PLANT SCIENCE TODAY
ISSN 2348-1900 (online)
Vol 10(sp2): 304–312
https://doi.org/10.14719/pst.2546

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MINI REVIEW ARTICLE

Bioactive Compounds and Pharmacological Potential of Hojasen (*Flourensia cernua*): A Mini review

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OPEN ACCESS

ARTICLE HISTORY
Received: 29 March 2023
Accepted: 23 May 2023
Available online
Version 1.0 : 27 December 2023
Version 2.0 : 12 January 2024

Check for updates

Additional information

Peer review: Publisher thanks Sectional Editor and the other anonymous reviewers for their contribution to the peer review of this work.

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CITE THIS ARTICLE
Linares-Braham A, Palomo-Ligas L, Nery-Flores S D. Bioactive Compounds and Pharmacological Potential of Hojasen (*Flourensia cernua*): A Mini review. Plant Science Today. 2023; 10(sp2) : 304-312. https://doi.org/10.14719/pst.2546

Abstract

Flourensia cernua, commonly known as hojasen, is a shrub that is widely distributed in northern Mexico and the southern United States. The presence of this shrub indicates the characteristic flora of the Chihuahuan desert and southern Arizona, and it is an endemic plant of the Coahuila region in Mexico. The leaves and flowers of *F. cernua* are commercially available in Mexican markets for preparing infusions and are used as traditional medicine, mainly for gastrointestinal disorders such as indigestion, diarrhea, stomach pain, and dysentery, among others. Several studies have shown that *F. cernua* extracts contain bioactive compounds that can act as antioxidants *in vitro* by stopping free radicals from doing damage. In addition, *F. cernua* extracts have antifungal activity against phytopathogenic fungi. Additionally, *F. cernua* extracts have demonstrated antibacterial effects against *Mycobacterium tuberculosis*. Also, the anti-inflammatory effect of leaf extract at different doses has been studied to see how it affects the production of inflammatory cytokines and nitric oxide (NO) in macrophage cultures. Therefore, identifying its components and pharmacological properties can promote its use as an adjunct or therapeutic candidate in controlling various diseases. With its potential to alleviate gastrointestinal issues, provide antioxidant protection, and inhibit fungi and bacteria, hojasen extract may prove to be a valuable addition to the treatment of many diseases. This minireview aims to expand the existing knowledge about hojasen, a semi-desert shrub that possesses different bioactive compounds belonging to families of interest such as flavonoids, sesquiterpenoids, and coumarins, hoping to arouse the interest of other researchers to further investigate the activities, properties and uses attributed to *Flourensia cernua*.

Keywords

Antioxidants; antimicrobial; anti-inflammatory; hojasen; *Flourensia cernua*; polyphenols.

Introduction

Research on plants from arid and semi-arid zones of Mexico has progressively increased over the years. The identification of bioactive compounds in these plants has led to the development of new therapeutic alternatives, including agents capable of eliminating or containing invading microorganisms, as well as natural sources of antioxidants. Many plants are rich in polyphenolic compounds, which give them antioxidant activity and the ability to protect cells from oxidative damage caused by free radicals. Oxidative stress is a precursor of various diseases, such as cancer, diabetes mellitus, arthritis, atherosclerosis, and inflammation, among others (1, 2, 3, 4). One of the Chihuahuan desert plants with antioxidant properties is hojasen (*Flourensia cernua*), whose pharmacological potential is described in this article.

Materials and Methods

A systematic review was conducted using electronic databases such as Google Scholar, Pubmed, Elsevier, SciELO, Science Direct, and Springer Link. Literature from any date was included if it was relevant to the scope of the bibliographic research. The keywords used were "*Flourensia cernua*", "hojasen", and "tarbush" as well as combinations with other words such as "*Flourensia cernua* pharmacology", "phytochemicals *Flourensia cernua*", "traditional uses *Flourensia cernua*", "*Flourensia cernua* antiinflammatory", and "*Flourensia cernua* antioxidant".

Results

Taxonomic classification and morphology

Kingdom: Plantae

Subkingdom: Viridiplantae

Infrakingdom: Streptophyta

Division: Tracheophyta

Subdivision: Spermatophytina

Class: Magnoliopsida

Superorder: Asteranae

Order: Asterales

Family: Asteraceae

Genus: *Flourensia* DC.

Species: *cernua* (https://www.itis.gov/)

F. cernua is a shrub with a light brown or gray stem that is short, typically around 1 meter tall, highly branched, resinous, and has a characteristic tar-like or hop-like odor. Its leaves are alternate, ovate to oval, and dark green, measuring 17-25 mm in length and 6.5-11.5 mm in width, with a paler underside and a petiole of 1-2.5 mm (Fig. 1) (5, 6, 7). The leaves of various species possess properties that confer resistance to drought, allowing them to thrive in arid environments. The size and degree of leaf loss depend on the duration and severity of the dry periods to which the plant is subjected (8). The plant produces a first set of small leaves in the dry spring and a second larger set as humidity increases. Most *Flourensia* species have capitula arranged in secondary cymes, occasionally arranged in panicles or clusters. *F. cernua* can be easily distinguished by its small, entire, ovate to elliptic leaves, and compact discoid flower heads. The plant's pale yellow flowers are grouped in panicles measuring 1 cm in diameter. The one-seeded dry fruit, called achenes, is compressed, narrowly oblong-cuneate, callous, and very downy (9). The plant typically blooms during the rainy season, which occurs from September to December (10).

Distribution and habitat

The Chihuahuan Desert is an arid zone with a significant diversity of flora. It occupies the northern portion of the Mexican Altiplano, at variable altitudes between 1,000 and 2,000-2,200 m amsl (11). This region includes parts of Mexican states such as Chihuahua, Coahuila, Durango, Zacatecas, San Luis Potosí, Nuevo León, and Tamaulipas, where the endemic species *Flourensia cernua* is found. In the United States of America, *F. cernua* can be found in the deserts of southern Arizona, New Mexico, and western Texas (Fig. 2). The plant exhibits well-adapted features to thrive in the Chihuahuan desert, including an extensive root system for efficient water and nutrient acquisition, resin on its leaves that acts as a protective barrier against dehydration, and polyphenol-rich resin that deters insects and herbivores attacks (12). The plant is known as blackbrush, tarbush, varnish bush, hojasen, in United States of America and in Mexico as "hojasén", "arbusto de alquitrán", "hojasé", "hoja ancha" (13, 14). At least nine of the 42 species that make up the genus *Flourensia* have been found in Mexico (12), three of which are endemic to the Coahuila region: *F. cernua*, *F. microphylla*, and *F. retinophylla* (13).

Phytochemistry

The levels of bioactive compounds in plants are influenced by several factors, including the age of the plant, the age of the leaves, seasonal variations, soil moisture and nutrient levels, geographical location, and solar radiation. (15). The phytochemical composition of *F. cernua* consists of a variety of polyphenolic compounds and essential oils (Table 1 and Fig. 3). Among the polyphenolic compounds,

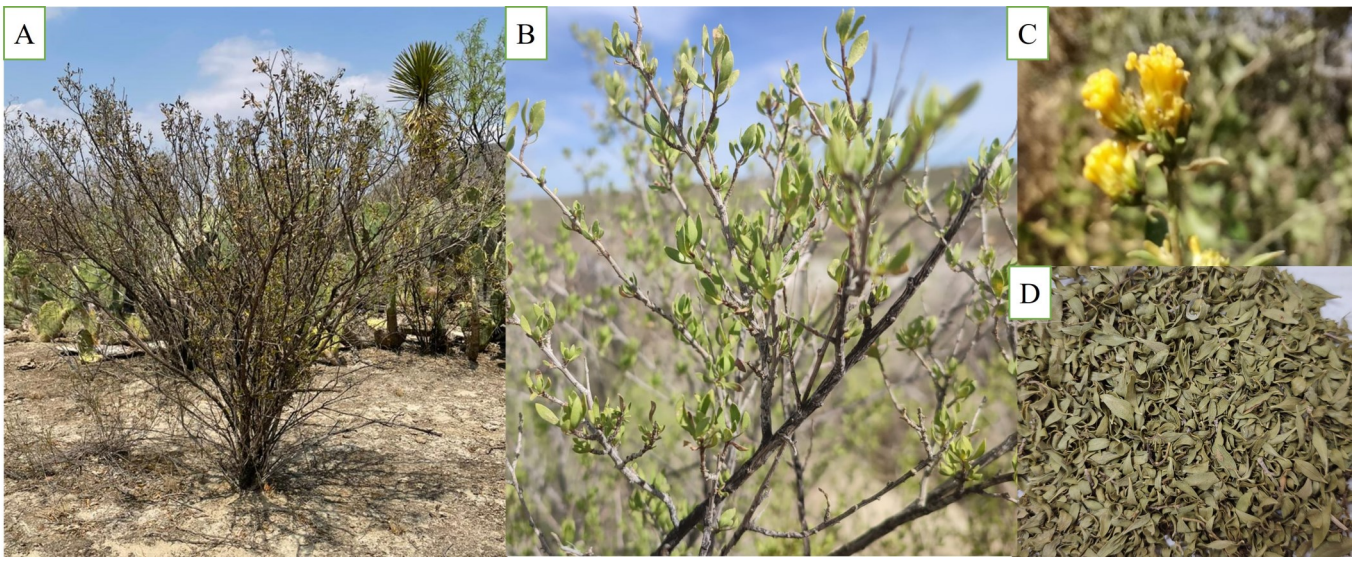

Fig. 1. A) *Flourensia cernua.* B) Details of the branch and leaves and C) flowers. D) Dry leaves are used for medicinal uses.

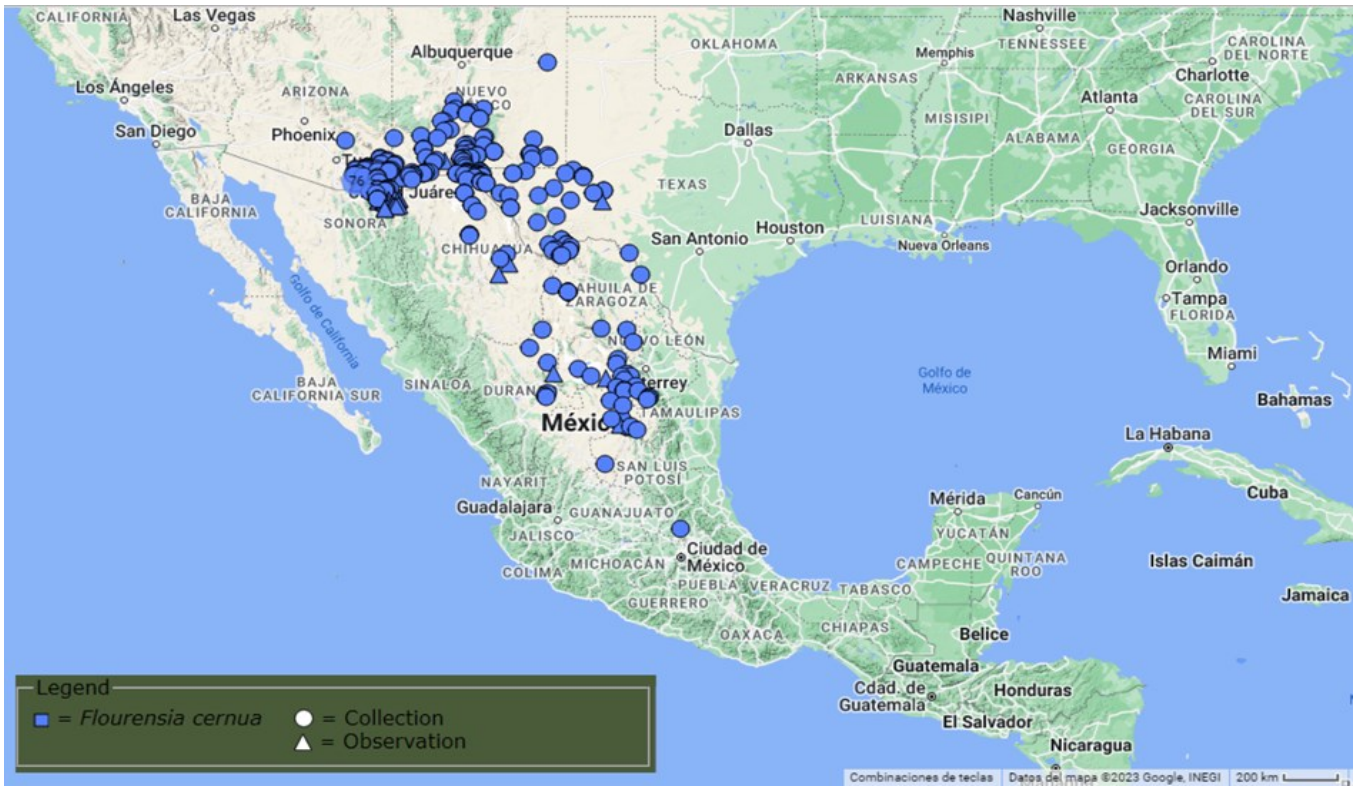

Fig. 2. Geographic distribution of *Flourensia cernua* in North America (https://swbiodiversity.org).

flavonoids such as flavones, flavanones, and flavonols have been reported as the main constituents (16). Additionally, *F. cernua* is a source of other polyphenolic compounds such as quercetin, catechin, ellagic acid, quinic acid, and methyl oscillate (12, 14). Regarding the compounds present in the essential oil of *F. cernua*, the main constituents are sesquiterpenes, which are characterized by a basic structure of 15 carbons. The major sesquiterpenes isolated from the essential oil include flourensadiol, ledol, caryophyllene, α-Endemol, limonene, γ-eudesmol, myrcene, borneol, δ-3-carene, α-himachalene and α-gurjunene (14, 17). Other reported compounds found in the resin are benzofurans, benzopyrans, chromenes, cinnamic acids, and coumarins (13).

Ethnomedical uses

The use of natural products from plants in arid regions can serve as an alternative for the treatment of diseases, especially in communities that have limited access to

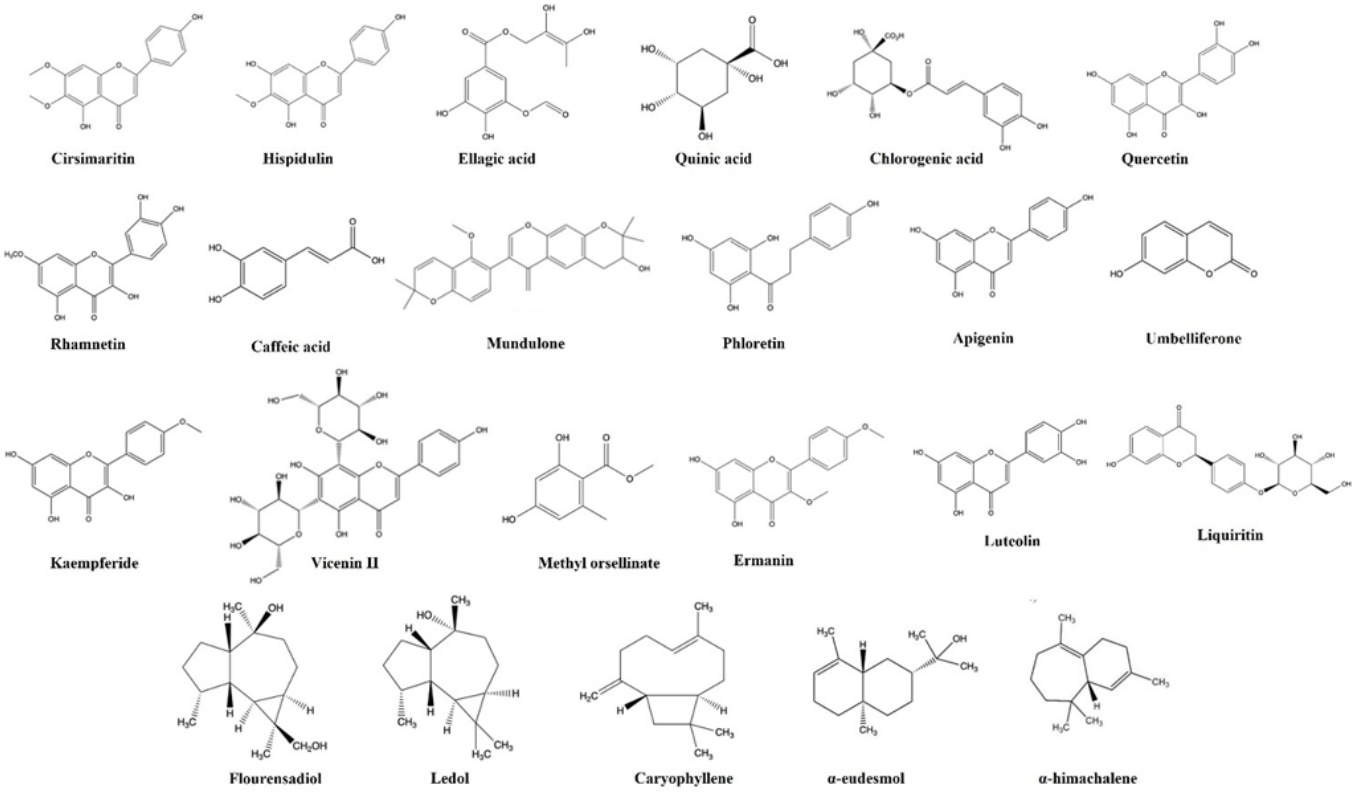

Fig. 3. Chemical structures of phytochemical compounds isolated from *Flourensia cernua*.

Table 1. Summary of compounds isolated from different parts of *Flourensia cernua*

Name of the compound	Type of compound	Plant part	Process of extraction	Reference
Cirsimaritin Hispidulin	Methoxyflavones	Plants heads	The extraction was carried out with petroleum ether, later with absolute ethanol to finally extract the flavonoids of interest with 10% Na_2CO_3.	(16)
Ellagic acid	Hydroxybenzoic acid dimers			
Quinic acid	Cyclohexanecarboxylic acid			
Chlorogenic acid	Hydroxycinnamic acids			
Quercetin	Flavonol			
Rhamnetin	Flavonol			
Caffeic acid	Hydroxycinnamic acids	Leafs	Extraction was carried out with a Soxhlet extractor with ethanol as solvent.	(24)
Mundulone	Isoflavones			
Phloretin	Dihydrochalcone			
Apigenin	Flavone			
Umbelliferone	Coumarin			
Kaempferide	Flavonol			
Vicenin II	Flavonoid 8-c-glycosides			
Methyl orsellinate	Hidroxybenzoic acid	Aerial parts	The extraction was carried out by maceration with dichloromethane and methanol (1:1) and to purify the resulting extract, it was done by column chromatography on silica gel.	(14)
Ermanin	Flavonol			
Flourensadiol	Sesquiterpenes			
Luteolin	Flavone	Leaves	Extraction was carried out with distilled water in a water bath at 60°C for 30 min. The purification of the polyphenolic compounds was carried out using Amberlite XAD-16. The extraction of essential oil was by steam distillation.	(17)
Liquiritin	Flavanone			
Ledol	Sesquiterpenes			
Caryophyllene	Sesquiterpenes			
α-eudesmol	Sesquiterpenes			

healthcare services. Traditional knowledge regarding the use of plants in arid zones is typically passed down through intergenerational dialogue, with older individuals (such as parents and grandparents) sharing their experiences with younger generations (18). In the case of *F. cernua*, its main traditional use is the treatment of gastrointestinal disorders, as reported by communities residing in the endemic regions where the plant grows and is still traded in markets in central Mexico (9, 19). It is commonly prepared as an infusion using its leaves or flowers to treat indigestion and various gastrointestinal ailments such as diarrhea, indigestion, and stomach pain. Furthermore, the plant is utilized for its purgative, astringent, expectorant, antirheumatic, and female ailment-relieving properties (7, 9, 14, 20, 21). The ethnomedicinal uses of *F. cernua* are reviewed in Table 2.

Antioxidant activity

Extracts from hojasen are abundant in bioactive compounds that exhibit antioxidant properties. For example, an aqueous extract of hojasen demonstrated a high inhibitory potential against free radicals, particularly 2,2-diphenyl-1-picryl-hydrazyl-hydrate (DPPH) and 2,2-azinobis-(3-ethylbenzothiazoline-6-sulfonate) ($ABTS^{\bullet+}$), with inhibition rates of 85.82% and 58.15%, respectively (22). In a previous study, an extract of stems and leaves that was made with ultrasound-assisted extraction only stopped the DPPH radical by about 62%. These results are different from that study. In another study, a Soxhlet extractor was used to find that an ethanolic extract of hojasen leaves had 53.07 mg GAE/g of total polyphenols. (23). Another investigation determined the total polyphenol content of an ethanolic extract of hojasen

Table 2. Summary of ethnomedicinal uses of *Flourensia cernua*.

Region	Plant part	Type of formulation	Ethnomedicinal uses	Reference
U.S.A. (Southwest) .	Leaves and flower heads	Infusion	Indigestion, stomach colic	(14)
Mexico (North-Central)	Leaves	Decoction	Dysentery and diarrhea	(20)
Mexico (North-Central)	Stems and leaves	Herbal baths (decoction)	Stiff joints	(20)
Mexico (North)	Leaves and flower heads	Decoction	Vaginal hemorrhages	(21)
México (North-Central)	Leaves	Tincture along or mixed with another beverage	Indigestion	(9)
Mexico (North-Central)	Leaves	Decoction	Expectorant, Respiratory infections	(42)
Mexico (North-Central)	Leaves	Herbal baths (decoction) with leaves of *Datura stramonium*	Rheumatism	(14)
Mexico (North)	Leaves	Decoction with leaves of *Artemisia frigida*	Yellow jaundice	(21)

leaves using a Soxhlet extractor, with a value of 53.07 mg GAE/g. The study also described that the antioxidant capacity was linked to a high value of total polyphenol content, with IC_{50} values for ABTS and DPPH at 69.27 and 174.37 µg TE/mL respectively (24). Furthermore, studies have reported that *F. cernua* leaves exhibit antioxidant activity by effectively inhibiting lipid oxidation *in vitro*. This characteristic makes hojasen extract a promising candidate as a natural substitute for synthetic preservatives (17).

Anti-inflammatory activity

A recent study investigated the anti-inflammatory activity of various *Flourensia* species, including *cernua*, *microphylla*, and *retinophylla* (24). They reported that ethanolic extracts showed anti-inflammatory effects. The extract was used at concentrations of 3.1, 6.5, 12.5, and 25 g/mL, and the amount of NO and TNF–α, release by RAW 264.7 macrophages was measured. A concentration-dependent inhibition of NO production was demonstrated and the lowest IC_{50} value was obtained by the *F. cernua* extract at a concentration of 17.8 µg/mL. Also, *F. cernua* was found to be the species with the lowest IC_{50} value for TNF-α inhibition. The study also suggested that the presence of hydroxyl groups in the phenolic structures may enhance the anti-inflammatory activity.

Antidiabetic activity

The potential antidiabetic activity of extracts from *F. cernua* leaves was evaluated *in vitro* by examining their ability to inhibit the enzymatic activity of α-amylase and α-glucosidase. The effect of the polyphenolic extract and the essential oils were analyzed, and the results demonstrated that polyphenols, primarily flavonoids, inhibited α-amylase activity by 10.14-44.93%, while essential oils predominantly inhibited α-glucosidase activity by 92.57-97.07%. Inhibition of α-glucosidase and α-amylase is a therapeutic approach to delay carbohydrate digestion and absorption, suggesting that hojasen extract could serve as an alternative for managing blood glucose levels (17).

Anticancer activity

An investigation has reported the potential anticancer activity of ethanolic extracts from *F. cernua* leaves against A549 cells. The treatment with the extract exhibited cytotoxic effects, with an IC_{50} value of 27.9 µg/mL. The observed cytotoxic activity is likely attributed to the presence of flavonoids, which act as cytostatic agents (24). Based on these findings, the authors propose *F. cernua* as a natural alternative for the treatment of lung cancer.

Antifungal activity

The antifungal activities of *F. cernua* have been reported mainly in phytopathogenic organisms, making it a

potential strategy for pest control in industrial crops. An investigation evaluated the effect against *Penicillium expansum* and *Fusarium oxysporum* using the products of tarbush leaf fermentation. Results showed that fermentation increases the antifungal effect in comparison to aqueous extracts, in a concentration-dependent effect. In addition, the highest inhibition was against *F. oxysporum* at 23.33% at a concentration of 1 g/L. A detailed characterization of the compounds obtained was not performed (25). Other studies have described the effect of extracts of hojasen, mainly using leaves. For example, the influence of solvents was tested against *Rhizoctonia solani.* The highest mycelial inhibition (100%) was found using cocoa butter as solvent at 1000 ppm of total tannins, in comparison to lanolin and water (26). Aqueous extracts of hojasen leaves have also exhibited inhibitory effects on *Rhizopus stolonifer*, *Botrytis cinerea*, *Fusarium oxysporum,* and *Colletotrichum gloeosporioides* with IC_{50} values ranging from 1.519 to 3.310 mg/L. This antifungal activity was mainly attributed to the presence of gallic acid and flavonoids such as luteolin 7-O-rutinoside and apigenin (6). Similarly, another study confirmed these effects and demonstrated activity against *Mucor* sp, *Penicillium* sp, *Alternaria alternate*, and *Sclerotinia sclerotiorum*, showed the greatest inhibitory effect against *Mucor* sp (268.32 mg/L). The phytochemical composition of the extract included 15 flavonoids, with luteolin 7- O-rutinoside and 6-C-glucosyl-8-C-arabinosyl apigenin as the main compounds (22). Furthermore, extraction using other solvents has also been effective. The use of 1 µg of the essential oil (volatile fraction) in a hexane extract of *F. cernua* had an antifungal effect on *Colletotrichum* species. In their composition, 41 compounds were identified, with higher amounts of monoterpenes, highlighted myrcene, 3-δ-carene, and limonene (27). Recently, another investigation reported the antifungal effect of ethanolic extracts of hojasen against *Fusarium solani*. These extracts enriched in polyphenols (8000 ppm) showed even greater activity than a commercial fungicide called thiabendazole (28).

Antibacterial activity

In addition to its antifungal properties, the hexane extract of hojasen has shown antibacterial activity. For example, the efficacy of *F. cernua* crude extracts against *Mycobacterium tuberculosis* strains has been reported, particularly in a multidrug-resistant strain of *M. tuberculosis*. The study demonstrated that only hexane and acetone extracts were active against this pathogen (29). Another investigation by the same authors confirmed that the fractionation using hexane increases mycobactericidal activity, even in crude aqueous extracts. These results suggested that the obtained compounds are amphipathic, and in the hydrophobic medium are more active against resistant strains, however, a detailed characterization of the components was not performed (30). On another hand, the effects of tarbush on cyanobacteria also have been reported. The essential oils from a hexane extract demonstrated an inhibitory effect on the growth of *Oscillatoria perornata* and *Oscillatoria agardhii*, exhibiting a concentration-dependent mode of action (27).

Toxicity

Concerning the plant's possible toxicity, a study described that ingestion of ripe fruit of *F. cernua* caused loss of sheep and goats due to inflammation, ulceration, and perforation of the gastrointestinal tract (31). However, the research also mentioned that the green leaves of the plant are harmless to cattle and no deaths have been reported when they consume them. Another study determined that chronic consumption of *F. cernua* leaves causes apoptosis in hepatocytes, as well as elevation in the levels of serum gamma glutamyl-transpeptidase and aspartate aminotransferase activities and platelet count in lambs that consumed the leaves (32). In recent studies, a study reported the toxicological effect of oral administration of an alcoholic extract from *F. cernua* leaves to Wistar rats at a limited dose of 2000 mg/kg (33). The study found that the limited dose did not cause death in the animals that received the extract, although there were mild signs of toxicity such as lethargy and drowsiness. However, there were no changes in body weight and macroscopic pathological studies did not show alterations in the organs studied, indicating that the LD_{50} of the extract was above 2000 mg/kg. Therefore, the toxicity of *F. cernua* depends on the part of the plant, with the fruits and flowers being toxic to livestock, while the leaves are relatively innocuous and can be used to obtain pharmacologically interesting compounds.

Discussion

F. cernua represents a promising source of compounds, predominantly flavonoids and sesquiterpenes, which may be responsible for its biological effects. Flavonoids possess a fundamental 15-carbon flavone structure, C6-C3-C6, consisting of two benzene rings connected by a three-carbon pyran ring. The antioxidant potential of flavonoids is due to their molecular structure, wherein hydroxy groups can donate electrons through resonance, thus scavenging free radicals (34). Moreover, flavonoids exhibit anti-inflammatory activity regulating transcription factors involved in the inflammatory process, such as NF-κB, and inhibiting enzymes like cyclooxygenase (COX-2) and lipoxygenase (LOX) (35). Among the compounds identified in *F. cernua*, including apigenin, kaempferol, kaempferide, and quercetin, as well as the potential synergistic effects of all the compounds present in the extracts, contribute to the observed anti-inflammatory effect. Therefore, the discovery of the anti-inflammatory activity of hojasen and its rich content of polyphenolic compounds suggests that it could be a promising natural source for developing new treatments for inflammatory diseases. Further studies on the specific compounds responsible for the anti-inflammatory effect of leaves could help identify potential targets for drug development (24).

The antimicrobial action of *F. cernua* is well-documented, although the specific mechanisms involved in its effects have not been extensively characterized. Reports suggest that the antimicrobial effects of hojasen may be attributed to various mechanisms, including enzyme inactivation, disruption of membrane permeability, and impairment of cell integrity, ultimately

leading to cell death (22). However, a detailed characterization of the antifungal or antibacterial effects of extracts has not been reported. Furthermore, several compounds identified in *F. cernua* have been isolated from other sources and have demonstrated pharmacological effects. For example, luteolin 7-O-galactoside rutinoside and 6-C-glucosyl-8-C-arabinosyl apigenin, are compounds that can form complexes with proteins and polysaccharides inhibiting electron transport through membranes and ions. These effects could be involved in the damage to microorganisms (36).

Sesquiterpenes are another group of compounds found in *F. cernua*. They are both terpenes with the same basic 15-carbon structure, which is made up of three isoprene units, a cyclic structure, and a -methylene-lactone ring that has been fused. These types of compounds are commonly found in plants of the Asteraceae family (37). Sesquiterpenes have been associated with various effects, including anti-inflammatory and antimicrobial activities, as well as potential herbicidal effects (27, 38, 39). The essential oils of *F. cernua* have also demonstrated inhibitory activity against α-glucosidase, with values greater than 90%. The authors propose that this inhibition may be attributed to a non-reversible competitive inhibition mechanism or a non-competitive allosteric inhibition of the enzyme. Therefore, the essential oil of hojasen could serve as a viable alternative for inhibiting intestinal glucose absorption, similar to the effect generated by acarbose (17). Additionally, certain polyphenolic compounds found in *F. cernua* extracts, such as apigenin, cirsimaritin, and hispidulin, have modulating capacities over $GABA_A$ channels, suggesting their potential use as anxiolytics (40, 41). Table 3 provides a summary of the pharmacological effects of *F. cernua* extracts and the possible compounds responsible for these effects.

Regarding the scientific investigation of hojasen's traditional uses, there is currently a lack of studies specifically analyzing its effects on gastrointestinal diseases and its use as an antirheumatic agent. The potential antidiarrheal effect of *F. cernua* could be attributed to the inhibition or elimination of intestinal pathogenic bacteria or parasites. Similarly, the antirheumatic effect may be linked to the anti-inflammatory activity of flavonoids present in hojasen. However, further research is necessary to provide evidence and validate the various biological activities attributed to hojasen.

Prospects and conclusions

This study presented a comprehensive overview of *Flourensia cernua*, including its physical characteristics, bioactive compounds, medicinal uses, and pharmacological effects. *F. cernua* has undergone extensive research in recent years, revealing its diverse range of bioactive compounds and therapeutic potential. The plant exhibits remarkable activities such as antioxidant, antifungal, antibacterial, and anti-inflammatory, among others, which can be attributed to its rich variety of bioactive compounds, mainly flavonoids and sesquiterpenes. Furthermore, *F. cernua* has seen an increase in abundance within the Chihuahuan desert, making it a potential alternative for treating various diseases in local communities in northern Mexico and the southwestern United States of America. Given these findings, hojasen shows great promise as a platform for the development of natural therapies to address a wide range of ailments. However, further research is necessary to fully comprehend the pharmacological properties and potential applications of *F. cernua* and its bioactive compounds. By conducting additional investigations, we can establish a solid foundation for the advancement of hojasen-based treatments and unlock their full medicinal potential.

Acknowledgements

This work was supported by the project “Fondo Destinado a Promover el Desarrollo de la Ciencia y la Tecnología en el Estado de Coahuila COAH-2022-C19-C064”.

Authors' contributions

L.B.A. Conducted the information search and drafted the manuscript. P.L.L. Created the figures and tables and reviewed the final document. N.F.S.D. conceived of the study and participated in its design and coordination. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest: Authors do not have any conflict of interest to declare.

Ethical issues: None.

Table 2. Summary of ethnomedicinal uses of *Flourensia cernua*.

Pharmacological properties	Possible phytoconstituent responsible for the pharmacological effect	Reference
Antioxidant	Apigenin, luteolin, ellagic acid, cirsimaritin, chlorogenic acid, quercetin, caffeic acid, kaempferide, vicenin II, mundulone, and caryophyllene.	(17, 22)
Anti-inflammatory	Ellagic acid, apigenin, kaempferide, quercetin, apigenin and caryophellene.	(24)
Antirheumatic	Apigenin, quercetin.	(43)
Antimicrobial	Luteolin, apigenin, myrcene, 3-δ-carene, limonene and caryophyllene,	(22)
Antidiabetic	Apigenin, luteolin and caryophyllene.	(17)
Anticancer	Umbelliferone, quinic acid, apigenin and ellagic acid,	(24)

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