



PHARMACOLOGICAL STUDIES OF *CELTIS IGUANAEA*: A MEDICINAL PLANT
REVIEW

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ABSTRACT

Celtis iguanaea commonly known as iguana hackberry is a deciduous tree in the genus *Celtis*. The phytochemical content in this plant includes flavonoids, coumarins, mucilage, pentacyclic triterpenes, friedelin, and epifriedelanol. Currently, there have been many studies that prove that *C. iguanaea* has several pharmacological activities, including anti-inflammatory, antinociceptive, antihyperlipidemic, antidiabetic, antioxidant, antiproliferative, anti-ulcerogenic and antisecretory. Currently, there is no detailed evaluation report on the potential that shows the effectiveness of the *C. iguanaea* plant, therefore this review article will discuss the potential pharmacological activities of the *C. iguanaea* plant.

KEYWORDS: *Celtis iguanaea*, Anti-inflammatory, Antinociceptive, Antihyperlipidemic, Antidiabetic, Antioxidant, Antiproliferative, Anti-ulcerogenic, Antisecretory.

INTRODUCTION

Medicinal plants are plants that can be used to maintain health and/or treat a disease. The use of herbal medicines is currently growing rapidly. This is because more and more types of new herbal plants are being discovered and more and more research is being done on medicinal plants, in order to obtain pharmacological effects that can prevent and treat diseases. Through exploration and research of plant biopharmaceuticals and nutraceuticals, more and more plants have been discovered that can be used as medicine,^[1] one of which is the *Celtis iguanaea* plant. *C. iguanaea* is a plant from the Ulmaceae family that has a height of 3-6 m. This plant has a main stem without thorns with few branches, bald and equipped with thread-like trichomes. The leaves have a leaf stalk size of 3-11 mm, smooth, rarely hairy, oval or elliptical leaf blades, stalked, rounded base, heart-shaped, asymmetrical, with pointed tips, serrated upper edges, scales on the surface near the stem, smooth or pubescent stem surface, with 5-7 pairs of secondary veins. The flowers of this plant are yellowish green. The fruit is elliptical, smooth, grows in pairs or singly, green, yellow or brown in color. Meanwhile, the flower stalk reaches 2-8 mm.^[2] The *C. iguanaea* plant is reported to have various properties as anti-inflammatory, antinociceptive, antihyperlipidemic, antidiabetic, antioxidant,

antiproliferative, anti-ulcerogenic and antisecretory. Currently, there is no detailed evaluation report on the potential that shows the effectiveness of the *C. iguanaea* plant, therefore this review article will discuss the potential pharmacological activity of the *C. iguanaea* plant.

TAXONOMIC CLASSIFICATION

Kingdom	: Plantae
Subkingdom	: Tracheobionta
Superdivision	: Spermatophyta
Division	: Magnoliophyta
Class	: Magnoliopsida
Subclass	: Hamamelididae
Order	: Urticales
Family	: Ulmaceae
Genus	: <i>Celtis</i>
Species	: <i>Celtis iguanaea</i> (Jacq.)
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PHARMACOLOGICAL STUDIES

Anti-inflammatory

Inflammation is one of the major problems that significantly affects the lifestyle of millions of people.^[3,4] However, existing therapies are not always effective and can cause several side effects, especially related to the

gastrointestinal tract,^[5,6] thus posing a challenge in finding drugs with better therapeutic effects and mild side effects. In this regard, medicinal plants, which are sources of various pharmacologically active molecules, have emerged as important tools in the search for new, safer and more effective drugs, one of which is the *C. iguanaea* plant. Oral administration of *C. iguanaea* extract at doses of 100, 300, and 1000 mg/kg has been reported to reduce carrageenan-induced pleurisy in mice. In addition, this *C. iguanaea* extract has also been reported to reduce tumor necrosis factor-alpha (TNF- α) levels.^[7]

Antinociceptive

Pain is an unpleasant experience caused by intense or damaging stimuli, mainly protective in nature and can act as a sensory modality to indicate tissue injury.^[8,9] There are various types and causes of pain, but all are associated with a sensation of physical or emotional discomfort that negatively impacts daily routines. Despite efforts to relieve pain, harmful physiological effects can occur, including sleep loss, fatigue, disorientation, anxiety, tachycardia, increased myocardial oxygen demand, immunosuppression, and increased catabolism.^[10] Currently available analgesic drugs such as opiates and nonsteroidal anti-inflammatory drugs (NSAIDs) are not useful in all cases because their effectiveness is overshadowed by various side effects.^[9] Therefore, the search for new analgesic drugs with promising pharmacological actions is an urgent need. Medicinal plants are believed to be an important source of new chemicals that have potential therapeutic effects to relieve pain and accelerate healing,^[11] one of which is the *C. iguanaea* plant. Oral administration of *C. iguanaea* extract at doses of 100, 300, and 1000 mg/kg has been reported to reduce pain stimuli by reducing the number of mice writhing induced by acetic acid and inhibiting nociception in mice induced by formalin.^[7]

Antihyperlipidemic

Cardiovascular disease (CVD), a group of disorders of the heart and blood vessels, is considered the number one cause of death globally. The risk of developing cardiovascular diseases such as atherosclerosis increases significantly with increasing levels of total cholesterol and LDL cholesterol and decreasing HDL cholesterol values.^[12] Administration of *C. iguanaea* extract at doses of 150, 300, and 600 mg/kg was reported to significantly reduce total and LDL cholesterol levels in a rat model fed high cholesterol, and was able to inhibit the HMG-CoA-reductase enzyme.^[13]

Antidiabetic

Diabetes mellitus (DM) is one of the major public health problems in the world. This disease is a metabolic disorder caused by failure of glucose homeostasis with impaired carbohydrate, fat, and protein metabolism as a result of defects in insulin secretion and/or insulin action.^[14,15] Modern drugs currently available for the treatment of DM are often associated with limitations

such as inadequate efficacy, high cost, and various side effects.^[16] Given the weaknesses of conventional drugs mentioned above, medicinal plants with antidiabetic activity are claimed to be used as an alternative approach in the management of DM especially in developing countries due to their cost-effectiveness, accessibility, broad cultural acceptance, and lower side effects.^[17] Administration of *C. iguanaea* extract at doses of 300 and 600 mg/kg was reported to reduce blood glucose levels, reduce sucrase and maltase activity, and significantly increase muscle glycogen levels in a mouse model fed high cholesterol.^[13]

Antioxidant

Free radicals are molecules that lose electrons so that the molecule becomes unstable so that it tries to return electrons from other molecules or cells.^[18,19] In the body, free radicals are very reactive and will interact through destructive oxidation reactions with certain body parts or cells composed of protein, fat, DNA, carbohydrates, and RNA, thereby triggering the development of various chronic degenerative diseases including coronary heart disease, cancer, and aging.^[20,21] Antioxidants are compounds that can protect cells from damage caused by free radicals.^[22] Administration of *C. iguanaea* extract at a dose of 600 mg/kg has been reported to significantly reduce TBARS levels and increase non-protein thiol levels in the plasma of mice fed high cholesterol.^[13]

Antiproliferative

Cancer is a complex group of diseases characterized by the rapid and irregular growth of abnormal (malignant) cells that invade tissues and organs and can spread to other parts of the body. These cells tend to be very aggressive and uncontrolled, thus determining the formation of tumors or malignant neoplasms.^[23] It is one of the main causes of death worldwide, with more than 22 million deaths estimated from the disease and complications of its treatment in the next two decades.^[24] Anticancer agents aim to destroy tumor cells, representing the main treatment at various stages of the disease.^[25] However, most of these drugs have low selectivity, causing severe side effects. In addition, many cancers still show a modest clinical response to the usual protocols or develop resistance to chemotherapy.^[26] Therefore, to achieve more effective and safe molecules, pharmacological studies with substances isolated from plants have been intensified,^[27-29] one of which is the *C. iguanaea* plant. Administration of *C. iguanaea* extract has been reported to have strong cytostatic activity against ovarian cell lines (OVCAR-3), glioblastoma (U-251), and colon tumor cells (HT-29), with GI50 values of 4.65 μ g/mL, 6.40 μ g/mL, and 3.16 μ g/mL, respectively.^[30]

Anti-ulcerogenic and Antisecretory

For more than a century, peptic ulcer disease has been a major cause of morbidity and mortality.^[31] Factors such as stress, malnutrition, smoking and continuous use of nonsteroidal anti-inflammatory drugs (NSAIDs) have led

to an increase in the incidence of peptic ulcers.^[32] The etiology of gastroduodenal ulcers is usually due to an imbalance between aggressive factors (hydrochloric acid and pepsin) and mucosal defensive factors (blood flow, mucus, bicarbonate secretion and epithelial lining).^[33] Treatment of peptic ulcers is generally based on inhibition of gastric acid secretion by H₂ antagonists, proton pump inhibitors and antimuscarinic agents.^[34] However, long-term use of these drugs can cause a series of side effects.^[35,36] Therefore, the search for new therapeutic antiulcer agents derived from medicinal plants is an important element in maintaining health, one of which is the *C. iguanaea* plant. Administration of *C. iguanaea* extract at doses of 25, 50, 100, and 200 mg/kg was reported to have anti-ulcerogenic and antisecretory effects by blocking bethanecol and histamine in NSAID-induced ulcer mice models.^[37]

CONCLUSION

The use of herbal medicines is currently growing, including in pharmacological practices that can prevent and treat diseases. Through the exploration of plant biopharmaceuticals and nutraceuticals, herbal medicines have reached the international market. It is seen that the *C. iguanaea* plant is a versatile plant through a number of pharmacological activities. Information on the *C. iguanaea* plant that currently exists can be used as basic data for further research, to find the active compounds contained and newer and more complete pharmacological activities.

REFERENCES

- Smith-Hall C, Larsen HO, Pouliot M. People, plants and health: a conceptual framework for assessing changes in medicinal plant consumption. *J Ethnobiol Ethnomed*, 2012; 8: 1-11.
- Zamengo H, Chamorro D, Houtepen E, Gaglioti A, Pederneiras L, Prado D, et al. A revision of the *Celtis iguanaea* complex (*Cannabaceae*) and the reinstatement of an additional species from southern South America. *Authorea*, 2024: 1-28.
- Nathan C, Ding A. Nonresolving inflammation. *Cell*, 2010; 140(6): 871-882.
- Manjiani D, Paul DB, Kunnumpurath S, Kaye AD, Vadivelu N. Availability and utilization of opioids for pain management: global issues. *Ochsner J*, 2014; 14(2): 208-215.
- Harirforoosh S, Asghar W, Jamali F. Adverse effects of nonsteroidal antiinflammatory drugs: an update of gastrointestinal, cardiovascular and renal complications. *J Pharm Pharm Sci*, 2013; 16(5): 821-847.
- Geczy QE, Thirumaran AJ, Carroll PR, McLachlan AJ, Hunter DJ. What is the most effective and safest Non-steroidal anti-inflammatory drug for treating osteoarthritis in patients with comorbidities?. *Expert Opin Drug Metab Toxicol*, 2023; 19(10): 681-695.
- Moraes WF, Silva DPBD, Florentino IF, Almeida DS, Moreira LKS, Nascimento MVM, et al. Antinociceptive and anti-inflammatory effects of extract of *Celtis iguanaea* (Jacq.) Sargent leaves in mice. *An Acad Bras Cienc*, 2022; 94(suppl 3): 1-15.
- Bektas N, Nemutlu D, Ulugbay G, Arslan R. The role of muscarinic receptors in pain modulation. *World J Pharm Med Res*, 2015; 1(1): 40-49.
- Zendehdel M, Taati M, Jadidoleslami M, Bashiri A. Evaluation of pharmacological mechanisms of antinociceptive effect of *Teucrium polium* on visceral pain in mice. *Iranian J Vet Res*, 2011; 12(4): 292-297.
- Helms JE, Barone CP. Physiology and treatment of pain. *Crit Care Nurse*, 2008; 28(6): 38-49.
- Kinghorn AD, Pan L, Fletcher JN, Chai H. The relevance of higher plants in lead compound discovery programs. *J Nat Prod*, 2011; 74(6): 1539-1555.
- Alkandahri MY, Kusumiyati K, Renggana H, Arfania M, Frianto D, Wahyuningsih ES, et al. Antihyperlipidemic activity of extract and fractions of *Castanopsis costata* leaves on rats fed with high cholesterol diet. *RASĀYAN J Chem*, 2022; 15(4): 2350-2358.
- Zanchet B, Gomes DB, Corraloa VS, Diel KAP, Schönell AP, Faust C, et al. Effects of hydroalcoholic extract of *Celtis iguanaea* on markers of cardiovascular diseases and glucose metabolism in cholesterol-fed rats. *Brazilian J Pharmacogn*, 2018; 28: 80-91.
- Barcelo A, Rajpathak S. Incidence and prevalence of diabetes mellitus in the Americas. *Pan Am J Public Health*, 2001; 10(5): 300-308.
- Tafesse TB, Hymete A, Mekonnen Y, Tadesse M. Antidiabetic activity and phytochemical screening of extracts of the leaves of *Ajuga remota* Benth on alloxan-induced diabetic mice. *BMC Complement Altern Med*, 2017; 17(243): 1-9.
- Bastaki A. Diabetes mellitus and its treatment. *Int J Diabetes Metab*, 2005; 13(3): 111-134.
- Sakthiswary R, Zakaria Z, Das S. Diabetes mellitus: treatment challenges and the role of some herbal therapies. *Middle East J Sci Res*, 2014; 20(7): 786-798.
- Tena N, Martin J, Asuero AG. State of the art of anthocyanins: antioxidant activity, sources, bioavailability, and therapeutic effect in human health. *Antioxidants*, 2020; 9(5): 1-28.
- Alkandahri MY, Nisriadi L, Salim E. Secondary metabolites and antioxidant activity of methanol extract of *Castanopsis costata* leaves. *Pharmacol Clin Pharm Res*, 2016; 1(3): 98-102.
- Kusumawati AH, Farhamzah F, Alkandahri MY, Sadino A, Agustina LS, Apriana SD. Antioxidant activity and sun protection factor of black glutinous rice (*Oryza sativa* var. glutinosa). *Trop J Nat Prod Res*, 2021; 5(11): 1958-1961.
- Alkandahri MY, Arfania M, Abriyani E, Ridwanuloh D, Farhamzah, Fikayuniar L, et al. Evaluation of antioxidant and antipyretic effects of ethanolic extract of Cep-cepan Leaves (*Castanopsis*

- costata* (Blume) A.DC). *J Adv Pharm Educ Res*, 2022; 12(3): 107-112.
22. Lü JM, Lin PH, Yao Q, Chen C. Chemical and molecular mechanisms of antioxidants: experimental approaches and model systems. *J Cell Mol Med*, 2010; 14(4): 840-860.
 23. Fantini M, Benvenuto M, Masuelli L, Frajese GV, Tresoldi I, Modesti A, et al. In vitro and in vivo antitumoral effects of combinations of polyphenols, or polyphenols and anticancer drugs: perspectives on cancer treatment. *Int J Mol Sci*, 2015; 16(5): 9236-9282.
 24. Siegel RL, Miller KD, Jemal A. Cancer statistics. *CA Cancer J Clin*, 2016; 67: 7-30.
 25. Costa-Lotufo LV, Montenegro RC, Alves APNN, Madeira SVF, Pessoa C, Moraes MEA, et al. Contribuição dos produtos naturais como fonte de novos fármacos anticâncer: estudos no Laboratório Nacional de Oncologia Experimental da Universidade Federal do Ceará. *Rev Virtual Quim*, 2010; 2(1): 47-58.
 26. Alfarouk KO, Stock CM, Taylor S, Walsh M, Muddathir AK, Verduzco D, et al. Resistance to cancer chemotherapy: Failure in drug response from ADME to P-gp. *Cancer Cell Int*, 2015; 15: 1-13.
 27. Lee KH. Discovery and development of natural product derived chemotherapeutic agents based on a medicinal chemistry approach. *J Nat Prod*, 2010; 73: 500-516.
 28. Kinjo J, Nakano D, Fujioka T, Okabe H. Screening of promising chemotherapeutic candidates from plants extracts. *J Nat Med*, 2016; 70(3): 335-360.
 29. Newman DJ, Cragg GM. Natural products as sources of new drugs over the period 1981-2014. *J Nat Prod*, 2016; 79: 629-661.
 30. Zanchet B, Miorando D, Gomes DB, Locateli G, Vecchia CAD, Serpa PZ, et al. In vitro antiproliferative potential of *Celtis iguanaea* against ovarian (OVCAR-3) and colon (HT-29) tumor cell. *European J Med Plants*, 2019; 30(3): 1-9.
 31. Higham J, Kang JY, Majeed A. Recent trends in admissions and mortality due to peptic ulcer in England: increasing frequency of haemorrhage among older subjects. *Gut*, 2002; 50(4): 460-464.
 32. Belaiche J, Burette A, De Vos M, Louis E, Huybrechts M, Deltenre M, et al. Observational survey of NSAID-related upper gastro-intestinal adverse events in Belgium. *Acta Gastroenterol Belg*, 2002; 65(2): 65-73.
 33. Wallace JL, Granger DN. The cellular and molecular basis of gastric mucosal defense. *FASEB J*, 1996; 10(7): 731-740.
 34. Bighetti AE, Antônio MA, Kohn LK, Rehder VL, Foglio MA, Possenti A, et al. Antiulcerogenic activity of a crude hydroalcoholic extract and coumarin isolated from *Mikania laevigata* Schultz Bip. *Phytomedicine*, 2005; 12(1-2): 72-77.
 35. La Vecchia C, Tavani A. A review of epidemiological studies on cancer in relation to the use of anti-ulcer drugs. *Eur J Cancer Prev*, 2002; 11(2): 117-123.
 36. Raghunath AS, O'Morain C, McLoughlin RC. Review article: the long-term use of proton-pump inhibitors. *Aliment Pharmacol Ther*, 2005; 22 Suppl 1: 55-63.
 37. Martins JLR, Sousa FB, Fajemiroye JO, Ghedini PC, Ferreira PM, Costa EA. Anti-ulcerogenic and antisecretory effects of *Celtis iguanaea* (Jacq.) Sargent hexane leaf extract. *Rev Bras Pl Med Campinas*, 2014; 16(2): 250-255.