as chloroform, petroleum ether, ethyl acetate and aqueous fraction of aerial parts of *H. bacciferum* showed significant antibacterial activity against *S. aureus*, *B. cereus*, *E. coli*, *Salmonella enteritidis*and *P. aeruginosa.* The chloroform and petroleum ether fraction showed that it inhibits the growth of *S. aureus*, *B. cereus* and *P. aeruginosa* with MIC of 15.625 µg/ml, *S. enteritidis*with 62.5 µg/ml and *E. coli* with 125 µg/ml respectively. The aqueous extract exhibited that it prevents the growth of *S. aureus*,*B. cereus* and *S. enteritidis*with MIC of 7.8125 µg/ml and *E. coli*, *P. aeruginosa* with 15.625 µg/ml correspondingly (42).

Antifungal activity

Different fractions of methanolic extract of whole part of *H. strigosum* revealed prominent antifungal activity. The chloroform and n-hexane fractions exposed antifungal activity against *Aspergillus niger*, *A. fumigatus*,*Fusarium solani and A. flavus* with the MIC of 2.5 mg/ml. Crude extract was inactive against *A. flavus*but showed activity against *A. niger*, *A. fumigatus* and *F. solani* with MIC of 2.5 and 3.5 mg/ml. Ethyl acetate and aqueous fractions did not show activity against any fungal strain (14). The ethanolic, chloroform, petroleum ether, aqueous and residue extracts of stem and leaves of *H. curassavicum* exhibited significant in vitro antifungal activity. The diffusable metabolites of *H. curassavicum* demonstrated noticeable inhibitory effects against *Penicilliumcitrinum* followed by *Candida albicans*(43).The alcoholic extract of whole plant including roots of *H. indicum* was tested against certain fungi named as *A. niger*, *A. wentii*and *Rhizopusoryzae*. The extract exhibited significant activity at the concentration of 100 µg/ml with the inhibition area logged against *A. niger*, *A. wentii*and *R. oryzae* is 8.00, 9.00, 8.00 mm respectively as compared with the standard fluconazole (44).

Antioxidant activity

The crude extract and subsequent sub-fractions of whole plant of *H. strigosum* were screened for antioxidant activity by using 1,1-diphenyl-2-picrylhydrazyl scavenging assay (DPPH). The n-hexane fraction of methanolic extract displayed strong antioxidant activity with an EC_{50} value of 35.53 µg/ml while ethyl acetate fraction also showed significant antioxidant activity with an EC_{50} value of 30.34 µg/ml. The aqueous fraction also revealed good antioxidant activity and had an EC_{50} value of 20.51 µg/ml. The crude extract did not show any antioxidant activity, same was true about the chloroform sub-

fraction (14).The flavonoids isolated from the resinous exudate of *H. sinuatum* revealed significant antioxidant activity (45). The chloroform and methanolic extract of whole plant material of *H. zeylanicum* hold substantial antioxidant activity along with itsantidiabetic andantihyperlipidemic effects(46).

Anti-inflammatory activity

The crude extract of the whole plant of *H. strigosum* and its subsequent solvent fractions showed anti-inflammatory activity in carrageenan-induced edema and xylene-induced ear edema. In carrageenan-induced edema, the ethyl acetate fraction was most dominant with 73.33% inhibition followed by hexane fraction (70.66%). When the extracts were tested against xylene-induced ear edema, ethyl acetate and hexane fractions were found active with 38.21% and 35.77% inhibition, respectively (47). The chloroform extract of dried leaves of *H. indicum* demonstrates significant anti-inflammatory activity in carrageenan-induced edema and cotton pellet granuloma models of inflammation. The extract of *H. indicum* with a concentration of 150mg/kg body weight showed maximum 80.0% inhibition on carrageenan-induced raw paw edema compared with the positive control drug, diclofenac sodium (48).

Antinociceptiveand anticonvulsant activity

The crude extracts and subsequent solvent fractions of *H. strigosum* were tested for antinociceptive and anticonvulsant activity in animal models. In acetic acid-induced writhing test, crude extract, n-hexane, ethyl acetate and aqueous fractions established marked reduction of nociception at test doses 50, 100 and 200 mg/kg intraperitoneally. When challenged against thermally induced pain model, pretreatment of extracts demonstrated prominent enhancement at test doses 50, 100 and 200 mg/kg intraperitoneally. In both tests, inhibition of noxious stimulation was in a dose-dependent manner, and the ethyl acetate fraction was most dominant. Thus, the extracts of *H. strigosum*showed significant antinociceptive effect in both centrally and peripherally acting pain models (49). The chloroform extract ofdried leaves of *H. indicum* was examined for antinociceptive activity in hot plate model in male swiss albino mices. The extract of *H. indicum* with a concentration of 150 mg/kg body weight showed maximum 82.79% antinociception in the hot-plate test as compared to a control drug, pentazocine(48). The methanol extract of the dried roots of *H. indicum* was observed for substantial antinociceptive activity in acetic acid-induced writhing mices. The extract produced significant inhibition in acetic acid-induced writhing mices at the oral doses of 250 and 500 mg/kg body weight comparable to the standard drug diclofenac sodium at the dose of 25 mg/kg of body weight (50).

Antineoplastic and antiviral Activity

The n-hexane, dichloromethane fractions of ethanolic extract of aerial parts of *H. subulatum* and its subsequent crude extract was examined forsignificant antineoplastic and antiviral activities. For

antineoplastic activity, it was found that ethanol extract, n-hexane and dichloromethane fractions revealed significant activity with the inhibition of 19.3 &32.2 %, 22.5 & 16.1 %, 09.6 & 06.4 % at the dose of 50 and 100 µg/kg/day. For antiviral activity, it was revealed that theethanol and hexane crude extracts showed significant activity to *Coxsackie, Poliomyelitis* and *Measles* at concentrations of 500 & 100 µg/ml respectively (51).

Cytotoxicity and phytotoxicity

The crude extract of *H. strigosum* and its resultant fractions possessed strong cytotoxic and phytotoxic activity. In brine shrimp toxicology assays, the fractions of ethyl acetate and chloroform showed strong cytotoxic actions with LD_{50} 8.3µg/ml and LD_{50} 8.8µg/ml respectively, followed by relatively weak crude methanolic extractwith LD_{50} 909µg/ml and n-hexane fraction with LD_{50} 1000µg/ml while in the case of phytotoxic activity against *Lemnaacquinoctialis*, strong phytotoxic effect was showed by ethyl acetate fraction with LD_{50} 91.0µg/ml respectively while chloroform fraction, plant crude extract and n-hexane fraction caused 50%, 30.76 ± 1.1% and 30.7 ± 1.1% inhibitory action respectively at maximum concentration that is 1000 µg/ml (52). From the ethanolic extract of aerial parts of *H. subulatum*, n-hexane, dichloromethane fractions of extract and crude extract were examined for cytotoxic activity. It was revealed that that n-hexane fraction showed potent cytotoxic activity at a concentration of 3mg/ml (51). The aqueous extract of senescent leaves of *H. foertherianum* and one of its isolated compounds rosmarinic acid were assessed for its effects against a pacific ciguatoxin (P-CTX-1B) in the neuroblastoma cytotoxicity assay and the receptor-binding assay. The cytotoxicity elicited by P-CTX-1B was inhibited by the aqueous extract of *H. foertherianum* at concentrations up to 2734µg/ml and by rosmarinic acid up to 607 µg/ml, the concentrations at which they began to be cytotoxic (53). The methanolic extract of dried plant material of aerial parts of *H. zeylanicum* was examined for cytotoxicity *in vitro* against MRC5 human cell line. The extract demonstrated significant cytotoxic activity with an IC_{50} of 13.00 µg/ml (54).The methanolic extract of the dried roots of *H. indicum* was studied for considerable cytotoxic activity by using the brine shrimp lethality bioassay. The extract showed different mortality rate at different concentrations with the LC_{50} of 47.86 µg/ml and LC_{90} of 75.85 µg/ml respectively (50).

Antiproliferative and antitumor activity

Ethanolic extract of whole plant of *H. indicum* revealed substantial anti-proliferative activity against SK-BR-3 human breast adenocarcinoma cell line using MTT [3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide]assay. The IC_{50} value of extract is 34 ± 9.09 µg/ml as compared to the standard drug used, paclitaxel with IC_{50} value 22.20 ± 2.30 µg/ml (55). The petroleum ether extract of aerial parts of *H. ovalifolium* were tested to identify its ability to inhibit specific cytokines, interleukin-6 (IL-6) at the dose of 7.6 µg/ml respectively (56).The methanolic extracts of stem and leaf of *H.*

*indicum*possessed a significant antitumor activity andIC_{50} for both the extracts found to be 200µg/ml, whereas stemextracts exhibited excellent activity up to 64.5% at 200µg/mlfollowed by leaf extract up to 49.67% at 200µg/ml respectively (57).

Antituberculosisactivity

The volatile oil isolated from the aerial parts of *H. indicum* was tested for antituberculosis activity and the outcomes exhibited significant activity against *Mycobacterium tuberculosis* attenuated strain with the MIC of 20.8 µg/ml as compared to the standard drugs used that were isoniazide and kanamycin (58).*Antidiuretic activity*

The methanol extract of the dried roots of *H. indicum* was examined for antidiuretic activity by observing different urination parameters of mices. The study revealed that the extract has a marked diuretic effect by the electrolyte loss ratio (Na^+/K^+ excretion ratio was 1.38 and 1.45 at the doses of 200 and 400 mg/kg respectively) as that of the standard diuretic furosemide whose ratio was 1.37 (50).

Histo-Gastroprotective activity

The histo-gastroprotective activity of the aqueous extract of the dried leaves of *H. indicum*was evaluated in wistar rats, where ulceration of the gastric mucosa was induced by the oral administration of 80mg/kg/body weight of Indomethacin. The aqueous extract exhibited histo-gastroprotective effect at the dose of 100, 200 and 400mg/kg/body weight respectively in a dose dependent manner. This effect of the aqueous extract might be due to the presence of its tannins, alkaloids and saponins (59).

Nephroprotective effect

The nephroprotective effect of methanolic extract of dried roots of *H. eichwaldi* was estimated in male swiss albino mices against cisplatin-induced acute renal damage. The results revealed that methanolic extract can be reflected as a potential contestant for protection of nephrotoxicity induced by cisplatin at the dose of 200 mg/kg and 400 mg/kg (60).

Wound healing activity

The petroleum ether, chloroform, methanol, and aqueous extracts of leaves of *H. indicum*were separately evaluated for their wound healing activity in rats using excision (normal and infected), incision, and dead space wound models. In the incision wound infection model, group of animals treated with methanolic extract demonstrated significant healing activity with the period of epithelialization that was 16.23 ± 0.98 days as compared to the group of animals treated with standard drug nitrofurazonewith the period of epithelialization 13.5 ± 1.54days. It is also observed in this model that the methanol and aqueous extract treated animals showed significant increase in the wound breaking strength up to 478.55 ± 12.63g and 378.63 ±18.02gwhereas the other extracts are unsuccessful to produce significant effects (61).

Anti-plasmodial activity

The ethanolic extract of flowers, roots and stems of *H. europaeum var*. *lasiocarpum* revealed significant anti-plasmodial properties against *Plasmodium falciparum*. At the concentration of 100, 50, 25 μg/ml, the ethanolic extract of flowers demonstrated 33, 10, 6 % of inhibition while the extract of roots revealed 91, 59, 19 % of inhibition and the extract of stems shown 80, 72, 37 % of inhibition at the same concentration (62). The dichloromethane, methanol and aqueous extracts of fresh plant material of *H. indicum* were tested for significant anti-plasmodial activity against *P. falciparum*. The dichloromethane extract was generally more active than other extracts but among these extracts, no one exposed the substantial anti-plasmodial activity. *H.indicum*revealed some anti-plasmodial activity because of its only use in the treatment of few malarial symptoms named as hyperthermias or colics(63). The methanolic extract of dried plant material of aerial parts of *H. zeylanicum* was examined for anti-plasmodial activity *in vitro* against chloroquine-resistant strain (KI) and sensitive strain (FCR3). The extract demonstrated significant anti-plasmodial activity with an IC_{50} of 8.41 μg/ml (54).

Antifertility activity

The n-hexane and benzene fractions of the ethanol extract of *H. indicum*were studied for antifertility activity in rats using anti-implantation and abortifacient models. The study revealed that the effect of ethanolic extract and its n-hexane and benzene fractions on percentage pre-implantation lost in pregnant rats as 30% and 35%, 40% and 60%, 30% and 50% at the dose of 200 & 400 mg/kg body weight respectively while the effect of ethanolic extract and its fractions on percentage abortion in pregnant rats as 50% and 60%, 50% and 60%, 30% and 60% respectively at the same dose. Thus, the *H. indicum* study revealed better abortifacient activity and moderate anti-implantation and sperm motility (64).

Anti-cataract activity

The ethanolic leaf extract of *H. indicum*was found to be having anti-cataract activity in the galactose induced rats. The results revealed that ethanolic extract at the dose of 200 mg/kg along with Vitamin E whose dose was 50 mg/kg and 30% galactose diet leads to the significant increase in the glutathione lens, soluble proteins and water contents as compared to the standard galactose diet given to the rats. Thus, it was concluded that *H. indicum* leaf extract possessed protective action against galactose induced cataract in rats (65).

Analgesic activity

The aqueous and ethanolic extract of fresh plant material of *H. indicum* demonstrated the significant analgesic activity in formalin-induced pain model in mice. For comparison of analgesic effect, morphine and diclofenac sodium were used as a reference opioid and NSAID, respectively. At the dose of 30-300 mg/kg, the aqueous and ethanolic extracts inhibited both the first and second phases of formalin-induced nociception in a dose dependent manner. Oral administration of aqueous extract at the dose of 1-5 g/kg in

formalin-induced mice were tolerated in acute toxicity studies but oral administration of 1-2 g/kg of the extracts in sprague-dawely rats produced pathologic effects on heart, kidney, liver and lungs. Therefore, instead of the fact that aqueous and ethanolic extracts have analgesic activity, it could have a cumulative toxic effects. Thus, prolonged and continuous use is not recommended (66).

Table 2. Pharmacological activities of some selected phytoconstituents of genus *Heliotropium*

Species	Extract	Isolated compounds	Biological activities evaluated	References
*H. subulatum*Hochst.	Ethanolic extract of aerial parts	Subulacine-N-oxide, 7-angeloyl heliotrine, retronecine, heliotric acid, heliotrine	Antibacterial, antifungal, antineoplastic, antiviral and cytotoxicity	(38, 51)
*H. ellipticum*Ledeb.	Ethanolic extract of whole plant	β-sitosterol, stigmasterol, β-amyrin, friedelan-β-ol, cycloartenone, β-amyrin acetate, friedelin, europine, heliotridine, lasiocarpine, lasiocarpine-N-oxide	Antibacterial and antifungal	(67, 68)
H. marifolium Koen.	Ethanolic extract of whole plant	β-sitosterol, stigmasterol, β-amyrin, friedelan-β-ol, cycloartenone, β-amyrin acetate, friedelin, epifriedenyl acetate	Antibacterial and antifungal	(69)
*H. filifolium*Miers.	Dichloromethane extract of cuticle	3′-hydroxy-2′,2′,6′-trimethyl-3H-spiro[1-benzofuran-2,1′-cyclohexane]-5-carboxylic acid, methyl 3′- acetyloxy-2′,2′,6′- trimethyl-3H-spiro[1-benzofuran-2,1′-cyclohexane]-5-carboxylate, methyl 3’-isopentanoyloxy-2’,2’,6’-trimethyl-3H-spiro[1-benzofuran-2,1’-cyclohexane]-5-carboxylate, methyl 3’-benzoyloxy-2’,2’,6’,-trimethyl-3H-spiro[1-benzofuran-2,1’-	Antibacterial	(70)

		cyclohexane]-5- carboxylate		
H. glutinosum Phil.	Dichloromethane extract of fresh plant material	4-methoxy-3-[(2)-7'-methyl-3'-hydroxymethyl-2',6'-octadienyl] phenol, 5,3'-dihydroxy-7,4'-dimethoxyflavanone, 5,4'-dihydroxy-7-methoxyflavanone, 4'-acetyl-5-hydroxy-7-methoxyflavanone	Antioxidant	(71)
H. taltalense Phil.	Dichloromethane extract of fresh plant material	Naringenin, 3-O-methylgalangin, 7-O-methyleriodictiol, filifolinol, filifolinylsenecionate	Antioxidant	(72)
H. sclerocarpum Phil.	Dichloromethane extract of fresh plant material	Filifolinol, naringenin, 3-oxo-2-arylbenzofuran	Antioxidant	(73, 74)
*H. filifolium*Miers.	Dichloromethane extract of fresh plant material	Filifolinol, filifolinylsenecionate, filifolinone, filifolinoic acid	Antiviral	`(75)
H. floridum A.	Ethanolic extract of aerial parts	3'-acetyltrachelanthamine, floridine, floridinine, floridimine, heliovicine	Anti-feedant	(76)
*H. filifolium*Miers.	Dichloromethane extract of fresh plant material	Filifolinone	Immunostimulant	(77)
*H. ovalifolium*Forssk.	Petroleum ether extract of aerial parts	4, 7, 8-trimethoxy-naphthalene-2-carboxylic acid, 6-hydroxy-5,7-dimethoxy-naphthalene-2-carbaldehyde	Anti-inflammatory	(56)

Table 3. Antibacterial, antifungal, cytotoxic, antiviral and anti-inflammatory activities of some bioactive constituents of genus *Heliotropium*

Pharmacological activity	Species	Compound	Results	Reference
Antibacterial	*H. subulatum*	7-angeloyl heliotrine	ZoI: 16mm	(38)
	H. ellipticum	Cycloartenone	ZoI: 12mm	(67)
		Friedelin	ZoI: 9mm	
		β-amyrin	ZoI: 4mm	
		β-amyrin acetate	ZoI: 8mm	
		Europine	ZoI: 10mm	(68)
		Lasiocarpine	ZoI: 12mm	
		Lasiocarpine-N-oxide	ZoI: 9mm	
	H. marifolium	Epifriedenyl acetate	ZoI: 17mm	(69)
		Friedelan-β-ol	ZoI: 15mm	
		β-sitosterol	ZoI: 16mm	
		β-amyrin acetate	ZoI: 14mm	
	H. filifolium	Filifolinol	MIC: 512µg/ml	(70)
Antifungal	*H. subulatum*	7-Angeloyl heliotrine	ZoI: 10mm	(38)
	H. ellipticum	Cycloartenone	ZoI: 7mm	(67)
		Friedelin	ZoI: 9mm	
		β-amyrin	ZoI: 4mm	
		β-amyrin acetate	ZoI: 7mm	
		Europine	ZoI: 7mm	(68)
		Lasiocarpine-N-oxide	ZoI: 8mm	
	H. marifolium	Epifriedenyl acetate	ZoI: 8mm	(69)
		Friedelan-β-ol	ZoI: 10mm	
		β-sitosterol	ZoI: 8mm	
		β-amyrin acetate	ZoI: 9mm	
	H. floridum	3'-acetyltrachelanthamine	ZoI: 49mm	(76)
Antiviral	*H. filifolium*	Filifolinylsenecionate	ZoI: 43mm	(75)
		Filifolinone	ZoI: 21mm	
Anti-feedant	*H. floridum*	3'-acetyltrachelanthamine	EC_{50}:1.79µgcm^{-2}	(76)
Anti-inflammatory	*H. ovalifolium*	4, 7, 8-trimethoxy-naphthalene-2-carboxylic acid	IC_{50}: 2.4µg/ml	(56)
		6-hydroxy-5,7-dimethoxy-naphthalene-2-carbaldehyde	IC_{50}: 2.00µg/ml	
Antineoplastic	*H. subulatum*	Subulacine-N-oxide	% Inh.: 30.2	(51)
		7-angeloyl heliotrine	% Inh.: 41.7	
		Heliotrine	% Inh.: 25.8	
Cytotoxicity	*H. filifolium*	Filifolinylsenecionate	EC_{50}: 400 µg/ml	(75)

ZoI = Zone of inhibition; EC_{50}= Effective concentration that gives half-maximal response; IC_{50}= Inhibitory concentration where the response is reduced by half; % Inh.= % inhibition.

PHYTOCHEMICAL EVALUATION OF GENUS *HELIOTROPIUM*

A variety of constituents are identified and isolated from different species of genus *Heliotropium*which are phytochemically active and have significant therapeutic effects. Many classes of organic compounds such as pyrrolizidine alkaloids (PAs), phenolic compounds, terpenoids and quinones are very abundantly present in *Heliotropium*. Pyrrolizidine alkaloids (PAs) are mainly occur as esters being accompanying with characteristic mono or dibasic acids known as necic acids. Triterpenoids are the compounds which contain almost 30 carbon atoms and occur as esters or glycosides. Flavonoids are the largely occurring phenols formed of three acetate units and a phenylpropane unit (78). A list of phytochemically active constituents is shown as under (see Table 4).

Table 4. Chemical constituents isolated from plants of genus *Heliotropium*

Class	Species	Compounds	References
Pyrrolizidine alkaloids (PAs)	*H. acutifolium*Kir.	Heliotrine	(79)
	*H. amplexicaule*Vahl.	Indicine	(80)
	*H. angiospermum*Murr.	Subulacine, lindelofidine, retronecine, supinidine, trachelanthamidine	(81)
	*H. arbainense*Fres.	Europine, heliotrine, lasiocarpine	(82)
	H. arborescens L.	Indicine, 3'-acetylindicine, lasiocarpine	(83)
	*H. arguzioides*Kir.	Heliotrine, trichodesmine	(84)
	*H. bacciferum*Forssk.	Europine, heliotrine, heleurine and their N-oxides, supinine	(85, 86)
	*H. bovei*Boiss.	Europine, 7-acetyleuropine, lasiocarpine, 5'-acetyllasiocarpine, lasiocarpine N-oxide, 5'-acetyllasiocarpine N-oxide	(87)
	H. bracteatum R.	Helibractinecine, retronecine, helibracteatinine, helibracteatine	(88, 89)
	H. bursiferum C.	7-Angeloylretronecine	(90)
	*H. circinatum*Griseb.	7-angeloylheliotrine, echinatine, europine, heleurine, heliotrine, lasiocarpine	(91)
	H. crassifolium Phil.	Ilamine, europine and their N-oxides	(92)
	H. curassavicum L.	Coromandaline, coromandalinine, curassavine, curassavinine, curassanecine, heliocurassavine, heliocurassavinine, heliocurassavicine, heliocoromandaline, heliovicine, 7-angeloylheliotridine, trachelanhamidine, retronecine, supinidine	(81, 93-95)
	*H. curassavicum*var. *argentium*nJohnst.	9-(3'-isovaleryl) viridiflorylretronecine, 9-(3'-acetyl) viridiflorylretronecine	(96)
	*H. dasycarpum*Ledeb.	Heliotrine	(97)
	*H. digynum*Forssk.	Europine, heliotrine, 7-angeloylheliotrine, lasiocarpine	(98)

	*H. dissitiflorum*Boiss.	Heliotrine, heliotrine N-oxide, europine, 5'-deoxylasiocarpine	(99)
	*H. eichwaldii*Steud.	Heliotrine, 7-angeloylheliotrine, lasiocarpine	(100)
	H. esfandiarii A.	Europine, europine N-oxide	(101)
	H. europaeum L.	Europine, acetyleuropine, heleurine, heliotrine, 7-angeloylheliotrine, lasiocarpine, 6-acetyllasiocarpine, heliotrine N-oxide, dehydroheliotrine, 5'-acetyllasiocarpine N-oxide, N-(dihydropyrrolizinomethyl)-heliotrine, supinine	(102, 103)
	H. hirsutissimum Gr.	Europine, heliotrine, heleurine, lasiocarpine, 3'-acetyllasiocarpine, 5'-acetyllasiocarpine, supinine, N-oxides of acetylasiocarpine, 3'-acetyleheliosupine	(80, 104)
	H. indicum L.	Echinatine, helindicine, heliotrine, heleurine, indicine, acetylindicine, indicinine, lasiocarpine, lycopsamine, rinderine, supinine, lindelofidine, retronecine, supinidine, trachelanthamine	(81, 93, 105, 106)
	H. keralense S.	Intermedine, isolycopsamine, retronesine	(107)
	*H. megalanthum*Johnst.	Lycopsamine, megalanthonine	(108)
	H. olgae B.	Heliotrine, incanine	(109)
	*H. ovalifolium*Forssk.	Heliofoline, retronecine	(110)
	*H. rotundifolium*Lehm.	Europine, 5'-acetyleuropine, heliotrine, lasiocarpine	(111, 112)
	*H. spathulatum*Rydb.	Amabiline, coromandaline, coromandalinine, heliovicine, curassavinine, curassavine, heliospathine, heliospathuline, lindelofidine, retronecine, supinidine, trachelanthamidine	(93, 113)
	*H. steudneri*Verdc.	Lycopsamine	(114)
	H. strigosum Willd.	Strigosine, trachelanthamidine	(115, 116)
	H. supinum L.	Echinatine, heliosupine, heliotrine, 7-angeloyl heliotrine (and its trachelanthic and viridifloric esters), lasiocarpine, supinine	(114, 117)
	*H. transalpinum*Vell.	Intermedine, indicine, lycopsamine, rinderine, 3'-acetylrinderine, supinine	(118)
	*H. transalpinum*var. *transalpinum*	Transalpinecine, subulacine	(119)
Terpenoids	*H. ellipticum*Ledeb.	β-sitosterol, stigmasterol, β-amyrin, friedelan-β-ol, cycloartenone, β-amyrin acetate, friedelin	(67)
	H. marifolium Koen.	β-sitosterol, stigmasterol, β-amyrin, friedelan-β-ol, cycloartenone, β-amyrin acetate, friedelin, epifriedenyl acetate	(69)

Geranyl aromatic derivatives (Flavonoids)	*H. glutinosum*Phil.	4-methoxy-3-[(2)-7'-methyl-3'-hydroxymethyl-2',6'-octadienyl] phenol, 5,3'-dihydroxy-7,4'-dimethoxyflavanone, 5,4'-dihydroxy-7-methoxyflavanone, 4'-acetyl-5-hydroxy -7-methoxyflavanone	(71)
	H. taltalense Phil.	Filifolinol, filifolinylsenecionate, naringenin, 3-O-methylgalangin, 7-O-methyleriodictiol	(72)
	H. sclerocarpum Phil.	Filifolinol, naringenin, 3-oxo-2-arylbenzofuran	(73, 74)
	*H. filifolium*Miers.	Filifolinol, filifolinylsenecionate, filifolinone, filifolinoic acid	(75)
		Filifolinone	(77)
	H. strigosum Willd.	Taxifolin (Dihydroquercetine), quercetin	(120)
Quinones	*H. ovalifolium*Forssk.	Heliotropinones A, heliotropinones B	(121)

(Necine) (Otonecine)

R_1= H ; R_2 = H R_1= H ; R_2 = H

IsoretronecanoleSupinidine

R_1= OH ; R_2 = H R_1= H ; R_2 = H

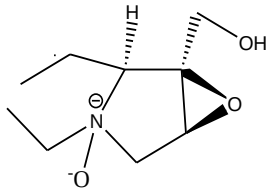
PlatynecineRetronecine

R_1= OH ; R_2 = H R_1= H ; R_2 = H

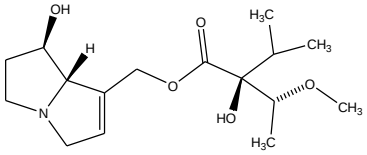
HastanecineHeliotridine

R_1= OH ; R_2 = OH

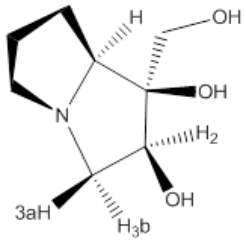
Rosmarinecine



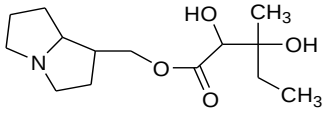
(Amabiline) (Indicine) (Subulacine-N-oxide)

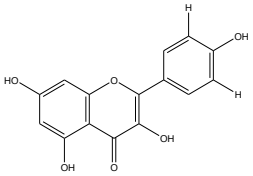


(Heliotrine) (Lycopsamine) (Megalanthonine)

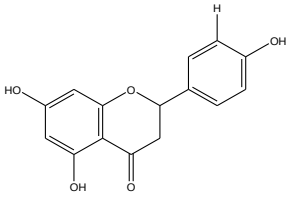


(Monocrotaline) (Helindicine) (Transalpinecine)



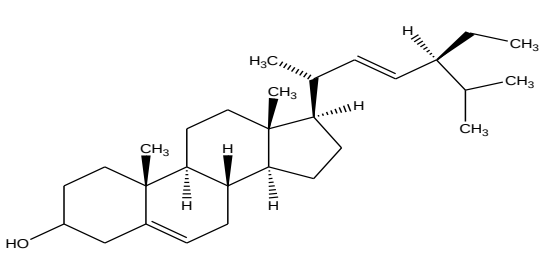


(Strigosine) (Taxifolin) (Quercetin) (Kaempferol)

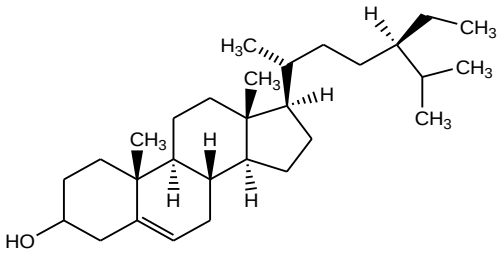


(Naringenin) (Filifolinol)

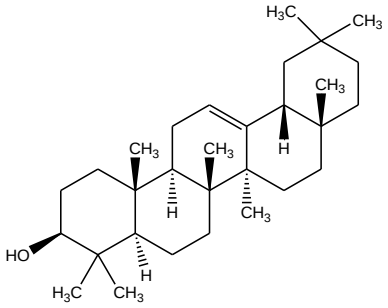
Figure 1. Structures of some of the pyrrolizidine alkaloids (PAs) and flavonoids from genus *Heliotropium*



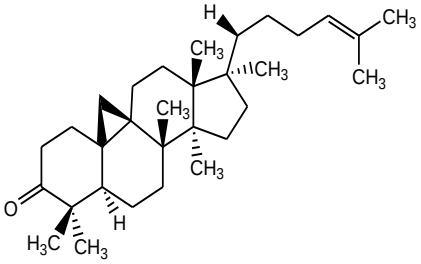
(Stigmasterol)



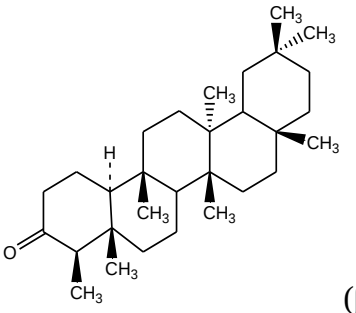
(β-sitosterol)



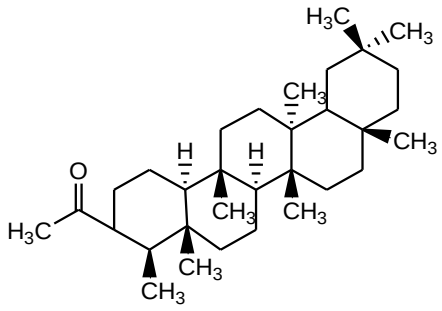
(β-amyrin)



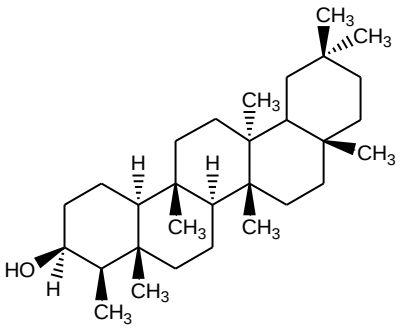
(Cycloartenone)



(Friedelin)



(Epifriedenyl acetate)



(Friedelan-3β-ol)

(Heliotropinones A)(Heliotropinones B)

Figure 2. Structures of some of the triterpenoids and quinones from *Heliotropium* species

TOXICOLOGY STUDIES ON DIFFERENT SPECIES FROM GENUS *HELIOTROPIUM*

In spite of enormous benefits, species of genus *Heliotropium* are very poisonous in nature due to presence of pyrrolizidine alkaloids. Human deaths reported due to accidental consumption of these species in many countries. Liver damage was caused by pyrrolizidine alkaloids because they were responsible for hepatic-veno occlusive disease. A disease which became endemic in Afghanistan due to consumption of wheat crop was spread due to contamination with seeds of *Heliotropium* species (122). The clinical symptoms associated with the liver damage resemble those of cirrhosis, hepatic tumors, Budd-Chiari Syndrome with portal hypertension and obliteration of small hepatic veins due to cross linking of DNA strands, hepatocytes damage occur because of formation of pyrrole metabolites from pyrrolizidine alkaloids by liver microsomal oxidation. Pyrrolizidine alkaloids produce necrosis or inhibition of mitosis that depend upon the dose but independent on route of administration (123, 124). In Australia, a disease in broiler chickens was reported due to heliotrine, a pyrrolizidine alkaloid isolated from *H. indicum*. The clinical signs associated with this disease were depression, hepatic degeneration and ascites. Experimental work showed that intake of *H. europaeum* in Australia produced identical lesions that were seen in the natural disease due to presence of heliotrine and lasiocarpine in this species (125).

ANATOMICAL AND MORPHOLOGICAL STUDIES OF GENUS *HELIOTROPIUM*

A systemic anatomical and morphological studies on leaves and stems of different species of genus *Heliotropium* namely *H. strigosum*, *H. arbainense*, *H. longiflorum* DC., *H. petrocarpum* DC., *H. lasiocarpum* F., *H. zeylanicum*Burm. and *H. jizanense* O. was described by demonstrating the most valuable characters such as stem anatomy, pollen grains, hairs and stomata (126). Moreover, the leaf anatomy of four different *Heliotropium* species such as*H. strigosum,H. curassavicum,H. digynum, H. subulatum* were investigated (127). The stomatal analysis of leaves of *H. indicum*was also recognized (28). Furthermore, the comparison of anatomical characteristics of *H. ovalifolium*, *H. strigosum,H. bacciferum,H. supinum*, *H. sudanicum* A.was reported (128). Ghazaly, (129) conducted the pollen morphology of *H. bacciferum*. The epidermal morphology of *H. europaeum*, *H. dasycarpum* and *H. rigidum* DC. was also studied (130). In short, during these critical studies, the scientists mainly focused upon some of the leading anatomical and morphological features of leaves and stems of these species. These primary characteristics include venation of leaves, leaf measurements including length (cm), width (cm) and form of leaf, inflorescence measurements, different features of stomata mainly types and no. of stomata, length (mm) and width (mm) of stomata, different types and measurements of pollen grains and different studies of epidermal layers, cortex cells and pith cells.

CONCLUSION

Heliotropium has been traditionally used for treatment of gout, various inflammations, rheumatism, poisonous bites and skin diseases as a healing agent in various countries of the world. The medicinal importance of *H. indicum* is recognized worldwide and described in Indian, Brazilian, Ivorian and African folk medicine. In this paper, it is reviewed that *Heliotropium* species are highly valued for antimicrobial and antioxidant activities due to isolation of secondary metabolites like alkaloids, flavonoids and terpenoids. So it must say that *Heliotropium* can be used for the treatment of various bacterial and fungal infections in modern medicine as it is proved from folk medicinal studies. In addition with anti-inflammatory, antiviral, antitumor, antidiabetic and antihyperlipidemic as well as gastroprotective activities also enhance the medicinal value of *Heliotropium* in future. Moreover, the medicinal importance of pyrrolizidine alkaloids (PAs), flavonoids and terpenoidshas enhanced during the last few years, particularly due to the advancements in different analytical and preparative methods such as liquid chromatography (LC), spectroscopic techniques and availability of faster biological screening methods. All these techniques have been extensively applied. However, knowledge on biotechnology and molecular biology of these chemical groups in plants and their functions in plant insect interactions is still under observation. The pyrrolizidine alkaloids that are abundantly found in *Heliotropium* are responsible for its poisonous nature like hepatotoxicity, mutagenicity and hepatocarcinogenicity. The toxic nature of pyrrolizidine alkaloids is due to many reasons such as the plants which are the main source of these alkaloids are consumed in food and sometimes used in the form of herbal medicines. Food is contaminated with pyrrolizidine alkaloids because of the elongated storage of many plants such as *symphytum* and *petasites* that used as green vegetables. The other reason behind this toxicity is the contamination of food grains with the seeds of plants containing pyrrolizidine alkaloids. This was the case behind the epidemic poisoning of *Heliotropium* reported in different areas of the world (131). To overcome the poisoning of pyrrolizidine alkaloids, the intake of further plant material must be avoided. Usually, the nature of toxicity can be diagnosed on the basis of clinical signs and symptoms, the compatible changes occurred in biochemical mechanisms and the history of exposure. Inspiteof this strong evidence regarding the data that the plants of the genus *Heliotropium* have many effective therapeutic actions in the management of various sicknesses, some questions looking for reasonable answers. For example, the revolution of clinical trials, using a large number of patients, is still necessary to know about the unwanted effects, for the better examination of the mechanism of action of the active ingredients and an evaluation of the possible drug interactions among the active principles present in such plants needs to be approved before their use in clinical practice. Finally, the clinical use of these plants as phytopharmaceuticals will depend on the development of suitable analytical procedures necessary for

standardization of the numerous secondary metabolites existing in such herbals preparations. Thus, we conclude that plants of genus *Heliotropium* become a decent source of native medicines in upcoming era.

ACKNOWLEDGMENTS

I am really thankful to Prof. Dr. Muhammad Uzair, Dr. Tariq Javed, Dr. NaeemQaiser and Dr. Farooq-e-Azam for helping me in the preparation of this article.

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