A panoramic review on ethnomedicinal, therapeutic, phytochemical, and advance attributes, of the genus *Ziziphus* Mill., native to Pakistan

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Review

Abstract

Background: Medicinal plants have gained prime importance in treating several fatal diseases, such as cancer, diabetes, and eczema, because they are a rich source of bioactive phytochemicals and a safer alternative to synthesized chemical compounds. Genus *Ziziphus* Mill. belongs to the family Rhamnaceae, which comprises 100 accepted plant species and is well known for multipurpose applications such as food, fodder, fuels, medicine, timber, alcohol, cosmetics, poison, etc. Six species of the genus *Ziziphus* are indigenous to Pakistan, famous as *Ziziphus nummularia* (Burm.f.) Wight & Arn., *Ziziphus mauritiana* Lam., *Ziziphus jujuba* Mill., *Ziziphus spina-christi* (L.) Desf., *Ziziphus rugosa* Lam., *Ziziphus oxyphylla* Edgew.

Method: Several search engines and online databases, including Sci-hub, PubMed, Google Scholar, Flora of Pakistan, research gate, and Science Direct, were used to perform an exhaustive literature survey for this review. Both original research studies and relevant review articles done till 2022 were included.

Result: These species have been used in traditional and Ayurveda medicine to treat diseases like fever, skin infections, urinary problems, diabetes, etc. Numerous components of *Ziziphus* species have been found, alkaloids, flavonoids, phenols, terpenoids, and organic acids, to exhibit a variety of biological properties, including anticancer, antimicrobial, anti-hair fall, antinociceptive, antipyretic, larvicidal, and anti-diabetic actions.

Conclusion: This review demonstrates the phytochemical composition, traditional uses, pharmacological properties, and nanoparticle-based activity of the genus *Ziziphus* and lays down a scientific foundation for further investigation on the usage of *Ziziphus*. Moreover, this review indicates that jujube has a hair growth effect because of its high nutritional value and pharmacological activities.

Keywords: Cancer; Ethnobotany; Nanoparticles; Pharmacology; Phytochemical; *Ziziphus.*

Background

Plants have been used as remedies since immemorial times (Tripathi *et al.* 2019).The plant kingdom has at least 250,000 species, of which only 10% have been investigated for potential pharmaceutical uses (Muhammad *et al.* 2022). Any plant with chemicals having therapeutic-potential in its one or more parts and have been used in producing plant-based drugs is referred to as a medicinal plant. Active ingredients of medicinal plants have been used in drug discovery known as phytochemicals and plant secondary metabolites (Odieka *et al.* 2022). These Phytochemicals build the skeletal framework of Phytomedicine, also beyond 25% of the manufacturing of drugs relies on phytochemicals (Yeshi *et al.* 2022). Biologically, Phytomedicine is the primary source of active compounds. Additionally, the scientific community and clinicians in contemporary drug research have taken cognizance of their nontoxic effect on healthy cells and improved toleration (Najmi *et al.* 2022). Indeed, many drugs used today are based on natural plant sources.

Genus *Ziziphus* belongs to the family Rhamnaceae and consists of evergreen or deciduous trees and shrubs in warm, temperate, tropical, and subtropical regions of Asia, Europe, Pakistan, India, China, Iran, Russia, middle east (Riaz *et al.* 2021, Aafi *et al.* 2022). Approximately the genus comprises 100 plant species, including shrubs and trees. (Uddin *et al.* 2022). Leaves of *Ziziphus* plants have prominent veins and are fragrant. At the same time, flowers are small in size and yellow to green in color (Stoli & Stanica, 2021). The fruit has a color range from yellow to red. Economically, it is a very important fruit bearing plant genus. Almost 5425 acres of land are covered with jujube orchards in Pakistan, producing 28 thousand tons of the fruit annually (Uddin *et al.* 2021). Moreover, *Ziziphus mauritiana* and *Ziziphus jujuba* have tasty fruit assurance as a food cash crop, especially in the desert region of Pakistan. Fruit is consumed in dried and fresh form due to its sweet taste, nontoxic nature, and rich source of energy (Sakna *et al.* 2022). Fruit contains proteins, carbohydrates, vitamins, minerals, and organic acids. In addition, it contains polyphenols, flavonoids, terpenoids, anthocyanins, alkaloids, and carotenoids (Aafi *et al.* 2022).

The land of Pakistan is rich in medicinal flora, and the mainstream people depend on plant-based medicine to treat various diseases (Saeed *et al.* 2022). In Pakistan, there are six species, *Ziziphus jujuba, Ziziphus nummularia, Ziziphus mauritiana, Ziziphus spina-christi, Ziziphus oxyphylla, Ziziphus rugosa* (Muhammed *et al.* 2022). In the traditional medicinal system of Pakistan, the *Ziziphus* plant is commonly used to treat headaches, liver diseases, anemia, urinary infections, diabetes, dermatitis, fever, pharyngitis, digestive disorders, blood diseases, hypertension, rheumatism, bronchitis, and insomnia (Rauf *et al.* 2016, Beg *et al.* 2020, Muhammad *et al.* 2022).

Previous publications have included genus *Ziziphus*'s chemical constituents and biological activities. This review will provide updated and comprehensive information on the traditional uses, pharmacological effects, and phytochemical composition of *Ziziphus* plant species in Pakistan. Further, it includes compilation and critical examination of the pharmacological effects of the biosynthesized nanoparticles of *Ziziphus* plants to support their therapeutic potential and highlight the prospects for future investigation.

Plant habit, distribution & morphological description

Ziziphus mauritiana is a tropical fruit-bearing tree known as Ber, Indian jujube, Desert apple, and Indian plum. It is native species of the Indo-Pak subcontinent (Prakash *et al.* 2021). It reaches a height of 15 meters with small spiny branches (Vinod *et al.* 2022). *Ziziphus nummularia* is a small thorny shrub reaching 6–8 feet in height and distributed in Pakistan, India, and China (see Fig. 1). It is famous for various vernacular names such as Jharberi and Bhor, which are more common. *Ziziphus jujuba* is famous as Chinese jujube or Chinese date (Wu *et al.* 2019). It is a tree in habit with 20 to 30 feet in height, ovate leaves, aromatic flowers, and round seeds (see Table. 1). *Ziziphus spina-christi* is originally a Sudanese tropical tree, about 20 m tall, commonly called Christ's thorn (Maaiden *et al.* 2019). *Ziziphus oxyphylla* is a small size glabrous tree (Saeed *et al.* 2022). *Ziziphus rugosa* is a with large elliptic leaves, flowers that are paniculated, and white drupe fruit. Primarily found in dry deciduous woodlands. It is a 3-6 m tall small tree or large straggly thorny evergreen shrub. The tree's relatively firm, reddish-colored wood has five obovoid-globose or sub-globose fruits ranging from orange to black and is 9 to 12 mm long and 8 to 10 mm wide (Manjunatha *et al.* 2020).

Table 1. Plant habit, morphological description and distribution of the genus *Ziziphus.*

Plant Species	Habit	Morphological description	Distribution	References
Ziziphus mauritiana	Evergreen Shrub Tree.	**Leaves:** Alternate, ovate. **Flower:** greenish-white with five petals. **Fruit:** soft, fleshy,drupe.	**Punjab** (Bahawalpur, Multan, D. G. Khan, Attock, Chakwal, and Mianwali districts). In **KPK,** Karak, Bannu, Kohat, Swabi, Charsada, Swat, Peshawar, Dir, and Malakand.& In **Sindh** (Multan, Nawab Shah, Hyderabad, Karachi, etc.).	Ashraf *et al.* 2015, Prakash *et al.* 2020, Uddin *et al.*2021, Mohankumar *et al.* 2022.
Ziziphus nummularia	Shrub	**Leaves:** Ovate-orbicular, tomentose with serrate margin & rounded base. **Flower:** pale yellow, 6–8 mm, axillary cymes inflorescence. **Fruit:** drupes of brown to orange, round.	Distributed all over the Pakistan.	Pandey *et al.* 2010,Uddin *et al.*2021.
Ziziphus jujuba	Tree	**Leaves:** Ovate, adaxially green blades, while adaxially dark green & papery. **Flower:** bisexual, glabrous , pentamerous, **Fruit:** drupe, red–purple color.	Khyber Pakhtunkhwa, Azad Jammu & Kashmir, and Gilgit Baltistan.	Liu *et al.*2021,Uddin *et al.*2021.
Ziziphus spina-christi	Tree	**Leaves:** small & shiny **Flower:** cluster, 3 mm in diameter, greenish. **Fruit:** 1cm wide Fruit	Punjab, Khyber Pakhtunkhwa, Sindh, & Balochistan.	Asgarpanah *et al.* 2012,Almalki *et al.* 2017, Uddin *et al.* 2021.
Ziziphus rugosa	Tree or Shrub	**Leaves:** subcordate, big elliptical leaves. **Flower:** Paniculated. **Fruit:** white, glabrous, drupe.	Sindh (Hyderabad).	Bulbul *et al.* 2016,Uddin *et al.* 2021.
Ziziphus oxyphylla	Tree	**Leaves:** cordate base, cordate, acuminate, glabrous, ovate to lanceolate. **Flower:** glabrous, fascicled, cymes. **Fruit:** ovoid, flattened pyrene, red-orange-black	Khyber Pakhtunkhwa Swat, Buner, Dir Malakand, Mardan, Kohistan, Hazara, and also in Sindh, Punjab, and Balochistan.	Ahmed *et al.* 2017,Zahoor *et al.* 2021,Uddin *et al.*2021.

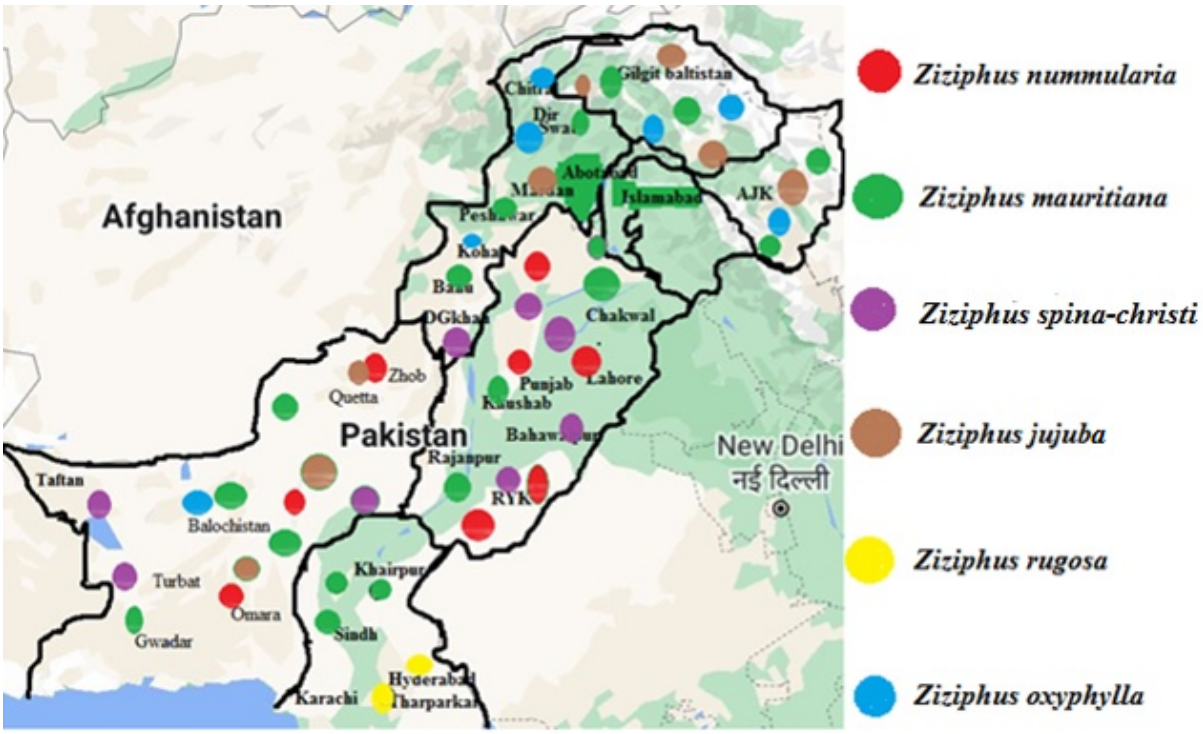

Figure 1. Map of Pakistan showing where various Ziziphus species are found. The image was manually altered after being downloaded from Google Earth Map. The locations of the six stated Ziziphus species that can be found in Pakistan are indicated by the various hues (Mohammed *et al.* 2022.)

Traditional Uses

Ziziphus mauritiana is known for its application in traditional medicine, such as inflammations, asthma, depression, allergies, insomnia, indigestion, and ulcers (Amin *et al.* 2019). *Ziziphus nummularia* fruits are eaten fresh and dried, and their juice is taken as a drink (Uddin *et al.* 2020). Leaves are used for the treatment of infectious diseases and cancer as well. Plants contain bioactive constituents like tannins, steroids, glycosides, and alkaloids used in traditional medicines for colds, anemia, indigestions, inflammation, diarrhea, and bronchitis (Mesmer *et al.* 2021). *Ziziphus jujuba* is in Chinese medicine. Jujuba fruit increases appetite and treats fatigue and diarrhea (Aafi *et al.* 2022). The leaves, bark, fruits, and seeds have pharmacological properties, including neuroprotective, cardioprotective, and hepatoprotective activities (Alhassan *et al.* 2019). It also has health-promoting effects and anti-aging properties. *Ziziphus spina-christi* leaves are used in folk medicine and as a soap for dermatitis (Nazemoroaya *et al.* 2022). Biological reports demonstrated that all parts are used in various remedies such as urinary disorders soothing, weakness, anodyne, typhoid, emollient, liver complaints, detoxification, obesity, astringents, toothache, and diarrhea (Alwossabi *et al.* 2022, Abdulrahman *et al.* 2022). *Ziziphus oxyphylla* plant parts are used in folk medicine as an anti-inflammatory, analgesic, and antidiabetic agent. It is also used in liver ailments and hypertension (Abdullah *et al.* 2022, Shaukat *et al.* 2022, Saeed *et al.* 2022). *Ziziphus rugosa* has been regarded as a plant with nutrients and therapeutic properties. Its fruit, roots, and stems are used medicinally to treat ulcerative tongue, carbuncle, syphilis, menorrhagia, and dysentery (Hossain *et al.* 2015). Traditionally, cheroots are prepared from dried leaves. The bark is used in beverage alcohol and its Paste to cure gastric disorders. Fruit is edible and nutrient-rich (Hassan *et al.* 2021). However, Flowers and bark are used as an astringent, antidiarrheal, menorrhagia, hemorrhage, antifungal, antidiabetic, and anti-inflammatory (Manjunatha *et al.* 2020).

Table 2. Ethnomedicinal information of genus *Ziziphus*.

Plant names	**Common name**	**Images**	**Plants part used**	**Mode of utilization**	**Medicinal uses**	**References**
Ziziphus nummularia (Burm. f.) Wight & Arn.	Mala, kokni ber		Leaves, Flower, fruits, roots, bark,	Fresh, dried, infusion decoction, juice, Powder, paste	Infectious diseases, cold, anemia, indigestions, inflammation, diarrhea, bronchitis.	Uddin *et al.* 2020, Mesmer *et al.* 2021.
Ziziphus jujuba Mill.	Chinese date, Chinese jujube.		Leaves, fruit, bark ,seeds	Powder, paste	Appetite, treat fatigue, diarrhea anti-aging, neuroprotective, cardio protective& hepatoprotective.	Aafi *et al.* 2022, Alhassan *et al.* 2019.
Ziziphus mauritiana Lam.	Ber, Indian jujube		Leaves fruit, bark	Fruit raw eat , dried powder	Inflammations, asthma, depression, allergies, insomnia, indigestions, ulcers.	Amin *et al.* 2019
Ziziphus spina-christi (L.)Willd.	Nabag		Leaves, bark roots, fruits, seed	Decoction, Paste, powder,	Dermatitis urinary disorders soothing, weakness, anodyne, typhoid, emollient, liver complaints, detoxify, obesity, astringents, toothache, diarrhea	Nazemoroaya *et al.* 2022; Alwossabi *et al.* 2022, Abdulrahman *et al.* 2022.

Ziziphus oxyphylla Edgew.	Elanai		Leaves flower bark,	Raw Fruit, paste	Diabetes, liver , skin, tongue, carbuncle, syphilis, menorrhagia, and dysentery diseases.	Abdullah *et al.* 2022, Shaukat *et al.* 2022, Saeed *et al.* 2022.
Ziziphus rugosa Lam.	Churan		Leaves, flower, bark,	Powder, paste	Diabetes, liver, skin, tongue, carbuncle, syphilis, menorrhagia, Dysentery hypertension, rheumatism.	Manjunatha *et al.* 2020, Hossain *et al.* 2015, Hassan *et al.* 2021.

Pharmacological properties of *Ziziphus*

Many studies have been conducted in recent years to look into and highlight *Ziziphus* plants' biological and pharmacological properties (see Fig. 2).

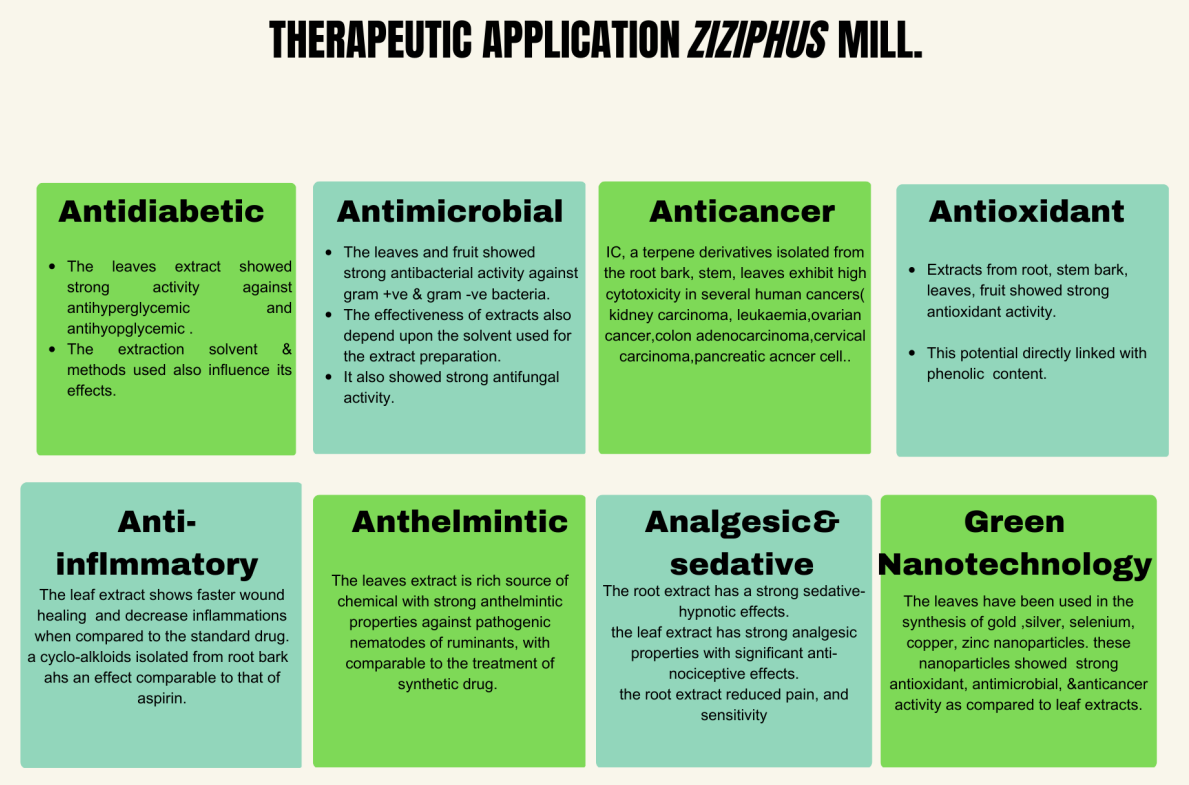

Figure 2. Therapeutic Applications of the genus *Ziziphus* Mill.

Anti-diabetics

Diabetes mellitus is a deregulation of blood glucose-type chronic diseases and is more common in developing countries (Mesmer *et al.* 2021). In the modern era, because of natural compound availability, low price, and few side effects, herbal therapies are preferable in diabetes patients (Mesmer *et al.* 2022). Conventionally, many plants have been employed to cure diabetes (Prathyusha & Velraj, 2022). Regarding antidiabetic potential, the aqueous and methanolic fractionated extract of *Ziziphus nummularia* were treated with an alpha-amylase process. Results revealed that all the fractionated extracts showed pronounced antidiabetic efficacy (Dubey *et al.* 2017). Prathyusha and Velraj investigated leaves antidiabetic potential in *Ziziphus mauritiana*'s methanol extracts under *in vitro* conditions. The results revealed that extracts showed alpha-glucosidase and alpha-amylase inhibitory activity, and due to the presence of high phenol content, *Ziziphus mauritiana* exhibited a prominent effect. (Prathyusha & Velraj, 2022).

Al-Ghamdi. (2017) investigated the hypoglycemic and antidiabetic activities of *Ziziphus spina-christi.* Methanol, ethyl acetate, n-butanol, and aqueous extract fractions on rats. The antidiabetic and hypoglycemic potential increases with the continuous increase in the doses of all tested fractions (Al-Ghamdi *et al.* 2017). In the latest study, leaves of *Ziziphus jujuba* have been used as methanol extract and isolated phenolic compounds. These phenolic compounds' antidiabetic activity has been evaluated using alpha-amylase and alpha-glucosidase. Results demonstrated solid antidiabetic activity in these compounds (Mahmoud *et al.* 2022).

In a recent study, Zahoor *et al.* 2021 identified some bioactive compounds from the root of *Ziziphus oxyphylla* named p- coumaric acid (V)and 3,4-dimethoxy benzoic acid(VI). The compounds (V)exhibited the highest inhibition against alpha-amylase, while alpha-glucosidase was more efficiently inhibited by compounds (VI)(Zahoor *et al.* 2021). All these data suggest the importance of the genus *Ziziphus* as a source of bioactive compounds, especially against diabetes (Mahmoud *et al.* 2022). All mentioned plants had significant antidiabetic potential and held future potential as nutraceuticals in treating diabetes and various free radicals-dependent ailments. Moreover, the six compounds have been isolated from the crude extract of *Ziziphus rugosa,* which showed various ranges of alpha–glucosidases inhibitory activity. Betulinic acid displayed potent yeast alpha–glucosidases inhibitory activity,

whereas lyoniresinol and (+)-lyoniresinol-3α-O-β-D-glucopyranoside showed less inhibition against the rat intestine. This molecular docking result revealed that betulinic acid has carboxyl species inhibiting yeast alpha glucosidases (Sichaem *et al.* 2017).

Table 3. Antidiabetic potential of the *Ziziphus* species.

Plant Species	Sample analyzed	Experimental model	Observation	References
Ziziphus nummularia (Burm. f.)Wight & Arn.	Aqueous, methanolic, & n-butanol, saponins extract	Alpha Amylase	Saponins showed maximum inhibition of 88.38 %, more active than other extracts. The IC50 values were 114.16 g/ml to 137.87µg/ml confirming 50% enzyme inhibition.	Dubey *et al.* 2017
Ziziphus jujuba Mill.	Ethanolic fruit extract	Male adult Albino rats	Constant supplementation of extract (4%) for 14 days produced a momentous decrease in blood glucose.	Jamshidi *et al.* 2014
Ziziphus mauritiana Lam	Methanol extracts of Seed and stem bark.	Swiss albino male Rat	Showed hypoglycemic activity in a dose-dependent manner, with 44.27% blood glucose reduced after 3 h, at 400 mg/kg body weight dose.	Akanda *et al.* 2021
Ziziphus spina-christi (L.)Willd.	Seed embryo extract	Male albino Diabetic rat	Oral administration of the extract caused a significant reduction in blood glucose level with significant raise in insulin. insulin release from the remnant β-cells, inhibiting glucagon secretion from alpha-cells paving way to amoriliation in the animal.	Mohammed *et al.* 2019
Ziziphus oxyphylla Edgew.	Crude and methanol extracts of stem	Male albino rat **Methods:** α-glucosidase ,α-amylase	Methanol extract reported a slight inhibition of 220 and 180 µg/ml with α-glucosidase, α-amylase respectively.	Khan *et al.* 2020
Ziziphus rugosa Lam.	Crude ethanol extract of bark	*Yeast,* rat intestine **Methods:** *α-glucosidase inhibition*	The active compound betulinic acid displays strong antidiabetic potential with IC_{50} 16.3 µg.	Sichaem *et al.* 2017.

Anti-Microbial

Antibacterial

The ability of compounds to limit the growth of microorganisms like bacteria, fungi, and viruses under their influence is known as antimicrobial activity. Ahmadi *et al.* 2022 evaluated the antimicrobial activity of *Ziziphus nummularia* fruit extract using the microdilution method against different strains of gram-positive and gram-negative bacteria. GC-MS analysis confirmed the antimicrobial compounds presence, which showed remarkable results against foodborne pathogens (Ahmedi *et al.* 2022). A study was undertaken (Nurrahma *et al.* 2022) to determine the antibacterial efficiency of *Ziziphus mauritiana* by using the agar well diffusion method and MIC test, and the ethanolic extract of *Ziziphus mauritiana* leaves showed strong antibacterial potential against ten different bacteria samples. A study in 2022 by Dilshad *et al.* confirmed the presence of various phytochemicals in *Ziziphus jujuba* by chemical analysis of ethyl acetate and ethanol extract. Ethyl acetate fraction gave potent results in

inhibiting the gram-positive and gram-negative bacteria (Dilshad *et al*. 2022). In a recent study, various fractionated extracts prepared using leaves of *Ziziphus oxyphylla* were screened for their antibacterial potential against bacterial strains. The result revealed that methanol extract exhibited higher activity against *Bordetella bronchiseptica, Staphyllococcus aureus, Pseudomonas aeruginosa,* and *Micrococcus luteus*. It was also found that methanol extract has significant antibacterial activity so it may be used for isolation (Naheed *et al*. 2022). In the latest study, Ads *et al*. 2022, isolated and partially purified the bioactive components from the crude ethanol extract and solvent fractions of *Ziziphus spina-christi* the stem bark. Results demonstrated that the n-butanol fraction has greater antibacterial efficiency and may be used as an antibacterial candidate in future clinical and pharmaceutical applications. It was found that solvent and aqueous extract from leaves and bark of *Ziziphus rugosa* showed antibacterial activity due to various phytochemicals. *In vitro*, the study by disc diffusion method was done, and leaf extract of acetone and methanol was reported as a maximum antibacterial activity with a 15mm inhibition zone (Chandukishore *et al*. 2019).

Antifungal

El-shahir *et al. (2022)* confirmed the presence of bioactive compounds in *Ziziphus spina-christi* by using gas chromatography (GC) and High-performance liquid chromatography (HPLC). These biologically active compounds obtained from leaves and fruits of *Ziziphus spina-christi* demonstrated potent results *in vitro* fungal activity against the fungal strain *Alterania alternata*. Naz *et al*. (2021) demonstrated the antifungal activity using the agar slant technique against *Rhizopus stolonifera, Aspergillus niger,* and *Aspergillus flavus. Ziziphus mauritiana* leaves extract showed significant results against R. stolonifera than other strains *A. niger* and *A. flavus*. Concerning antifungal activity, ethanolic extract of *Ziziphus nummularia* exhibited strong efficacy against *Candida albicans, Aspergillus flavus, Aspergillus niger,* and *Trichophyton rubrum*. The result demonstrated that ethanol fraction is more effective than the aqueous fractioned extract, and the susceptible fungi were *T. rubrum* (Gautem *et al*. 2011). Ahmad *et al*. 2016 evaluated the antifungal activity attribute of crude extract of leaves and roots of *Ziziphus oxyphylla* using the serial dilution method in microtiter plate against *Aspergillus fumigatus, Trichophyton rubrum, and Candida albicans*. The result revealed that plant crude extract and its fraction showed no antifungal activity. Rajai *et al*. (2020) performed the antifungal activity of seed and pulp ultrasonic extract of *Ziziphus jujuba* against the *Aspergillus niger, Rhizopus stolonifera*, and *Penicillium expansum*. Results revealed that the extract had not shown any antifungal efficiency but enhanced the fungal strain because of the presence of carbohydrates in the plant extract. All the data mentioned above on the genus *Ziziphus* showed that the plant could be a potential basis for novel antimicrobial candidates. All these findings may be helpful in the search for new drug discoveries to decrease antimicrobial resistance.

Table 4. Antimicrobial properties of the *Ziziphus* species.

Plant Species	**Sample analyzed**	**Experimental model**	**Observation**	**References**
Antibacterial				
Ziziphus nummularia (Burm.f.)Wight & Arn.	Methanol, hexane, the aqueous fraction of Fruit, leaves, bark	**Strains**: E. Coli, S. aureus, E. coli **Method:** Agar well diffusion.	The methanol fraction of fruit showed good antimicrobial activity.	Beg *et al*. 2016
Ziziphus jujuba Mill.	Ethanolic and aqueous extract of Leaves	**Strains:** *Escherichia coli, Staphloccoccus aureus, Klebsiella pneumoniae* **Method:** Disc diffisuion	The result showed that leaves could be used as good antibacterial agents because of their phytochemical composition.	Alhassan *et al*. 2019
Ziziphus mauritiana Lam.	Solvents extract from Leaves	**Strains:** *Vibrio parahemolyticus* **Method:** Disc diffusion, MIC, MBC	Ethyl acetate extract was reported as the highest antibacterial against vibrio.	Jain *et al*. 2019

Ziziphus spina-christi (L.)Willd.	Leaves, fruit, bark extracts.	**Strains;** *Streptococcus mutans* (dental cement) **Method:** Disc diffusion	Efficacy of each extract different Leaves extracts showed potent antibacterial activity than other sample extracts.	Mathew *et al.* 2020.
Ziziphus oxyphylla Edgew.	Compounds from stem and root Oxyphylline B Oxyphylline C	**Strains:** *Escherchia coli, Bacillus subtilis Shigella flexeneri Staphylococcus aureus, Pseudomonas aeruginosa Salmonella typhi* **Method:** Disc diffusion	Comparatively, Oxyphylline B showed better antibacterial activities	Kaleem *et al.* 2012
Ziziphus rugosa Lam.	Hexane, chloroform, and methanol extracts of bark and leaf.	**Strains:** *Staphylo-coccus aureus ,Escherichia coli* **Method:** Agar well diffusion	Leaves methanol extract potent against test organism.	Vinakaya *et al.* 2009
	Aqueous extract of *Ziziphus rugosa*	**Strain:** *Lactobacisllus acidophilus,S. mutansm,Bacillus subtilis, Acinetobacter baumannii,Raoultella ornithinolytica, Streptococcus thoraltensis* **Method:** Agar well diffusion	The aqueous extract was more effective against the performed biofilm formation. It also showed potent antibacterial activity.	Al-makhzomi *et al.* 2020
Antifungal				
Ziziphus spina-christi (L.)Willd.	Leaves methanol extract from localities of Tozeur Dgueche, Metlaoui, provenance.	**Strains:** *Candida albicans, Candida sake, Candida parapsilosis* ***Method.*** Agar well diffusion**.**	Tozeur leaves extract could be a good candidate for fungal infection.	Elaloui *et al.* 2022
Ziziphus jujuba Mill.	Aqueous and ethanolic extract of mesocarp.	**Strains:** *Exophiala dermatitidis, Saprochaete clavata, Rhodotorula mucilaginosa, Candida albicans, Aspergillus fumigatus, Candida parapsilosis, Fusarium dimerum,Aureobasid ium pullulans* **Method:**Broth dilution	No antifungal activity was reported.	Visnjevec *et al.* 2019.
Ziziphus mauritiana Lam.	Crude methanolic extract	**Strains:** *Candida albicans* **Methods:** Disc diffusion.	Showed antifungal activity with a 10mm zone of inhibition and MIC: 125 µg/mL).	Ghasham *et al.* 2017

Ziziphus oxyphylla Edgew.	Crude methanolic and various fractions	**Strains:** *Candida albicans, Aspergillus flavus, Microsporum canis, Fusarium solani, Candida glaberata* **Method:** Agar tube dilution	No significant result	Nasir *et al.* 2011

Anticancer

Over the past 25 years, about 65% of new anticancer medications have come from natural sources. These naturally occurring chemicals were produced in vast amounts, and their novel analogs were created through chemical synthesis (either partial or whole) (Newman *et al.* 2020). Tabassum *et al.* 2021 planned research to explore the anticancer potential of methanolic extracts of *Ziziphus mauritiana* and *Triticum aestivum*. The highest crude extracts percentage was observed with *Ziziphus mauritiana* on breast and ovarian cancer cell lines. MTT assay and Incucytes imaging analysis (live cell analysis) demonstrated that *Ziziphus mauritiana* extract had a more substantial anticancer potential against breast and ovarian cancer cells. Consequently, these extracts could be used as chemotherapeutics due to their low cost and easy accessibility. (Tabassum *et al.* 2021). Pancreatic Cancer (PC) is the fourth chief basis of all cancer-related deaths. Mesmer *et al.* 2021 have used an ethanolic extract of leaves of *Ziziphus nummularia* to treat human pancreatic ductal adenocarcinoma cells. Results revealed that the ethanolic extract of *Ziziphus nummularia* possesses anti-proliferative and anti-invasive action on the Capen -2 of PC cells. Moreover, the extract suppressed nitric oxide levels and VEGF(Vascular endothelial growth factor) and reduced ovo angiogenesis. Results suggested that *Ziziphus nummularia* extract can weaken the malignant phenotype of Capan-2 by stopping marks of PC. Evidence demonstrated that *Ziziphus nummularia* showed anticancer potential, which may lead to the discovery of novel anticancer compounds (Mesmer *et al.* 2021). Concerning antitumor activity, polysaccharides extracted from *Ziziphus jujuba* seeds exhibit more significant potential against HeLa cells. Flow cytometry and Fluorescent microscopic reported that *Ziziphus jujuba* seed suppressed the spread of HeLa cells by apoptosis. It has been concluded that *Ziziphus jujuba* seeds are the best sources of antitumor polysaccharides (Wu *et al.* 2019). It is well established that *Ziziphus spina-christi* has potent cytotoxic effects on human cancer cell lines. With apoptotic induction, the G2M phase cell cycle is arrested and stimulates apoptosis in the SCC-9 cell line. Against oral cancer drug development, the seed of *Ziziphus spina-christi* may be a novel agent (Al Shahrani *et al.* 2021). However, the inclusive study is mandatory for additional characterization and purification of bioactive target compounds and *in-vivo* activity validations. Ahmed *et al* (2016) put forward a comparative study on the cytotoxicity of *Ziziphus oxyphylla* and *Cedrela serrata*. Fractionated leaves bark and root extract were applied on the MRC- 5 cell line. The CHCl3 fractions of *Ziziphus oxyphylla* roots, leaves, and the bark of Cedrela serrata were the ones that were the most toxic to MRC-5 cells. In contrast, the n-hexane fraction appeared more hazardous than the CHCl3 fraction solely for the *Cedrela serrata* leaves (Ahmed *et al.* 2016).

Table 5. Cytotoxic and anticancer studies on the genus *Ziziphus*.

Plant Species	**Sample Analyzed**	**Experimental Model**	**Pharmacological active**	**References**
Ziziphus nummularia (Burm. f.)Wight & Arn.	Ethanolic extract from the root bark	Female Swiss albino mice against Ehrlich ascites carcinoma	The dose decreased tumor volume, size, and cell count and increased body weight.	Ray *et al.* 2015
	Methanolic Fruit extract	Hela cells **Methods:** MTT assay.	Showed significant cytotoxicity.	Beg *et al.* 2016
Ziziphus jujuba Mill.	Aqueous Fruit extract	MDA-MB-468 cell line of breast cancer cell **Methods:** MTT assay.	Showed significant effect on NMU carcinogenesis and curing mammary tumors in humans.	Hoshyar *et al.* 2015
	Aqueous fruit extra	Cervical and breast cancer cell line **Methods:** MTT	Reported as an anti-tumor agent by apoptosis induction and inhibition of cell growth.	Abedini *et al.* 2016

Ziziphus mauritiana Lam.	Dichloromethane & methanol Root extracts	MCF-7 cell line **Method:** MTT assay	Exhibited significant anticancer activity	Batool *et al.* 2019
Ziziphus spina-christi (L.)Willd.	Leaves methanolic extract	Hepatocarcinoma in rats	Targeting oncogenes and oxidative stress Showed strong anticancer activity.	El Din *et al.* 2019
Ziziphus oxyphylla Edgew.	$Chcl_3$ fractions of Leaves, root extract	MRC-5 cell lines	Chloroform fractions of root leaves showed strong cytotoxicity with 5.1 and 18.99 IC50.	Ahmed *et al.* 2016

Anti-oxidant Activity

Human diseases, such as gastrointestinal, cancer, inflammatory disorder, and nervous and digestive diseases, are due to the overproduction of free radicals and reactive oxygen species (ROS). Concerning antioxidant activity, Uddin *et al.* (2020) evaluated the antioxidant activity of six different genotypes of *Ziziphus nummularia* (coded as ZNP01-06) fruit extract *in vitro* methods are mentioned in Table 4. The extract showed the highest antioxidant potential because of polyphenols, which may lead to new drug discovery (Uddin *et al.* 2020). It was confirmed that *Ziziphus jujuba* possesses polysaccharides which showed the highest antioxidant activity *in vitro* study. Results revealed that in functional foods, *Ziziphus jujuba* could be used as an antioxidant (Yang *et al.* 2021). In the latest study, Shady *et al.* 2022 investigated *Ziziphus mauritiana* fruit extracts' antioxidant activity using an *in-vitro* assay. The result reveals the potent antioxidant potential because of the presence of antioxidant compounds (Shady *et al.* 2022). Frequent studies have concentrated on plant-based antioxidant compounds and compared the leaves bark and root fractionated extract of *Ziziphus oxyphylla* and *Cedrela serrata*. The result demonstrated that ethyle fractions of *Ziziphus oxyphylla* and *Cedrela serrata* leaves barks showed the highest antioxidant IC50 < 10 mg/mL. Leaves and bark exhibited higher antioxidant activity than roots to neutralize free radicals that defend against many ailments (Ahmed *et al.* 2016). Previous studies on the *Ziziphus spina-christi* leaves extract in methanol, ethanol, and ethyl acetate showed suitable scavenging activities. Among all these fractions, ethyl acetate showed strong antioxidant properties compared to others. It was also confirmed that leaves contained high levels of phenols and flavonoids (Mohammed *et al.* 2019). Compared to other solvent extracts, the highest level of antioxidant activity was seen in ethanolic extracts of *Ziziphus spina-christi* roots. Compared to other antioxidant determination activities, Fe2+-chelating was the most effective test (0.24 IC 50 0.4). The second-highest test utilized to gauge the antioxidant activity of ZCR was the ABTS. This sensitivity to the Fe2+-chelating assay may support the safe application of ZCR. The IC50 levels went from 0.33 0.14 to 0.5 0.07 mg/ml, a slight reduction. Antioxidant response to DPPH was reduced, and IC 50 values ranged from 0.41 to 0.01 (EE) to 0.6 to 0.05 mg/ml (ACE) (Elaloui *et al.* 2021). It has been confirmed that the chloroform fraction of *Ziziphus oxyphylla* exhibited intense antioxidant activity compared to other studied soluble fractions. Further statistical results are mentioned in the table (Mazhar *et al.* 2015). Manjunatha *et al* demonstrated the potential radical scavenging activity of the ethanolic extract of *Ziziphus rugosa* bark. The DPPH experiment, at a 125 g/ml concentration, showed a more significant scavenging effect of 55.84% than other concentrations. At a concentration of 1000 g/ml exhibits a more significant scavenging effect than other compounds in the ABTS experiment (81.69%). Since high concentrations have the less scavenging effect, the DPPH assay demonstrates that the scavenging action is not dosage dependent. Moreover, the ethanolic extract has antiulcer effectiveness against stomach lesions. Reduced gastrointestinal volume, gastric ulcer index, and percentage protection are signs of the antiulcer action, as are decreased acid secretory parameters (such as total and free acid) (Manjunatha *et al.* 2020).In conclusion, the bioactive components and parts of the *Ziziphus* plant have shown substantial antioxidant efficacy both *in vitro* and in animal tests, suggesting their potential use in antioxidant therapy for chronic illnesses caused by ROS (reactive oxygen species).

Table 6. Analysis of *Ziziphus* species against oxidative stress.

Plants Species	**Sample analyzed**	**Methods**	**Pharmacological active**	**References**
Ziziphus nummularia (Burm.f.)Wight & Arn.	Fruit extract	DPPH	Result of Radical scavenging against ABTS (65.3 ± 1.74 µg/mL) and DPPH (67.03 ± 1.04 µg/	Uddin *et al.* 2020
		ABTS	mL) compared to ascorbic acid (68.7 ± 0.47 µg/mL).it reported	

			as strong antioxidant potential due to confirmed presence of polyphenols.	
Ziziphus jujuba Mill.	A neutral polysaccharide (HJP-1a)& three acid polysaccharides (HJP-2, HJP-3 and HJP-4).	In Vivo and in-vitro methods , ABTS,	The four isolated fractions, particularly HJP-2 in vitro and HJP-1a in vivo, demonstrated dose-dependent radical scavenging activity on ABTS+ radicals and lowering capacity as well as outstanding protective impact on H2O2-induced HepG2 cells and metronidazole-damaged zebrafish embryos.	Yang *et al*. 2021
Ziziphus mauritiana Lam.	Fruit extracts	hydrogen peroxide and superoxide radical scavenging	Three phenolic chemicals may be active, according to PASS computational calculations of antioxidant activity (Pa score > 0.5). Consequently, due to ZFE's antioxidant and anti-inflammatory properties, it may be an alternative treatment that aids in wound healing.	Shady *et al*. 2022
Ziziphus spina-christi (L.)Willd.	Aqueous, Methanolic, Ethanolic and Acetonic extract of roots.	DPPH,ABTS, Fe2+ - chelating	The highest level of antioxidant activity was seen in Ethanolic extracts with IC_{50} values ranged between 0.41 ± 0.01.	Elaloui *et al* . 2021
Ziziphus oxyphylla Edgew.	Chloroform ,n-butanol ,methanol, chloroform fractions of leaves barks.	DPPH	Ethyl acetate fraction of leaves showed strong antioxidants activity between the range of IC50 < 10-100 mg/mL.	Ahmed *et al*. 2016
	Chloroform,n-hexane, ethyl acetate, n-butanol	DPPH,FRAP	Chloroform fraction showed highest antioxidant with IC5013.20±0.27µg/mL, relative to standard, having 12.10±0.29µg/mL.	Mazhar *et al*. 2015
Ziziphus rugosa Lam.	Ethanolic extract of stem bark	ABTS ,DPPH	In DPPH and ABTS assays, the extract had a maximal radical scavenging efficacy of 55.84% and 81.69%, respectively.	Manjunatha *et al*. 2020

Anthelmintic Activity

Ruminants are significant targets of helminthic infections, which limit livestock production (Abrar *et al*. 2018). Synthetic anthelmintic drugs improperly administrated in animals possess many health hazards. Furthermore, invertebrates have developed resistance to these drugs (Mesmer *et al*. 2021). It is documented that *Ziziphus spina-christi* leaves extract showed anthelmintic potential against infection caused by *Eremophila papillata* in rats. Dose-dependent results reported that death decreases with increases in extract (Alzahrani *et al*. 2016). Authors found that *Ziziphus nummularia* The IC50 of this fraction was 13.20±0.27µg/mL, relative to butylated hydroxytoluene (BHT, a reference standard), having IC50 of 12.10±0.29µg/mL. It also showed the highest total antioxidant activity, i.e., 1.723±0.34, exhibited the anthelmintic effect by causing the death of worms and inhibiting egg and larval development in sheep. *In vitro* and *in vivo* studies have demonstrated that *Ziziphus nummularia* holds anthelmintic activity. In Pakistan, they were used as traditional veterinary medicine (Bachaya *et al*. 2009). There is great potential in developing anthelmintic activity using an extract of *Ziziphus mauritiana*. It is concluded that *Ziziphus mauritiana* Lam. exhibited a wormicidal effect, and extracts have shown anthelmintic potential against Haemonchosis contortus (Abrar *et al*. 2018). Another study reported that *Ziziphus spina-christi* has a protective role against malaria. Hafiz evaluated the antiplasmodial activity of *Ziziphus spina-christi* leaf extract against plasmodial berghei-induced spleen and liver injury. Histopathological images showed improvement in spleen and liver-damaged cells after the implication of leaf extract (Hafiz *et al*. 2016). Various extracts of *Ziziphus jujuba* were screened to evaluate the anthelmintic potential against the Phertima Posthuma. Results demonstrated that methanol extract had been

shown more potential because of the presence of tannins, steroids, and flavonoids (Venkatachalam *et al.* 2019). Thirty-three constituents were isolated from *Ziziphus lotus*. The especially major identified compound was Di-isooctyl phthalate, which has been used against the intestinal microbiota (Bekker *et al.* 2021). This suggests that the genus *Ziziphus* offers a cost-effective and inoffensive approach to new anthelmintics. Studying the structure, activity, and molecular relationship may lead to drug discovery. It would be remarkable to recognize the compounds that are potent against nematodes.

Table 7. Anthelmintic properties of the genus *Ziziphus* native to Pakistan.

Plant Species	**Sample analyzed**	**Experimental model**	**Pharmacological active**	**References**
Ziziphus jujuba Mill.	Fractionated extracts of Bark	*Phertima posthuma,*	Methanol and aqueous extract revealed remarkable anthelmintic activity compared to Piperazine citrate(standard drug).	Veeresh *et al.* 2010
	Water, Benzene, Diethyl Ether extract of fruit.	Mature earthworm	Benzene extract showed more efficient activity than the others of at concentrations 5, 10, and 20mg/ml. At 10mg/ml Dose increases reported the shortest time of paralysis and death.	Keerthi *et al.* 2016
Ziziphus mauritiana Lam.	Crude aqueous and crude aqueous methanolic extract from leaves	Nematode ova **Method:** Egg hatch test	For this vitro ovicidal effects Lethal concentration 50 (LC50) values of CAE and CAME were 0.1773 and 0.6778 respectively.it possesses anthelmintic activity and uses as veterinary medicine.	Bhutta *et al.* 2011
Ziziphus spina-christi (L.)Willd.	Leaves methanolic and aqueous extract	In vitro, live *Haemoncus contortus*	Crude aqueous extract(25mg/ml) at 6, 12, 24hrs post treatment showed 14%, 20%and 74%mortality rate. While the crude methanolic extract produced a mortality rate of 84%,100%and 100% in the same conditions.	Intisar et al. 2015
		In vivo *Haemoncus contortus* infection in Nubian goats	After ingesting the extract orally, blood glucose levels significantly decreased, and insulin levels significantly increased. Animal amoriliation is facilitated by the release of insulin from the remaining -cells, which prevents glucagon secretion from alpha cells.	

Anti-inflammatory activity

It was found that leaves cream prepared from the ethanolic extract of *Ziziphus mauritiana* showed solid anti-inflammatory activity in mice. The cream affects the descriptive observation subjective to the microscopic image of inflammatory cells and COX-2 enzyme expression in mice induced by croton oil (Kurniawan *et al.* 2020). Ethanolic extract of *Ziziphus jujuba* leaves has been found to give anti-inflammatory activity against kaolin and carrageenan-induced inflammation rats. Weak anti-inflammatory activity was detected due to both inflammation models (Hovanet *et al.* 2016). The *Ziziphus nummularia* root bark is used as an anti-inflammatory component in traditional medicine. octadecahydro-picene-2,3,14,15-tetranone (IC) was isolated from crude ethanolic extract of the plant and proved to be an anti-inflammatory agent (Rey *et al.* 2015). Aqueous, chloroform, ethyl acetate, and methanol extract of root bark from *Ziziphus rugosa* were analyzed for their anti-inflammatory activity. Results revealed that

an aqueous extract of 50,100mg/kg showed remarkable activity. Significant results were reported with the increase in dose (Abhimany *et al.* 2010).

Table 8. Anti-inflammatory properties of *Ziziphus* extracts.

Plants	Sample analyzed	Experimental model	Observation	References
Ziziphus jujuba Mill.	Ethanolic extract of the fruit	Carrageenan-induced paw oedema in female Wistar rats	Results revealed that the extract inhibited paw oedema significant degree ($p \leq 0.05$) and the paw volume and thickness were affected compared to the control	Mesaik *et al.* 2018
Ziziphus mauritiana Lam.	Benzene and methanol extract of Leaves	Male Wistar & female balb rats.	After 2, 3, and 4 hours of pretreatment with MEZ at 250 and 500 mg/kg, there was 12.1%, 20.6%, 16.2%, and a 19%, 23%, 33% protection, respectively.	Mohankumar *et al.* 2022
Ziziphus nummularia (Burm. f.)Wight & Arn.	Leaf alcoholic extract	Albino rats	Topical administration of 0.5 g of the extract's gel formulation was employed separately to promote both anti-inflammatory and wound-healing effects in wister albino rats.	Ray *et al.* 2015

Analgesic & sedative activity

In traditional medicine, the genus *Ziziphus* has been widely used for relieving pain. Hence, Mohankumar *et al.* investigated the analgesic property of *Ziziphus mauritiana* in rats using the hot plate method. At 500mg/kg, the methanolic extract significantly reduced pain. The result revealed that methanol extract has analgesic potential in dose-dependent manners (Mohankumar *et al.* 2022). Rauf *et al.* 2016 investigated the analgesic and sedative activity using solvent extract of the root of *Ziziphus nummularia*. The biological efficacies were most noticeable from 50 to 100 mg/kg.Furthermore, the extract significantly (p 0.05) reduced the abdominal constraints induced by acetic acid. Ethyl acetate and chloroform extract proved to be dose-dependent strong candidates for antipyretic and sedative-hypnotic activities (Rauf *et al.* 2016). Application of *Ziziphus jujuba* fruit lotion in females against nipple fissure pain confirmed the analgesic property of fruit by faster and better healing breast nipple fissure as compared to the breast milk used as the control group (Shahrahmani *et al.* 2018). The methanolic extract of *Ziziphus rugosa* demonstrated a considerable (p 0.01) dose-dependent antinociceptive effect in the analgesic activity test. The extract inhibited writhing response by 51.87% at a 300 mg/kg dose, equivalent to the reference medication indomethacin (55.20%). In contrast, the plant extract showed a substantial (p 0.01) sdose-dependent reduction of locomotor and exploratory behaviors in the open field and hole cross tests. The extract against Balb/c mice (Brewer's yeast-induced hyperthermia and acetic acid-induced writhing) may have analgesic and CNS-depressant properties because it contains biologically significant chemical components (Babul *et al.* 2015).

Antischistosomal Activity

Only Praziquantel (PZQ) has been licensed by the World Health Organization (WHO), but its efficacy was subpar in individuals with early illness. As a result, scientists have worked harder to discover novel complementary therapies for treating schistosomiasis. Egyptian Schistosoma strain (*Schistosoma haematobium*) was 100% declined under 6 to 12 hours of incubation after applying *Ziziphus spina-christi* extracts. It was reported that the extract may be effective for schistosomiasis (Fadladdin *et al.* 2021).

Repairing Hair Damaged

Hair loss and baldness are problems often experienced by men and women. Leaves extract acts as hair fertilizer as compared to other chemical shampoos. The confirmed presence of alkaloids, flavonoids, riboflavin, and saponins, has hair fertility activities, which promotes hair growth (Hakim *et al.* 2020).

Table 9. Analgesic, Sedative & Antischistosomal activity of the genus *Ziziphus* native to Pakistan.

Plant Species	Sample Analyzed	Experimental Model	Pharmacological Active	References
Ziziphus mauritiana	Methanolic extract of leaves	Rats **Method** :Hot plate.	MEZ significantly (p 0.001) lowers the pain sensation induced by, mechanical, thermal, and chemical pain models at a dose of 500 mg/kg. In 1-4h after carrageenan injection of MEZ at 500 mg/kg, paw edema is significantly decreased. The results supported the claim of traditional use by demonstrating potential analgesic, effects of the MEZ at the dosages examined.	Mohankumar *et al.* 2022
Ziziphus nummularia	Methanolic, Ethyl acetate & chloroform extract of Roots.	Balb/c mice of both gender **Method:** Open field method	The effectiveness of bromazepam and *Z. nummularia* root extract given intraperitoneal to mice at 50 and 100 mg/kg. A notable sedative effect with reduced motility was demonstrated by the extract in a dose-dependent manner. At 50 and 100 mg/kg, the chloroform fraction was significantly more prevalent than ethyl acetate (p 0.05 and p 0.01), respectively.	Rauf *et al.* 2016
Ziziphus jujuba	Fruit lotion	*Female fissure*	The findings demonstrated that lotion of *Ziziphus jujuba* Fruit speeds up the healing of painful nipples compared to breast milk. In comparison to breast milk, a significant decrease in mean nipple damage, pain intensity, and nipple discharge was seen on the seventh- and fourteenth-days following therapy. This finding suggests that sore nipples healed more quickly in the fruit lotion group than in the lactation group.	Shahrahmani *et al.* 2018
Ziziphus rugosa	Methanolic extract	Balb/c mice (Brewer's yeast-induced hyperthermia and acetic acid-induced writhing)	The plant's anti-nociceptive potential is indicated by the methanol extract's dose-dependent suppression of abdominal constrictions. The enforced inhibition of writhing was comparable to the usual non-narcotic analgesic medication, Indomethacin, at a dose of 300 mg/kg body weight.	Babul *et al.* 2016).
Ziziphus spina-christi (L.)Willd.	Leaves extracts	*Schistosoma haematobium*	After ingesting the extract orally, blood glucose levels significantly decreased, and insulin levels significantly increased. Animal amoriliation is facilitated by the release of insulin from the remaining -cells, which prevents glucagon secretion from alpha cells.	Fadladdin *et al.* 2021

Phytochemical composition

Several research studies have been undertaken to assess the chemical composition of the genus *Ziziphus*. Genus *Ziziphus* is a rich source of bioactive compounds, especially cyclopeptide alkaloids. One of the earliest research conducted in 1989 demonstrated that cyclopeptide alkaloids named nummularine-P, sativanine-H, and rugosanine-B isolated from the *Ziziphus rugosa* bark (Tripathi *et al.* 1989). Further study by the jossang led to the

identification of mauritine J, an alkaloid from the root bark of *Ziziphus mauritiana* (Jossang *et al*. 1996). From the stem bark extract of *Ziziphus spina christi,* two major compounds, betulinic acid, and botulin, were isolated. These compounds were used as anticancer and antibacterial candidates (Ads *et al*. 2022). Novel saponins were isolated from the butanol extract of *Ziziphus spina christi*, named Christinin A, B, C, D, studied by (Mahran *et al*. 1996).Chemical studies of the stem bark of *Ziziphus jujuba* revealed the presence of Jubanine -C, scutianine-C, and ziziphine-A, type cyclopeptide alkaloids (Tripathi *et al*. 2001). Moreover, spectroscopic analyses of the root of *Ziziphus jujuba* have been found to contain jubanines F–J, nummularine B, daechuine-S3, and mucronine K and reported as antiviral agents (Kang *et al*. 2015). The literature review demonstrated that 431 compounds, mostly alkaloids and flavonoids, have been isolated and identified from the *Ziziphus* genus. According to date information, 165 alkaloids, 151 flavonoids, 43 terpenoids, 31 saponins, and 40 other compounds have been identified (Maaiden *et al*. 2020). Table no 1 summarizes the information on the phytochemical composition of the genus *Ziziphus*. Leaves of *Ziziphus mauritiana* exhibited many Phytoconstituents, such as tannins, saponins, flavonoids, resins, polyphenols, and glycosides (Rahman *et al*. 2021). In the genus *Ziziphus*, Cyclopeptide is 13, 14, and 15-membered cyclopeptide alkaloids include nummularine-C and ziziphine-A, frangulanine-B, aduotine-Z, amphibine-B, amphibine-F, pandamine, and integerrine, mucronine-A type (Maaiden *et al*. 2020). Adam and his colleagues isolated and identified six 14-member ring cyclopeptide alkaloids mentioned in (Table 1.) From the root bark of *Ziziphus spina-christi* (Adam *et al*. 2022) from LC-MS/MS, there were 12 alkaloids isolated and identified from the methanolic fruit extract of *Ziziphus mauritiana* (Soraya *et al*. 2022, Choudhary *et al*. 2011, Panseeta *et al*. 2011, Teunter *et al*. 2017, Kang *et al*. 2015). Recent studies by Qin *et al* reported 60 alkaloids from the *Ziziphus jujuba*. In addition, 295 compounds were isolated from this species, of which 270 were identified first (Qin *et al*. 2022). *Ziziphus oxyphylla* stem and root extracts contained 13 and 14-membered alkaloids that showed strong antibacterial, antinociceptive, and antioxidant activity (Kaleem *et al*. 2012, Kaleem *et al*. 2013, Kaleem *et al*. 2015). This plant species is enriched with cyclopeptide alkaloids, catechin, quercetin, and kaempferol derivatives. (Shaukat *et al*. 2022). The term "flavonoid" primarily refers to two benzene rings (A and B) with phenolic hydroxyl and refers to a group of compounds with the basic carbon skeleton C6-C3-C6 joined by three major carbon chains. There are several subgroups of flavonoids, including flavonoids, flavonols, isoflavones, anthocyanins, chalcone, nerone, and flavane. Flavonoids are extensively dominant in various foods in varying amounts and are stored in plants' roots, stems, leaves, flowers, and fruits (Chen *et al*. 2022). UHPLC-Q-Exactive Orbitrap MS analysis identified 69 flavonoids from the fruit juice of *Ziziphus jujuba*, as mentioned in Table 9 (Qin *et al*. 2022). Phenolic compounds in plants play a significant role as primary antioxidants or free radical scavengers. When 1.0 g of polyphenolic compounds are consumed daily from a diet high in vegetables and fruits, it has been suggested that these compounds have anti-mutagenic and anticarcinogenic characteristics in humans (Maaiden *et al*. 2019). Phenolic compounds, non-volatile acids, and soluble sugar were isolated from different parts (leaves, bark, fruit, seed) extract of *Ziziphus* by using TLC and HPLC, GC-MS technique (Soraya *et al*. 2022 , Uddin *et al*. 2022, Ads *et al*. 2022, Mahmoud *et al*. 2022, Ozturk *et al*. 2021). Triterpenoids are also important and abundant bioactive components in jujube. Forty-three terpenoids have now been isolated from the leaves, flowers, fruits, and seeds of *Ziziphus jujuba*, *Ziziphus mauritiana*, and *Ziziphus spina christi*. Several studies have revealed that terpenoids from the genus *Ziziphus* have biological activities such as inhibitory activities, cytotoxicity, antimicrobial, anti-inflammatory, antiplasmodial, anticomplememtry, antimycobacterial, and anticancer oxidation, lowering blood lipids, lowering blood sugar, protecting liver (Shen *et al*. 2022). Twelve terpenoids have been isolated and identified from *Ziziphus mauritiana* fruit extracts (Soraya *et al*. 2022, Maaiden *et al*. 2020). From the stem bark extract of *Ziziphus spina christi*, two major compounds, betulinic acid, and botulin, were isolated by Ads *et al*. 2022. Both of these compounds were used as anticancer and antibacterial candidates. Metabolic characterization and fractions were performed using LC-HR-ESI-MS, and the results demonstrated the presence of 36 compounds of different chemical classes, especially triterpenes, and flavonoids. *In vitro*, investigation revealed that *Ziziphus spina-christi* and its isolated compounds act as antimicrobial and antioxidant candidates for pharmacological applications (Ads *et al*. 2022, Shaukat *et al*. 2022). A number of sugars and proteins was determined using HPLC analysis. Other techniques were used to determine the total amount of carbohydrates, ash, moisture, fiber, lipids, and protein from the fruit of *Ziziphus spina christi*. According to the findings, the average concentrations of the different minerals were Ca (57.22 mg/100g), Mg (72.11 mg/100g), Na (9.12 mg/100g), V (0.14 mg/100g), Fe (2.81 mg/100g), Cu (0.34 mg/100g), Ni (0.25 mg/100g), Al (3.42 mg/100g), As (0.37 mg/100g), and Pb (0.31 mg/100g). Fructose (175.58 g/kg), glucose (158.34 g/kg), and sucrose (132.02 g/kg) made up the majority of the sugars. According to the results of manual methods, the ash content was 3.34%, moisture was 8.16 %, protein was 5.3 %, fiber was 4.7 %, fat was 1.0 %, and total carbs were 77.2 %. Overall findings demonstrated that Nabag fruit pulp was rich in sugars and nutritionally important elements (Ishag 2021).

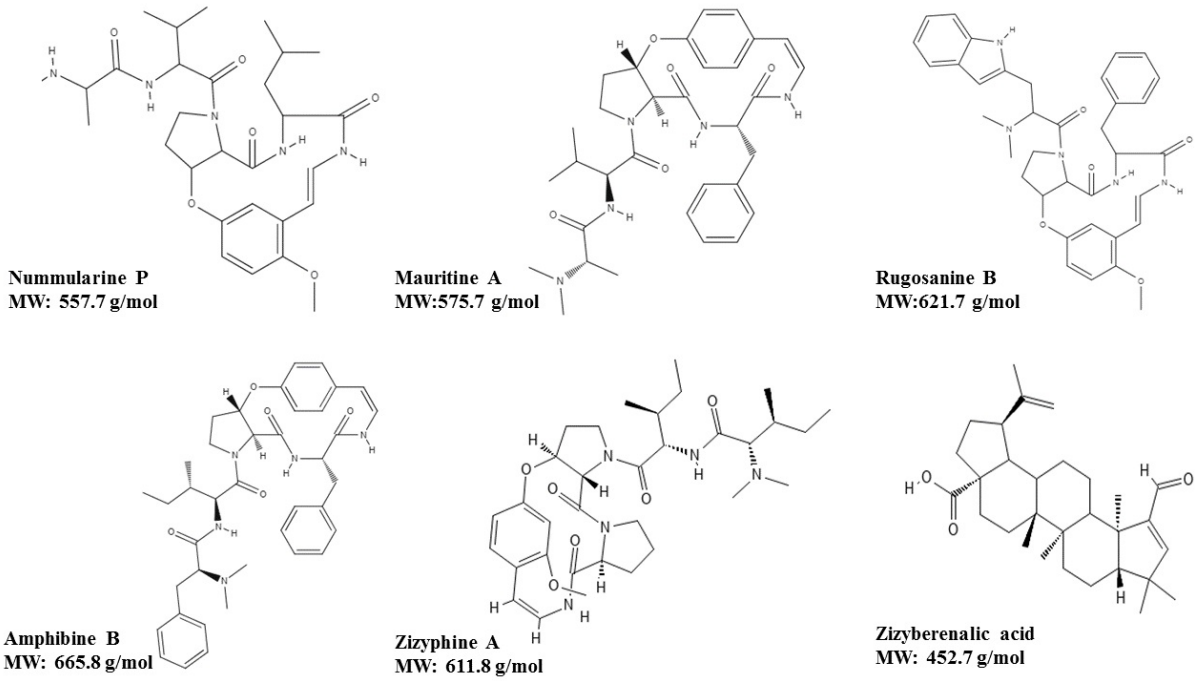

Figure 3. Structural representation of compounds identified from the genus *Ziziphus* plants.

Advanced formulation of the plant genus

Nanotechnology is an emerging field with the application of molecular imaging, catalysis, drug discovery, and other diagnostic purposes; it involves the production of molecules with a range of 1-100 nanometers in length (Kumar *et al.* 2022). "Green synthesis" of nanoparticles is the most fascinating technique now a day. Using the different plant parts, microbes and metals ion are reduced into their nanoparticle form (Khani *et al.* 2018). In addition to producing more stable nanoparticles than other techniques, green synthesis is more scalable and environmentally sustainable as it does not involve hazardous chemicals, high temperatures, or pressure.Unlike bulk materials, nanoparticles displayed entirely new or better characteristics because of their small size and high surface-to-volume ratio (Padalia *et al.* 2021). Species of the genus *Ziziphus* extract have been used in the biosynthesis of copper, silver, gold, zinc, and selenium nanoparticles (Khani *et al.* 2018, Seku *et al.* 2021, Alzahrani *et al.* 2022, Rahman *et al.* 2021). The antibacterial properties of Cu-NPs nanoparticles synthesized from *Ziziphus spina-christi* fruit extract were studied against *Escherichia coli* and *Staphylococcus aureus*. The result revealed that a higher concentration of nanoparticles showed solid antibacterial activity than low concentrations and aqueous fruit extract (Khani *et al.* 2018).

Silver nanoparticles biosynthesized from leaves extract of *Ziziphus mauritiana* showed antibacterial potential against *Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa,* and *Bacillus subtilis*, bacterial strains. Nanoparticles inhibit the growth of *Staphylococcus aureus* and show a mild effect on *Escherichia coli* (Asimuddin *et al.* 2020). Capped silver nanoparticles biosynthesized from *Ziziphus jujuba* fruit extract showed strong antimicrobial potential against tested fungal and bacterial strains. The tested bacterial and fungal strains were *Bacillus subtilis, Streptococcus, Escherichia coli, Pseudomonas Aeruginosa, and Aspergillus niger* and *Aspergillus fumigatus* respectively (Seku *et al.* 2021). Kumar *et al.* biosynthesized silver nanoparticles from roots extract of *Ziziphus nummularia.* The result revealed that nanoparticle possesses significant antimicrobial potential against *Staphylococcus aureus, Enterococcus faecalis, Pseudomonas aeruginosa, Escherichia coli, Aspergillus niger,* and *Candida albicans* strains (Kumar *et al.* 2022). Similar improvement was observed in another study, using synthesized nanoparticles from fruit extracts of *Ziziphus nummularia*, which found strong potential against gram-negative and gram-positive bacteria, fungal strain, as well as showing better hair growth (Khalil *et al.* 2022). The antimicrobial potential of silver nanoparticles synthesized with *Ziziphus spina-christi* leaf extract was tested against ten bacterial strains (five gram-positive and five gram-negative). The result proved that prepared AgNPs might be strong antibacterial candidates for bacterial infection treatment (El-Ansary *et al.* 2018). Due to their potential for widespread biological applications compared to conventional techniques, the green production of gold nanoparticles (AuNPs) utilizing plants has attracted much interest (Padalia *et al.* 2021).

Table 10. Isolation and studies of active components from selected *Ziziphus* species.

Chemical Compounds	Species	Sample Analyzed	Extracting Solvent	Separation & detection Method	Bioactive Compounds	References
Alkaloids	*Ziziphus nummularia*	Stem, Root Bark	Methanol	HPLC-PDA-(HRMS)-SPE-NMR	Nummularine P-U, spinanine-B,C mauritine-F, nummularine-D, E amphibine-D.	Teunter *et al.* 2017
	Ziziphus mauritiana	Root bark, fruit extracts	MeOH	NMR, X-ray	Mauritine L, M nummularine H, B hemsineA ,methiodide	Panseeta *et al.* 2011, Soraya *et al.* 2022.
					Benzoylhypaconine	
					Dauricicoline	
					Ephedradine	
					Magnoflorine	
					Neojiangyouaconitne	
					Nortropanoline	
					Benzoylaconine	
					D-Lirioferine	
					Ephedradine	
					Gentianamine	
					Sanjoinine A	
	Ziziphus rugosa	Bark	Methanol	Spectroscopic& chemical degradation	Nummularine P	Tripathi *et al.* 1989
					Satianine-H	
					Rugosanine-B	
	Ziziphus spina-christi	Stem, root bark	Methanol	Spectroscopic& chemical degradation	Zizyphine-F, jubanine-A amphibine-H spinanine-A mauritine-A mauritine C	Galil *et al.* 1991, Adam *et al.* 2022
					Amphibine-A amphibine-E	
	Ziziphus jujuba	Root	Methanol	spectroscopic analyses	Jubanines F–J nummularine B daechuine-S3, mucronine K	Kang *et al.* 2015; Qin *et al.* 2022.
		Fruit			Sinomenine Magnoflorine Magnocurarine	
					4-keto-magnoflorine	
					Desmethyl magnoflorine tembetarine	
					Nuciferine chiloenaminen-methylcoclaurine	
					Reticulin	
					Norreticuline	
					Coclaurine	
					Juzirine, asimilobine	
					Asimilobine	

	Ziziphus oxyphylla	Root stem	Methanol	1D,2D-NMR	Nummularine-R nummularin-C hemsine-A Oxyphylline D	Choudhary *et al.* 2011 , Kaleem *et al.* 2012
Flavonoids &flavones	*Ziziphus oxyphylla*	Root bark	MeOH	HPLC & ESI-	Kaempferol, quercetin	Shaukat *et al.* 2022
	Ziziphus mauritiana	Fruit extracts	Methanol	GC-MS analysis	6Hydroxykaempferol-3-O-glucoside	Soraya *et al.* 2022
					Cyanidin3,5-diglucoside_1	
					Gallocatechin	
					Isoetin-7-O-β-D-glucopyranosyl-2'-O-β-D-xyloypyranoside	
					Licurazide	
					Nelumborosideb	
					Quercetin-3-gentiobioside	
					Quercetin-3-rhamnogentiobioside	
					Undulatosidea	
					Hydroxykaempferol-3-O-glucoside	
	Ziziphus jujuba	Plant powder	Methanol extracts	LC-MS/MS	Procyanidin B2, catechin, quercetin3-O-rutinoside, hyperoside, isoquercitrin, luteolin-7-O-glucoside, kaempferol-3-O-neohesperidosidenicotiflorin, quercitrin, phlorizin, trilobatin, quercetin, proanthocyanidins,	Qin *et al.* 2022
	Ziziphus rugosa	Root bark	MeOH, CH_2Cl_2	Spectroscopic technique	Kaempferol afzelin	Kaennkam *et al.* 2013
					Quercitrin catechin	
Terpenoids	*Ziziphus mauritiana*	Fruit extract	Methanol extracts	HPLC & GC-MS	Betulonicacid	Soraya *et al* . 2022
					Ganodericacid	
					Istanbulina	
					Ecliptasaponinb_1	
					E-p-Coumaticacid	
					Ginsenosiderh4_1	
					Lactiflorin	
					Phytolaccagenin_1	
					Poricoicaciddm	
					Qinghaosuiv	
					Sweroside	
					Yemuosideym12_1	
	Ziziphus oxyphylla	Rootbark	MeOH	HPLC& ESI-MS/MS	Caenothic acid	Shaukat *et al.* 2022
	Ziziphus rugosa	Root bark	MeOH	Spectroscopic	Lupeol	

					Betulin betulinic aldehyde betulinic acid alphitolic acid euscaphic acid zizyberenalic acid	Kaennkam *et al.* 2013
					B−sitosterol coumarin scopoletin	
Phenols &Polyphenols Total	*Ziziphus nummularia*	Fruit	MeOH	HPLC /UV analysis	Chlorogenic acid, quercetin,	Uddin *et al.* 2020, Uddin *et al.* 2022.
					Morin,	
					Rutin,	
					Pyrogallol, mandellic acid chlorogenic acid, hydroxy benzoic acid	
					Gallic acid,	
					Caffeic acid, Cinamic acid, Ellagic acid, Quercetin 3- rutinosides, Caffeic acid hexoside, 5-O-Caffeoylquinic acid,	
					Qurecetin-3-O-galactoside, Luteolin-7-O-glucoside,	
					Spinacetine-3-O-glucopyranoside, Kaempferol-3-O-,	
					Glucoside-7-O-glucoside,	
	Ziziphus jujuba	Leaves	MeOH	Folin-Ciocalteu method	Gallic acid	Mahmoud *et al.* 2022
					Resorcinol	
					Catechol	
					Epigallocatechin-3- gallate	
					Chlorogenic acid	
					Ferulic acid	
					Rutin	
					Protachatechuic acid	
					Ethyl ester	
					Ellagic acid	
					Rosmarinic acid	
					Apigenin	
					Amentflavone	
	Ziziphus oxyphylla	Fruit extract	MeOH	HPLC-DAD	Proanthocyanidin B1	Uddin *et al.* 2022
					Ellagic acid pentoside, Quercetin 3-glucoside, Qurecetin-3-D-galactoside, Luteolin-7-O-glucoside, Salicylic acid,	
					P-Coumaric Acid, 5-O-p-Coumaroylquinic acid,	
					Caffeic acid hex, Ellagic acid ,	
					Gallic acid	

	Ziziphus mauritiana	Fruit extracts	MeOH	LC/MS-MS	2,4,6-Trihydroxyacetophenone-2,4-di-O-β-D-glucopyranoside	Soraya *et al.* 2022
					Cimidahurine	
					Koaburaside	
					Kukoamine A	
Organic acid& Glycosides	*Ziziphus mauritiana*	Fruit	Methanolic extracts	LC/MS-MS	4-O-β-dglucopyranosyl-cis-cinnamic acid	Soraya *et al.* 2022
					9-octadecenoicacid	
					Coronaricacid	
					Quinicacid	

Nowadays, biosynthesized Gold nanoparticles are applied against bacterial infection and found fruitful results. Alzahrani *et al*. studied the comparative analysis of the antibacterial activity of gold, silver, and gold-silver alloy nanoparticles synthesized from *Ziziphus spina-christi* leaf extract against multi-drug resistance bacteria. The result reported that gold-silver alloy nanoparticles showed strong antibacterial potential with the minimum inhibitory bactericidal concentration of 77.33 to 93.33µg/ml (Alzahrani *et al.* 2022). The latest study, undertaken by Padalia *et al*. confirmed that gold nanoparticles synthesized from *Ziziphus nummularia* leaves extract showed potent antioxidant, anticancer (cytotoxicity against human cervical cell line) potential in a dose-dependent manner (Padalia *et al.* 2021). Zinc nanoparticles which are also exhibited antimicrobial potential. Zinc oxide nanoparticles synthesized with the leaves of *Ziziphus mauritiana* showed antimicrobial properties against the tested strain *Staphlococcus aureus* and *Escherichia coli* (Rahman *et al*., 2021). The antimicrobial activity of zinc oxide and selenium nanoparticles prepared from callus extract of *Ziziphus spina-christi* leaves was done. The result demonstrated that these nanoparticles exhibited antimicrobial potential against gram-negative, gram-positive, and fungal strain and possesses antioxidant effect (Hasanin *et al.* 2021). In recent studies, Cobalt nanoparticles have reported a broad spectrum of antimicrobial properties. Saeed *et al*. (2022) prepared cobalt nanoparticles from the *Ziziphus oxyphylla* root extract showed pronounced antibacterial activity against different strains of gram-positive and gram-negative bacteria (Saeed *et al*. 2022). Therefore literature reported that nanoparticles prepared from plant species of *Ziziphus* have significant antioxidants and antimicrobial properties and could be very significant in pharmaceutical and medical science.

Table 11. Other activity of the genus *Ziziphus* based on nanoparticles.

Nanoparticles	**Plant**	**Observation**	**References**
Copper Nanoparticles	*Ziziphus spina-christi*	Dose decreased tumor volume, size, cell count and increased body weight.	Khani *et al*. 2018
Silver Nanoparticles	*Ziziphus spina-christi*	Suppressed the growth of 5 gram-positive and gram - negative bacterial strains, which showed auspicious antimicrobial agent for successful treatment of bacterial infection especially in bacterial resistance.	El-Ansary *et al*. 2018
	Ziziphus mauritiana	Inhibited the growth of *S. Aureus* and E.coli with a minimum inhibitory concentration (MIC) of 2.5 µg/ml and 5 5 µg/ml respectively .	Asimuddin *et al*. 2020
	Ziziphus nummularia	Against *Staphylococcus aureus, Enterococcus faecalis, Pseudomonas aeruginosa, Escherichia coli Aspergillus niger,* and *Candida albicans ,* AgNPs showed promising antimicrobial activity.	Kumar *et al*. 2022
Gold Nanoparticles	*Ziziphus nummularia*	Showed hypoglycemic activity in dose dependent manner, 44.27% blood glucose reduced after 3 h, at 400 mg/kg body weight dose.	Akanda *et al*. 2021
Zinc Nanoparticles	Ziziphus mauritiana	Oral administration produced momentous reduction in blood glucose level with significant raise in insulin.	Mohammed *et al*. 2019
	Ziziphus spina-christi	Insulin discharge from the remnant β-cells, inhibiting glucagon secretion from alpha-cells pave way to amoriliation in animal.	Hasanin *et al*. 2021
Selenium Nanoparticles	*Ziziphus spina-christi*	Se NPs have pronounced antimicrobial property against Gram-negative, Gram-positive	Hasanin *et al*. 2021

		bacteria, and fungi, more it showed potent antioxidant activity	
Cobalt oxide nanoparticles	*Ziziphus oxyphylla*	At 16 mg ml−1 dilution of cobalt oxide nanoparticle, 23.1 and 14.8mm maximum zone of inhibition was recorded against E. Coli and S. Aureus. This confirmed the antibacterial activity of the synthesized nanoparticle because confirmed presence of phenols.	Saeed *et al*. 2022

Conclusion

For many decades, plants have been used as natural sources of bioactive constituents for treating various lethal diseases. The present review focuses focussing the *Ziziphus* plant species native to Pakistan on explaining the bioactive phytochemical constituents, traditional uses, and pharmacological activities. The review is organized as follows: first, the traditional uses of all six species of the genus *Ziziphus*; then, the pharmacological properties of plant extract and different nanoparticles are discussed. These include their antidiabetic, anticancer, antioxidant, antimicrobial, anthelmintic, and anti-inflammatory activities. In the end, the phytochemicals compounds of *Ziziphus* present in the plant's parts leaves, fruits, roots, fruit, and seed are highlighted. Papers with mere abstracts, unpublished manuscripts, conference proceedings, and publications in languages other than English were not considered. The review reported the activity of different parts of the plants and their pharmacognostic profile. Extracts and nanoparticles prepared from plants have been reviewed for various pharmacological responses, including anticancer, antidiabetic, antimicrobial, antioxidant, cytotoxic, anti-inflammatory, analgesic, sedative, and other effects. The described pharmacological properties showed that *Ziziphus* is an auspicious plant genus, and because of its nontoxicity and effectiveness, it could be applied and studied for other therapeutic applications. In conclusion, additional research on this plant may be helpful for new drug discovery.

Declarations

List of abbreviations: E.: *Escherichia*, HPLC.: High Performance Liquid Chromatography, Lam.: Lamarck, mm.: millimeters, spp.: several species, GC-MS.: Gas Chronmatography-Gas Spectrometry, TLC.: Thin Layer Chromatogarphy, LC-HR-ESI-MS.: Liquid Chromatography-High Resolution Electrospray Ionization Mass Spectrometry, ZCR.: *Ziziphus spina-christi* Root, PC.: Pancreatic Cancer.

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