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A REVIEW ON THE PHARMACOLOGICAL POTENTIAL OF THE GENUS *HELIOTROPIUM* (BORAGINACEAE)

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ABSTRACT

Plants provide an unlimited source of bioactive compounds that have immense potential applications in pharmaceutical industry. Phytomedicine is highly valued in the world and has high demand in many nations. A large number of medicinal plants are explored for the development of commercial drugs. It provides an area of better treatment with fewer side effects in the human physiological system. Most of the plants in the genus *Heliotropium* are considered as weed by farmers but finds a place in folk medicine by traditional medicinal practitioners due to its immense pharmacological potential. These plants have been used as traditional medicines by local heelers, where they prepared medicines in the form of decoction, pastes, juices and some have been taken orally. The plants belonging to the genus *Heliotropium* contain many pharmacologically important phytochemicals in the various parts of the plants and are reported to possess anti-microbial, anti-tumor, anti-tuberculosis, antiplasmodial, anti-cataract, anti-fertility, wound healing, anti-inflammatory, antinociceptive, analgesic and histo-gastro protective properties and many more. So, the present review on the genus *Heliotropium* opens a gateway to find out the promising species in the genus for the development of novel drugs that could combat various diseases including cancer.

KEYWORDS: *Heliotropium*, Boraginaceae, Pyrrolizidine alkaloids, antiproliferative activity.

INTRODUCTION

Herbal medicines are nowadays commonly used for the development of many drugs. In the United States, about 25% of the medicines dispensed contain an active plant derived material. Natural plant extracts as well as synthetic drugs that mimic the natural plant compounds are used to develop drugs.[1] Medicinal plants are found to contain substances that could be useful for the treatment of diseases or for the production of drugs. The healing power exhibited by the plants lies in the phytochemical constituents present in the different parts of the plant body and could elicit specific pharmacological actions in the human body. These phytochemicals which are referred to as secondary metabolites include alkaloids, flavonoids, phenolics, steroids, tannins, saponins and coumarins.[2] Most of the phytochemicals of plants possess medicinal potentials which are active against many diseases. The phytochemical analysis and bioactive studies of the plants is very important commercially and has great interest in pharmaceutical companies for the production of the new drugs for curing of various diseases.[3,4] *Heliotropium* is the large genus of the family Boraginaceae are mostly herbs and rarely shrubs or trees. *Heliotropium* is derived from the Greek word, 'helios' for 'sun' and 'trope' for 'turning', suggesting that the leaves and flowers of the plant turn towards sun.[5] Most of the plants of the family Boraginaceae are used as garden plants, and few others are found as weeds. The genus comprises about 300 different species, which are collectively known as "heliotropes". These are distributed in the tropical and temperate regions of the world in different habitats but only a few species have been systematically investigated.[6] Most of the plants are seen in waste places and unsettled lands.[7] The present review highlights the immense pharmacological potential of the genus *Heliotropium* and it is expected that the important phytochemical and bioactivity studies will be very useful for the researchers to find out the possibilities in the development of new drugs.

Taxonomic classification

Domain	Eukaryota
Kingdom	Plantae
Phylum	Spermatophyta
Subphylum	Angiospermae
Class	Dicotyledonae
Order	Boraginales
Family	Boraginaceae
Genus	*Heliotropium*
Species	*Heliotropium indicum*

Traditional uses of *Heliotropium*

Traditionally, the plant is widely used in different folklore systems of medicine all over the world. *Heliotropium indicum* is used to cure skin diseases, poison bites, stomachache and nervous disorders in Kancheepuram district of TamilNadu, India.[6] The leaf juice boiled with coconut oil is used to treat dandruff by the Malasar tribes of Coimbatore, India.[8] External application of fresh leaf extract in fresh cuts and wounds by the different tribe of Cachar district of Assam.[9] Rheumatism is treated with external application of leaf paste in Rayal Seema in Andhra Pradesh, India and for skin infection in Nicaragua. *H. indicum* is believed to be useful in treatment of malaria, abdominal pain and dermatitis in some African countries. The decoction of both leaf and root together is used for the treatment of whooping cough in children in Eastern Nicaragua.[6] The Africans used the plant as an analgesic, diuretic and for wound cleansing.[10] In Jamaica, the decoction of the plant is applied external to the vaginal cavity to induce abortion in females and also administered rectally to treat local sores in the rectum. The decoction of the leaves is abortive in large dose and emanagogue in small doses.[11] The sap of the stem is orally administered by the females for treating dysmenorrhea.[12] The infusion of the flower is taken orally for the treatment of menorrhagia in Jamaica.[8] In Thailand it is believed that the dried inflorescence can produce permanent sterilization when taken orally in females.[13] Leaf and root paste together is applied externally for treatment of sores and warts in Taiwan.[14] The plant is applied to treat pyoderma and ringworm infection in Malaysia. In Burma the whole plant decoction is used to treat gonorrhea and leaves infusion is used to soothe mouth sprue. In Philippines, the dried roots are taken orally to promote menses and the seeds are used to treat cholera, malaria, and for wound-healing.[15] The curative property of *H. indicum* against typhoid was mentioned in Rajanighantu—an important lexicon Ayurvedic material media written in the 12th/13th century.[16] The whole plant exhibits its potential use in traditional medicine.

The review highlights the bioactive studies of *Heliotropium* in different solvent extracts and are reported to possess antimicrobial, histogastroprotective, antihypertensive, antidiabetic, anti-inflammatory, cytotoxic, antiproliferative, wound healing, antiplasmodial and antitrypanosomal, antihelminthic, antifertility, antiulcerogenic, anti-inflammatory and antinociceptive, antioxidant, antihyperlipidemic, antituberculosis, antiviral, antipyretic, analgesic, anticataract, neuroprotective potential etc. Table No.1 shows the different solvent extracts and the plant parts used for the assessment of different bioactive studies by the different researchers.

1. Antimicrobial activity

Alcoholic whole plant extract of *Heliotropium indicum* has been investigated for its antimicrobial activity against bacterial species like *Bacillus subtilis, Bacillus pumilus, Staphylococcus aureus, Micrococcus glutamicus, Pseudomonas aeruginosa, Proteus vulgaris, Serratia marcescens* and *Escherichia coli. Heliotropium indicum* not only showed a dose dependent inhibition against bacterial species but also inhibited fungal species like *Aspergillus niger, Aspergillus wentii* and *Rhizopus oryzae* and the yeast, *Saccharomyces cerevisiae* and *Candida albicans*.[17] Antimicrobial screening showed that the methanolic leaves extract of *H indicum* was effective against *Escherichia coli, Pseudomonas aeruginosa, Klebsiella spp, Proteus mirabilis* and *Staphylococcus aureus* at different concentrations. The study showed that *S. aureus* and *Klebsiella* spp. were inhibited at 50, 100 and 200 mg/ml concentrations with MIC of 3 mg/ml. *P. aeruginosa* and *P. mirabilis* were inhibited at 100 mg/ml and 200 mg/ml with MIC of 10 mg/ml and *E. coli* was inhibited only at 200 mg/ml with MIC of 20 mg/ml.[7] When methanol and ethyl acetate stem extracts of another species of *Heliotropium* was tested, significant antibacterial activity was observed. For example *H. curassavicum* L. showed inhibitory activity against *Bacillus pumilis, Enterococcus faecalis, Micrococcus luteus, Streptococcus faecalis, Escherichia coli, Klebsiella pneumoniae* and *Proteus vulgaris*.[18] In another study, methanolic extract of whole plant of *H. curassavicum* L also showed significant antibacterial activity against *Pseudomonas aeruginosa, Acetobacter motfi, Enterococcus hirae* and *Bacillus cereus* with highest activity against *Pseudomonas aeruginosa*.[19] With another species, *Heliotropium marifolium* Retz. antimicrobial activity was studied in hexane, chloroform, ethyl acetate methanol and water whole plant extracts which also showed significant inhibitory activity against *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae, Salmonella typhii, Proteus mirabilis, Salmonella paratyphii A and Salmonella paratyphii B.*[20] In another study, *Heliotropium bacciferum* was studied for its antimicrobial activity. Methanol, hexane, ethyl acetate, butanol and aqueous aerial parts extracts showed inhibitory activity against bacterial and fungal strains[21] but no active principles have been isolated. When the antimicrobial activity of isolated pyrrolizidine alkaloids viz, europine, heliotridine, lasiocarpine and lasiocarpine n- oxide from ethanolic extract of aerial parts of *Heliotropium ellipticum* have been studied against four bacterial strains and four fungal strains, the maximum MIC was demonstrated by europine (12mm) against *Escherichia coli* and lasiocarpine against *Fusarium*

moniliforme (11mm) as compared to lasiocarpine-N-oxide and heliotridine, but it was not much exhibited as compared to the crude ethanolic extract against the test organisms. The study showed that the efficacy of the crude extract against the test organisms might be due to the presence of pyrrolizidine alkaloids and /or by other metabolites present in the extract.[22] Ethanoic leaf and root extract of *H. indicum* was investigated for its antimicrobial activity against six human pathogens. The study revealed that the ethanolic leaf extract possessed higher inhibitory activity when compared to the root extracts and the extract caused dose dependent inhibition against *Staphylococcus aureus* and *Candida albicans*. GC-MS analysis revealed the presence of terpenes, fatty acids, phytol, alkaloids and organic derivatives in the plant that contributes to its therapeutic activity.[23] Crude extract and ethyl acetate, n- hexane, chloroform and aqueous whole plant extracts of *Heliotropium strigosum* was tested for its antibacterial in six bacterial strains and antifungal activity in four fungal strains. Crude extracts and fractions exposed excellent antibacterial activity against *Staphylococcus epidermidis* while all fractions showed good activity against *Pseudomonas aeruginosa.* The chloroform and n- hexane fractions showed excellent antifungal activity against all the four fungal strains.[24] Ethanol, ethyl acetate, chloroform, hexane and aqueous whole plant extracts of *Heliotropium zeylanicum* (Burm.f.) Lam was also tested against six pathogenic bacteria. The ethanolic extract exhibited significant antibacterial activity against *Escherichia coli, Pseudomonas aeruginosa, Salmonella typhi*.[25]

2. Histogastroprotective activity

The histogastroprotective activity of aqueous leaf extracts of *H. indicum* was studied against indomethacin-induced ulceration in Wistar rats. The histogastroprotective effects were revealed from the histological studies of the stomach body wall which showed normal morphological appearance of the different components of the mucosa layer. The aqueous extract showed dose dependant histo - gastroprotective effects.[26]

3. Antihypertensive activity

Antihypertensive activity was studied with crude extracts of the stem with leaves and roots of *H. indicum* in wistar rats. Pharmacological effects of the extracts revealed that both the aqueous extracts of the stem with leaves and roots induced a significant decrease of blood pressure in L- NAME - induced hypertensive rat. In addition it was also found that at 500mg/kg, the stem with leaves extract had normalized the blood pressure in hypertensive rats.[27]

4. Antidiabetic activity

Antidiabetic activity was investigated with hexane, ethyl acetate, methanol and aqueous extracts of whole plant of *H. indicum* in streptozotocin (STZ) induced diabetic rats. Fasting blood sugar levels were analyzed after the treatment in diabetic rats. The methanolic and aqueous fractions each at a dose of 500mg/kg exhibited significant antidiabetic activity in diabetic rats. The study revealed that the methanolic active fraction of *H. indicum* possibly showed significant antidiabetic activity.[28] In another study, *Heliotropium. zeylanicum* (Burm.f.) Lam methanolic whole plant extract was used to determine the antidiabetic activity on streptozotocin – induced diabetic rats. The blood glucose levels of the diabetic rats were analysed after the treatment with the administration of methanolic extract 150 and 300 mg/kg body weight, and tolbutamide 10 mg/kg. The extract showed significant reduction in blood glucose in diabetic rats.[29] When the ethanolic whole plant extract of *H. indicum* was investigated on Alloxan and streptozotocin induced albino wistar rats and the serum glucose levels and serum lipid profiles were analysed in diabetic rats a significant reduction in serum glucose levels on 14 days, 21st and 28th days was observed. The serum lipid profiles showed decreased total cholesterol, triglycerides and LDL and no change in VLDL levels and an increase in HDL.[30] The aqueous leaf extract of *H. indicum* was also investigated on Alloxan (ALX) induced hyperglycemic rats. The FBG and serum lipid profiles were investigated in diabetic rats after 14 days of treatment. After the 14 days of treatment with metformin 14.2mg/kg and the folkloric dosage of the extract of either 30 or 75mg/kg b.wt, a significant normal blood glucose levels was observed in the diabetic rats. The serum lipid profile results indicated that the aqueous extract also showed improvement in lipid abnormalities in hyperglycaemic condition, triglyceride levels, significant reduction in total cholesterol and LDL – cholesterol and increase in HDL – cholesterol resulted in improved artherogenic index.[31] The ameliorative effect of aqueous leaf extract of *H indicum* was also studied on Alloxan (ALX) induced hyperglycemic rats. The test groups were treated with 30 and 75 mg/kg b.wt, extract for fourteen days. The significantly increased serum concentrations of tissue membrane bound enzymes (ALT, AST, ACP and ALP), direct and total bilirubin, urea and creatinine were observed in hyperglycemic control compromised tissue structures. It was also found that the significantly reduced serum total protein, globulin and albumin in HC were significantly increased by both doses of the extract. The ameliorative role of the aqueous extract at the test doses was supported from the histological assessment of liver and kidney of the animals and therefore the study supported the ethnobotanical dose of 30 and 75 mg/kg b.wt aqueous leaf extract of *H. indicum* for the management of some of the tissue-specific disarrays associated with diabetes.[32]

5. Antiinflammatory activity

The anti-inflammatory activity of ethanolic whole plant extract of *H. indicum* was studied on lipopolysaccharide-induced uveitis in white rabbits. The level of protein, and the concentrations of TNF-α, PGE2 and MCP-1 in the aqueous humor and the histopathological studies were investigated after the treatment with the extract and prednisolone. After the treatment it was found that the

ethanolic extract of *H. indicum* inhibited both the clinical scores of inflammation and inflammatory cells infiltration. In addition, the level of protein and the concentrations of TNF-α, PGE2 and MCP-1 in the aqueous humor were also significantly reduced. Furthermore, the histopathological studies showed normal uveal morphology in the treated rabbits. Therefore, the study proposed the potential of ethanolic whole plant extract and prednisolone possibly to reduce the production of pro-inflammatory mediators on LPS – induced uveitis. [33] The anti-inflammatory activity of *H. indicum* leaf was found to possess significant activity on carrageenin induced hind paw oedema for acute inflammation and cotton pellet granuloma for subacute inflammation in rats.[34] When the petroleum ether and ethanolic whole plant extracts of *H. indicum* was investigated for its anti-inflammatory activity in albino rats using egg white induced acute paw edema model the extracts at the dose of 25mg/kg body weight produced a significant inhibition for acute inflammation.[35] *H. indicum* whole plant ethanolic and water extracts was studied on lipopolysaccharide (LPS)-stimulated RAW 264.7 macrophages. It was revealed that the ethanolic whole plant extract demonstrated the most potent inhibitory activity on nitric oxide production while water extract was found inactive. [36] From the whole plant and fractions of *H. strigosum*, carrageenan - induced edema and xylene – induced ear edema in wistar rats and albino mice was studied. The study revealed marked attenuation of edema induced by carrageenan injection in a dose-dependent manner. In both inflammations significant anti-inflammatory effect was observed with ethyl acetate and hexane fractions.[37]

6. Cytotoxic activity

The antitumor activity of different extracts of *H. indicum* was evaluated in several experimental tumor systems. Ethanolic and water extracts of the whole part of *H. indicum* was studied in lung cancer cell lines (A549 and NCI- H226). The study revealed that the ethanolic extract showed cytotoxic activity against NCI-H226 and it exhibited no cytotoxic activity against A549. The ethanolic whole plant extract exhibited good cytotoxic activity when compared to water extract.[36] Methanolic leaf and stem extracts of *H. indicum* was also studied on HELA cell lines. The study indicated that the methanolic extracts of leaf and stem of *H. indicum* possessed good anticancer activity. The stem extracts showed excellent activity up to 64.5% at 200 µg/ml and leaf extract showed activity up to 49.6% at 200 µg/ml.[38] In another study, aqueous, chloroform, and hexane extracts of dried whole plant powder of *H. indicum* was tested against three cervical cancer cell lines. HeLa (HPV 18positive), Si Ha (HPV 16 positive) and C33A (HPV negative). The study revealed that the chloroform and hexane fractions of *H. indicum* was found to be most efficient in inhibiting cell growth and inducing apoptosis in cervical cancer cells at lower concentrations.[39] The active principle was isolated and found to be N- oxide of the alkaloid, indicine. The pyrrolizidine alkaloid, Indicine N-oxide isolated from *H. indicum*, was studied in Phase 1 clinical trial patients with advanced cancer. In the study, thirty-seven patients including 15 men and 22 women (mean age, 53 years) with solid tumors received the drug. Toxic side effects were leukopenia and thrombocytopenia, and the toxicity was cumulative with repeated doses and many other. The study revealed that indicine N – oxide had no complete or partial responses in the advanced cancer patients. It was found that one patient with skin melanoma and another with ovarian carcinoma showed improvement that lasted 2 months.[40] In another research study the molecular mechanism of the toxicity of indicine - N- oxide was evaluated. It was found that Indicine N-oxide, a pyrrolizidine alkaloid was present in *H. indicum* which showed promising cytotoxic activity in various tumor models (cervical, breast, prostate and cervical squamous). Indicine N-oxide exhibited severe toxicity to hepatocytes and bone marrow cells. Most of the alkaloids are found to be hepatotoxic and internal use is not recommended. The study revealed that the toxicities of indicine N-oxide were due to its DNA damaging effects and depolymerization of microtubules.[41]

7. Antiproliferative activity

The antiproliferative activity of ethanolic whole plant extracts of *H. indicum* was investigated against SKBR3 human breast adenocarcinoma cell line using MTT assay. Significant antiproliferative activity was exposed in the study.[42]

8. Wound healing activity

The wound healing potential of petroleum ether, chloroform, methanol and aqueous leaves extracts of *H. indicum* was investigated using excision (normal and infected), incision and dead space models in rats. The study showed that in the excision wound models, faster epithelialisation was found with the methanol extract treated animals than aqueous extract. The percentage of wound closure with the methanolic extract was similar to that of the standard drug. In incision wound model studies it was observed that the methanol and aqueous extract treated animals showed significant increase in breaking strength. The wound infection model studies with *S. aureus* and *P. aeruginosa*, the methanol extract showed significant healing activity. The methanol extract of *H. indicum* also exhibited significant increase in the granulation tissue weight, increased hydroxyproline content and increased activity of SOD and catalase level in the animals. It was observed that in this model, the methanolic extracts of *H. indicum* exhibited significant wound healing activity when compared with other extracts.[43] With the ethanolic extracts of *H. indicum*, wound healing activity was tested by using excision and incision wound in rats following topical application. The study revealed that *H. indicum* exposed better wound healing activity.[44] n-butanol extracts of leaves and stem of *H. indicum* was also examined to determine the wound healing effect in H292- cells. The column chromatography using Sephadex LH-20 revealed the

presence of two alkaloids namely, Pestalamide B and Glycinamide, N-(1- oxooctadecyl) glycyl- L- alanyl glycyl- L- histidyl. These compounds were first isolated from *H. indicum* which exhibited better wound healing activity.[45]

9. Anti-plasmodial and Anti-trypanosomal activities

The anti-plasmodial and anti-trypanosomal activities of methanolic extract of *H. zeylanicum* (Burm.f.) Lam was evaluated. The methanolic extract of *H zeylanicum* showed good antiplasmodial activity against chloroquine-resistant strain (K1) and sensitive strain (FCR3) and also good antitrypanosomal activity against Trypanosoma brucei brucei GUT at 3.1 strain.[46] In another study, dichloromethane, methanol and aqueous extracts of leaves, twigs, aerial parts and roots of *H. indicum* was also evaluated. The antiplasmodial activity of extracts was evaluated using the measurement of the plasmodial lactate dehydrogenase activity on chloroquine-sensitive (3D7) and resistant (W2) strains of *Plasmodium falciparum*. The extracts of *H. indicum* did not show any anti-plasmodial activity.[47]

10. Antihelminthic activity

The antihelminthic activity of acetone, ethanol, hydro-alcohol and distilled water root extracts of *H indicum* was evaluated to justify the folkloric medicinal use as worm expeller in South West of Nigeria. The study revealed that all the extracts of *H indicum* exhibited good antihelminthic activity against the nematodes larvae from sheep and adult earthworm in a dose-dependent manner. [48]

11. Antifertility activity

The antifertility potential of ethanolic leaves extract and its n- hexane and benzene fractions of *H. indicum* was investigated using Antiimplantation and Abortifacient models. Better anti implantation activity was exhibited with n-hexane extract and in abortifacient model, higher dose of 400 mg/kg body weight showed better activity. In addition, the sperm motility study exposed better activity at 10% concentration. The n – hexane extract of *H. indicum* possessed better abortifacient activity and moderate anti-implantation activity.[49]

12. Anti-ulcer activity

The anti-ulcer activity of ethanolic leaves and root extracts of *H. indicum* was investigated for against pylorous ligation induced gastric ulcer in rats. Decrease in gastric juice volume, decrease in the acidity and increase in P^H exposed the anti-ulcer potential of *H. indicum* leaf and *H. indicum* root extracts. The study concluded that *H. indicum* leaf and root extract possessed bioactive compounds which account for its antiulcerogenic activity.[50]

13. Anti-inflammatory and antinociceptive activity

The anti-inflammatory and antinociceptive activity of chloroform leaves extract of *H. indicum* was studied in albino wistar rats with carrageenan induced paw edema model. The chloroform extract of *H. indicum* showed significant anti – inflammatory activity in carrageenan – induced paw edema and cotton pellet granuloma models of inflammation which accounts for its significant anti-nociceptive and anti-inflammatory activities.[51]

14. Antioxidant activity

The antioxidant activity of ethanolic whole plant extract of *H. indicum* was investigated for its antioxidant effect by evaluating DPPH and reducing power scavenging activities. The study showed that the ethanolic extract possessed significant reducing power and free radical scavenging and was concentration dependant.[52] In another study, the antioxidant activity of ethanolic and aqueous leaves extract of *H. indicum* was investigated by DPPH radical scavenging and hydrogen peroxide scavenging. The free radical scavenging of both aqueous and ethanolic extracts of *H. indicum* was found to be concentration dependent.[53] Crude extract, ethyl acetate, n-hexane, chloroform and aqueous whole plant fractions were of *Heliotropium strigosum* was analyzed for its antioxidant activity. The study showed that the n – hexane fraction showed strong antioxidant activity followed by ethyl acetate extract which showed significant antioxidant activity.[24] Further resinous extract of *H. sclerocarpum* Phil. was analyzed to determine the chemical composition of the resin and the antioxidant potential of the phenolic compounds and the resin. A new type of 3-oxo-2- arylbenzofuran derivative 3 and was identified as 2-(4', 6'-dihydroxy-3'-methylphenyl)-4-hydroxy-6- methoxy-3-oxo-benzofurylium in the resinuous extract. Two additional compounds identified were filifolinol (1), isolated previously from *H. filifolium* and *H. taltalense* and the flavonoid naringenin (2), identified previously in the resinous exudates of *H. stenophyllum*, *H. sinuatum*, *H. chenopodiaceum* and *H. taltalense*. 2-(4', 6'-dihydroxy-3'-methylphenyl)-4-hydroxy-6- methoxy-3-oxo-benzofurylium is a new compound in nature. The antioxidant activity of *H. sclerocarpum*. Phil was mainly due to the compound naringenin.[54] In another research study the plant exudate of *H. sinuatum* was studied to determine the relationships between the structural characteristics of flavonoids and their antioxidant activity. The antioxidant activity of the flavonoids depends on the substitution pattern of the hydroxyl groups of the flavonoid skeleton and the presence of an unsaturation at the C2 – C3 bond.[55]

15. Antihyperlipidemic activity

The antihyperlipidemic activity in streptozotocin induced diabetic rats was analysed with methanolic extract of *Heliotropium zeylanicum* (Burm.f.) Lam. The treatment of animals with methanol extract of *H. zeylanicum* caused a decrease in total cholesterol levels, although this was less marked than the decrease in triglycerides. Repeated administration of methanol extract of *H. zeylanicum* showed a beneficial effect on the hyperlipedimia associated with hyperglycemia.[29]

16. Anti-tuberculosis activity

Volatile oil from the aerial parts of *H. indicum* was analysed to determine the compounds which exhibit anti-tuberculosis activity by a combination of gas chromatography (GC–FID) and gas chromatography–mass spectrometry (GC–MS) techniques. The major constituents of the volatile oil of *H. indicum* analysed were phytol (49.1%), 1-dodecanol (6.4%) and *β*-linalool (3.0%). The volatile oil of *H. indicum* showed significant antituberculosis activity against *Mycobacterium tuberculosis* attenuated strain.[56]

17. Antiviral activity

The antiviral potential of resinous exudates of *H. filifolium* was studied to determine the anti‑viral effect of a group of natural compounds (geranyl aromatic derivatives) viz. filifolinol, filifolinyl senecionate, filifolinone and filifolinoic acid isolated from Heliotropiaceae semi‑synthetics compounds obtained from them, and the resinous exudates was evaluated on CHSE‑214 cell line infected with infectious pancreatic necrosis virus (IPNV) using a virus plaque inhibition assay at various concentrations. It was found that the compound ester filifolinyl senecionate was found to be the best anti‑viral and the compound produced inhibition of viral genomic RNA synthesis. These results indicated that the ester filifolinyl senecionate can be used in antiviral therapy for IPN virus in salmon fry.[57]

18. Antipyretic activity

The antipyretic activity of ethanolic leaves extract of *H. indicum* was investigated using Brewer's yeast induced pyrexia. The study showed that the ethanolic leaves extract in doses of 250 and 500mg/kg showed a significant reduction in the rectal temperature of pyretic rats in a dose dependent manner.[58]

19. Analgesic activity

The analgesic activity and safety assessment of ethanolic and aqueous aerial parts extracts was studied using formalin induced pain model in mice. The aqueous and ethanolic extracts exhibited a dose-dependent inhibition in both the first and second phases of the formalin-induced nociception. Pathologic conditions were observed on the heart, kidney, liver and lungs of rat models after 14-days of oral administration of the extracts. Therefore, the aqueous and ethanolic extracts of *H. indicum* have analgesic activity but it could have a cumulative toxic effect on prolonged and continuous use.[59]

20. Anti-cataract activity

The anticataract potential of aqueous whole plant extracts of *H. indicum* was studied on sodium-selenite induced cataract in 10 – day – old rat pups. *H. indicum* extracts showed the greatest activity against selenite-induced cataracts at the highest dose of 300 mg kg−1. Significantly high levels of GSH in the extract-treated eyes supported the activity of the extract. There were significantly high concentrations of total protein, CRYAA, and CRYAB depending on the transparency of the lens which indicated the transparency of the lens. The estimated levels of AQP0 water channel was significantly high when treated with the extract. The histopathological assessment showed that the integrity of the lens epithelium and also the architecture of the lens fibers in all the *H. indicum* aqueous extract treated rats and normal rats was maintained. There was observable epithelial erosion of the lens and abnormal morphology of the lens fibers.[60] With the ethanolic leaf extract of *H. indicum* anti-cataract potential on galactose induced rats was also studied. The results showed that ethanolic leaf extract at a dose of 200mg/kg along with Vitamin E at a dose of 50mg/kg and 30% galactose diet produced a significant increase in the glutathione lens, soluble proteins and water contents when compared to the standard galactose diet given to the rats. The ethanolic leaf extract of *H. indicum* was found to be having anti-cataract activity in the galactose induced rats.[61]

21. Neuroprotective potential

The neuroprotective potential of ethanolic whole plant extract of *H. indicum* was studied on cerebral ischemia/reperfusion induced brain damage in rats. The biochemical and histopathological studies of brain infarct area showed that the ethanolic whole plant extract of *H. indicum* significantly reduced relative infarct size and rescued neural dysfunction very effectively. The study proposes that *H. indicum* could be explored for treating stroke and neurological disorders.[62]

Table No. 1: Plant parts and solvent extracts used for the bioactive studies in the genus *Heliotropium*.

Sr. no	Bioactivity	Plant species	Parts used	Extract	Reference
1.	Antimicrobial	*H. indicum* L.	Whole plant	Alcohol	[17]
		H. indicum L.	Leaves	Methanol	[7]
		H. indicum L.	Leaves, roots	Ethanol	[23]
		H. curassavicum	Stem	Ethylacetate, methanol	[18]
		H. curassavicum	Whole plant	Methanol, chloroform and aqueous	[19]
		H. marifolium Retz.	Whole plant	Hexane,chloroform, ethyl acetate, methanol and water	[20]
		H bacciferum	Aerial parts	Methanol, n – hexane, ethyl acetate, butanol and aqueous	[21]

		H. strigosum	Whole plant	Crude extract and ethyl acetate, n – hexane, chloroform and aqueous	[24]
		H. ellipticum	Aerial parts	Ethanol	[22]
		H. zeylanicum (Burm.f.) Lam	Whole plant	Ethanol, ethyl acetate, chloroform, hexane and aqueous	[25]
2.	Histogastoprotective	*H. indicum* L.	Leaves	Aqueous	[26]
3.	Antihypertensive	*H. indicum* L.	Stem, leaves and roots	Aqueous	[27]
4.	Antidiabetic	*H. indicum* L.	Whole plant	Hexane, ethyl acetate, methanol, aqueous	[28]
		H. indicum L.	Whole plant	Ethanol	[30]
		H. indicum L.	Leaves	Aqueous	[32]
		H. zeylanicum (Burm.f.) Lam	Whole plant	Methanol	[29]
5.	Anti-inflammatory	*H. indicum* L.	Whole plant	Ethanol	[33]
		H. indicum L.	Whole plant	Ethanol and water	[36]
		H. indicum L.	Whole plant	Petroleum ether, ethanol	[35]
		H. indicum L.	Dried leaves		[34]
		H strigosum	Whole plant	Ethyl acetate and hexane	[37]
6.	Cytotoxicity	*H. indicum* L.	Whole plant	Ethanol and water	[36]
		H. indicum L.	Leaves, stem	Methanol	[38]
		H. indicum L.	Whole plant	Aqueous, chloroform, hexane	[39]
7.	Antiproliferative	*H. indicum* L.	Whole plant	Ethanol	[42]
8.	Wound healing	*H. indicum* L.	Leaves	Petroleum ether, chloroform, methanol, aqueous	[43]
		H. indicum L.	Leaves, stem	n - butanol	[45]
		H. indicum L.		Ethanol	[44]
9.	Antiplasmodial and Antitrypanosomal	*H. indicum* L.	Leaves, twigs, aerial parts,roots	Dichloromethane, methanol, aqueous	[47]
		H. zeylanicum Burm.f.) Lam	Aerial parts	Methanol	[46]
10.	Antihelminthic	*H. indicum* L.	Roots	Acetone, ethanol, hydro-alcohol, distilled water	[48]
11.	Antifertility	*H. indicum* L.	Leaves	Ethanol	[49]
12.	Antiulcer	*H. indicum* L.	Leaf and roots	Ethanol	[50]
13.	Anti-inflammatory and Antinociceptive	*H. indicum* L.	Leaves	Chloroform	[51]
14.	Antioxidant	*H. indicum* L.	Whole plant	Ethanol	[52]
		H. indicum L.	Leaves	Ethanol, aqueous	[53]
		H. sinuatum	Plant exudates		[55]
		H. sclerocarpum	Resinuous extract		[54]
		H. strigosum	Whole plant	Ethyl acetate, n – hexane, chloroform, aqueous	[24]
15.	Antihyperlipidemic	*H.zeylanicum* (Burm.f.) Lam		Methanol	[29]
16.	Antituberculosis	*H. indicum* L.	Aerial parts	Volatile oil	[56]
17.	Antiviral	*H. filifolium*		Resinuous exudate	[57]
18.	Antipyretic	*H. indicum* L.	Leaves	Ethanol	[58]
19.	Analgesic	*H. indicum* L.	Aerial parts	Aqueous and ethanol	[59]
20.	Anticataract	*H. indicum* L.	Whole plant	Aqueous	[60]
		H. indicum L.	Leaves	Ethanol	[61]
21.	Neuroprotective	*H. indicum* L.	Whole plant	Ethanol	[62]

SUMMARY AND CONCLUSION

The review summarizes the pharmacological and medicinal values of the genus *Heliotropium.* Various research has been conducted to evaluate the traditional uses of the genus *Heliotropium* and all of the different parts of the plants have been reported to have medicinal values which supported the traditional claims. It is remarkable that the crude extracts of the members of Boraginaceae family have diverse biological effects due to the presence of flavonoids, phenols, sterols, terpenoids and alkaloids. Among the plants belonging to the genus studied, *Heliotropium indicum* L. finds a remarkable place in having immense bioactive potential.

H. indicum L.is a weed in waste places but also finds a place in traditional medicine due to its immense bioactive properties. Hexane and chloroform fractions of the whole plant of *H. indicum* L. was found to be effective in inhibiting cell growth and inducing apoptosis in cervical cancer cell lines at low concentrations. The ethanolic whole plant extract of *H. indicum* L. showed good antiproliferative activity against SKBR3 human breast cancer adenocarcinoma cell line. The wound healing potential of *H. indicum* L. methanolic, ethanolic and n – butanol leaves extract showed significant activity. Two alkaloids namely Pestalamide – B and Glycinamide were found to possess wound healing property. Aqueous and ethanolic aerial parts extract of *H. indicum* L. exhibited good analgesic properties.

Various alkaloids containing pyrrolizidine groups are isolated from *Heliotropium* species namely, echinatine, heleurine, heliotriene, lasiocarpine, indicine N – Oxide, retronecine, cynoglossine and supinine. Different extracts of *H. indicum* L. have been studied for the possible biological activities in various animal models and reported to possess anti-inflammatory, cytotoxic, wound healing and abortifacient activities. Various animal studies have assessed the safety of the crude extracts and have found to be hepatotoxic due to the presence of pyrrolizidine alkaloids. The alkaloids, mainly pyrrolizidine alkaloids are the main constituents of *Heliotropium* species, which are responsible for biological activities viz, cytotoxic, antimicrobial and anti-viral effects. The active compound responsible for antitumor activity is indicine N – Oxide, which is a pyrrolizidine alkaloid. Unfortunately, the pyrrolizidine alkaloids show a hazardous potential with mutagenic, teratogenic, carcinogenic and fetotoxic properties in humans and animals. It causes some side effects such as liver damage and so it is not recommended for internal use. Phenolics, flavonoids, terpenoids and quinones have been reported from this genus which are also promising anticancer, antiviral, antimicrobial and wound healing agents, and future research could be extended with these compounds. The *in vitro* and animal model studies indicated that the various extracts of *H. indicum* L. possess good pharmacological potential which supports the folk medicine. However, still more research utilizing the different biotechnological tools is needed in *H. indicum* L. and warrants extensive studies in antiproliferative, wound healing, antimicrobial and anti-inflammatory activities.

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