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REVIEW ARTICLE

A Review of the Pharmacological Activities and Safety of *Heliotropium indicum*

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Abstract

Heliotropium indicum L. is distributed over Africa, Asia, Europe and North America. Its use in folkloric medicine covers treatment for asthma, rheumatism, skin disorders, snakebites, and inflammation. However, there are misgivings about its safety due to reports of adverse events and the presence of toxic alkaloids. This study thus summarizes the various pharmacological activities and safety studies on *H. indicum* through a scoping review. Sixty-eight (68) publications were retrieved from SCOPUS, CINAHL Complete, PubMed, and Cochrane Library, of which 19 articles were analyzed. The major pharmacological activities investigated in these articles included the anti-allergic, anti-glaucoma, wound healing, histo-gastro-protective, antitumor, antimitotic, neuroprotective, anti-proliferative, anti-nociceptive, anti-ulcer, cytotoxic, anti-inflammatory, antioxidant, anti-dyslipidemia, anti-cataractogenic and cytostatic activities. Two studies on the safety of *H. indicum* were performed in horse and mouse models, and two other studies on the plant pyrrolizidine alkaloid indicine N-oxide, in human and cell lines. Recorded adverse effects were bile pigment accumulation in the spleen, and brain abnormalities in the cerebral cortex in animal model. Indicine N-oxide, a highly toxic substance, caused dose-dependent mortality in Swiss mice, at a lethal dose of 9.78 grams per kilogram of body weight, with adverse effects seen on the liver and kidneys. Also, inflammatory alterations were observed in the testicles. Pharmacological studies on *H. indicum* revealed noteworthy potential as a rich source of bioactive substances. The reported side effects highlight the need for a cautious approach to its use and to prioritize safety assessments.

Major Findings: *Heliotropium indicum* has been investigated for a wide range of pharmacological activities; however, there have also been a reports of possible injuries to the spleen and brain in animals.

Keywords: *H. indicum*, Medicinal Uses, Pharmacological Activity, Safety

1. Introduction

Medicinal plants are a variety of plants with therapeutic characteristics, which are relevant for their pharmacological components, and their usage as alternative drug sources[1]. The World Health Organization (WHO) estimates that over 65% to 80% of low-income countries depend on Herbal Medicines (HMs) as a primary source of healthcare, and in developed countries, there were about 25% of prescribed herbal medicines being sourced from different plant species[2-4].

Heliotropium indicum, also known as the Indian heliotrope of the family *Boraginaceae* has been identified as a notable source of medicines due to its widespread medicinal usage; several studies have assessed its pharmacological importance[5-7]. *H. indicum* is reportedly used widely in folkloric medicine, in the treatment of glaucoma, cataracts, conjunctivitis, and uveitis, among others[8,9]. Biomedically, the aqueous-whole plant extract has shown anti-cataract activity by inhibiting the development of glycation end products, which contribute to cataract formation[7,10]. The aqueous and ethanolic extracts from the leaves also

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demonstrated anti-inflammatory activity by blocking the synthesis of pro-inflammatory enzymes and cytokines. The aqueous extracts also possess microbial inhibitory activity against a range of fungi, bacteria, and viruses. Additionally, the plant has demonstrated antitubercular effects by preventing the growth of *M. tuberculosis*, [8].

The ethanolic extract has also been found to possess cytotoxic and apoptotic effects against various cancer cell lines of the breast, lung, and liver[2,11].This plant may offer a natural reservoir of potent and affordable lead compounds with reduced adverse effects for cancer treatment, but for the toxic nature of constituent alkaloidal compounds such as indicine N-oxide[8]. *H. indicum* extracts, and its compound, indicine N-oxide, have been evaluated in clinical trials for the management of cancer and liver conditions and yielded varying results[12]. Prolonged use of the whole plant's aqueous and ethanolic extracts showed cumulative toxicity on the liver, lungs and kidneys[13].

Human fatalities from the unintentional intake of several *Heliotropium* species have been reported in South Africa, Jamaica, and Barbados[14]. *H. indicum* has several pyrrolizidine alkaloids such as indicine, heleurine, indicine N-Oxide, acetyl indicine, supinidine, lindelofidine and heliotrine, all of which have been associated with hepatotoxic properties[15,16]. Hepatic metabolism of pyrrolizidine alkaloids generates highly reactive adducts, including 2, 3-dihydro-1H-pyrrolizine protein, which exhibit high reactivity towards protein and nucleic acids, such as DNA and RNA[13]. This reactivity leads to the development of veno-occlusive disease in the liver. Acute pyrrolizidine alkaloid poisoning induces severe hepatotoxicity, hemorrhagic necrosis, and eventual death. Furthermore, pyrrolizidine alkaloids may also possess tumorigenic potential, particularly in relation to skin cancer via photosensitization[13].

Some studies have also shed light on the presence of toxic components of *H. indicum,* raising safety concerns. Heliotrine, lasiocarpine and retrorsine are reported to induce hepatotoxicity in, as well as developing cancerous growth in animal studies, and exertion of an adverse effect on human embryo liver cells development[13]. It is postulated that the synthesis of pyrrole products from pyrrolizidine alkaloid through oxidation by liver microsomal, results in the DNA strands cross-linking, which is associated with genotoxic effects[17]. Subject to the dose, but regardless of the method of administration, pyrrolizidine alkaloids cause necrosis and hinder mitosis[18].

Heliotrine, is also reported to be responsible for significant disease outbreak in broiler chickens in Australia that was marked by depression, fluid accumulation, and liver deterioration[19]. A case report on a farm in Costa Rica, over the course of 4 years found that more than 75 % of 110 horses died after exhibiting neurological signs, kidney discoloration and adhesion to the capsule, lungs nodules containing a purulent exudate, meningeal swelling and congestion in their brains, damage to the liver including fibrosis between lobes, anemia in hepatocytes with enlarged cells, accumulation of bile pigments, presence of vacuoles and fatty changes, increased bile ducts and localized bleeding in the liver tissue, kidney epithelial degeneration, cytoplasmic accumulation of bile pigment, pneumonia ranging from areas of purulent to granulomatous in the lungs, and splenic retention of bile pigments. These are indicative of liver, kidney and lung injury. Taxonomic and toxicologic investigations pointed to *H. indicum* as the most likely culprit[20].

Extremely lethal reactions result in response to internal treatment with indicine-N-oxide; thus, using *Heliotropium* species internally is not advised[21]**.** The toxicity of indicine N-oxide from *H. indicum* is related to the breakdown and damage to microtubules [22]. The impact on kidney health is, however, inconclusive as different studies have presented contrasting findings. According to Abdullah *et al.,* ethanolic extracts from *H. indicum* showed the potential to protect the kidneys against rifampicin-induced nephrotoxicity. These extracts had an effect by decreasing uric acid and creatinine levels in blood and urine while increasing protein levels, thus indicating improved kidney function[23]. Another study, however, found that *H. indicum* extracts can be harmful to kidney cells through cytotoxicity studies on HeLa cells. The results showed a reduction in up to 64.5% HeLa cell viability[24,11].

Heliotropium indicum contains diverse phytocompounds such as flavonoids, alkaloids, terpenoids, saponins, cyanogenic glycosides, hydrolizable tannins, reducing sugars, and steroids, which are responsible for its pharmacological activities[7,9,10,16,19,25]. Echinatine, heleurine, heliotrine, heliotridine, supinine, indicine, lasiocarpine and indicine *N*-oxide are some

alkaloids found in the aerial parts[26-30]. Sterols found in the entire plant material included campesterol, β-sitosterol, chalinasterol, stigmasterol and hexacosane-1-ol[31]. The leaves are reported to contain putrescine, spermidine, and spermine amines[15]. 1-Dodecanol, β-Linalool and phytol were some volatile oils isolated from the total biomass[32]. Trachelanthamidine and retronecine alkaloids were also isolated from the leaves[15,33]. Squalene, phytol and 1,2 Benzenedicarboxylic acid disooctyl ester are reported to be present[34]. *H. indicum* seeds have been reported to contain europine *N*-oxide, heliotridine *N*-oxide, heliotrine *N*-oxide, heleurine *N*-oxide, and alkaloids[30]. β-amyrin and rapanone are some more alkaloids obtained from the entire plant part of *H. indicum*[31]. The roots have also been documented to contain helindicine, lycopsamine alkaloids and estradiol sterol[35].

2. Materials and Methods

2.1 Search Strategy

The search strategy utilized terminologies including pharmacological activities, safety, and *H. indicum*, along with their synonyms and MeSH terms. These were combined using Boolean operators and adjusted

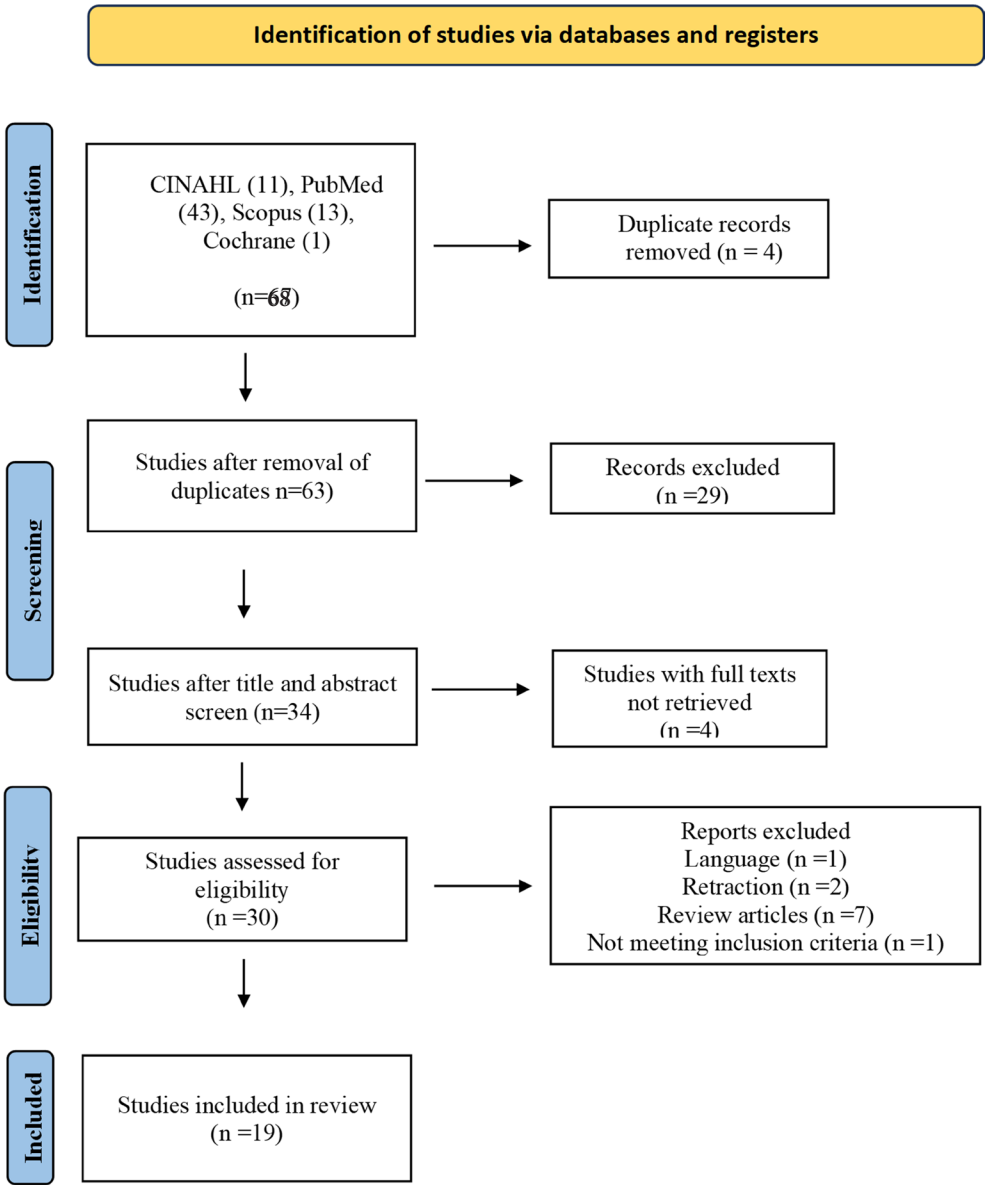


Figure 1. Flowchart of the search strategy and articles included in this review.

as necessary to optimize results. The search was conducted between 16th May and 31st May 2023 without restrictions across the following databases: PubMed, CINAHL Complete (Ebsco), Scopus (Elsevier), and Cochrane CENTRAL. The Clinical Trials register was also searched for ongoing trials.

2.2 Inclusion Criteria

All studies involving pharmacological activities, like *in vitro*, *ex vivo* and *in vivo* studies on *H. indicum*.

2.3 Exclusion Criteria

Studies of *H. indicum* that were not published in English, studies that involved the pharmacological activities and the safety of plants other than *H. indicum,* and data not related to the focus of the study.

2.4 Data Extraction

Data on the safety of *H. indicum* extracts and various preparations, as well as pharmacological and toxicological properties. Extraction of the data was done using Microsoft Excel 2019 under the heading's country of origin of study, author and year, pharmacological activity, specific investigations and findings. The data were gathered on various extract types, pharmacological substances, biological activities, tests model (using rats, mice, and clinical trials as the test subjects), extract dosages or medication dosages, and effects.

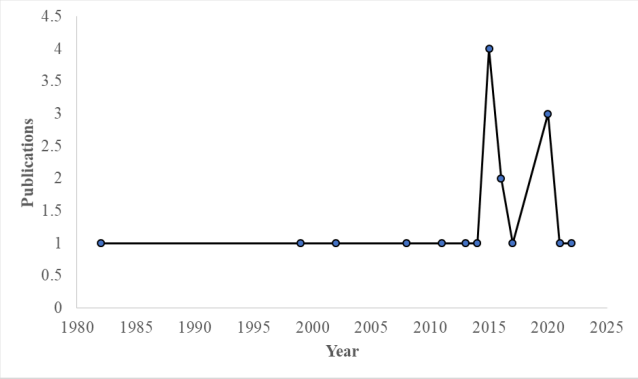


Figure 2. Theyear and the number of publications.

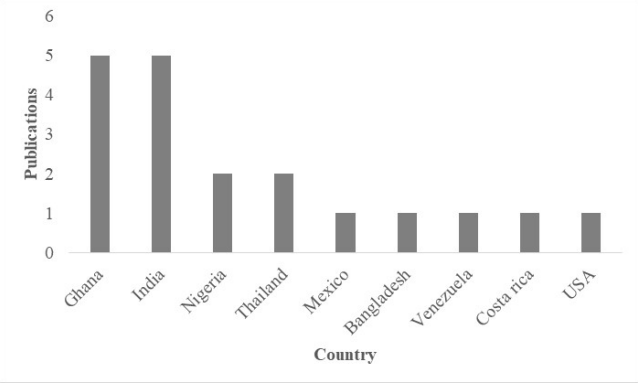


Figure 3. Geographical location and number of publications on *H. indicum*.

3. Results

The search produced 68 articles in total after four duplicate articles were removed. These articles were categorized as 13 articles from Scopus, 11 articles from CINAHL Complete, 43 articles from PubMed, and 1 article from Cochrane.. A total of 34 full articles were retrieved, 15 excluded, and ultimately, a total of 19 articles were included in this review.

The studies span 39 years from the year 1982 to 2021, with 2015 publishing the highest number of studies[4], followed by 3 in 2020 (Figure 1). From the reviewed articles, Ghanaian and Indian researchers conducted the most studies on this plant, with 5 publications each (Figure 2)[36-44]. Two articles, each included in this study, were by Nigerian and Thai researchers, followed by others from Mexico, Bangladesh, Venezuela, Costa Rica, and the USA[47-48]. Details are displayed in Figure 3.

3.1 Pharmacological Activities of *H. indicum*

Heliotropium indicum has a wide variety of pharmaco logical activities (details displayed in Table 1) associated

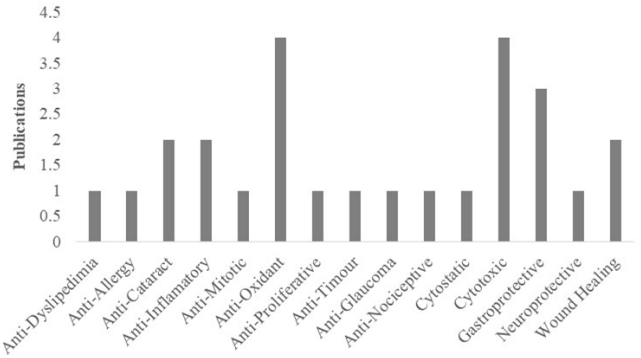


Figure 4. Major pharmacological properties described for *H. indicum*.

Table 1. Pharmacological activities of *H. indicum*

S. No	Country	Author	Pharma cological Activity	Specific Investigation	Findings
1	Ghana	Kyei *et al.*,[36]	Anti-allergic effect	30-300mg kg^{-1} doses of *H. indicum* whole plant part extract (HIE) compared with 30 mg prednisolone, 10 mg chlorpheniramine, or 10 mL phosphate buffered saline all given per kg body weight. The treatment, with HIE, showed an antiallergic effect, which was statistically significant ($p \leq 0.001$).	Exhibits anti-allergic effect in ovalbumin-induced conjunctivitis in guinea pigs *via* a probable immunomodulation or immunosuppressive action.
2	Ghana	Kyei *et al.*,[38]	Anti-glaucoma and antioxidant effect	The whole plant extract showed a decrease, in intraocular pressure (IOP) ($p \leq 0.05$-0.001), in both acute and chronic glaucoma cases. Additionally, it helped maintain levels of glutathione and glutamate levels ($p \leq 0.01$–0.001).	The whole plant extract of *H. indicum* possesses ocular hypotensive and anti-glaucoma activity with antioxidant and possible neuroprotective activities.
3	India	Reddy *et al.*,	Wound healing effect	A comparative study of the wound healing activity of ethanolic extracts from the whole plant of *H. indicum, Plumbago zeylanicum,* and *Acalypha indica* in a rat model with dermatological application of a 10% w/v formulation.	The whole plant extract of *H. indicum* possessed the highest wound healing activity with rapid wound epithelization and collagenization.
4	India	Dash *et al.*,[42]	Wound healing effect	Investigation of wound healing properties of leaf extracts from *H. indicum*, in male Wistar albino rats using petroleum ether, chloroform, methanol and aqueous solvents.	*H. indium's* effects on incision and excision ewound healing showed a considerable enhancement of wound healing with both the methanol and water extracts. The methanol extract had faster wound epithelialization than those treated with aqueous leaf extract, however the chloroform, and petroleum ether extracts had no discernible action.
5	Nigeria	Adelaja *et al.*,[45]	Histo-gastro-protective activity	Wistar rats with indomethacin-induced gastric mucosal ulcers (80 mg/kg/bodyweight) were used to evaluate the gastroprotective potential of the aqueous leaves extracts.	The aqueous extracts of *H. indicum* exhibited dose-dependent histo-gastro-protective effects at 100 and 200 mg/kg/bodyweight.
6	Mexico	López-Lorenzo *et al.*,[49]	Gastric ulcer healing activity	Comparative investigation of hexane, dichloromethane, and methanol leaf extracts of *H. indicum* at 30 mg and 100mg/kg doses were investigated in CD1 mice for gastroprotective effect in ethanol-induced gastric injury.	(E)-Ethyl-12-cyclohexyl-4, 5-dihy droxydodec-2-enoate was isolated from the dichloromethane extract and found to have a significant gastroprotective effect.

Table 1. Continued...

S. No	Country	Author	Pharma cological Activity	Specific Investigation	Findings
7	India	Basak *et al.*,[41]	Anti-ulcer activity	Ethanolic extract of the leaves of *H. indicum* was evaluated in albino rats. In 200 mg/kg body weight of aspirin plus pylorus ligation-induced ulcer model	The ethanolic leaf extract of *H. indicum* possesses significant dose-dependent anti-ulcer effects
8	Ghana	Kyei *et al.*,[39]	Anti-inflammatory activity	Whole plant part aqueous extract of (30 to 300 mg/kg) of *H. indicum* (HIE) was evaluated in New Zealand white rabbits with uveitis, induced with 1.0 mg/kg lipopolysaccharide	The extract and standard prednisolone significantly reduced inflammation in rabbits, leading to reduction in inflammatory cells.
9	Ghana	Kyei *et al.*,[39]	Anti-cataract activity	Evaluation of whole plant part aqueous extract of *H. indicum* on galactose-induced cataract in Sprague-Dawley rats	The whole plant part aqueous extract when administered at 30 and 100 mgkg−1, effectively delays cataract development induced by galactose and reduces blood glucose levels.
10	Ghana	Kyei *et al.*,[37]	Anti-cataractogenic and antioxidant activities	The effects of 30, 100, and 300 mg kg-1 ofthe whole plant aqueous extract, and 10 mL kg-1 of normal saline was investigated selenite-induced cataracts in Sprague-Dawley rats.	The extract significantly showed anti-cataractogenic activity against selenite-induced cataracts in Sprague-Dawley rats and reduced biomarkers alpha A, B crystallins, and aquaporin 0 which indicate lens transparency. Additionally, lens glutathione and total lens proteins concentrations were significantly preserved (p = 0.01-0.001).
11	Bangladesh	Sifat *et al.*,[50]	Anti-dyslipidemia activity	Assessment of the aerial plant part extract of *H. indicum* on a high-fat-high-cholesterol diet (HFHC)induced female Wistar albino rats.	*H. indicum* powder effectively manages weight, reduces belly fat, improves glucose intolerance, and reduces dyslipidaemia in obese rats, while also improving liver function by its antioxidant effect.
12	Thailand	Chunthorng-Orn *et al.*,[47]	Cytotoxic, anti-inflammatory, and antioxidant activities	Comparative evaluation of whole plant part aqueous and ethanolic extract of *H. indicum* for cytotoxic activity.	The ethanolic extract (EA) inhibited NCI-H226 (IC_{50} = 51.90+2.35 µg/mL) while the water extract had no activity against both A549 and NCI-H226. Ethanolic extract exhibited the most potent inhibitory activity on nitric oxide production (IC_{50} = 24.17+2.12). For antioxidant activity, the ethanol extract had EC_{50}= 28.91+4.26 µg/mL, but the water extract showed minimal EC_{50} >100 µg/mL.
13	Thailand	Tuy-on *et al.*,[48]	Cytotoxic activity	Comparative study of various plants including *H. indicum* stem extract for *in vitro* inhibitory activity against ovarian, cervical, and breast cells.	The stem extract of *H. indicum* exerted moderate cytotoxicity to the various cancer cells and low toxicity to normal cells

Table 1. Continued...

S. No	Country	Author	Pharma cological Activity	Specific Investigation	Findings
14	Venezuela	Taylor *et al.,*[51]	Cytotoxic and cytostatic activities	Comparative study of plant extracts for cytostatic and cytotoxic activity against tumour cell lines.	*H. indicum* possessed cytotoxic and cytostatic activities with mean LC50 values less than 750 mg/mL.
15	India	Gosh *et al.,*[43]	Cytotoxicity and antioxidant activities	An examination of leaf extracts to determine the levels of phytochemicals and assess their antioxidant properties, as well as potential cytotoxic effects.	Leaf extract of *H. indicum* possesses *in vitro* antioxidant activity and promising cytotoxic activity.

with different extracts, fractions, and compounds. The major pharmacological properties demonstrated include antioxidant activity, cytotoxic activity, gastroprotective activity, wound healing activity, anti-cataract activity, and anti-inflammatory activity. Additionally, *H. indicum* aided in wound healing and exhibited anti-ulcer effects. Details of the activities are displayed in Figure 4.

3.2 Safety of *H. indicum*

The safety of *H. indicum* is in doubt, mainly due to reports of toxicity from the plant or its constituent alkaloids. There are reports of the toxicity of *H. indicum* in horses, which resulted in bile pigment accumulation in the spleen, as well as satellitosis, neuronophagia, and gliosis in the cerebral cortex. This effect, which resulted in mortality was because of intoxication attributed to Pyrrolizidine Alkaloids (PA) from the plant[20]. There are several such reports of fatality from PA[54]. A classical toxidrome of pyrrolizidine alkaloid intoxication results in liver fibrosis along with megalocytosis, bile pigment retention, interlobular fibrosis, and an increase in the number of bile ducts[55]. The principal alkaloidal compound, indicine N-oxide (INO), has also been reported to exhibit severe hepatotoxicity and bone marrow depletion[22], though the exact molecular mechanism remains uncertain. This finding corroborates other published literature about indicine N-oxide isolated from *H. indicum* exhibiting similar toxic properties of hepatotoxicity and myelosuppression[56,57].

Oral administration of the ethanol extract was also found to cause dose-dependent mortality in mice[58]. The LD_{50} was 9.78 grams per kilogram of body weight. No adverse effects were, however, observed on the hepatic and renal organs, but the testes showed signs of inflammation when exposed to a dose of 2.0 grams per kilogram of body weight per day after 5 months of treatment. The findings of no hepatotoxicity and renal toxicity were at variance with other studies that have reported hepatotoxicity with the use of this plant[24,59,60]. Phase I trials on the lead compound, INO, in human patients with advanced cancer, induced hepatic dysfunction during drug administration in seven treatment courses in patients[12]. The data suggests that the liver plays a critical function in the metabolism and excretion of INO. Sixty percent (60%) of the compound is eliminated through urine without undergoing any changes after intravenous administration. The remaining portion of the drug enters the intestinal tract through passive diffusion, where it is metabolized by gut bacteria into indicine, a form that can be harmful to the liver[61]. Details of the safety assessments are displayed in Table 2. INO present in the plant is also reported to display extreme toxicity to liver and bone marrow cells[22].

4. Discussion

Heliotropium indicum boasts of a rich history of medicinal uses. Notable applications are in treating bites, skin infections, stomach issues, and nervous system disorders as shown by the ethnopharmacological survey conducted in Tamil Nadu in India[62]. In the Amazon rainforest, people have traditionally used poultices made from the leaves and roots to treat scorpion stings and insect bites[63]. Additionally, in Mali, the decoction

Table 2. Safety of *H. indicum*

S. No	Country	Author	Experimental Model	Specific investigation	Findings
1	Costa Rica	Van Weeren *et al.,*[52]	Horse	A case report on mortality because of intoxication by pyrrolizidine alkaloids from *H. indicum.*	The results revealed the presence of bile pigment accumulation in the spleen, as well as satellitosis, neuronophagia, and gliosis in the cerebral cortex.
2	India	Appadurai *et al.,*[40]	Cell lines	The study evaluated the mechanism of toxicity of indicine N-oxide, analkaloid isolated from *H. indicum.*	INO is highly cytotoxic against tumour cel lines at higher concentrations due to its potent DNA damaging activity and its inhibitory effect on tubulin polymerization.
3	Nigeria	Owolabi *et al.,*[46]	Sprague Dawley rats	Evaluation of the toxicity of *H. indicum* ethanolic extract in Sprague Dawley rats after oral administration.	The mortality rate was dosage dependent. In the rats, the LD_{50} was 9.78g/kg body weight. Notable, no adverse effects were observed on the kidney and liver except for the testes which exhibited inflammatory changes at the highest dose of 2.0g/kg body weight, after a prolonged treatment of five months.
4	USA	Ohnuma *et al.,*[53]	Human	Phase 1 study of INO in patients with advanced cancer.	A dose limiting toxic effect of INO at maximal dose of 9 g/m^2.

of the foliage is drunk to treat nausea and vomiting[64]. In Ghana, a decoction of *H. indicum* leaves is used to treat paludism and eye infections for a period of seven days[65]. Research conducted on the components and raw extracts of *H. indicum* has shown a range of effects providing initial backing for traditional assertions. Nevertheless, some aspects also necessitate further scientific investigation and exploration.

The different biological actions exhibited by the crude extracts and their bioactive compounds serve as the foundation for understanding the underlying mechanisms of action[66]. The pharmacological properties investigated on this plant included antioxidant activity, cytotoxic activity, gastroprotective activity, wound healing activity, anti-cataract activity, and anti-inflammatory activity. Additionally, *H. indicum* aided in wound healing and exhibited anti-ulcer effects[37,41,42,44,45,49].

4.1 Cytotoxic Activity

Four studies reported on the cytotoxic properties of *H. indicum,* while 3 reported on the activities of the ethanolic extract of *H. indicum* against breast and lung cancer cells[6,11,67]. This result is supported by other literature that found an ethanolic extract derived from *H. indicum* inhibiting the growth of both breast and lung cancer cell lines[21]. One study reported on cytotoxicity in mouse leukemic monocyte macrophage cell line[68]. The cytotoxicity was attributed to the presence of pyrrolizidine alkaloids, particularly INO. INO exhibits potent depolymerizing activity on both interphase and spindle microtubles, leading to severe disruption of microtubule dynamics. The toxic effects are attributed to its ability to cause DNA damage and microtubule depolymerization, resulting in significant cellular harm[22]. Other studies suggest that the compound hampers the formation of microtubules by interfering with the assembly process of tubulin, ultimately leading to damageto DNA[22].

4.2 Antioxidant Activity

For the antioxidant activity of *H. indicum*, 4 studies obtained results suggesting that the ethanolic extract possesses significant antioxidant properties. In one of the studies, the ethanolic extract was found to have an EC_{50} value of (28.91 ± 4.26µ/mL) as compared to a superior butylated hydroxytoluene extract of *H. indicum* , which was 13.08 ± 0.29 µ/mL[69]. The antioxidant property of *H. indicum* was linked to the plant's secondary metabolite, flavonoids[11]. Flavonoids have strong antioxidant, antimicrobial, and chelating properties[70]. In a comparative study of the antioxidant capacity of various methanol extracts in scavenging for DPPH[71], *H. indicum* showed the highest level of

activity as indicated by its IC_{50} value of 120.81 ± 0.58 µg/mL compared to standard ascorbic acid.

4.3 Gastroprotective Activity

The ethanol leaf extracts of *H. indicum,* have been in shown in several studies to possess dose-dependent anti-ulcer effects. Three studies reported on the gastroprotective property and the anti-ulcer effect. One study attributed the gastroprotective and antiulcer properties to the phytochemical component (*E*)-Ethyl-12-cyclohexyl-4,5-dihydroxydodec-2-enoate[72]. The 2nd study validated the proof that the ethanolic extract exhibited properties in treating ulcers and protecting the stomach[34]. When given to rats with induced ulcers, the plant extracts reduced factors that contribute to ulcer formation by a reduction the ulcer index and acidity of gastric juice, with effects similar to the standard drug ranitidine[73]. These findings lend support the use of *H. indicum* as an antiulcer treatment in folkloric medicine. In an aspirin and pylorus ligation model induced gastric ulcer, the ethanol extract showed a reduction in gastric volume, free acidity levels, and ulcer score relative to the control[74]. Similar conclusions are found in other studies[75].

4.4 Wound Healing Activity

Two studies also reported the wound-healing properties of *H. indicum.* According to one, the strength of the skin and tissues in wound models suggests that collagen maturation was enhanced[76]. This could be attributed to its components, such as flavonoids, which inhibit lipid peroxidation and improve blood flow[77]. These phytoconstituents may also enhance collagen fibers, promote DNA synthesis, prevent cell damage, and promote overall tissue health[78]. The wound healing properties may also be linked to its constituents' antioxidant and antibacterial effects[42,44,47].

4.5 Anti-cataract Activity

The anti-cataract potential of *H. indicum* was mentioned in 2 studies. Both studies were authored by the same authors in separate years[10,79]. Kyei *et al.,* concluded that the extract of *H. indicum* possessed anti-cataract activity. Even though the mechanism of action was not conclusive, therapeutic activity was attributed to the presence of bioactive components of the extract[80]. It was deduced that *H. indicum* possessed anti-cataract activity in galactose-induced cataracts in Wistar rats. It was also suggested that this action was due to antioxidant activity. Kyei *et al.,* in their 2nd study, which investigated the anti-cataract potential of *H. indicum* in a galactose-induced cataract model in Spague-Dawley rats. The aqueous extract obtained from the entire plant part of *H. indicum* proved to be effective in delaying the formation of cataract in Sprague Dawley rats. Both the extract and prednisolone treatment effectively reduced inflammation in rabbits, resulting in delayed cataract development, weight gain, and loss of lens weight[37,81].

4.6 Anti-inflammatory Activity

Two studies investigated the anti-inflammatory effects of *H. indicum.* Chunthorng-Orn *et al.,* determined this activity by investigating the reduction in nitric oxide generation in RAW246.7 cells, with the ethanolic extract having the highest inhibitory activity. Indomethacin, as the positive control, showed a lower inhibitory effect as compared to the ethanolic extract which had an IC_{50} value about 1.43 times higher. The study by Kyei *et al.* used uveitis in New Zealand white rabbits that was induced by an endotoxin. Findings indicate a possible inhibition of the production of pro-inflammatory mediators as a mechanism of action of *H. indicum* extract. Both findings of anti-inflammatory properties of *H. indicum* extract align with other published literature. The extract of *H. indicum* has been reported to prevent anti-inflammatory activities in hind paw oedema induced by carrageenan and granuloma induced by cotton pellet in rat models[82,83].

4.7 Anti-dyslipidemia Activity

Heliotropium indicum powder was reported to be effective in managing body weight, reducing fat accumulation, improving glucose tolerance, and mitigating dyslipidemia in rats[69]. *H. indicum* showed effects in improving obesity and related metabolic disorders caused by a high-carbohydrate, high-fat diet. It had effects on impaired glucose metabolism in rats, confirming its folkloric use while also reducing high levels of triglycerides, low-density-lipoprotein cholesterol, and total cholesterol. Additionally, supplementation with *H. indicum* powder was found to improve liver function as evidenced by lowered alkaline phosphatase, aspartate amino transaminase, and alanine aminotransferase enzyme activities[84].

The findings of this study highlight the potential of *H. indicum* in mitigating stress, inflammation, and fibrosis induced by a high-carbohydrate, high-fat diet, obesity and its associated metabolic disorders . Another study drew a similar conclusion for *H. indicum* aqueous extract. There was a reduction in the concentrations of total cholesterol, LDL, and TG, while HDL increased, suggesting that this particular extract exhibits anti-dyslipidemia activities[85].

4.8 Other Pharmacological Properties

Pretreatment with an aqueous extract of *H. indicum* significantly prevented the expected rise in intraocular pressure in New Zealand White rabbits with dextrose induced ocular hypertension. The effect was comparable to acetazolamide pretreatment[7]. The anti-allergy, anti-mitotic, anti-tumor, anti-proliferative, anti-nociceptive, cytostatic, and neuroprotective activities were other pharmacological properties that were explored by various studies[7,11]. Given the combination of pharmacological characteristics displayed and its safety record, the results of this review presuppose that further exploration can be conducted on *H. indicum* as a promising option for an affordable and safe remedy for a range of diseases, particularly in poor regions.

4.9 Safety of *H. indicum*

Due to safety concerns with the use of *H. indicum* extracts, and some of its isolated compounds, there is a need to establish the safety of various extracts at specific doses and for its isolated constituents. Further studies will be needed to determine the specific bioactive components of the plant and those that can be exploited by chemical modifications for drug development. The focus on medicines from plants has garnered interest due to the prospects of their effectiveness, quality, and safety[86,87].

5. Conclusion

Even though there is still skepticism about the safety and therapeutic efficacy *H. indicum,* literature shows it has been widely used in various countries to treat several ailments. *H. indicum* is rich in compounds having a wide range of therapeutic activities that includes anti-allergic effect, anti-glaucoma effect, wound healing effect, histo-gastro-protective activity, antitumor activity, antimitotic, neuroprotective, anti-proliferative, anti-nociceptive, anti-ulcer activity, cytotoxic activity, anti-inflammatory activity, antioxidant activity, lipid lowering activity, anti-cataractogenic activity and cytostatic activity, thus making it promising.. Therefore, comprehensive studies are needed to better understand its medicinal composition and its effects on biological systems to improve its safety while streamlining its use. Some specific constituents like indicine N-oxide, heliotrine and retrorsine have shown toxic effects in animal models and human cells, which further complicates its use as a remedy. To establish the credibility of incorporating this remedy into mainstream medicine, it is crucial to back up justifications with evidence-based scientific data.

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7. Author Contribution

The study was conceptualized and overseen by EOB and EAP. All authors executed the study. SA and NA were responsible for searching and collecting data, while BBW handled the data extraction and analysis. All authors have read and agreed to the published version of the manuscript.

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