



Cardiospermum halicacabum Linn.: Food and Drug

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Abstract

Medicinal plants are natural sources of bioactive phytochemical constituents which, for the physiological actions produced on the human organism, can be used against many diseases. For this reason, it is necessary for medicinal plants to be assessed for their phytochemistry in order to ascertain the potential of these indigenous sources of medicinal products. Today, people around the world are interested in using herbal medicines rather than synthetic drugs because of their minor side effects and low cost; however, there is little scientific evidence for the healing properties of these natural drugs. Scientific validation of their properties is required for their safe use. *Cardiospermum halicacabum* L., from the family Sapindaceae, is a widespread perennial plant, different parts of which have been used by indigenous populations in various parts of the world both as food and in the treatment of many pathologies. Knowledge of the plant's chemical components and their standardization and in vitro and in vivo experimentation to evaluate its pharmacological activity are means by which the quality of the drug and its possible toxicity can be controlled and adulterations with other similar species can be revealed in order to guarantee the safety and well-being of the consumer. The complex chemical composition and multiplicity of applications of *C. halicacabum* L. have attracted the attention of researchers who, applying modern methodologies, have ascertained the safety and validity of its use in the treatment of many pathologies.

Keywords: *Cardiospermum halicacabum*, Sapindaceae, Cardiospermin

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Introduction

Cardiospermum halicacabum L. of the Sapindaceae family is a creeping herbaceous plant which propagates easily. It is a tropical genus, widespread in India, South America, and central Africa. In warm climates it is a perennial species, whereas in rigid winter climates, it has an annual biological cycle. Its ascent in height takes place through opposing tendrils present at the height of the inflorescence which, using suitable supports, make the plant reach heights of more than 3 m. The leaves area flowers appear, aesthetically insignificant, gathered in axillary corymbs. The true attraction of this plant is its fruit. The membranous capsules are first lantern-shaped green, then brown; slightly hairy, tripartite internally, and generally contain three seeds that are firmly attached to a central membrane, dark brown in color with a white heart-shaped stain with two dots in the center which are traces of the seed attachment to the inner membrane.¹

The morphological characteristics of the plant are the preconditions for the scientific denomination. From Latin, “cardiospermum” means heart-shaped seed, while “halicacabum” means container for salt. In the German language, the plant is known as “herzsamen”; in Tamil it is known as “Modakathon”, i.e. disabling pain and remedy; in North America it is referred to as “balloonvine” (that is, climbing balloon) due to the fact that the plant is a creeper

and produces globose capsules similar to small balloons.

In the middle of the last century, Willmar Schwabe picked up this plant in Africa, where it was popularly used as a medicine for various applications: as an anti-rheumatic, for digestive and respiratory disorders, joint pain, back pain, sprains, muscle tears, and inflammation. Over a period of 70 years, the cortisone effects of this plant were discovered.² Subsequently, the plant was the subject of study by many researchers who were driven by the importance it had among poor populations and experimentally highlighted its phytotherapeutic properties.

In rural areas of southern India, this plant is sold in local markets as a green vegetable and provides a source of income for poor families. The whole plant has been used for several centuries in the treatment of rheumatism, stiffness of the limbs, and snake bite; the decoction from its roots is used as a diaphoretic, diuretic, emetic, laxative, and for sweating; the decoction of its leaves and stems is used in cases of diarrhea, dysentery, and headaches; a poultice of them as a cure for swelling. The juice of the leaves has even been used as a treatment for earache.³⁻⁵

Due to the presence of saponins, substances that for a foam in water when they undergo agitation, *C. halicacabum* is used in its regions of origin as a detergent for the hair and as a laundry soap. Every part of this plant is useful, as food and as a remedy for diseases.

Chemical Composition

The many species of cardiosperma widespread in India, America, Africa and include *C. halicacabum*, *Cardiospermum corindum*, *Cardiospermum ovatum*, *Cardiospermum grandiflorum*, *Cardiospermum hirsutum*, *Cardiospermum barbicaule*, *Cardiospermum vesicarium*, and *Cardiospermum canescens*, the morphological characteristics and chemical compositions of which differ among species. *C. halicacabum* and *Cardiospermum canescens* are the most studied species.

Aqueous, chloroformic, and methanolic extracts of the leaves of *C. halicacabum* have a panned appearance of dark brown color; the solvent evaporation powder is highly soluble in water, chloroform, and methanol. The main active constituents of the plant are extracted from the flowered aerial parts, and the chemical composition is very complex. The analysis of an ethanolic extract highlighted the presence of several compounds including phenolic acids (p-coumaric acid, 4-hydroxybenzoic acid, hydroquinone, protocatechuic acid, gallic acid); flavonoids (apigenin, kaempferol, luteolin, quercetin); glycosidic compounds; tannins; and sterols including β -sitosterina, Campestrina, and stigmasterin. All compounds have been isolated and evaluated for antioxidant and anti-inflammatory activity.⁶⁻⁸

The watery extract of the leaves is rich in mucilage that has been isolated and purified. Its analysis has highlighted the presence of very interesting compounds. The percentage yield of the isolated mucilage was found to be 2.5%, soluble in water, and insoluble in acetone, ethyl alcohol, ethyl acetate, and toluene. Chemical analysis revealed carbohydrates and nitrogenated substances, while tannins, chlorides, and sulphates were absent.⁹

Among the carbohydrates identified were pinitol, 3-O-methylether of D-chiroinositol, and both its enantiomers. Pinitol is present in many vegetables and has a great pharmacological importance for its antidiabetic, anti-inflammatory, and antioxidant activities and its use in the treatment of hypertension, rheumatism, cardiovascular disease, AIDS, and neurological disorders. The mucilage is also a chemically inert, non-toxic, biocompatible, natural material with good rheological properties. Its extraction is economically advantageous and, therefore, can be applied as an excipient thickening agent in many pharmaceutical formulations.¹⁰⁻¹³ Very interesting is the presence of L-quebrachitol (2-O-methyl-L-inositol) in the aqueous extract, which has attracted the attention of researchers. The infusion of this plant is used to treat diabetes in the practice of local traditional medicine and, therefore, it could be used as a substitute for sugar. Discovered for the first time by Tanret in the bark of *Aspidosperma quebracho* as a component of the resin, it was later found in many plants, especially those of the Sapindaceae family. It is a colorless, crystalline compound, which melts at 192-193°C and can be sublimated under a reduced pressure; the boiling point in the vacuum is about 210°C; it is easily soluble in water, and insoluble in alcohol and ether.^{14,15} Atomic absorption spectrophotometry also revealed the presence of mineral elements: macronutrients (nitrogen, phosphorus, potassium) and micronutrients (iron, manganese, copper and zinc).

The roots of *C. halicacabum* have traditionally been used for the treatment of epilepsy and anxiety disorders. Epilepsy is a common neurological disorder affecting over 40 million people around the world, and its incidence is higher among children at an early age and in individuals aged over 55 years. Anticonvulsant medications are the most commonly prescribed medications for epilepsy and convulsive disorders for their high treatment efficacy, but they produce a number of undesirable side effects, including teratogenesis, drowsiness, mental dullness, nausea, ataxia, paraesthesia, hematologic alterations, hirsutism, weight gain, gingival hypertrophy, and congenital malformations.^{16,17}

Anxiety is a major problem for public health; important associations between psychiatric illness and chronic medical conditions have been clinically highlighted. Most research has focused on depression, because it can negatively affect self-care and increase the risk of disease, complications, and mortality. Anxiety disorders are less studied, but solid epidemiological and clinical evidence shows that they play an equally important role. Recent articles have raised a debate over the efficacy of some plant-derived extracts in anxious models in mice.¹⁸

Some researchers have tested an alcoholic extract of *C. halicacabum* L. root on various mouse models affected by epilepsy induced with pentylenetetrazole, isoniazid, and picrotoxin to evaluate the anticonvulsant effects. From the trials it was found that mice treated with oral solutions of *C. halicacabum* at concentrations of 100 and 300 mg/kg showed significantly delayed onset of clone and tone convulsions. Significant motor toxicity was not observed even at a maximum dose of 900 mg/kg. Levels of cerebral monoamine were determined after 2 days of administration, and a significant increase in GABAergic activity in the cerebellum was revealed, with increased convulsive thresholds with increasing doses of extract. The results showed that the extract possesses a significant anticonvulsant activity that can occur through activation of the GABA receptor with a consequent increase in GABAergic activity. Altered locomotor activity and coordination are known undesirable side effects that are observed with the use of barbiturics and benzodiazepines; these effects were not observed with the extract of the *C. halicacabum* root, which did not influence motor coordination in animals even for values closer to its LD50 value. The phyto-constituent responsible for the anxiolytic activity is cardiospermine, a cyanogenic glucoside that has been isolated and identified.^{19,20}

The seeds of *C. halicacabum* have been studied at both macro/microscopic and physico-chemical levels for their importance in food and medicine. They are of a hard and globular shape, dark brown in color with a heart-shaped stain of grayish white. The size varies between 4 to 6 mm in diameter, and they have a smooth surface. Inside, they contain a floury almond of yellowish-white color that has an astringent, bitter, odorless flavor. Microscopic studies have clearly shown the presence of irregular masses of oily blood cells dispersed between parenchymatous layers. Various physical parameters, of both the whole seeds and the flour obtained after grinding, have also been determined, such as moisture content, total ashes,

acid-insoluble ashes, water-soluble ashes, pH values, and extractive power in different solvents. Among the extracts examined, it was observed that the best yield for the oily component was obtained in hexane, while the extract obtained with the aqueous mixture of methanol was richer in flavonoids, phenols, saponins, and alkaloids.²¹

The structural characterization assumes a great value for the standardization of the plant for the preparation of herbal extracts, including the oil of *C. halicacabum* that, in addition to food use, is mentioned for the treatment of various forms of cancer. Saturated and unsaturated fatty acids have been identified in the composition of the oil obtained by extraction with various solvents. The major component is 11-eicosenoic acid, the presence of *Cardiospermum* oil in comparison with other oils; palmitic, linolenic, linoleic, oleic, stearic, archaic, and small amounts of behenic acid are also present.²²

The unsaponifiable fraction of the *C. halicacabum* oil, both of the cortical and inner part of the seed, extracted with oil ether 40°-60° in Soxhlet apparatus, was analyzed by highlighting a different chemical composition.²³ The various components have been identified both by TLC and GC-MS. The unsaponifiable fraction of the inside contains substances of a sterolic and terpene nature, while the unsaponifiable fraction of the outside contains above all saturated and unsaturated hydrocarbons. The Prussian blue test was negative for the oil extracted from the inside, while, with the appearance of an intense blue coloration, it was positive for the oil extracted from the cortical part, indicating the presence of nitrile. The cyanolipids that are present in various concentrations, from 13%-55% in the oils of the various species of Sapindaceae, have been studied and distinguished in four different groups formed by a base structure of long-chain fatty acids esterified with an isoprenoid group hydroxy or dihydroxy-nitrile. The large amounts of C20 acids that are usually found in these oils indicate an appreciable content of cyanolipids, because these acids are preferentially incorporated in fractions containing nitrile.^{24,25}

The combinations of chromatographic and spectrophotometric techniques have made it possible to highlight and determine the tocopherolic component with great precision. Due to the low concentration of this fraction in the unsaponifiable matter and its high oxidability, it was necessary to proceed with caution, avoiding alteration in the components caused by a different number of methyls present in the structure, which are responsible for both oxidation reactions and ease of polymerization following chemical and physical treatments of various kinds. The presence of tocopherols and a polymeric compound, presumably a dimer, were determined.²⁶

Pharmacological Activity

The drug comprises the flowering aerial parts of the plant that manifest an important cortisone-like action and act favorably on inflammatory allergic reactions of the skin and itching. Currently, *Cardiospermum* preparations are used for the treatment of inflammatory dermatitis, hives, eczema, and insect bites. The active ingredients responsible for the cortisone-like effect are phytosterols that exhibit anti-inflammatory, moisturizing, sebum-regulating, anti-pruriginous, soothing

skin redness, avoiding flaking activities.²⁷⁻²⁹ The antioxidant activity also manifests itself in relieving pain caused by arthritis and rheumatism, because the phytosterols, due to their antioxidant power, inhibit the action of the inflammatory enzymes and peroxilipids that damage the cells, carrying out antiphlogistic action.^{4,30}

The antibacterial properties of various parts of the plant extracted with different solvents (diethyl ether, chloroform, acetone) were tested against gram-negative (*Escherichia coli*, *Pseudomonas*, *Aeromonas*, *Salmonella*) and gram-positive (*Staphylococcus aureus*) bacterial strains. Evaluation was performed 24 hours after the minimum zone of inhibition with respect to the control with ofloxacin.

The flavonoid, terpene substance and tannin contents, present in all the extracts, were responsible for the antibacterial activity.^{31,32}

The flavonoids apigenin and luteolin present in the plant have been shown to possess anti-hyperglycemic, antioxidant, and antineoplastic activity. It has been shown that apigenin has an inhibitory effect on the aldose-reductase enzyme and is, therefore, useful in the prevention of chronic complications of type 2 diabetes, such as peripheral neuropathy, retinopathy, and cataracts occurring because of the intracellular accumulation of sorbitol.³³⁻³⁵

Luteolin, having been endowed with interesting biological properties, has been extensively investigated in studies linked to the field of oncology. Numerous published scientific articles have evidenced the effects of luteolin on various types of experimental tumors, its ability to influence the activity of certain cellular enzymes such as 15-lipoxygenase, its involvement in inflammatory reactions with the genesis of leukotrienes 5'-nucleotidase which scinds the AMP in phosphate and adenosine, and its mediation of multiple biochemical effects. Moreover, it inhibits the onset and progression of cancer by interfering with transcription factors and kinases, which intervene in tumor transformation, such as phosphatidylinositol-3-kinase (PI-3k) which regulates insulin-ruled glucose metabolism, and other cellular functions linked to oncogenesis.

Luteolin is a common food flavonoid which has long been used in traditional Chinese medicine for the treatment of hypertension and inflammatory diseases, indicating its safety for clinical use; it could be a good candidate for cancer therapy.³⁶⁻³⁸

From the first works it was realized that the alcoholic extract of the aerial parts produces sedative effects and pain-relief. It showed an action comparable to that of phenylbutazone in the test of edema induced by carrageenan. Investigation of the inhibiting effects of the ethanolic fraction of *C. halicacabum* leaves extract on the production of pro-inflammatory mediators nitric oxide (NO) and tumor necrosis factor alpha (TNF- α), administered intraperitoneally in the mouse, showed a marked depressive effect on the central nervous system without acute toxic effects up to 50 g/kg orally; the decoction of the leaves at the dose of 2 g/kg showed a strengthening of the hypnotic effect induced by pentobarbitone and at doses up to 20 g/kg showed sedative activity on the central nervous system. The aqueous extracts also showed a myocardial

depressive effect similar to that obtained with cholinergic agents, which was partially blocked by atropine.³⁹⁻⁴³

Some research has shown antimalarial activity of the extracts of this plant as well as anti-inflammatory and analgesic, antiparasitic, anti-diarrheal, anti-diarrhoil, anti-hysterility, anti-sterility, nephroprotective; hepato-protective and anticancer activity.⁴⁴⁻⁵²

Conclusions

Recent clinical studies have confirmed the efficacy of *C. halicacabum* extracts for many pathologies, highlighting perfect tolerability and safety even after prolonged use. The variety of active substances present in the phytocomplex along with its high anti-inflammatory activity have made known this plant as “natural cortisone”, and it was first used for the treatment of rheumatic pathologies. Subsequent experiments showed sedative activity on the central nervous system as well as antibacterial, anti-malaria, anti-diarrheal, anti-ulcer, and anticancer activity. It was mainly the absence of unwanted side effects and the preference of consumers for natural drugs compared to synthetic ones which prompted researchers to deepen their understanding of the potential activities of the phytocomplex. *Cardiospermum* helps maintain the good health of an organism and is also used as food. The mucilage present in the leaves, as well as highlighting anti-hyperglycemic and antitumor activity due to the presence of pinitol and quebrachitol, can be used as a thickening agent in pharmaceutical, food, and cosmetic preparations; the amino acids, tocopherols, flavonoids, and mineral substances present in the plant are useful for integrating a deficient diet. The flour obtained by grinding the inner part of the seeds, mixed with cereals flour, is an excellent basis for baking. The use of its oil, rich in unsaturated fatty acids, is a valuable aid in the prevention of cardiovascular diseases.

People around the world are very interested in using phytotherapeutic products instead of synthetic drugs because of their minor side effects and low cost. Studies on *C. halicacabum* L. have verified its use in traditional medicine by demonstrating the relationship between activities and chemical components present, but further insights are needed to isolate, characterize, and elucidate the structure of bioactive compounds and their mechanism of action for the formulation of industrial drugs.

Conflict of Interest Disclosures

The author declares she has no conflicts of interest.

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