Scientific Research Publishing

Advances in Biological Chemistry, 2026, 16(4), 45-65
https://www.scirp.org/journal/abc
ISSN Online: 2162-2191
ISSN Print: 2162-2183

Biological Activities and Chemical Composition of *Heliotropium Indicum* L.: An Overview

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How to cite this paper: Arama, D.P., Diop, R., Diallo, B., Diallo, T., Koumaré, B.Y., Bah, S. and Sanogo, R. (2026) Biological Activities and Chemical Composition of *Heliotropium Indicum* L.: An Overview. *Advances in Biological Chemistry*, **16**, 45-65.
https://doi.org/10.4236/abc.2026.164005

Received: June 28, 2026
Accepted: August 11, 2026
Published: August 14, 2026

Abstract

This work was carried out between March 2020 - July 2026. Chemical composition and biological activities of *Heliotropium indicum* L. (Indian heliotrope) are deeply explored in this work. The analysis highlights the predominance of pyrrolizidine alkaloids, as well as the significant presence of triterpenoids, sterols, flavonoids and polyamines. These compounds are responsible for a wide range of biological activities, mainly including antioxidant, anti-inflammatory, wound healing, antimicrobial, hypolipidemic and antitumor effects. Focus has been placed on structure-activity relationships (SAR), particularly in pyrrolizidines, triterpenoids and sterols, to demonstrate the influence of structural elements such as double bonds, hydroxyl and ester groups on biological activity and toxicity of these compounds. The study also shows that complexation with cyclodextrins, in particular for amyrins, is one of the promising strategies aimed at improving the bioavailability of compounds. Despite its therapeutic potential, the use of *Heliotropium indicum* L. remains limited by the well-documented toxicity of pyrrolizidines, notably liver toxicity and genotoxicity. This review highlights the need for targeted studies on standardized extracts and isolated compounds, in order to optimize the benefit/risk ratio and to support a rational integration of compounds from this plant into modern therapeutics.

Keywords

Heliotropium indicum L., Pyrrolizidine Alkaloids, Triterpenoids, Sterols, Biological Activities, Structure-Activity Relationships

1. Introduction

In many regions of developing countries, access to conventional healthcare remains limited, pushing a large part of the population to use medicinal plants to treat common ailments. The *Heliotropium* genus (*Boraginaceae*) includes more than 250 species distributed in tropical and subtropical areas, which are particularly valued for their richness in bioactive secondary metabolites [1] [2]. *Heliotropium indicum* L. is a vigorous annual plant, with an average height of 0.3 to 1 m, almost continuous flowering, and fruits composed of 2 to 4 nutlets measuring 4 to 5 mm in length [3]. It is widely distributed in South Asia and West Africa, where it is integrated into traditional medicine for wound healing, treatment of eye infections, menstrual cycle regulation, and as an antidote against envenomations [1] [3].

Phytochemical studies indicate the presence of pyrrolizidine alkaloids as well as triterpenoid derivatives, sterols, and tannins [4]-[6]. Pyrrolizidine alkaloids are biosynthesized following a process described by Hartmann & Ober [7]. Pharmacologically, *Heliotropium indicum* L. exhibits anti-inflammatory effects demonstrated *in vivo* in rats and against experimental uveitis in rabbits [8] [9], antioxidant and antimicrobial properties [10], wound-healing actions confirmed in animal models [11], as well as anti-cataract activity *in vitro* and *in vivo* [9]. Earlier studies have also identified antitumor molecules in this plant [12]. The main components of *Heliotropium indicum*, the pyrrolizidine alkaloids, have a pharmacological potential for different pathologies or pathological processes so much so that its main alkaloid, Indicine *N*-oxide has been evaluated *in vivo* in cancer patients, although it has also been shown to be a hepatotoxic compound [13].

The aim of this work was to review the current knowledge on the phytochemistry, biological activities, and to identify characteristic structural elements of *Heliotropium indicum* L. main constituents, in a structure-activity relationship (SAR) approach, in order to guide future pharmacochemical research.

2. Methods

This systematic review realized between March 2020 and July 2026, was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations to ensure transparency, reproducibility, and minimization of bias (**Figure 1**). The literature search strategy was done using search engines such as PubMed, ScienceDirect, Google Scholar, ResearchGate, BioMed Central, Elsevier. The following keywords were used: "*Heliotropium indicum*" and "phytochemistry" or "biological activities" or "toxicity" or "structure activity relationship" in both French and English.

For studies selection, criteria for identification, screening, inclusion, non-inclusion, and traceability of exclusions were observed. The first step of selection listed a total of 158 articles from bibliographic databases using a combination of keywords such as "*Heliotropium indicum*", "pyrrolizidine alkaloids", "triterpenoids", "phytosterols", and "biological activities".

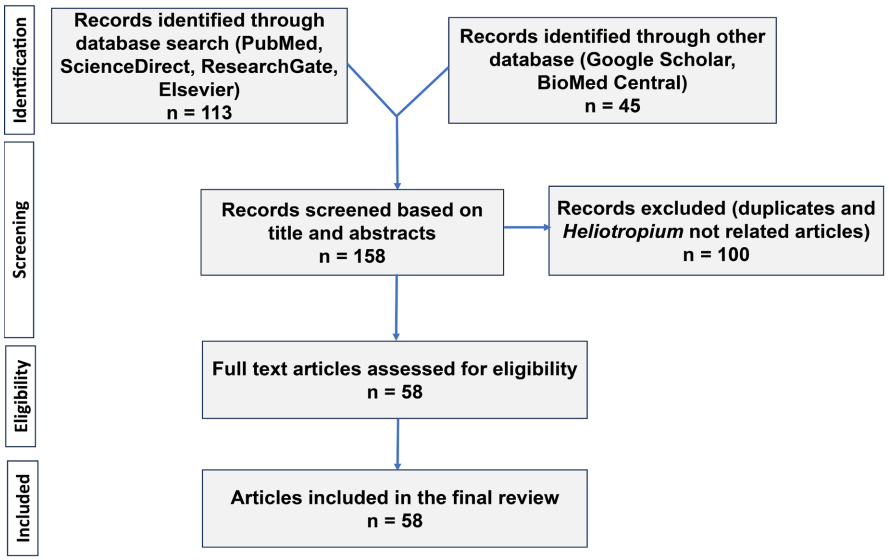

Figure 1. Review process diagram, according to the PRISMA methodology.

For the screening, titles and abstracts of 158 identified articles were independently examined by two reviewers. At the end of this screening, only studies specifically dedicated to *Heliotropium indicum* or those concerning the *Heliotropium* genus were selected for the next step. Articles mentioning *Heliotropium indicum* or the *Heliotropium* genus and peer-reviewed publications (scientific journal articles) were included. Studies not concerning the *Heliotropium* genus, articles not peer-reviewed, academic documents not published in journals (theses, internal reports), and residual duplicates identified in the databases were excluded. At each stage, the reasons for rejection were recorded to ensure transparency of the selection process for traceability. At the end of the selection and eligibility process, 58 studies were selected for the final analysis according to the defined criteria. The studies such selected cover all targeted aspects: chemical composition, biological activities, structure-activity relationships, and toxicity of *Heliotropium indicum* L. For articles concerning the genus **Heliotropium**, only data relating to the species **indicum** were used for the purposes of the review.

For data management, a collection form in Excel was previously validated during a pilot phase (5% of the corpus), then applied to all studies. Regarding extraction, two examiners worked independently on the following data: i) Full reference, year, type of study (*in vitro*, *in vivo*, review), ii) Plant organ studied, iii) Chemical family (pyrrolizidine alkaloids, triterpenes, sterols, etc.), iv) Analytical method (GC-MS, HPLC-MS, NMR, TLC, etc.), v) Quantitative results (concentrations, % of extract) and qualitative results (nature of the activities), vi) Experimental conditions (animal model, dose, cell line, etc.). The disagreements were resolved through discussion and, if necessary, by a third reviewer. As for the data synthesis, the results are presented in narrative form, supplemented by summary tables (chemical profile, distribution by organ, pharmacological activities), and structural figures; no meta-analysis was conducted due to the heterogeneity of protocols (*in*

vitro vs *in vivo*, variability in dosages). The discrepancies between studies were subject to critical discussion, in connection with methodological quality.

In this study, reference management was handled using the Zotero software (version 5.0.96.2). Extraction forms and tables were created with Microsoft Excel 2016 and Word 2016. Chemical structures were drawn with ChemDraw Professional 12.0.2. The PRISMA diagram was created in PowerPoint 2016.

3. Results and Discussion

The search produced 158 articles in total identified through several database search. From the retrieved full articles, 100 were excluded due to duplicated records and those not related to *Heliotropium* genus. A total of 58 articles were included in this review. These studies cover a 58-year period, from 1967 to 2025, with the years 2011 and 2020 recording the highest number of publications (5 articles each).

3.1. Limitations of the Review

This review is limited by some methodological constraints that temper the scope of its conclusions. The heterogeneity of experimental protocols (*in vitro* and *in vivo* models, extraction solvents, varied doses and exposure durations) made it difficult to conduct a quantitative meta-analysis, limiting the synthesis to a simple narrative. Furthermore, despite the use of a data collection validated form, the manual selection of studies and data extraction remain dependent on the reviewer's judgment, introducing a risk of error and subjective bias. In addition, the methodological quality of the various studies is very variable. Indeed, many authors do not specify either randomization or blind control, and few of them detail the reproducibility of their experiments. The diversity of phytochemical analysis techniques and extraction protocols also complicates the comparison of results. Finally, the restriction to publications in English and French up to July 2025 excludes any relevant studies published later or in other languages.

A detailed characterization of the phytochemical composition of *Heliotropium indicum* L. was provided in 45 studies (78%) among the 58 selected, while 39 studies (67%) described the metabolites distribution within the different organs of the plant. Only a few studies addressed the structure-activity relationships of identified compounds.

3.2. Phytochemical Composition

The major families of reported metabolites and their frequency of occurrence in the corpus (percentages rounded to the nearest whole number) are presented in Table 1.

The review showed that in the 58 studies analyzed, pyrrolizidine alkaloids and pentacyclic triterpenoids are the most reported chemical groups, respectively in 23 studies (40%) and 12 studies (21%). The phytochemical profile of *Heliotropium indicum* L. varies considerably from one organ to another and reveals a di-

versity of chemical compounds specific to each part of the plant.

Table 1. Main chemical groups identified in *Heliotropium indicum* L.

Chemical group	Number of studies (n = 58)	%	References
Pyrrolizidine alkaloïds	23	40	[1] [3]-[8] [11]-[25]
Pentacyclic triterpenoids	12	21	[3] [7]-[9] [11] [17] [21] [22] [24]-[27]
Sterols (phytosterols)	8	15	[6] [9] [13] [21]-[25]
Biogenic amines	5	10	[1] [2] [21]-[23]
Amides	6	12	[21]-[23] [26] [31]
Benzoquinones	4	8	[9] [21] [23] [26]
Essential oils	3	6	[4] [23] [29]

3.3. Distribution of the Identified Main Compounds According to *Heliotropium indicum* L. Plant Organs

The tables below summarize the presence or absence of the main compounds identified in the leaves, seeds, stems and roots of *Heliotropium indicum* L. according to chemical group: pyrrolizidine alkaloids (**Table 2**), triterpenoids (**Table 3**), sterols (**Table 4**), amines, amides, benzoquinones and essential oils (**Table 5**).

Table 2. Pyrrolizidine alkaloids.

Compound	Leaves	Seeds	Stems	Roots	References
Indicine	+	+	+	–	[4] [12]-[17] [23]
Lycopsamine	+	–	+	+	[4] [13]-[16] [23]
Lasiocarpine	+	+	–	+	[4] [5] [13]-[16]
Heliotrine	+	–	+	–	[5] [13]-[16]

Table 3. Pentacyclic triterpenoids.

Compound	Leaves	Seeds	Stems	Roots	References
β-Amyrin	+	+	+	+	[3] [22] [25]-[27]
Lupeol	+	–	+	+	[3] [22] [25]-[27]

Table 4. Sterols (phytosterols).

Compound	Leaves	Seeds	Stems	Roots	References
β-Sitosterol	+	+	+	–	[1] [6] [13] [23] [24] [26]
Campesterol	–	+	–	+	[1] [6] [13] [23] [24] [26]
Stigmasterol	+	–	+	–	[1] [6] [13] [23] [26]
Estradiol	–	–	–	+	[2] [6] [13] [26]

Table 5. Other phytochemical compounds.

Compound		Leaves	Seeds	Stems	Roots	References
Polyamines	Putrescine	+	–	–	–	[13] [28]
	Spermidine	+	–	–	–	
	Spermine	+	–	–	–	
Amides	Peslamide-B	+	+	–	+	[21] [26]
	Glycinamide	–	+	–	–	
Benzoquinones	Rapanone	+	+	–	+	[9] [26]
Huiles essentielles	Dodecanol	+	+	–	–	[4] [29]
	β-Linalol	+	+	–	–	
	Phytol	+	–	–	–	

Four pyrrolizidine alkaloids are reported to be in the leaves compared to three in the stems.

Pyrrolizidine alkaloids as well as their esters have been isolated and characterized in leaves, stems, and seeds by Pandey DP *et al*. [5] [14], Mattocks [15], Hoque *et al*. [4], Birecka *et al*. [16], and Souza *et al*. [17]. The presence of heliotrine and lasiocarpine has been demonstrated by Pandey DP *et al*. [5] and Rahman *et al*. [18] in the leaves and roots, with root-derived indicine *N*-oxide being identified as the main antitumor molecule by Kugelman *et al*. [12]. The rapid detection of these same alkaloids in various extracts (ethanol, methanol, aqueous) has been validated through colorimetric and chromatographic screenings (Dragendorff assay, TLC, HPLC) carried out by Adetuyi *et al*. [19], Basak & Dey [20], and other authors [21]-[24].

All organs contain *β*-Amyrin. Except the seeds, the other organs contain Lupeol. Da Silva Júnior *et al*. [25] and Sahu *et al*. [22] identified *β*-amyrin and lupeol in methanolic leaf extracts of *Heliotropium indicum* L., the former highlighting their ability to form inclusion complexes with cyclodextrins (*β*-CD, HP*β*-CD) to improve their solubility and *in vitro* anti-inflammatory activity, and the latter qualitatively confirming their presence through phytomorphological and chromatographic tests. Ghosh *et al*. [3], through a concise review, reported the predominant concentration of these triterpenoids in the foliar apparatus. In contrast, the work of Kyei *et al*. [26] and Kumar MS *et al*. [27], although interesting for their pharmacological and antioxidant evaluation, do not provide precise information on the anatomical distribution of triterpenoids within the plant.

Phytopharmacological analyses carried out by Ghori *et al*. [1], Sahu *et al*. [22] and Ovalle *et al*. [13] highlighted ubiquitous sterols (sitosterol, campesterol, and *β*-sitosterol) in leaf, stem, and root extracts of *Heliotropium indicum* L., while estradiol, detected exclusively in the root, was confirmed by Gopinathan & Balasubramanian [2] and Ovalle *et al*. [13].

Many other compounds of the polyamine, amide, benzoquinone, and essential oil types, found in the leaves, are absent from the stems.

3.4. Pharmacological Activities

Among the 43 studies that evaluated the biological activities of *Heliotropium indicum*, 27 were carried out *in vitro*, 13 *in vivo*, and 3 combined both approaches. Twelve (12) studies (28%) also reported toxic effects, mainly related to pyrrolizidine alkaloids. Table 6 presents the activities by chemical group, type of study, used model, and the described side effects.

Table 6. Biological activities of *Heliotropium indicum* L. according to the chemical group and the experimental format.

Chemical group	Study type	Biological activities	Side effects	References
Pyrrolizidine Alkaloids	*In vivo* & *in vitro*	Anti-inflammatory, Antitumor, Analgesic, Antioxidant, Antimicrobial, Antipyretic, Gastroprotective, Hypoglycemic, Anti-cataract, Larvicide, Anthelmintic	Hepatotoxicity, Cytotoxicity (rat, mouse)	[8] [10]-[13] [25] [27] [37]-[41]
Triterpenoids	*In vitro* & *in vivo*	Antioxidant, Anti-inflammatory, Healing	–	[9] [11] [26] [27] [33] [37]
Sterols	*In vitro* & *in vivo*	Hypolipidemic, Anti-inflammatory, Hypoglycemic	–	[6] [19] [27] [30] [31]
Biogenic amines	*In vitro*	Cellular regulation, Antioxidant,	–	[1] [2] [23] [29]
Benzoquinones	*In vitro*	Cytotoxic (Antitumor), Antioxidant, Antibacterial, Antifungal, Healing	–	[9] [11] [21] [29]
Amides	*In vivo*	Healing, Antibacterial	–	[11] [21] [22]
Essential oils	*In vitro*	Antimicrobial, Antituberculous	–	[4] [10] [32]

The described main activities for *Heliotropium indicum* are anti-inflammatory, antioxidant, and antimicrobial activities.

Systematic reviews by Dash and Abdullah [28], Ovalle *et al*. [13] reported the presence of polyamines (putrescine, spermine, and spermidine) in the leaves of *Heliotropium indicum* L., suggesting their essential role in cell division and plant defense mechanisms. Joshi *et al*. analyzed the leaves of *Heliotropium indicum* L. by gas chromatography coupled with mass spectrometry (GC-MS), identifying more than twenty-five volatile compounds, including linear alkanes such as hexadecane and nonacosane [29]. Using Gas chromatography-mass spectrometry (GC-MS), Faleye *et al*. identified twenty-nine (29) constituents in *Heliotropium indicum* ethanolic leaves extract, many of which are poorly soluble and have low gastrointestinal absorption (GIA). However, they found some of them soluble with high GIA and However, they found some of them soluble with high GIA and blood brain barrier (BBB) permeability. The results showed that (+)-Isomenthol and Ergost-22-en-3-ol are the two most active constituents of ethanolic leaves extract of *Heliotropium indicum,* targeting androgen receptor (AR) and transient receptor potential cation channel subfamily M member 8 (TRPM8), which have implication in prostate cancer [30]. The phytochemical screening of *Heliotropium indicum* methanol leaf extract revealed the presence of flavonoids, phenols, tannins, saponins, alkaloids, and steroids. The extract demonstrated a dose-dependent reduction in intestinal transit and frequency of watery stool, with promising results

compared to the positive control, loperamide [31]. A study carried out in 2024 by Mst *et al*. depicts the first and novel report of GC-MS compounds on in silico analysis. Chloroform (CHF), and ethyl acetate (EAF) extracts exhibit significant anti-inflammatory activity, indicating their potential as a source for developing new therapeutic agents for treating inflammation [32]. In their study on the whole-plant methanolic extract of *Heliotropium indicum*, Md Ekramul *et al*. demonstrated that the extracts protected against oxidative DNA damage induced by the water-soluble free radicals generator 2,2'-azobis(2-amidinopropane) dihydrochloride (AAPH), highlighting their antioxidant properties. In addition, in-silico PASS prediction suggested multiple pharmacological activities, including TNF inhibition, TP53 expression enhancement, and free radical scavenging [33].

In vitro callus culture of *Heliotropium indicum* L. revealed a high content of phenolic and flavonoid compounds, estimated at approximately 120 mg of gallic acid equivalent per gram [27]. Moreover, the green synthesis of zinc oxide nanoparticles (ZnO nanoconjugates) from leaf extracts [34] highlights the richness and versatility of the green chemistry developed based on this species.

3.5. Structure-Activity Relationships (SAR) Characteristic Elements

An analysis was carried out using a structure-activity relationship (SAR) approach to identify the characteristic structural elements of the main chemical groups to explain the link between some representative compounds and the described activities for this plant. In this review, we focus on describing the structure-activity relationships of compounds belonging to the following chemical groups: pyrrolizidine alkaloids, sterols, pentacyclic triterpenoids, and biogenic amines or polyamines.

3.5.1. Pyrrolizidine Alkaloids

The chemical structure of pyrrolizidine alkaloids can be described as a necine base core esterified with one or two necic acids, resulting in mono-, macrocyclic or diesters (**Figure 2**).

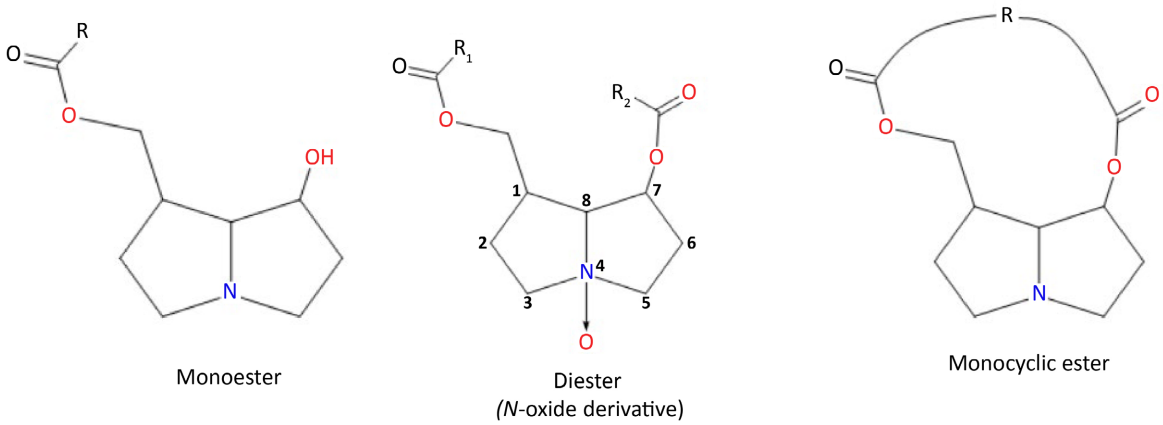

Figure 2. Esterified necine base core with necic acid.

There are four main necine bases which can be found as their corresponding *N*-oxides. The necine base is generally a bicyclic aliphatic hydrocarbon consisting of two fused five-membered rings with a bridgehead nitrogen atom. The ring is substituted with a hydroxymethyl group (–CH_2OH) at the C-1 position and sometimes bears a secondary alcohol function (–OH) at C-7 (retronecine, heliotridine, platynecine) (Figure 3).

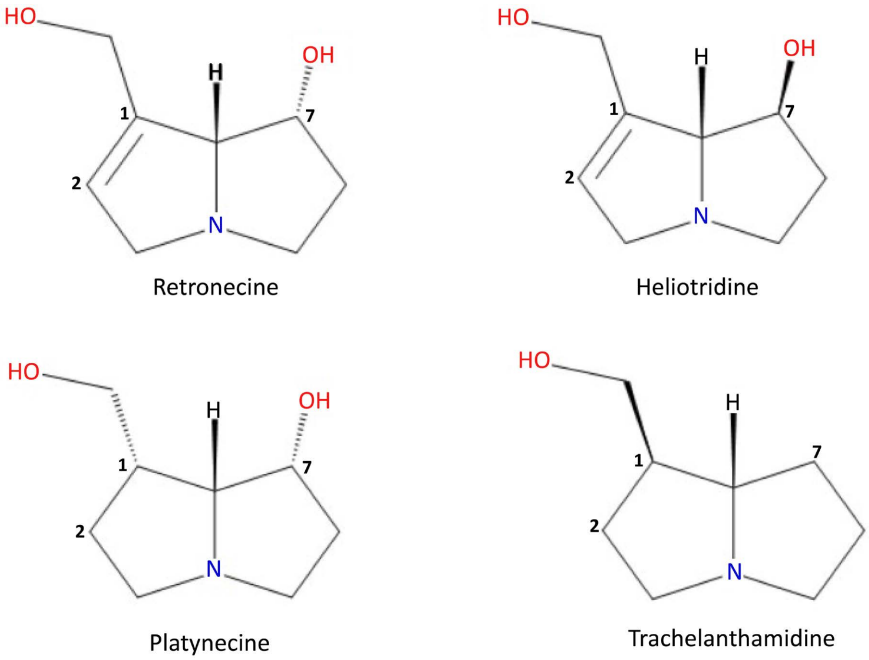

Figure 3. Structure of main necine bases: retronecine and heliotridine are enantiomers at the C7 position.

Hydroxylation of the necine base and/or the necic acid, acetylation of hydroxyl groups, *N*-oxidation of the necine tertiary nitrogen, and the presence of unsaturation in the C1-C2 bicyclic system constitute the main forms of diversification observed for this group (Figure 4).

In the pyrrolizidine alkaloids of *Heliotropium indicum* L., subtle structural modi-fications strongly dictate their toxicological and pharmacokinetic profile.

- **Double bond $\Delta^{1\text{-}2}$**: the presence of this unsaturation in the necine nucleus is essential, as it promotes the formation of free radicals under UV irradiation, leading to increased lipid peroxidation and generation of cellular oxidative stress. Furthermore, substitution at C-7 strongly modulates phototoxicity: 7-hydroxy derivatives produce lower levels of lipid peroxidation than their 7-acetoxyl homologues, indicating that polar substituents can mitigate damage to membrane lipids by trapping excited states before the formation of reactive oxygen species [35].
- **Hydroxyls at C-1/C-7 (retronecine)**: compared to methoxylated derivatives, unsubstituted retronecine at these positions shows a more pronounced hepatotoxic potential, due to more efficient bioactivation into reactive pyrrolic me-

tabolites in the liver [15] [36].

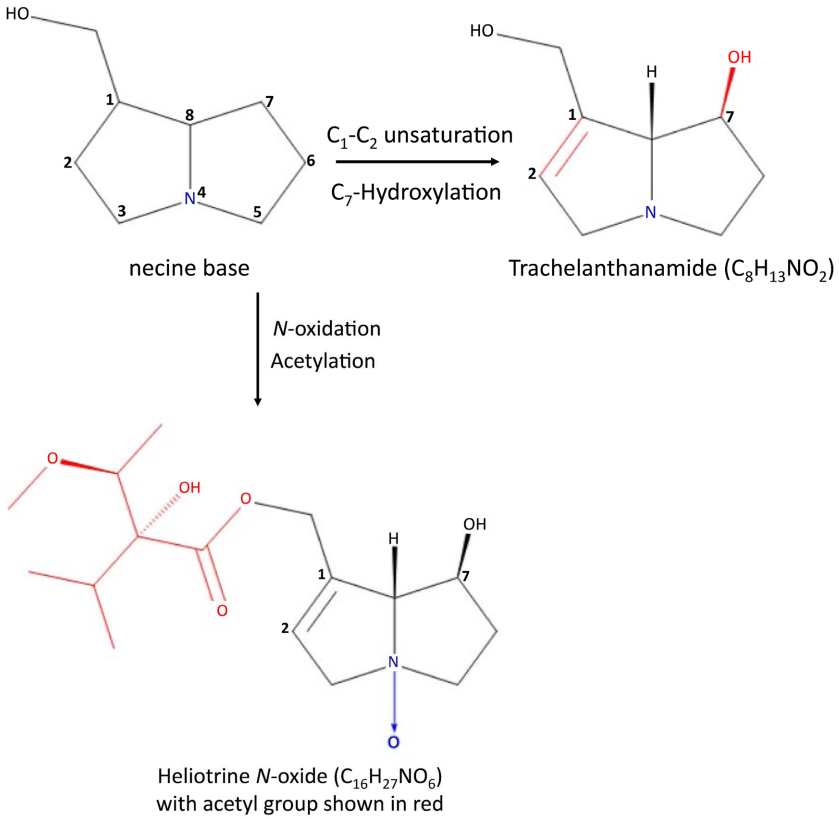

Figure 4. Illustration of possible modifications using examples of pyrrolizidine alkaloids described in *Heliotropium indicum* L.

- ***N*-oxide derivatives (heliotrine *N*-oxide, indicine-*N*-oxide)**: the conversion of the alkaloid base to *N*-oxide modulates excretion and tissue distribution, partially attenuating hepatic cytotoxicity but leading to an increase of hematological effects and specific nephrotoxicity [12] [36].
- **Retronecine esterification**: the nature and length of the acid chains esterifying the retronecine base directly influence lipophilicity and therefore cellular absorption and bioavailability, thereby determining the intensity and duration of tissue exposure [17] [20].

Pyrrolizidine alkaloids, characterized by the presence of a C1-C2 double bond on the necine nucleus (dehydro-pyrrolizidine), can give, after hepatic bioactivation, active metabolites that form covalent adducts with deoxyribonucleic acid (DNA) and hepatocyte proteins, thus explaining their hepatic and genotoxic toxicity [15] [23]. Esterification at C7 (formation of retronecine or heliotridine esters) increases lipophilicity and modulates tissue distribution, enhancing the compound toxic effect [36] (**Figure 5**). *N*-oxides derivatives (such as indicine-*N*-oxide) serve as circulating precursors which, once reduced to free alkaloids in the liver, induce more pronounced hepatic toxicity than their non-oxidized forms [15] [23].

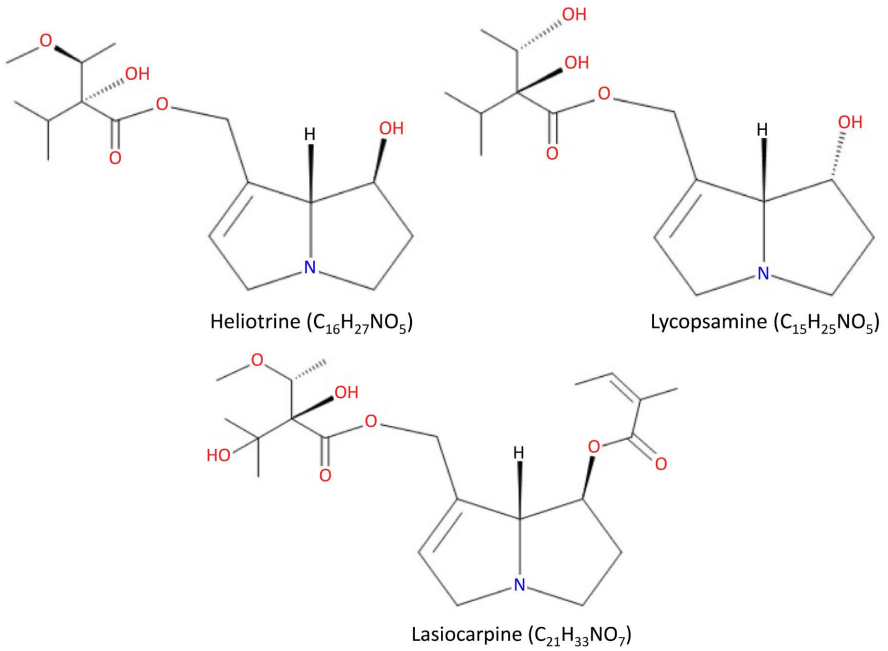

Figure 5. Example of esterified pyrrolizidine alkaloids described isolated from *Heliotropium indicum* L.

The pyrrolizidine alkaloids of *Heliotropium indicum* L. exhibit a broad pharmaco-logical spectrum. The anti-inflammatory activity was confirmed through several models. Kyei *et al*. [26] demonstrated a marked reduction of uveal edema in rabbits, while Kalyan *et al*. [37] and Srinivas *et al*. [38] reported a significant inhibition of carrageenan-induced paw edema in rats. In parallel, the analgesic effect was highlighted by Boye *et al*. [39] with a notable increase in pain latency in the hot tail test model.

Regarding the antitumor effect, Kugelman *et al*. [12] isolated indicine *N*-oxide, which showed selective cytotoxicity on several tumor cell lines with 50% inhibitory concentrations (IC_{50}) in the micromolar range. The antioxidant properties are also strong, with ethanolic extracts showing DPPH radical inhibition at an IC_{50} of about 25 µg/mL [8] [10] [27] [40].

The antimicrobial effects against *Staphylococcus aureus* and *Escherichia coli* are established by Adelaja *et al*. [41] and reinforced by Wani *et al*. [10], confirming the interest of these compounds against common pathogens. Systemically, Basak & Dey [20] reported an antipyretic effect reflecting a significant decrease in body temperature after administration of ethanolic extracts. Moreover, the his-to-gastroprotective capacity was documented by Adelaja *et al*. [41], while Mohammad *et al*. [21] highlighted a powerful hypoglycemic activity, with a reduction of nearly 60% in blood glucose in diabetic animal models (rats). In this same logic of metabolic activity, Sifat *et al*. [42] showed that, in rats made obese by a high-fat diet, chronic supplementation with *Heliotropium indicum* L. allowed to limit weight gain while improving the lipid profile and insulin sensitivity [42]. Properties against cataract [9] [43], the larvicidal against *Aedes aegypti* [44], and anthelmin-

tic [45] properties further expand the range of biological activities of these alkaloids, making *Heliotropium indicum* L. a plant resource of interest for the development of targeted natural therapeutics.

It was also reported that photoirradiation of pyrrolizidines generates reactive oxygen species and triggers lipid peroxidation of cell membranes [35], while repeated administration of extracts rich in pyrrolizidine alkaloids induces a significative elevation of liver transaminases and liver fibrous lesions [19] [36]. Along the same lines, according to Moreira *et al.*, pyrrolizidines are bioactivated by cytochrome P450 enzymes into reactive dehydropyrrolizidine derivatives, responsible for severe liver damage (veno-occlusive disease, fibrosis, carcinoma) and carcinogenic gene mutations. Therefore, their presence in plants and foods requires strict regulatory thresholds [46].

3.5.2. Phytosterols

Phytosterols compounds particularly β-sitosterol, campesterol, and stigmasterol, have a rigid Δ^5-cyclopentano-perhydrophenanthrene nucleus and a hydroxyl group at C3β (**Figure 6**), allowing effective competition with cholesterol at the intestinal Niemann-Pick C1-like 1 transporter (NPC1L1). This structural analogy could explain their hypolipidemic effect [6] [47]. The $\Delta^5/3\beta$-OH configuration is also essential for their anti-inflammatory activity observed *in vivo* in a uveitis model [9].

Due to their structural analogy, the phytosterols identified in *Heliotropium indicum* L. act by competing with dietary cholesterol at the intestinal level, thereby reducing its absorption and lowering plasma LDL-cholesterol rates [6] [48]. This richness in phytosterols gives *Heliotropium indicum* L. a hypolipidemic activity confirmed by *in vitro* studies and recent pharmacological reviews [47].

In addition to alkaloids and triterpenoids, sterols have an anti-inflammatory effect observed *in vivo*. In a model of lipopolysaccharide-induced uveitis in rabbits, the plant extract (containing a combined profile of sterols and other bioactive lipids) significantly reduced cellular infiltrate and the production of pro-inflammatory cytokines (IL-1β, TNF-α) in the aqueous humor, suggesting a concerted action on membrane receptors and the modulation of NF-κB and Mitogen-activated protein kinase (MAPK) pathways [26] [47].

Phytosterols also contribute to the improvement of carbohydrate metabolism. In a model of streptozotocin-induced diabetic rats, administration of a standardized hydro-alcoholic extract resulted in a significant reduction in fasting blood glucose and an improvement in glucose tolerance, partially attributed to the inhibition of hepatic gluconeogenesis enzymes and the sensitization of peripheral tissues to insulin [21] [47].

The phytosterols of *Heliotropium indicum* (β-sitosterol, campesterol, stigmasterol) derive their hypolipidemic effect from the Δ^5-3β-OH configuration, which allows them to compete with cholesterol on the NPC1L1 transporter [6] [47]. However, the actual competition between these sterols and cholesterol has never been validated by direct kinetic measurements or in human models, leaving doubt about the extent of this effect *in vivo*. Moreover, if the same $\Delta^5/3\beta$-OH configuration

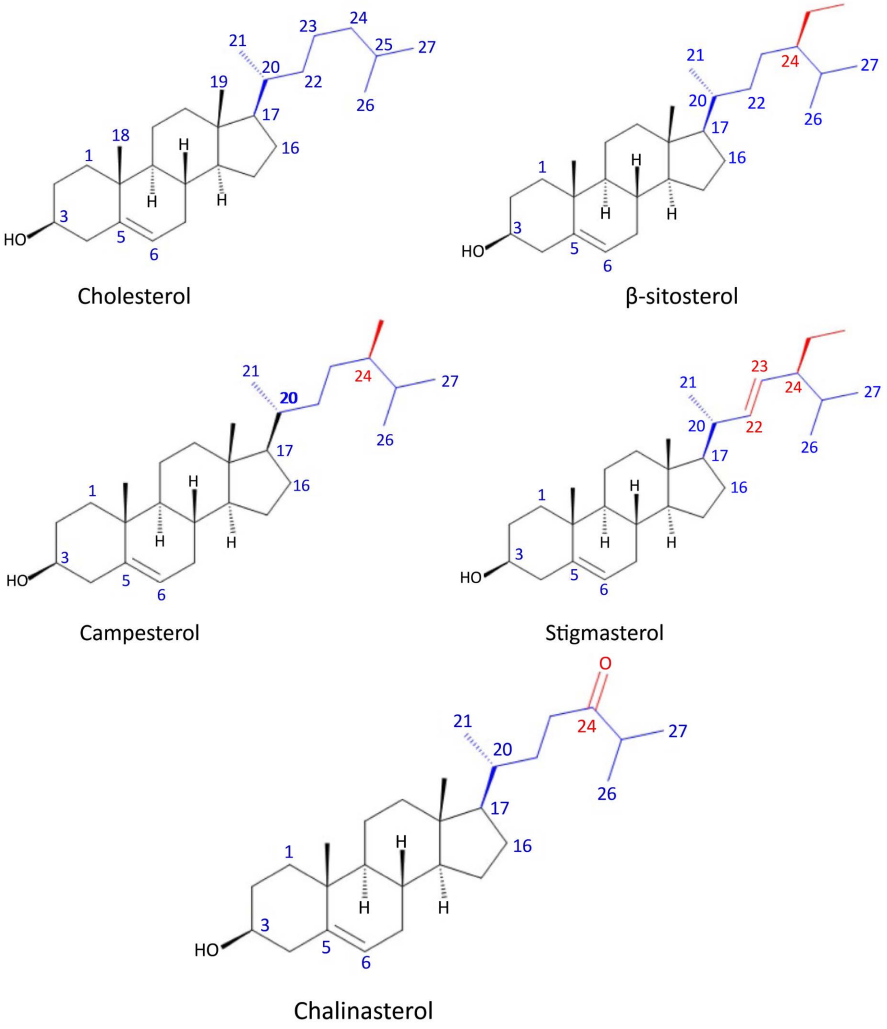

Figure 6. Structural analogy between cholesterol and phytosterols from *Heliotropium indicum* L. (variations sites depicted in red).

is necessary for the anti-inflammatory activity observed in experimental uveitis [9], the influence of the length and degree of saturation of the alkyl chain at C-17 remains unknown, whereas it could modulate the interaction with cyclooxygenase 2 (COX-2) or 5-lipoxygenase (5-LOX). The lack of pharmacokinetic data regarding hepatic metabolism and the bioaccumulation of phytosterols limits the prediction of their efficacy and long-term tolerance. This gap clearly identifies the need for future studies combining pharmacokinetic analyses, molecular modeling, and *in vivo* testing to clarify the structure-activity relationship of *Heliotropium indicum* L. isolated phytosterols and to optimize their therapeutic profile.

3.5.3. Pentacyclic Triterpenoids

Although pentacyclic triterpenoids such as *α*-amyrin, *β*-amyrin and lupeol (**Figure 7**) are among the most frequently identified compounds in *Heliotropium indicum* L., few studies to date have formally explored the link between their structures and their activities. The majority of research has been limited in describing

their biological effects without establishing rigorous structural correlations. However, some publications have proposed, in an extrapolative manner, potential structure-activity relationships (SAR) based on hydroxyl motifs and the rigidity of the pentacyclic skeleton, thus laying the basis for more in-depth analyses.

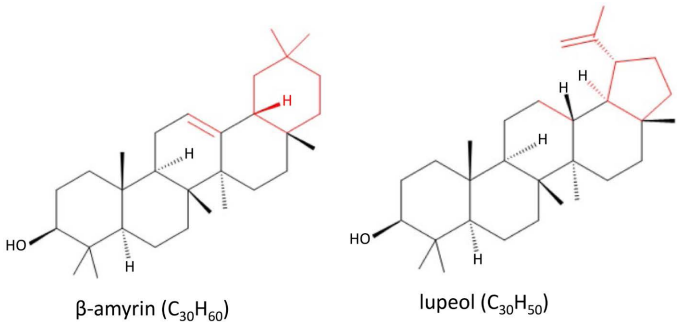

Figure 7. Chemical structures of *β*-amyrin and lupeol.

- **Pentacyclic nucleus (Δ^5-cyclopentano-perhydrophenanthrene nucleus):** the integrity and lipophilic nature of the pentacyclic skeleton (**Figure 7**) facilitate membrane penetration but limit aqueous solubility. Da Silva Júnior *et al*. demonstrated that the formation of *α*/*β*-amyrin-cyclodextrin inclusion complexes greatly increases solubility and bioavailability, without altering the anti-inflammatory profile *in vitro* [25].
- **Hydroxyl function at C-3:** the –OH group at position C-3 is essential for antioxidant activity. It provides the necessary hydrogen for neutralizing free radicals. Thus, *in vitro* calluses, the correlation between C-3 alcohol (including hydroxylated triterpenoids) and antioxidant capacity *via* the 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay highlights the importance of this site [27].

Triterpenoids (*α*- and *β*-amyrin, lupeol) isolated from *Heliotropium indicum* L. exhibited three major biological activities. First, they showed a powerful antioxidant activity by efficiently scavenging free radicals in the DPPH assay in correlation with their C-3 alcohol content, which results in a slowdown of lens opacification in an experimental cataract model [9] [27]. Moreover, when complexed with cyclodextrin, they reveal an anti-inflammatory effect, dose-dependently inhibiting the production of nitric oxide (NO) and TNF-*α*, significantly reducing edema and nociception, and alleviating experimental uveitis [25] [26] [36]. It was also noted that an *n*-butanol fraction rich in these triterpenoids accelerates *in vitro* wound healing by stimulating fibroblast proliferation and collagen deposition, attesting their role in the proliferative phase of tissue repair [11]. In addition to the *in vitro* data from Dodehe *et al*., it has been reported that an *in vivo* model in rats confirms the healing effect of *Heliotropium indicum* L. extract, with faster wound closure and collagen reorganization [11] [49]. The effect of lipophilicity of the pentacyclic triterpene core on interactions with membranes and biological targets could explain these properties [50]-[52].

Despite the limited number of studies formalizing the links between the struc-

ture and activities of *Heliotropium indicum* L. triterpenoids, several works suggest, by extrapolation, the role of key structural elements in their biological activities. The correlation between alcohol nature and DPPH power highlights the importance of the hydroxyl group at C-3 on the pentacyclic core [27].

- **Complexation with cyclodextrin:** the encapsulation of *α*/*β*-amyrin in beta-cyclodextrin (*β*-CD), or in hydroxypropyl-beta-cyclodextrin (HP*β*-CD), greatly increases their aqueous solubility, dissolution rate, and stability against oxidation [25]. This complexation gives the resulting compounds better bioavailability. This could facilitate the access of triterpenoids to the catalytic sites of COX-2 or to the transporters involved in the regulation of nitric oxide (NO)and TNF-*α*, explaining the faster and more pronounced inhibition observed *in vitro*.

The n-butanol fraction rich in triterpenoids favors the healing effect, proving its action on wound closure [11]. This could be explained by:

- The hydroxyl group (OH) at C-3: the action would be related to a hypothetical formation of H-bonds with fibroblast receptors, promoting adhesion and proliferation.
- Pentacyclic rigidity: this rigidity would provide better membrane anchoring, optimizing interaction with extracellular remodeling proteins.

Terpenic compounds can interact with sterols, leading to modulation of membrane fluidity and enhancement of the healing effect. These hypotheses, which nevertheless need to be formally validated by in-depth studies, provide a framework for targeted SAR studies, in order to clarify the exact role of each structural element in the antioxidant, anti-inflammatory, and healing activities of triterpenoids from *Heliotropium indicum* L.

3.5.4. Biogenic Amines (Polyamines)

Polyamines are organic compounds consisting of a carbon chain with at least two amino groups, positively charged at physiological pH. The presence of these positive charges facilitates close electrostatic interactions with negatively charged macromolecules. Compounds such as putrescine, spermidine and spermine from *Heliotropium indicum* L., exhibit an increasing polycationic charge, promoting their binding to anionic biomolecules (DNA, RNA, ATP, proteins, membrane phospholipids) and modulating processes such as cell growth and apoptosis (**Figure 8**). The linear structure and the free radical scavenging capacity also give these polyamines protective antioxidant activity. They are often presented as simple growth modulators due to the polycationic charge and as antioxidants by trapping free radicals [13].

Polyamines (putrescine, spermidine, spermine) are often presented as simple growth modulators due to their polycationic charge promoting interactions with DNA and membranes, and as antioxidants by trapping free radicals [13]. However, this model remains widely discussed, since no study has quantified these amines affinity for specific molecular targets (histones, membrane receptors) nor tested their ability to effectively penetrate the relevant cellular compartments. Fur-

thermore, the delicate balance between their pro-survival role and their pro-apoptotic potential (observed in other systems) has never been explored for *Heliotropium indicum* L., leaving the optimal therapeutic dose uncertain. The absence of specific pharmacokinetic and toxicological data prevents predicting their bioavailability and therapeutic margin. This is why structural modifications-based SAR studies and targeted functional assays are essential to validate or refine the exact biological role of *Heliotropium indicum* L. isolated polyamines. These polyamines derivatives appear to act as growth factors essential for cell division. For instance, putrescine—the simplest polyamine—reacts with decarboxylated *S*-adenosylmethionine to form spermidine. Spermidine can react with another molecule of decarboxylated *S*-adenosylmethionine to form spermine. These polyamines are involved in numerous cellular metabolic processes and thus exhibit pesticidal, fungicidal, herbicidal, analgesic, and antioxidant activities [50]-[52].

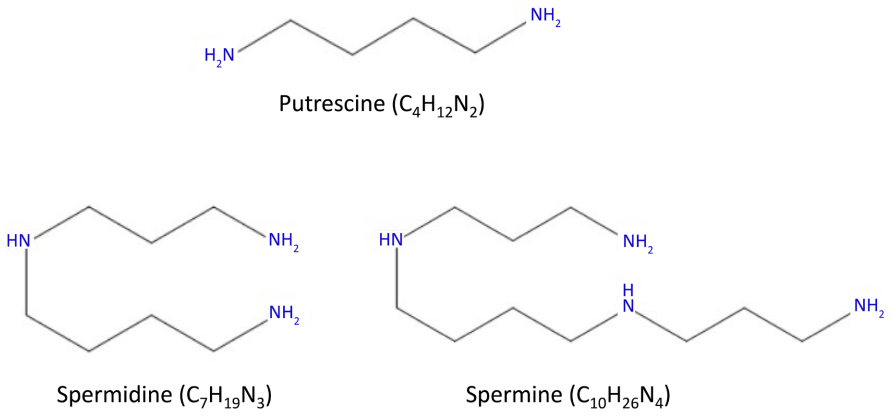

Figure 8. Chemical structures of representative biogenic amines from *Heliotropium indicum* L.

The bioactive constituents of *Heliotropium indicum* L. have outstanding pharmacological activities, which deserves further attention. In addition, several pyrrolizidine alkaloids isolated from the plant were shown to exhibit hepatotoxic effects in experimental animals [13] [53]-[58]. For this, further research on standardized extracts and isolated compounds in a bioguided fractionation context, with reported bioactivities would be pertinent to discover new active phytochemicals, thus clarifying their relationships, structure, activity, and possible synergistic effects.

4. Conclusions

This review highlighted the chemical richness and the numerous pharmacological activities of *Heliotropium indicum* L., a traditionally used plant in various diseases. Phytochemical studies have revealed the presence of several groups of bioactive compounds including pyrrolizidine alkaloids, triterpenes, sterols, and amines, each associated with varied biological activities.

The reported data show that this plant has several effects such as antioxidant,

healing, antimicrobial, and anti-inflammatory activities. However, the presence of potentially toxic compounds raises concerns about its therapeutic use. This highlights the importance of a rigorous evaluation of the safety and efficacy of extracts from this plant.

To strengthen the integration of this plant into conventional medicine, it is essential to convert empirical knowledge into robust scientific data. To do so, further research is needed to identify characteristic structural elements in a structure-activity relationship study approach, in order to establish safe therapeutic margins and minimize intoxication risks. In this perspective, *Heliotropium indicum* L. could become a valuable source of new phytotherapeutic treatments.

Acknowledgements

The authors thank the National Institute for Research on Traditional Medicine and Pharmacopoeia "Institut national de Recherche sur la Médecine et la Pharmacopée Traditionnelles (INRMPT)" and all those contributed to the review and correction of the manuscript.

Author Contributions

Dominique Patomo ARAMA and Rouguiatou Diop developed the protocol, collected and analyzed the data, and drafted the initial versions of the manuscript. Boubacar Diallo and Tidiane Diallo contributed to revising the various versions of the manuscript. Benoit Yaranga Koumaré, Sékou Bah and Rokia Sanogo reviewed and validated the protocol and revised the manuscript versions.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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