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Ethnobotany, phytochemistry and pharmacological activities of *Celtis australis*: A review

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ABSTRACT

Celtis australis is a deciduous plant used worldwide in folk medicine to treat various ailments, such as stomach disorders, cough, pimples, joint pain, amenorrhoea, rheumatism, menstrual disorders, and herpes. The present review aims to document and summarize different works regarding the ethnomedicinal uses, phytochemistry, and biological activities of different parts (fruits, barks, leaves, and seeds) of this medicinal plant. For data collection, Google scholar, Science direct, Scopus, PubChem, and PubMed databases were used. This study shows that *C. australis* contains several bioactive compounds, exhibiting various pharmacological activities mainly hepatoprotective, analgesic, anti-inflammatory, cytotoxic, antioxidant, and antimicrobial properties. Thus, *C. australis* is a promising plant that can be exploited in the treatment of various diseases.

Implication for health policy/practice/research/medical education:
The present review reports the ethnomedicinal uses of *Celtis australis* worldwide. It also provides a detailed insight into the pharmacological properties of this plant and highlights its richness in bioactive compounds, which can be involved in the development of new safe drugs, with no or little side effects, for human therapy.

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Introduction

Various plants are used and appreciated around the world for their ability to promote health (1). This is especially the case in rural societies where the healing disease process relies essentially on traditional medicine based on the use of medicinal and aromatic plants (MAPs) (2). This could be due to the strong attachment of people to their traditional heritage or their difficult access to health facilities. The traditional use of these plants as remedies has led many researchers to focus their work on ethnopharmacology. This interdisciplinary approach is based first on ethnobotanical surveys providing knowledge on medicinal plants exploited by indigenous populations, then on the botanical identification of these plants, and finally on the investigation of their chemistry and pharmacology (3).

Thus, several scientific works have confirmed the relevance of the ethnological uses of MAPs. The in vitro and in vivo experimental trials have revealed that thanks to their richness in bioactive compounds giving them interesting pharmacological properties (4), the MAPs are currently exploited in therapeutic systems, and could play an important role in the development of natural drugs (3).

Celtis australis is a deciduous tree (5) belonging to the *Cannabaceae* family (6,7), and commonly known as Mediterranean hackberry, European nettle tree, or lote tree (6). It is one of the medicinal plants that are used in different countries as a natural remedy for many diseases such as cough, colic, amenorrhoea, ulcers, and stomach disorder (8-10). It has been demonstrated that *C. australis* organs contain a variety of phytochemical molecules, including flavonoids (11-14), terpenoids (15), and anthocyanins (6). These compounds are known for their ability to exert different biological effects (16-18). Many studies have proved the pharmacological potential of this plant (11,19-22).

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To the best of our knowledge, no review has been dedicated exclusively to *C. australis*. However, there are some ethnobotanical books that have mentioned *C. australis* among other plant species. Moreover, the numerous published research papers, on which our work was based, bring only partial information on *C. australis.* They do not cover all the plant's organs, all bioactive molecules, or all the methods of extraction. Furthermore, these papers do not integrate both the ethnobotanical uses and the pharmacological properties of this species. In this context, the present review aims to summarize data on the ethnomedicinal uses of *C. australis*, its phytochemistry, and pharmacological potential. This review will therefore be beneficial to both society and researchers by providing them with a compilation of ethnomedicinal knowledge concerning this plant, and a suggestion of research leads for further studies.

Methods

This work was performed by using the search engines of several databases mainly Google Scholar, Scopus, Science Direct, Web of Science, PubChem, and PubMed. Search queries were a binary association between the keywords "*Celtis australis*" and the followings: "biological activities", "antimicrobial activities", "antioxidant activities", "phytochemicals", and "distribution". In order to give a broad view of the study subject, all obtained works published up to September 2022 were included. As regards the exclusion criteria, the only documents not mentioned were those which did not correspond to the objectives of the present study. Thus, 59 documents were mentioned, synthesized, and summarized, including 19 studies about the ethnomedicinal use of *C. australis,* 8 studies concerning its phytochemistry, and 18 studies related to its pharmacological properties (Figure 1). Most of the chemical structures were obtained from the DhemDraw database, while some were taken from the corresponding articles.

Botanical description and distribution

Celtis australis is a suckering tree, characterized by smooth whitish bark, deciduous leaves, young hairy branches, and subglobose drupes (5) (Figure 2). This species grows in mild semiarid and subhumid bio-climates (5). It is native to the Mediterranean basin and Western Asia and occurs from the Iberian Peninsula and Morocco to Syria, including the Mediterranean islands, up to the Black Sea and the Caucasus (23).

Ethnomedicinal uses of *Celtis australis*

According to several ethnobotanical surveys, *C. australis* has been used around the world in folk medicine to treat various ailments. Table 1 lists the traditional medicinal uses of different parts of *C. australis* and their preparation modes that have been reported by various ethnobotanical studies, conducted all over the world.

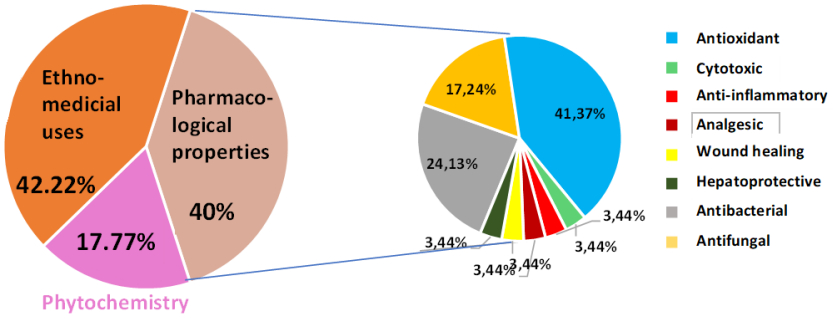

Figure 1. Distribution of the published studies according to *Celtis australis* uses, chemical composition, and bio-active properties.

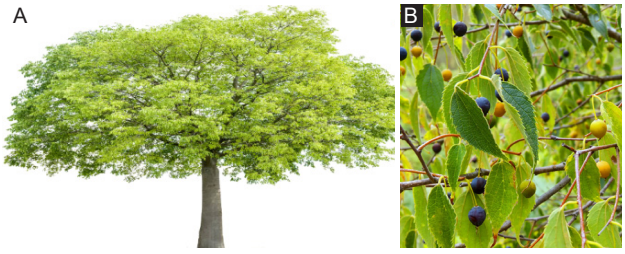

Figure 2. *Celtis australis*; A: Whole tree; B: Leaves and drupes.

Table 1. Ethnomedicinal uses of *Celtis australis* reported in scientific works

Part used	Geographic area	Preparation/use method	Diseases cured	Reference
Leaves	Different sites of lesser Himalayas	Fresh leaves decoction is taken orally	Stomach disorder and cough	(8)
	Swat Valley, Northern Pakistan	Decoction	Stomach disorder and cough	(24)
	Shankaracharya Hill, Srinagar, J&K, India	Infusion, crushed leaves in curd	Burning of soles, herpes	(32)
	Alt Empordà region (Catalonia, Iberian Peninsula)	Decoction, infusion	Anti-hypertensive	(35)
	Regions of L'Alt Empordà and Les Guilleries (Catalonia, Iberian Peninsula)	Infusion	Anti-hypercholesterolaemic	(36)
Fruits	Pak-Afghan border, near Bajaur, Pakistan	Fruits are directly consumed	-	(25)
	Jhelum valley, Azad Kashmir, Pakistan	Decoction	Amenorrhoea, menstrual disorder and peptic ulcer	(26)
	Kutlla Valley (Bheri), Muzaffarabad	Decoction	Amenorrhoea, menstrual disorder and peptic ulcer	(27)
	Khyber Pakhtunkhwa, northwestern Pakistan	-	Colic, amenorrhoea	(9)
	Alaşehir (Manisa) in Turkey	Raw, spice	Gastrointestinal diseases	(34)
	Sarigöl district (Manisa), Turkey	Fruits are eaten by chewing	Ulcers	(10)
	National Park of Cilento and Vallo di Diano, Campania, Southern, Italy	-	Antidiarrheal	(39)
Bark	Antakya: in Hatay Province of Turkey	Decoction (boiled until concentrated)/ applied externally	Itching-Scabies	(33)
Whole plant	Kalrayan hills of Villupuram district, Tamil Nadu, India	Decoction	Astringent and diuretic	(28)
Stem, bark	Pauri district of Uttarakhand, India	-	Joint pain, pimples	(29)
Fruits, seeds	Jammu, Kashmir and Ladakh (India)	-	Amenorrhoea, colic complaints, rheumatism	(30)
Leaves, fruits	Kathua district, J&K (Jammu & Kashmir), India	Decoction	Menstrual disorders	(31)
Fruits, bark	Pak-Afghan border area	Decoction + ghee	Amenorrhoea	(37)
Fruits, leaves and seeds	Central Zagros, Lorestan Province, Iran	Cataplasm	Astringent, digestive ulcers Dysentery	(38)

In Pakistan, leaves decoction of *C. australis* is taken orally (8) as a remedy for stomach disorders and cough (8,24), while fruits are consumed directly (25) or in decoction form (26,27) as a cure for colic (9), amenorrhoea (9,26,27), menstrual disorders, and peptic ulcer (26,27).

In India, the decoction of different parts of this plant is employed as astringent and diuretic (28). Stems and barks serve to treat joint pain and pimples (29). Fruits and seeds are used for their healing potential of amenorrhoea, colic complaints, and rheumatism (30). As for leaves, their decoctions are exploited to manage menstrual disorders (31), while their infusion or crushed form in curd is intended to medicate the burning of soles and herpes (32). In Turkey, bark decoction is applied externally to fight scabies itching (33), while fruits (raw, spice) are used to treat ulcers and gastrointestinal diseases (10,34). In Catalonia, leaf decoction is taken as anti-hypertensive (35), whereas leaf infusion is administrated as anti-hypercholesterolemic (36) and anti-hypertensive remedy (35). In Afghanistan, the decoction and the ghee of fruit and bark are used to treat amenorrhoea (37). In Iran, fruits, leaves, and seeds are exploited to heal digestive ulcers and dysentery (38). In Italy and Morocco, fruits are used to treat diarrhea (39,40).

The analysis of literature reported in this work (Table 1, Figure 3A) shows that the ethnomedicinal uses of *C. australis* were mainly highlighted by studies carried out by researchers in India (35%), Pakistan (25%) and Turkey (15%). Furthermore, the most frequent *C. australis* ethnomedicinal use cited is the treatment of digestive tract (30,76%) and genito-urinary (26,92%) diseases (Figure 3B). Figures 3C and 3D show that the most exploited part of *C. australis* is fruit (43,33%), and the dominant mode of preparation is decoction (50%). El Hachlafi et al indicated that plant decoction allows a good extraction of bioactive compounds and attenuates the toxic effect of herbal recipes (41). Therefore, this could explain the abundance of this preparation mode in the reported ethnomedicinal studies.

Phytochemistry

In spite of their limited number, studies dedicated to the

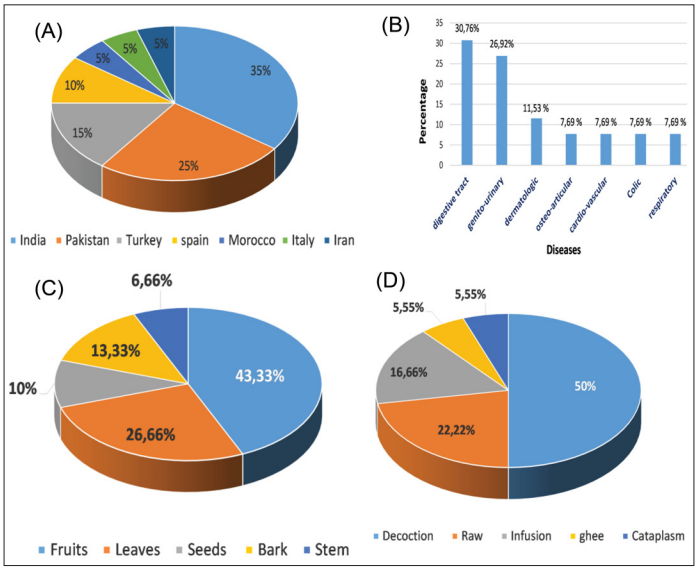

Figure 3. Distribution of ethnomedicinal use of *Celtis australis* according to different criteria: A) geographic location of the cited studies; B) treated diseases; C) exploited parts; (D) preparation mode.

phytochemistry of *C. australis* have demonstrated the richness of this plant in bio-active compounds (Table 2 and Figure 4). Moreover, Figure 5 clearly shows that the chemical composition of *C. australis*' extracts varies significantly between the plant parts. In fact, the most dominant compounds are flavonoids in leaves (Figure 5A), and flavonoids and triterpenoids in fruits (Figure 5B). In bark, only triterpenoids and bacteriohopanoid were reported (Figure 5C). Furthermore, as shown in Table 2, besides the plant's parts other factors may be responsible for the variation of the extract's chemical composition such as the plant's origin, the extraction solvent (42), and the harvest season (6).

Pharmacological properties

According to several studies, *C. australis* possesses several pharmacological properties, including antimicrobial, antioxidant, anti-inflammatory, hepatoprotective, analgesic, cytotoxic, and wound healing effects.

Antibacterial activity

The antibacterial activity of different parts of *C. australis* has been investigated against various gram-positive and gram-negative bacteria. Table 2 summarizes several studies carried out in this context.

Ahmad et al (44), assessed the antibacterial effect of aqueous and methanolic extracts of *C. australis*'s leaves against *Staphylococcus aureus* (ATCC 25923) and *Pseudomonas aeruginosa* (ATCC 27853) using disc diffusion method. The highest inhibition zone diameter (ϕ) was obtained with the methanolic extract at a concentration of 200 mg/mL; the most sensitive bacteria was *S. aureus* (ϕ = 10.50 ± 0.57 mm). In the same context, El Maliki et al, investigated the antimicrobial potential of *C. australis*'s leaves extracts using different solvents with increasing polarity, namely: dichloromethane, ethyl acetate, butanol, and methanol (45). Several bacterial strains were tested: *Bacillus* sp (CIP 104717), *Bacillus cereus* (ATCC 33019), *Listeria ivanovii* (ATCC 19119), *Citrobacter freundii* (ATCC 8090), *Staphylococcus aureus* (ATCC 25923), *Salmonella* sp, *Escherichia coli* (CIP 54127). *S. aureus,* and *B. cereus* showed the highest susceptibility (ϕ=13.5 ± 0.5 mm) to butanol extract of *C. australis's* leaves at a concentration of 8 mg/mL. In addition, butanol extracts were the most effective extracts against all bacteria tested when the tube dilution method was applied (minimal inhibitory concentration [MIC]= 5 mg/mL) (45). Similarly, Filali-Ansari et al evaluated the antimicrobial activities of hexane, ethyl acetate, and hydromethanol *C. australis*'s leaves extracts against the same bacterial strains listed previously, and showed that ethyl acetate extract at 1 g/mL induced the highest inhibition of *B. cereus and Listeria ivanovii* (ϕ= 17±2 mm) (46). These strains were also tested for their susceptibility to three isolated compounds from the leaves of *C. australis* (Vanillic acid, β-sitosterol-3-O-β-glucoside, and β-sitosterol) in another work. Vanillic acid exhibited the most important effect against *B. cereus* (MIC= 25 µg/mL) (31).

More interestingly, Ota et al (6) studied the antimicrobial effect of *C. australis*'s mesocarp and leaves extracts (aqueous and ethanolic extracts) at different growth stages (June, October) against four clinical isolated bacteria (*Escherichia coli* O157:H7 ŽMJ370, *Listeria monocytogenes* ŽMJ58a, *Pseudomonas aeruginosa* ŽMJ87, and *S. aureus* ATCC 25923). The obtained results revealed that *S. aureus* was the most sensitive bacteria (MIC= 1.25 mg/mL) toward ethanolic extracts of *C. australis*'s leaves

Table 2. Isolated compounds from *Celtis australis* according to the reported studies

Isolated compounds	Plant part	Extract	Collection origin	Method	Reference
Flavonoids					
Vitexin, orientin, isovitexin, isoorientin, rutin, 2''-O-β-galacto- pyranosylvitexin, 2''-O-β-D-galactopyranosylorientin, 4'''-α-rhamnopyranosyl-2''-O-β-D-galacto pyranosylvitexin	Leaves	Ethanolic	El-Orman Botanical Garden and the Agricultural museum, Giza, Egypt	Silica gel column chromatography	(11)
Apigenin, quercetin-glucoside, quercetin	Fruits	Ethanolic	Bhatwara, District of Tehri Garhwal (India)	Silica gel column chromatography	(12)
Acacetin 7-O-glucoside , Isovitexin (apigenin 6-C-glucoside), Cytisoside (acacetin 8-C-glucoside)	Leaves	Methanolic	-	Sephadex column chromatography	(13)
2''-α-rhamnopyranosylvitexin, 2"-α-rhamnopyranosyl-7-O-methylvitexin	Leaves	Methanolic	Italy	Sephadex column chromatography	(14)
Epicatechin	Leaves (June, October)	Ethanolic	Istria (Marasi village near Vrsar, Croatia)	Ultra-High-Performance Liquid chromatography (Ultra-HPLC)	(6)
Steroids					
(3β,9β,14β)-14-hydroxy-9,19-cyclocholan-3-yl β-D-glucopyranoside	Fruits	Ethanolic	Bhatwara, District Tehri Garhwal(India)	Silica gel column chromatography	(15)
β-sitosterol, β-sitosterol-3-O-β-glucoside	Leaves	Methanolic	El Jadida city (Morocco)	Flash chromatography on silica gel column	(20)
Anthocyanins					
Delphinidin-3,5-di-O-glucoside: R	Leaves and Mesocarp (October)	Aqueous	Istria (Marasi village near Vrsar, Croatia)	Ultra-HPLC	(6)
Cyanidin-3,5-di-O-glucoside	Leaves (October)	Aqueous	Istria (Marasi village near Vrsar, Croatia)	Ultra-HPLC	(6)
	Leaves and mesocarp (June, October)	Ethanolic	Istria (Marasi village near Vrsar, Croatia)	Ultra-HPLC	(6)
Pelargonidin-3,5-di-O-glucoside	Leaves and mesocarp (October)	Aqueous	Istria (Marasi village near Vrsar, Croatia)	Ultra-HPLC	(6)
	Leaves and mesocarp (June, October)	Ethanolic	Istria (Marasi village near Vrsar, Croatia)	Ultra-HPLC	(6)

Table 2. Continued

Isolated compounds	Plant part	Extract	Collection origin	Method	Reference
Terpenoids					
(9β, 31R)-9,25-cyclo-30 propylhopan-31-ol, (3β)-3-hydroxy-30-pro-pylhopan-31-one, (3β)-oleanan-3-ol	Bark	Ethanolic	Bhatwara, District Tehri Garhwal (India)	Silica gel column chromatography	(15)
(3β,9β)-9,25-cycloolean-12-en-3-yl β-D-glucofuranoside	Fruits	Ethanolic	Bhatwara, District Tehri Garhwal (India)	Silica gel column chromatography	(15)
Anthraquinone					
6-hydroxy-5,7,8-trimethoxy-9,10-dioxo-9,10-dihydroanthracen-2-yl acetate	Fruits	Ethanolic	Bhatwara, District Tehri Garhwal (India)	Silica gel column chromatography	(15)
Phenolic acids					
Gallic acid	Leaves (June) Mesocarp (October)	Aqueous	Istria (Marasi village near Vrsar, Croatia)	Ultra-HPLC	(6)
Vanillic acid	Leaves (June, October)	Ethanolic	Istria (Marasi village near Vrsar, Croatia)	Ultra-HPLC/ flash chromatography on silica gel column	(6, 20)
Phenolic aldehyde					
3,5-Dihydroxy-benzaldehyde	Leaves and mesocarp (June, October)	Ethanolic	Istria (Marasi village near Vrsar, Croatia)	Ultra-HPLC	(6)
Sulphonated phenolic					
Celtisanin	Fruits	Ethanolic	Bhatwara, Tehri Garhwal (India)	Silica gel column chromatography	(12)
Bacteriohopanoid					
3-βhydroxy-35-(cyclohexyl-5’ -propan-7’ -one)-33-ethyl-34-methyl-bactereohopane	Bark	Ethanolic	Bhatwara, District of Tehri Garhwal (India)	Silica gel column chromatography	(43)

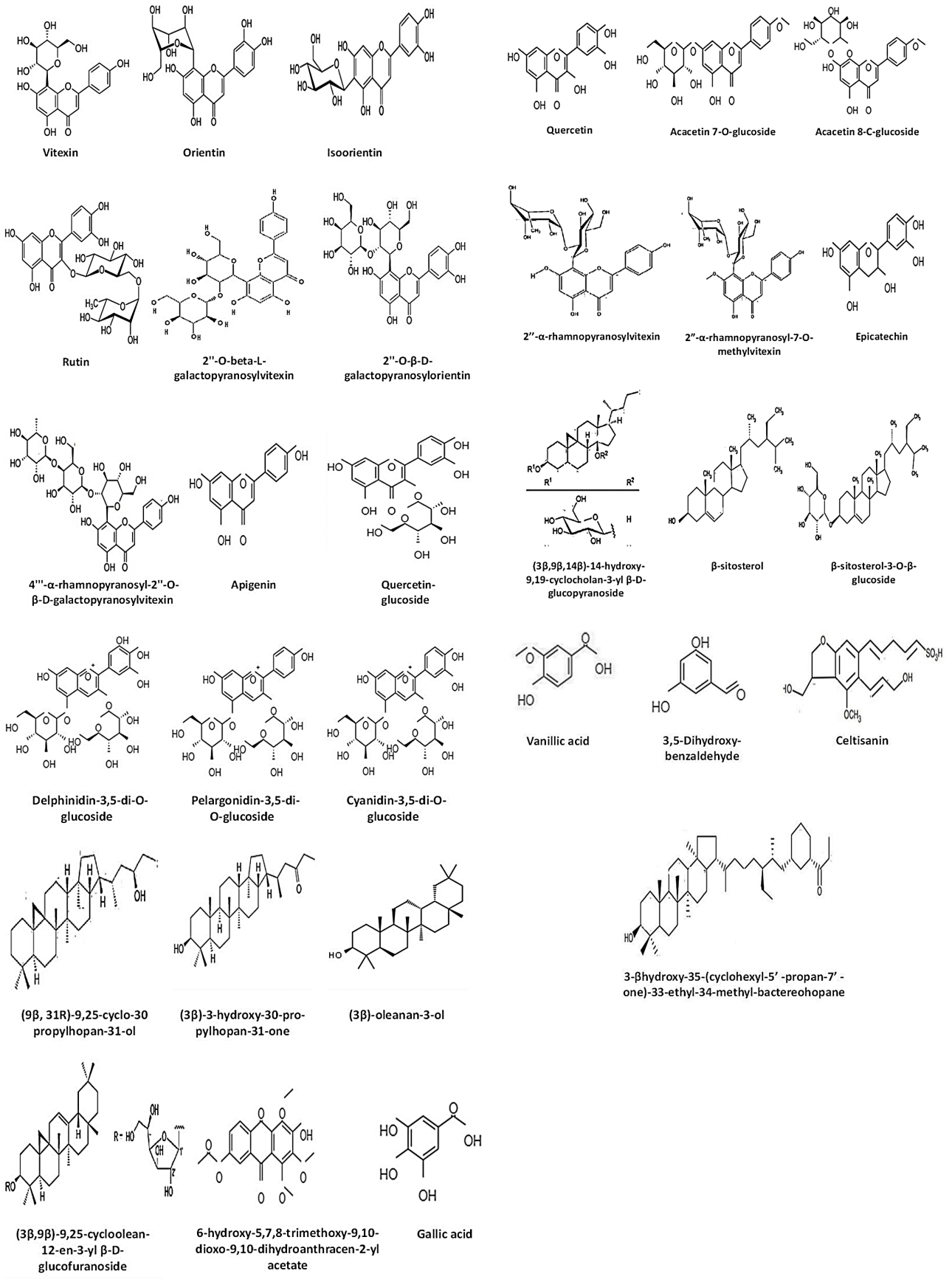

Figure 4. Chemical structures of the main compounds isolated from *Celtis australis*.

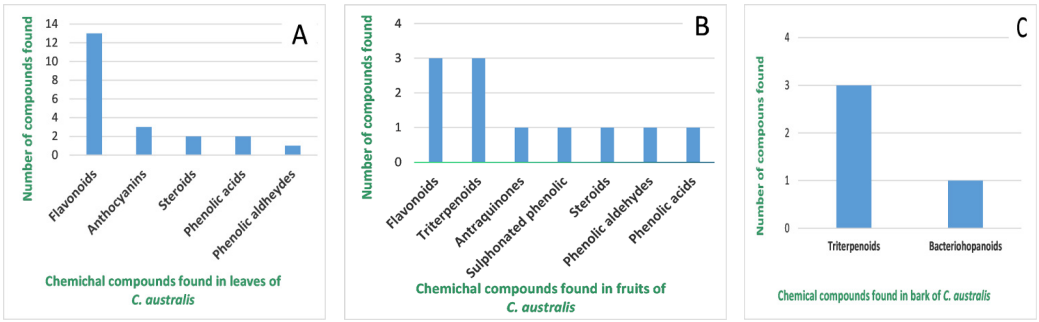

Figure 5. Variation of chemical compounds reported in different extracts of *Celtis australis* parts. A) Leaves; B) Fruits; C) Bark.

and mesocarp.

Badoni et al also assessed the antimicrobial activity of *C. australis*'s fruits, and reported a good effect of the ethanolic extract against all the bacteria investigated in this study: *Bacillus subtilis* ($\phi = 21.3 \pm 0.58$ mm), *Pseudomonas aeruginosa* ($\phi = 19.6 \pm 0.87$ mm), *Escherichia coli* ($\phi = 19.4 \pm 1.2$ mm), and *Staphylococcus aureus* ($\phi = 18.2 \pm 1.0$ mm) (47).

Concerning the *C. australis*'s seeds, their antibacterial potential was evaluated by Freitas et al against a panel of gram-positive and gram-negative bacteria using the microdilution method. The best results were obtained against *B. cereus* with a MIC and minimum bactericidal concentration (MBC) lower than that obtained with ampicillin (19). In addition, Filali-Ansari et al (46) investigated the antibacterial effect of *C. australis*'s seeds using three different solvents (hexane, ethyl acetate, and methanol) against the same bacterial strains tested by EL Maliki et al (45). *B. cereus* was the most sensitive ($\phi = 17 \pm 3$ mm) to ethyl acetate seeds extract at a concentration of 1 g/mL.

From these studies, it can be noted that as for the chemical composition, the antibacterial activities of *C. australis* vary according to different factors. It depends on the solvents used and also on the targeted bacteria. Moreover, as shown in Table 3, isolated compounds (vanillic acid, β-sitosterol-3-O-β-glucoside, β-sitosterol) exhibit a strong antibacterial activity (low MIC values). Hence, further studies on the pharmacological properties of *C. australis's* pure phytocompounds are necessary to perform.

Antifungal activity

The activity of *C. australis*'s extracts against different fungi has been proved in various studies. Ota et al investigated the antifungal activity of the ethanolic extract of *C. australis's leaves* and mesocarp harvested at different growth stages (end of June and end of October), on the most frequent fungal colonizers of dishwashers. *Aureobasidium pullulans* EX 3105, *Saprochaete clavata* EX 5631, *Candida parapsilosis* EX 9370, *Candida albicans* EX 9382, *Exophiala dermatitidis* EX 5586, *Aspergillus fumigatus* EX 8280, *Fusarium dimerum* EX 9214, and *Rhodotorula mucilaginosa* EX 9762 were tested. Results showed that the mesocarp extract had no antifungal activity, while the leaves extract harvested at the end of October (richer in phenolics) inhibited *Candida albicans* (MIC = 0.156 mg/mL), *C. parapsilosis* (MIC = 0.156 mg/mL), and *Rhodotorula mucilaginosa* (MIC = 0.313 mg/mL) (6).

In another study, Filali-Ansari et al (20) tested the antifungal activity of three isolated compounds from the leaves of *C. australis* (vanillic acid, β-sitosterol-3-O-β-glucoside, and β-sitosterol) against two yeasts "*C. albicans* and *Candida tropicalis*" and one filamentous fungus "*Aspergillus niger*". The minimum inhibitory concentration (MIC = 50 µg/mL) was obtained with vanillic acid against *C. albicans* and *C. tropicalis,* as well as β-sitosterol-3-O-β-glucoside against *C. albicans,* and β-sitosterol against *C. tropicalis.* The same fungal strains were tested by El Maliki et al (45) for their susceptibility to different solvent extracts (dichloromethane, ethyl acetate, butanol, and methanol) of C. *australis*'s leaves. The highest inhibition zone was obtained with dichloromethane extract against *C. tropicalis* ($\phi = 19.5 \pm 0.5$ mm). Similarly, using different solvent extracts (ethyl acetate, hexane, and hydromethanol extracts) of *C. australis*'s seeds and leaves, the antifungal activity against *C. albicans, C. tropicalis, and A. niger* was examined by Filali-Ansari et al (46). The results showed an important activity both for the leaves hydromethanol extract (at 0.5 and 1 g/mL) against *C. albicans,* and for ethyl acetate extract (1 g/mL) against *C. tropicalis*; with a similar inhibition zone diameter of 15 ± 3 mm (46).

The antifungal activities of *C. australis* seed extracts were also evaluated by Freitas et al (19). The best results were obtained against *Aspergillus ochraceus* and *Penicillium funiculosum* with MIC and MFC values lower than those obtained for ketoconazole.

Antioxidant activity

Thanks to their richness in phenolic compounds (48,49), different parts of *C. australis* (leaves, mesocarp, bark, and seeds) have been found to possess important antioxidant

Table 3. Antibacterial activities of *Celtis australis* reported in scientific works

Parts used	Extracts/isolated compounds	Methods used	Bacteria tested	Findings	Reference
Leaves					
	Aqueous extract	Disc diffusion	*Staphylococcus aureus*(ATCC25923) *Pseudomonas aerugenosa* (ATCC27853)	Inhibition zone diameter (IZ ϕ) at 200 mg extract/mL: ϕ = 8.56 ± 1.86 mm ϕ = 8.0 ± 1.0 mm	(44)
	Methanolic extract	Disc diffusion	*Staphylococcus aureus* (ATCC25923) *Pseudomonas aerugenosa* (ATCC 27853)	IZ ϕ at 200 mg extract/mL: ϕ = 10.50 ± 0.57 mm ϕ = 9.0 ± 1.0 mm	(44)
	Dichloromethan extract	Disc diffusion	*Escherichia coli* (CIP 54127) *Salmonella* sp *Citrobacter freundii* (ATCC 8090) *Staphylococcus aureus* (ATCC 25923) *Bacillus* sp (CIP 104717) *Listeria ivanovii* (ATCC 19119) *Bacillus cereus* (ATCC 33019)	IZ ϕ at 8 mg extract/mL: ϕ = 8.5 ± 0.5 mm ϕ = 8.5 ± 0.5 mm ϕ = 9.5 ± 0.5 mm ϕ = 9.5 ± 0.5 mm ϕ = 9.5± 0.5 mm ϕ = 9.5 ± 0.5 mm ϕ = 9 ± 0.5 mm	(45)
	Ethyl acetate extract	Disc diffusion	*Escherichia coli* (CIP 54127) *Salmonella sp* *Citrobacter freundii* (ATCC 8090) *Staphylococcus aureus* (ATCC 25923) *Bacillus sp* (CIP 104717) *Listeria ivanovii* (ATCC 19119) *Bacillus cereus* (ATCC 33019)	IZ ϕ at 8 mg extract/mL: ϕ = 9.5 ± 0.5 mm ϕ = 9.5 ± 0.5mm ϕ = 10.5 ± 0.5 mm ϕ = 12.0 ± 1.0 mm ϕ = 10.5 ± 0.5mm ϕ = 12.0 ± 1.0 mm ϕ = 10.5 ± 0.5 mm	(45)
	Butanol extract	Disc diffusion	*Escherichia coli* (CIP 54127) *Salmonella* sp *Citrobacter freundii* (ATCC 8090) *Staphylococcus aureus* (ATCC 25923) *Bacillus* sp (CIP 104717) *Listeria ivanovii* (ATCC 19119) *Bacillus cereus* (ATCC 33019)	IZ ϕ at 8 mg extract/mL: ϕ = 10.5 ± 0.5 mm ϕ = 12.5 ± 0.5 mm ϕ = 11.5 ± 0.5 mm ϕ = 13.5 ± 0.5 mm ϕ= 13.0 ± 1.0 mm ϕ = 11.5 ± 0.5 mm ϕ = 13.5 ± 0.5 mm	(45)
	Methanolic extract	Disc diffusion	*Escherichia coli* (CIP 54127) *Salmonella* sp *Citrobacter freundii* (ATCC 8090) *Staphylococcus aureus* (ATCC 25923) *Bacillus sp* (CIP 104717) *Listeria ivanovii* (ATCC 19119) *Bacillus cereus* (ATCC 33019)	IZ ϕ at 8mg extract/mL: ϕ = 10.5 ± 0.5 mm ϕ =11.5 ± 0.5 mm ϕ = 11.0 ± 1.0 mm ϕ = 9.5 ± 0.5 mm ϕ = 10.0 ± 1.0 mm ϕ= 12.5 ± 0.5 mm ϕ= 9.5 ± 0.5 mm	(45)

Table 3. Continued

Parts used	Extracts/isolated compounds	Methods used	Bacteria tested	Findings	Reference
				Minimal inhibitory concentration	
	Dichloromethane extract	Tube dilution	*Escherichia coli* (CIP 54127)	MIC = 40 mg/mL	(45)
			Bacillus sp (CIP 104717)	MIC = 10 mg/mL	
			Citrobacter freundii (ATCC 8090)	MIC = 10 mg/mL	
			Staphylococcus aureus (ATCC 25923)	MIC = 40 mg/mL	
			Listeria ivanovii (ATCC 19119)	MIC = 10 mg/mL	
			Bacillus cereus (ATCC 33019)	MIC = 10 mg/mL	
			Salmonella sp	MIC = 10 mg/mL	
	Ethyl acetate extract	Tube dilution	*Escherichia coli* (CIP 54127)	MIC = 5 mg/mL	(45)
			Bacillus sp (CIP 104717)	MIC = 5 mg/mL	
			Citrobacter freundii (ATCC 8090)	MIC = 10 mg/mL	
			Staphylococcus aureus (ATCC 25923)	MIC = 10 mg/mL	
			Listeria ivanovii (ATCC 19119)	MIC = 10 mg/mL	
			Bacillus cereus (ATCC 33019)	MIC = 10 mg/mL	
			Salmonella sp	MIC = 10 mg/mL	
	Butanol extract	Tube dilution	*Escherichia coli* (CIP 54127)	MIC = 5 mg/mL	(45)
			Bacillus sp (CIP 104717)	MIC = 5 mg/mL	
			Citrobacter freundii(ATCC 8090)	MIC = 5 mg/mL	
			Staphylococcus aureus (ATCC 25923)	MIC = 5 mg/mL	
			Listeria ivanovii (ATCC 19119)	MIC = 5 mg/mL	
			Bacillus cereus (ATCC 33019)	MIC = 5 mg/mL	
			Salmonella sp	MIC = 5 mg/mL	
	Methanolic extract	Tube dilution	*Escherichia coli* (CIP 54127)	MIC = 10 mg/mL	(45)
			Bacillus sp (CIP 104717)	MIC = 10 mg/mL	
			Citrobacter freundii (ATCC 8090)	MIC = 20 mg/mL	
			Staphylococcus aureus (ATCC 25923)	MIC = 20 mg/mL	
			Listeria ivanovii (ATCC 19119)	MIC = 20 mg/mL	
			Bacillus cereus (ATCC 33019)	MIC =20 mg/mL	
			Salmonella sp	MIC = 20 mg/mL	
	Hexane extract	Disc-diffusion		IZ ϕ at 1 g extract/mL:	(46)
			Bacillus sp (CIP 104717)	ϕ = 12 ± 2 mm	
			Bacillus cereus (ATCC 33019)	ϕ = 10 ± 1 mm	
			Listeria ivanovii (ATCC 19119)	ϕ = 12 ± 2 mm	
			Staphylococcus aureus (ATCC 25923)	ϕ = 10 ± 2 mm	
			Citrobacter freundii (ATCC 8090)	ϕ = 12 ± 2 mm	
			Escherichia coli (CIP54127)	ϕ = 10 ± 2 mm	
			Salmonella sp	ϕ = 9 ± 2 mm	

Table 3. Continued

Parts used	Extracts/isolated compounds	Methods used	Bacteria tested	Findings	Reference
	Ethyl acetate extract	Disc-diffusion		IZ ϕ at 1 g extract/mL:	(46)
			Bacillus sp (CIP 104717)	ϕ = 15 ± 2 mm	
			Bacillus cereus (ATCC 33019)	ϕ = 17 ± 2 mm	
			Listeria ivanovii (ATCC 19119)	ϕ = 17 ± 2 mm	
			Staphylococcus aureus (ATCC 25923)	ϕ = 11 ± 1 mm	
			Citrobacter freundii (ATCC 8090)	ϕ = 14 ± 2 mm	
			Escherichia coli (CIP54127)	ϕ = 14 ± 2 mm	
			Salmonella sp	ϕ = 10 ± 1 mm	
	Hydro-methanolic extract	Disc-diffusion		IZ ϕ at 1 g extract/mL:	(46)
			Bacillus sp (CIP 104717)	ϕ = 8 ± 1 mm	
			Bacillus cereus (ATCC 33019)	ϕ = 8 ± 2 mm	
			Listeria ivanovii (ATCC 19119)	ϕ = No effect	
			Staphylococcus aureus (ATCC 25923)	ϕ = 8 ± 2 mm	
			Citrobacter freundii (ATCC 8090)	ϕ = 9 ± 3 mm	
			E. coli (CIP 54127)	ϕ = 8 ± 2 mm	
			Salmonella sp	ϕ = 7 ± 1 mm	
	Vanillic acid	Tube dilution	*Bacillus sp*	MIC =50 µg/mL	(20)
			Bacillus cereus	MIC =25 µg/mL	
			Listeria ivanovii	MIC =100 µg/mL	
			Staphylococcus aureus	MIC =100 µg/mL	
			Citrobacter freundii	MIC = 50 µg/mL	
			Escherichia coli	MIC = 100 µg/mL	
			Salmonella sp	MIC = 50 µg/mL	
	β-sitosterol-3-O-β-glucoside	Tube dilution	*Bacillus sp*	MIC = 50 µg/mL	(20)
			Bacillus cereus	MIC = 200 µg/mL	
			Listeria ivanovii	MIC = 100 µg/mL	
			Staphylococcus aureus	MIC = 200 µg/mL	
			Citrobacter freundii	MIC = 100 µg/mL	
			Escherichia coli	MIC = 200 µg/mL	
			Salmonella sp	MIC = 100 µg/mL	
	β-sitosterol	Tube dilution	*Bacillus sp*	MIC = 100 µg/mL	(20)
			Bacillus cereus	MIC = 200 µg/mL	
			Listeria ivanovii	MIC = 200 µg/mL	
			Staphylococcus aureus	MIC = 100 µg/mL	
			Citrobacter freundii	MIC: Not determined	
			Escherichia coli	MIC = 200 µg/mL	
			Salmonella sp	MIC = 200 µg/mL	

Table 3. Continued

Parts used	Extracts/isolated compounds	Methods used	Bacteria tested	Findings	Reference
	Aqueous extract	Micro-dilution	*Escherichia coli* (O157:H7 ŽMJ370) *Listeria monocytogenes* (ŽMJ58a) *Pseudomonas aeruginosa* (ŽMJ87) *Staphylococcus aureus* (ATCC 25923) *Escherichia coli* (O157:H7 ŽMJ370) *Listeria monocytogenes* (ŽMJ58a) *Pseudomonas aeruginosa* (ŽMJ87) *Staphylococcus aureus* (ATCC 25923)	**Leaves collected in June** MIC = 5 mg/mL MIC > 10 mg/mL MIC > 10 mg/mL MIC > 10 mg/mL **Leaves collected in October** MIC = 2.5 mg/mL MIC = 10 mg/mL MIC > 10 mg/mL MIC = 5 mg/mL	(6)
	Ethanolic extract	Micro-dilution	*Escherichia coli* (O157:H7 ŽMJ370) *Listeria monocytogenes* (ŽMJ58a) *Pseudomonas aeruginosa* (ŽMJ87) *Staphylococcus aureus* (ATCC 25923) *Escherichia coli* (O157:H7 ŽMJ370) *Listeria monocytogenes* ŽMJ58a *Pseudomonas aeruginosa* ŽMJ87 *Staphylococcus aureus* ATCC 25923	**Leaves collected in June** MIC = 2.5 mg/mL MIC > 10 mg/mL MIC > 10 mg/mL MIC > 10 mg/mL **Leaves collected in October** MIC = 5 mg/mL MIC = 5 mg/mL MIC > 10 mg/mL MIC = 1.25 mg/mL	(6)
Meso-carp					
	Aqueous extract	Micro-dilution	*Escherichia coli* (O157:H7 ŽMJ370) *Listeria monocytogenes* (ŽMJ58a) *Pseudomonas aeruginosa* (ŽMJ87) *Staphylococcus aureus* (ATCC 25923) *Escherichia coli* (O157:H7 ŽMJ370) *Listeria monocytogenes* (ŽMJ58a) *Pseudomonas aeruginosa* (ŽMJ87) *Staphylococcus aureus* (ATCC 25923)	**Leaves collected in June** MIC> 10 mg/mL MIC> 10 mg/mL MIC> 10 mg/mL MIC> 10 mg/mL **Leaves collected in October** MIC = 5 mg/mL MIC > 10 mg/mL MIC > 10 mg/mL MIC = 5 mg/mL	(6)
	Ethanolic extract	Microdilution	*Escherichia coli* (O157:H7 ŽMJ370) *Listeria monocytogenes* (ŽMJ58a) *Pseudomonas aeruginosa* ŽMJ87 *Staphylococcus aureus* ATCC 25923 *Escherichia coli* (O157:H7 ŽMJ370) *Listeria monocytogenes* (ŽMJ58a) *Pseudomonas aeruginosa (*ŽMJ87) *Staphylococcus aureus* (ATCC 25923)	**Leaves collected in June** MIC > 10 mg/mL MIC > 10 mg/mL MIC > 10 mg/mL MIC > 10 mg/mL **Leaves collected in October** MIC = 5 mg/mL MIC = 5 mg/mL MIC = 2.5 mg/mL MIC = 1.25 mg/mL	(6)

Table 3. Continued

Parts used	Extracts/isolated compounds	Methods used	Bacteria tested	Findings	Reference
Fruits	Ethanolic extract	Agar diffusion and tube dilution		IZ ϕ at 10 mg extract/mL	
			Staphylococcus aureus	ϕ= 18.2 ± 1.0 mm, MIC: Not determined	(48)
			Bacillus subtilis	ϕ= 21.3 ± 0.58 mm, MIC = 250 µg/mL	
			Pseudomonas aeruginosa	ϕ= 19.6 ± 0.87 mm, MIC = 125 µg/mL	
			Escherichia coli	ϕ= 19.4 ± 1.2 mm, MIC: Not determined	
Seeds	Hydro-methanolic extract	Mirodilution	A panel of gram positive and gram negative bacteria	Best results were obtained against *Bacillus cereus*: MIC and MBC lower than ampicillin	(19)
	Hexane extract	Disc-diffusion		IZ ϕ at 1 g extract/mL:	(46)
			Bacillus sp (CIP 104717)	ϕ = 10 ± 2 mm	
			Bacillus cereus (ATCC 33019)	ϕ = 12 ± 1 mm	
			Listeria ivanovii (ATCC 19119)	ϕ = 9 ± 2 mm	
			Staphylococcus aureus (ATCC 25923)	ϕ = No effect	
			Citrobacter freundii (ATCC 8090)	ϕ = 8 ± 2 mm	
			Escherichia coli (CIP54127)	ϕ = 10 ± 1 mm	
			Salmonella sp	ϕ = No effect	
	Ethyl acetate extract	Disc-diffusion		IZ ϕ at 1 g extract/mL:	(46)
			Bacillus sp (CIP 104717)	ϕ = 16 ± 2 mm	
			Bacillus cereus (ATCC 33019)	ϕ = 17 ± 3 mm	
			Listeria ivanovii (ATCC 19119)	ϕ = 14 ± 2 mm	
			Staphylococcus aureus (ATCC 25923)	ϕ = 10 ± 2 mm	
			Citrobacter freundii (ATCC 8090)	ϕ = 14 ± 2 mm	
			Escherichia coli (CIP54127)	ϕ = 13 ± 2 mm	
			Salmonella sp	ϕ = 18 ± 4 mm	
	Hydro-methanolic extract	Disc-diffusion		IZ ϕ at 1 g extract/mL:	(46)
			Bacillus sp (CIP 104717)	ϕ = 7 ± 1 mm	
			Bacillus cereus (ATCC 33019)	ϕ = 7 ± 2 mm	
			Listeria ivanovii (ATCC 19119)	ϕ = No effect	
			Staphylococcus aureus (ATCC 25923)	ϕ = No effect	
			Citrobacter freundii (ATCC 8090)	ϕ = 7 ± 1 mm	
			Escherichia coli (CIP54127)	ϕ = 7 ± 2 mm	
			Salmonella sp	ϕ = 7 ± 2 mm	

activities revealed in several studies by various methods, including 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging, xanthine oxidase, conjugated dienes inhibition, ferric reducing antioxidant power (FRAP), thiobarbituric acid reactive substances (TBARS), phospho-molybdenum complex (PMA), 2,2′-azino-bis 3-ethylbenzothiazoline-6-sulphonic acid (ABTS), and β-carotene bleaching assays. Results of published works concerning the antioxidant activity of *C. australis* are presented in Table 4.

El-Alfy et al studied the antioxidant potential of ethanolic and aqueous extracts, n-butanol fraction, and an isolated compound (2"-O-β-galactopyranosyl-vitexin) obtained from the leaves of *C. australis* by using the DPPH radical scavenging and xanthine oxidase inhibition methods (11). The tested samples exhibited a high antioxidant effect with an inhibition percentage ranging from 55.6 ± 2.10% (aqueous extract) to 84.8 ± 2.44% (isolated compound) for DPPH assay, and an IC_{50} ranging from 24.2 ± 1.95 µM (isolated compound) to 76.8 ± 2.90 µM (ethanolic extract) for xanthine oxidase inhibition test (11).

The antioxidant capacity of isolated compounds from the leaves of *C. australis* have also been reported by Filali-Ansari et al (20). In fact, vanillic acid, β-sitosterol-3-O-β-glucoside, and β-sitosterol have shown interesting antioxidant activities revealed by different methods (DPPH radical scavenging, inhibition of conjugated dienes, and TBARS assays), with the highest activity obtained for β-sitosterol using DPPH test (IC_{50}=10 µg/mL). Other studies have also demonstrated the antioxidant ability of the leaves of *C. australis*. Shokrzadeh et al (22) found an IC_{50}= 80.5 ± 1.73 µg/mL and a FRAP value = 595.98 µM Fe(II)/g for the hydroethanolic leaves extract of *C. australis* with DPPH and FRAP assays, respectively. Hydromethanolic leaves extract has also exhibited a high percent of inhibition of DPPH radical (88%), conjugated dienes (92%), and TBAR substances (87%) in the study carried out by Filali-Ansari et al (50). Similarly, Hammash et al (49) investigated the antioxidant activity of hydromethanolic leaves extract of *C. australis*; for which an IC_{50} of 0.1169 ± 0.003 mg/mL was found using DPPH assay, and an important antioxidant ability slightly dependent on the concentrations was recorded through the FRAP Assay. Moreover, in another study (51), the antioxidant effect of hydromethanolic leaf extract of *C. australis,* tested by DPPH radical scavenging and TBARS methods, was reported to increase significantly during the growing season until midsummer due to the seasonal variations in phenolic compounds. In the same context, Ota et al (6) have studied the antioxidant ability of aqueous and hydroethanolic extracts of *C. australis*'s leaves and mesocarp collected at different growth stages (end of June, end of October), and showed the highest antioxidant capacity of the extracts of leaves harvested in October. In addition, other works have examined the antioxidant potential of *C. australis*'s fruits. Aqueous and hydroacetonic extracts of *C. australis*' fruits showed respective FRAP values of 90.43 µm GAE/100 g FW and 33.91 µm GAE/100 g FW, inhibition percent of DPPH radical of 88.60 ± 5.69% and 54.24 ± 4.69%, and respective PMA values of 240.96 µm AAE/100 g FW and 60.24 µm AAE/100 g FW (48). The antioxidant effects of fruit extracts of *C. australis* have also been demonstrated by Bhatt et al using ABTS, DPPH radical scavenging, and FRAP assays (52). Concerning the antioxidant ability of *C. australis* seed extracts, high inhibition percentages were obtained by DPPH assay (86%), measurement of conjugated dienes (91%), and TBARS method (80%) (50). Moreover, Freitas et al (19) have found through studying the antioxidant potential of *C. australis* seed hydromethanolic extract an effective inhibition of DPPH radical, TBARS, and a significant protection of β-carotene from the free radicals generated from linoleic acid.

Furthermore, the hydroacetone extracts of *C. australis* fruits showed respective FRAP values of 90.43 µm GAE/100 g FW and 33.91 µm GAE/100 g FW, DPPH radical inhibition percentages of 88.60 ± 5.69% and 54.24 ± 4.69%, and PMA values of 240.96 µm AAE/100 g FW and 60.24 µm AAE/100 g FW, respectively (48).

As for bark extract of *C. australis,* Hammash et al reported an IC50= 0.117 ± 0.005 mg/mL for DPPH assay and slight differences in the antioxidant ability depending on the extract concentrations for the FRAP assay (49).

Anti-inflammatory activity

Semwal et al have investigated the anti-inflammatory potential of *C. australis*'s bark and fruit extracts, in addition to that of fatty acids obtained from *C. australis*'s fruit extract (21). The anti-inflammatory activity was evaluated on Swiss albino mice using carrageenan for the induction of edema in the hind paws of the tested animals. The obtained results showed that all plant samples used exhibited anti-inflammatory effects at different concentrations (100, 200, and 500 mg/kg). Besides, at the highest concentration (500 mg/kg), the inflammation inhibition was 44.26%, 45.90%, and 42.62%, respectively for bark crude extract, fruit crude extract, and fatty acids.

Wound healing activity

El Abbouyi et al (53) investigated the wound healing ability of ethyl acetate extract of *C. australis* seeds using incision model in rats. The assessment of wound healing effect was based on the measurement of wound area every two days until recovery. Results showed that the tested extract has induced a decrease of wound size in a time dependent manner. Besides, the healing potential of *C. australis's* extract was similar (41%, 63% and 94% after 2, 4 and 6 days, respectively) to that exhibited by standard ointment (40%, 64% and 97%), and was significantly higher than the control group (23%, 38% and 47%). Moreover, the healing effect of *C. australis* was positively correlated with its phenolic content.

Table 4. Antioxidant effects of *Celtis australis*

Parts used	Extracts/ isolated compounds	Methods used	Findings	References
Leaves				
	Ethanolic extract	- DPPH assay - Xanthine oxidase inhibition assay	- Percent inhibition = 67.2 ± 2.10 % - Median inhibitory concentration (IC50) = 76.8 ± 2.90 µM	(11)
	Aqueous extract	- DPPH assay - Xanthine oxidase inhibition assay	- Percent inhibition = 55.6 ±2.10% - IC50 = 70.2 ± 2.18 µM	(11)
	n-butanol fraction	- DPPH assay - Xanthine oxidase inhibition assay	- Percent inhibition = 70.3 ± 2.20% - IC50 = 27.2 ± 2.10 µM	(11)
	2''-O-β-galactopyranosylvitexin	- DPPH assay - Xanthine oxidase inhibition assay	- Percent inhibition = 84.8 ± 2.44% - IC50 = 24.0 ± 1.95 µM	(11)
	Vanillic acid	- DPPH assay - Measurement of conjugated dienes - TBARS method	- IC50 = 8.2 µg/mL - IC50 = 7.4 µg/mL - IC50 = 7.0 µg/mL	(20)
	β-sitosterol-3-O-β-glucoside	- DPPH assay - Measurement of conjugated dienes - TBARS method	- IC50 = 9.5 µg/mL - IC50 = 8.1 µg/mL - IC50 = 9.0 µg/mL	(20)
	β-sitosterol	- DPPH assay - Measurement of conjugated dienes - TBARS method	- IC50 = 10.0 µg/mL - IC50 = 8.1 µg/mL - IC50 = 8.5 µg/mL	(20)
	Hydro-ethanolic extract	- DPPH assay - FRAP assay	- IC50 = 80.5 ± 1.73 µg/mL -FRAP value= 595.98 µmol Fe(II) /g	(22)
	Hydromethanolic extract	- DPPH assay - Measurement of conjugated dienes - TBARS method	- Highest percent of inhibition: 88% - Highest percent of inhibition: 92% - Highest percent of inhibition: 87%	(50)
	Hydro-methanolic extract	- DPPH assay - FRAP assay	- IC50= 0.1169 ±0.003 mg/mL - Antioxidant ability slightly dependent on the concentration of the extract	(49)
	Hydromethanolic solution	- DPPH assay - TBARS assay - Measurement of conjugated dienes	The Antioxidant potential increase significantly during the growing season until midsummer.	(51)

Table 4. Continued

Parts used	Extracts/ isolated compounds	Methods used	Findings	References
Mesocarp and leaves	Aqueous extract Hydro-ethanolic extract	DPPH assay	The highest antioxidant ability of plant material extracts when harvested in October. For mesocarp; water extracts are richer in antioxidants than ethanol extracts. For leaves, ethanol extracts are richer in antioxidants than water extracts	(6)
Fruits				
	Water extract	- DPPH assay - FRAP assay - PMA assay	- Percent inhibition= 88.60 ±5.69% - FRAP value= 90.43 µmole GAE/100 g FW - PMA value= 240.96 µmole AAE /100 g FW	(47)
	Hydroacetonic extract	- DPPH assay - FRAP assay - Phospho-molybdenum complex assay (PMA)	- Percent inhibition = 54.24 ± 4.69 % - FRAP value= 33.91 µmole GAE/100 g FW. - PMA value = 60.24 µmole AAE /100 g FW	(47)
	Acidic methanol extract	- ABTS - DPPH - FRAP	- 0.8 mmol AAE/g FW - 17.49 mmol AAE/g FW - 17.49 mmol AAE/g FW	(52)
Seeds				
	Hydromethanolic extract	- DPPH assay - Measurement of conjugated dienes - TBARS method	- Highest percent of inhibition: 86% - Higher percent of inhibition: 91% - Higher percent of inhibition: 80%	(50)
	Hydromethanolic extract	- DPPH assay - TBAR assay - β-Carotene test	Effective inhibition of DPPH, TBARS, and protection of β-carotene from the free radicals generated from linoleic acid	(19)
Bark	Hydro-methanolic extract	- DPPH assay - FRAP assay	- IC50= 0.117 ± 0.005 mg/mL - Antioxidant ability slightly dependent on the concentration of the extract	(49)

TBARS:Thiobarbituric acid reactive substances; DPPH: 2,2-diphenyl-1-picrylhydrazyl; ABTS: 2,2'-azino-bis 3-ethylbenzothiazoline-6-sulphonic acid; FRAP: Ferric reducing antioxidant power; GAE: gallic acid equivalent; AAE: acid ascorbic equivalent; FW: fresh weight;

Hepatoprotective activity

The hepatoprotective effect of *C. australis* hydroalcoholic extract was investigated by Shokrzadeh et al (22) using mice as an animal model for the *in vivo* study. The hepatotoxicity was induced by intraperitoneal injection of carbon tetrachloride (CCL4) at 0.5 mL/kg to mice after pretreatment with the extract at different concentrations (200 and 400 mg/kg). The assessment of the hepatoprotective activity of the tested extract was achieved through the determination of several biochemical parameters, including aspartate aminotransferase (AST), alkaline phosphatase (ALP), and alanine aminotransferase (ALT), in addition to histopathological studies. The results showed a significant reduction of all parameters when compared to control group. Moreover, histopathological analysis presented strong evidence for biochemical tests. Other plant extracts were found able to exert a potential hepatoprotective effect, such as the hydroalcoholic extract of *Teucrium polium* (54). The hepatoprotective activity of plant extracts was reported to be related to their phenolic compounds (55).

Analgesic activity

Semwal et al (21) have investigated the analgesic activity of *C. australis* bark and fruit extracts, in addition to that of fatty acid of fruit extract, by measuring the writhes induced in mice following acetic acid injection. The samples used at different concentrations (100, 250, and 500 mg/kg) were active when compared to the negative control group. Moreover, the higher concentration of bark crude and fruit crude extracts and of fatty acids (500 mg/kg) exhibited respective analgesic activities of 59.28%, 63.22%, and 45.79%, indicating an interesting analgesic potential of *C. australis*.

Cytotoxic activity

The cytotoxic activities of aqueous and ethanolic extracts of *C. australis*'s leaves were investigated by El-Alfy et al (11) using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) colorimetric assay. The cell lines examined in this study were: human hepatocellular carcinoma (HEP-G2), colon carcinoma (COLO 205), leukemia carcinoma (CCRF-CEM), ovary carcinoma (NIH: OVCAR) and gastric carcinoma (NCI-N87). The obtained results showed that the most sensitive cells were HEP-G2, COLO 205, and NCI-N87, followed by NIH: OVCAR. Furthermore, the ethanolic extract of *C. australis* was more effective against COLO 205, while the aqueous extract of this plant exhibited the highest activity toward HEP-G2. The cytotoxic activity of these extracts could be related to their richness in bioactive compounds (6,11,15,20). Furthermore, using ultra-high-performance liquid chromatography (Ultra-HPLC), aqueous extract of *C. australis* leaves contained a potential phenolic acid: 'gallic acid' (6). This compound exhibited a high anticancer effect against different cell lines, such as Jurkat cell line (54), breast cancer cells (55), and cervical cells (56). The activity of gallic acid was attributed to its ability to down-regulate the expression of molecular pathways involved in cancer progression (57).

Conclusion and perspectives

This review summarizes and lists the different ethnomedicinal uses, phytochemistry, and biological properties of an important medicinal plant: *C. australis*.

In fact, different parts of this promising plant have been reported, according to the ethnomedicinal studies, to treat diverse diseases mainly digestive tract, genito-urinary, dermatologic, osteo-articular, and respiratory ailments. Moreover, scientific works have demonstrated the richness of *C. australis* with bioactive compounds (flavonoids, terpenoids, anthocyanins), as well as its high pharmacological potential revealed by its antimicrobial, antioxidant, and anti-inflammatory activities, cytotoxicity, analgesic, hepatoprotective, and wound healing properties. Such properties should be more investigated through preclinical and clinical trials, so that new safer drugs with little or no side effects can be developed later from extracts or isolated compounds of *C. australis*. In addition, to verify the innocuity of this plant, various toxicity tests (acute, sub-acute, and sub-chronic assays) need to be performed.

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Authors' contributions

KB carried out data collection, literature survey, and prepared the first draft of the manuscript. SIK supervised the research. KFB supervised the research and improved the manuscript.

Conflict of interests

The authors declare no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication etc) have been completely observed by the authors.

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