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Journal of Applied Biotechnology and Bioengineering

Research Article
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Systematic review of the phytochemical compounds use of *Heliotropium indicum* taking advantage of its advantage in modern medicine

Abstract

Throughout history, some plants have been taken as a medicinal alternative, which has been little studied. Their phytochemical compounds have been used for many years by our ancestors, demonstrating that they have components capable of saving lives. *Heliotropium indicum* is quite common in tropical and subtropical countries, it has been reported as a common field weed, but its main components, 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. All parts of the plant have important compounds for pharmacological study and identification, individualizing each component and reviewing its potential is important for further study to better understand the plant.

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This review allows to have a potential vision for its use of the different compounds and their effect on humans for a massive use, in addition to analyze the phytochemical uses of *Heliotropium indicum* and its uses in traditional medicine and its possible arrival in modern medicine as an alternative to treatments currently used.

Keywords: *Heliotropium indicum*, pyrrolizidine alkaloids, volatile oils, sterols.

Volume 9 Issue 5 - 2022

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Received: August 26, 2022 | **Published:** September 6, 2022

Introduction

The interest in discovering new drugs that allow the use of natural substances as their main components and that are accessible to all populations has grown in recent years, this has led to the study of medicinal plants in modern science, opening the possibility of knowing new compounds capable of improving the current situation of humanity as far as medicines are concerned. The use of medicinal plants can be therapeutic, neoadjuvant or adjuvant in conventional treatments currently used. These advances have allowed to know compounds of plants such as Heliotropium indicum, used by ancestors as a healing plant in some cultures and is claimed to have medicinal properties, this plant has high concentrations of different compounds capable of providing an aid to the human being, among these compounds are pyrrolizidine alkaloids, ester compounds followed by distinctive mono or dibasic acids known as necic acids; sterols, volatile acids and amines.[1–4]

The genus Heliotropium comprises more than 250 species distributed in different tropical and subtropical zones in all continents but only a few species such as Heliotropium indicum have been investigated.[5] According to different studies this plant possesses significant pharmacological activity with anticancer activity, anti-inflammatory activity, anti-cataract activity, antimicrobial activity, and anti-tubercular activity. [2,6–9]

Materials and methods

For the present literature review, articles mentioning the term *Heliotropium indicum were* taken from digital databases through the internet, specifically Google Scholar, PubMed, Elsevier and ScienceDirect, where review and research articles from the year 1961 to the year 2021 were considered**.** Various sources were reviewed and used including research articles, review articles, web pages and books.

Results

Heliotropium indicum, is also known as Heliotrope or Hatishur, being easily found in places like India, parts of Africa and in Asian countries such as Bangladesh,[10–12] It is also found in countries such as Colombia, in the departments of Amazonas, Caldas, Cesar, Chocó, Santander and others.[13] *Heliotropium indicum* belongs to the Family *Boraginaceae,* order *Boraginales,* class *Dicotyledoneae,* phylum *Spermatophyta* and kingdom *Plantae.*[14]

Within its characteristics it can be found that it is a thick grass species, up to 61 centimeters in height, in sunny places, wastelands, ponds and dry ditches, as well as in artificial habitats; this plant is generally considered as a field weed, it grows in sunny places and prefers an altitude between 800 to 1000 meters above sea level.[10,15]

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The plant has been studied through the years due to all its phytochemical components in which stand out the triterpenes, amines, volatile oils and pyrrolizidine alkaloids, the latter being the most important. The pharmacological and phytochemical properties of the plant have been investigated to identify and verify its qualities according to the traditional medicine in which it is commonly used.

Heliotropium indicum is very rich in pyrrolizidine alkaloids, ester

compounds followed by distinctive mono or dibasic acids known as necic acids; alkaloids are molecules derived from amino acids and nitrogen carriers, they are known to have biological properties of toxicity or powerful pharmaceuticals, they have been used throughout the ages as pharmaceuticals, The alkaloids found so far are indicine, heliotrine, indicidin, indicine N-oxide, lasiocarpine, acetyl indicine, cinoglosine, helleurin, eurypine N-oxide, heliotridine N-oxide and heliotrine N-oxide; several amines have been studied in the leaves of the plant such as spermidine, spermine and putrescine. As far as sterols and volatile oils are concerned, we found estradiol, chalinasterol, campesterol, stigmasterol and phytol, 1-dodecanol and β-linalol respectively. All the components were isolated from different parts of the plant from the roots and seeds to the aerial part, leaves, and stem. [1–4,16–22]

Pyrrolizidine lactone alkaloids known as lycopsamine and helindicine have also been found, J Souza et al.,[23] reported these. The pharmacological activity has been evaluated in different presentations of the plant, either with aqueous, ethanolic or chloroformed extracts or with a specific part of the plant, either with leaves, stem, seeds etc. In the main investigations carried out to study its benefits, results have been found such as antioxidant effect, its anti-inflammatory, antinociceptive, antimicrobial and anti-tuberculosis activity, its anti-cataract, anticarcinogenic, gastroprotective, diuretic and antithrombotic effect. [2,6–8,16–22]

Some of the above compounds, including N-oxide of indicin, have been found to be toxic when used for prolonged periods of time, causing liver and lung damage. The cytotoxic effects are mainly due to the action of the pyrrolizidine alkaloid, indicin N-oxide which is the main pyrrolizidine alkaloid isolated from *Heliotropium indicum*, which alters the assembly of tubulin into microtubules, inducing DNA damage and has the potential risk of hepatotoxicity.[24–30,31] All this was demonstrated by Cook *et al.* in a case published in 1983, using the treatment in a 5-year-old male patient with refractory acute myelocytic leukemia, he was given N-oxide of indicin, however, nine days later the patient died with symptoms of liver failure and his autopsy showed massive liver necrosis.[1,32–34]

As mentioned above, the most important and varied compounds in *Heliotropium indicum*, are the pyrrolizidine alkaloids, which are represented by: Trachelanthamidin and retronicin which composes 94% of the total alkaloids found in the leaves of the plant.[19,35] The compound trachelanthamidine has different biological properties such as carcinogenicity, hepatotoxicity, and intoxication in animals.[36] The compound retronicin usually accumulates in plants as N-oxide, has toxic properties and has a bio impact on the soil where the plant is found.[37]

Echinatine like helleurin is a substance that has demonstrated inhibitory effects on acetylcholinesterase, preventing acetylcholine catalysis demonstrating a strong antagonistic power.[21,22] In the case of heliotrine, it has shown great anti-inflammatory power by inhibiting the production of nitric oxide, which is one of the major mediators of inflammation. In addition, heliothrin inhibits thymine uptake by all cell types, the higher the concentration of the alkaloid, the higher the inhibition; without the possibility of thymine uptake, cells are unable to synchronize the early G1/S phase and cell replication.[4,38–41] On the other hand, the compound heliotridine together with helindicin and lasiocarpine have been shown to cause liver, kidney, and lung toxicities, inducing both tumors and carcinomas in the parts in contact with it, being one of the most dangerous compounds of the plant.[21,42,43] The N-oxide of indicin has anticancer activity preventing proliferation in solid tumors and helping in the control of acute leukemias, although it has also been investigated for inducing liver toxicity in some patients treated with this compound.[1,32,44,45] Helindicin and its predecessor lycopsamine which, as described above, are toxic alkaloids for humans, in addition to generating carcinomas and necrosis in organs such as liver and kidney.[42]

Alkaloids are also commonly found in the form of N-oxides, which are bases in tertiary form synthesized by hydrolysis of necines and necic acids.[21] The compounds found in N-oxide form are europine N-oxide, heliotrine N-oxide, heliotridine N-oxide, heliotridine N-oxide and heliotridine N-oxide, these compounds have anti-inflammatory, anticancer activities, which allows them to act as acetylcholinesterase inhibitors, although, it has also been reported toxic activities in humans.[37,42] N-oxides are responsible for hepatic sinusoidal obstruction syndrome and exert hepatotoxicity through activation to form reactive metabolites that bind with cellular proteins to generate pyrrole-protein adducts.[46]

Finally, in the case of lupeol, this alkaloid has been shown to have anti-inflammatory and anticancer activities, but unlike others it does not cause any toxicity in any human tissue, being used in therapies and as prevention for cancers and inflammations.[47]

Within the phytochemical compounds of *Heliotropium indicum*, we find polyamines such as putrescine and spermidine, which are essential for cell growth, promoting events such as the synthesis of DNA, RNA and proteins; it should be noted effects have been seen as the stabilization of ribosomes or an increase of amino acids absorbed by cells for protein synthesis; its high concentration derives in a counterproductive effect on tissues inhibiting the growth of these.[48] On the other hand, spermine is a natural polyamine known to be an essential regulator of several cellular processes, including DNA stability, cell growth, differentiation, and apoptosis, it should also be mentioned that it is used to treat cancer, other pathologies, inflammation, immunity, infection and aging. Similarly, spermidine is a polyamine compound that counteracts aging and promotes cellular longevity.[49–51]

Sterols are part of the essential compounds for the life of *Heliotropium indicum*, being estradiol, a primary compound found only in the root of the plant, this has a wide variety of functions in plant physiology of the plant, such as the regulation of sodium and potassium, cell differentiation, proliferation and permeability of the membrane of the cells that compose it. Sterols such as β-Sitosterol, chalinasterol, campesterol, hexacosane-1-ol and stigmasterol; which like the estradiol, their functions are based on the plant physiology of the plant and help to keep it healthy.[52]

As for volatile oils, they are compounds that have been evaluated for antituberculosis activities in comparative trials with isoniazid and kanamycin, the oils identified were β-linalool, 1-dodecanol and phytol.[2] The following table presents the above-named compounds and where they can be isolated from Table(1-2).

Discussion

Pyrrolizidine alkaloids are the main bioactive constituents of *Heliotropium indicum*, in particular heliothrin, heliothrin N-oxide and indicine N-oxide. The anticancer activity of *Heliotropium indicum* indicated that the plant could be a natural source to find promising compounds, due to the presence of a large amount of pyrrolizidine alkaloids, this plant exerts potent anticancer activity.

The plasma cholinesterase receptor activity of *Heliotropium indicum* validates some of its traditional folk values, such as relief of abdominal pain, hypertension, impotence, and sexual weakness.

However, the occurrence of liver toxicity and even bone marrow aplasia has led to the withdrawal of this compound from clinical trials.[1,53]

Table 1 Part from which the phytochemicals of *Heliotropium indicum* are isolated

Part of the plant	Phytochemicals	References
Leaves	Trachelanthamidine Retronicin Putrescina Spermidine Spermine	10,19,23,35,37,49,51
Stem	Echinatine Heleurin Heliothrin Heliotridine Helindicin Lasiocarpina N-indicin oxide Lupeol	3,21,22,41,42,47
Root	Helindicin Licopsamine Estradiol	42,52
Seed	Europine N-oxide Heliothrin N-oxide Helleurin N-oxide Heliotridine N-oxide	21,37,46
Whole plant	β-linalool 1-dodecanol β-Sitosterol Calinasterol Campesterol Hexacosane-1-ol Stigmasterol Fitol	2,52

Table 2 Compound route of action for cytotoxic effects of most important compounds

Compound	Compound route of action	References
Heliotrine	Apoptosis by interrupting the G1 and G2 phase of cell replication.	3,8,19,23,30,53,54
Indicidine	Apoptosis	3,8,19,23,30,53,54
Indicine N-oxide	Apoptosis caused by altered cellular tubulin assembly.	3,8,19,23,30,53,54
Lasiocarpine	Apoptosis due to accumulation of vacuoles.	3,8,19,23,30,53,54
Cinoglossine	Apoptosis	3,8,19,23,30,53,54
Heleurine	Apoptosis by interrupting the G1 and G2 phase of cell replication.	3,8,19,23,30,53,54
Europine N-oxide	Apoptosis caused by depolymerization of microtubules.	3,8,19,23,30,53,54
Heliotridine N-oxide	Apoptosis caused by depolymerization of microtubules.	3,8,19,23,30,53,54
Heliothrin N-oxide	Apoptosis caused by depolymerization of microtubules.	3,8,19,23,30,53,54

However, one can find compacts such as lupeol, a dietary anti-inflammatory and anticancer triterpene, which has strong antioxidant, anti-mutagenic, anti-inflammatory, and anti-arthritic characteristics with potential pharmaceutical applications. It has been shown to possess several biological functions, including defense against herbivory, microbial attack, or other sources of injury. Lupeol induces G1 cell cycle arrest and G1 cell alterations. An effect on the protein level of cdk2 has also been seen, without having cytotoxic side effects against the human body.[47,54,55]

Several classes of phytochemical compounds have been isolated from this medicinal plant, furthermore, the biological activities evaluated on its phytocomponents are not enough. Although *Heliotropium indicum* can potentially contribute to the advancement of health care, to date, only a few studies have been conducted on its isolated constituents, limiting its translation to clinical practice. Available pharmacological studies on the ingredients and extracts indicated broad anticancer effects of *Heliotropium indicum*. Its bioactive constituents have outstanding pharmacological activities, which deserves further attention. For this, further research on identification and isolation of extracts, with reported bioactivities would be pertinent to discover new active phytochemicals, thus clarifying their relationships, structure, activity, and possible synergistic effects.

Acute and chronic toxicity should be studied extensively to establish toxicological and stability parameters, providing guidance for clinical applications. Several pyrrolizidine alkaloids isolated from the plant were shown to exhibit hepatotoxic effects in experimental animals; therefore, further studies are needed to ensure the stability of the use of this plant. Likewise, the use of plant extracts in experimentation involves several problems, among them changes in

their constituents depending on the climate or form of cultivation, presence of compounds with adverse or antagonistic effects, changes in bioactivity throughout their performance, storage or preparation of materials.

Conclusion

It can be concluded that *Heliotropium indicum* is a potential source of chemical compounds with promising biological occupations. However, at present, clinical trials are not enough, makes it more complicated than the use of its phytochemicals and their approval in new drugs to improve the quality of life of hundreds of thousands of people affected. It is necessary to do more clinical trials to verify its viability and how we can benefit from all the benefits offered by the plant.

Acknowledgement

None.

Conflict of interest

The authors declare there is no conflict of interest.

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Citation: Ovalle JDT, Ovalle JMM, Garcia OAT. Systematic review of the phytochemical compounds use of *Heliotropium indicum* taking advantage of its advantage in modern medicine. *J Appl Biotechnol Bioeng.* 2022;9(5):132–136. DOI: 10.15406/jabb.2022.09.00300