JOURNAL OF SCIENTIFIC RESEARCH IN ALLIED SCIENCES

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ZIZIPHUS JUJUBA: AN OVERVIEW ON ITS PHYTOCHEMICAL CONSTITUENTS, PHARMACOLOGICAL ACTIVITY AND TRADITIONAL USES

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ARTICLE INFO

Article History
Received: December 2024
Accepted: January 2025

ABSTRACT

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ORIGINAL RESEARCH ARTICLE

2024, www.jusres.com

INTRODUCTION

Jujube (*Ziziphus jujuba*) is an edible and nutritious fruit widely cultivated in tropical and subtropical regions, particularly in East Asia (China, India), North Africa, and Middle Eastern countries[1]. With increasing research focused on jujube, various beneficial nutrients have been identified, including carbohydrates, minerals, vitamins, sugars, and amino acids, establishing it as a popular nutritious food worldwide[2-6].

In India, herbs have traditionally served as natural medicine. Medicinal plants possess curative properties due to various complex chemical substances, including secondary metabolites such as alkaloids, flavonoids, terpenoids, saponins, and phenolic compounds distributed throughout different plant parts. While numerous drugs exist for disease management, common antihypertensive medications often come with side effects. Medicinal herbs contain multiple active substances with pharmacological and prophylactic properties beneficial for treating hypertension.

Ziziphus jujuba, belonging to the family Rhamnaceae, has a long history of use both as a fruit and medicinal remedy[11]. The plant's primary biologically active compounds include polysaccharides, triterpene acids, flavonoids, phenols, and saponins[12]. Research has demonstrated that *Z. jujuba* exhibits diverse pharmacological properties, including antioxidant[10][13], hepatoprotective[14], anti-inflammatory[7][15], anticancer[16], and sedative[8][9] effects, along with various protective actions in organs and tissues.

Morphologically, the species displays considerable variation, ranging from shrubs to small or medium-sized trees that may be erect, semi-erect, or spreading. Trees typically reach heights of 3-4 to 10-16 m, though specimens reaching 20 m are rare. These semi-deciduous trees feature extensive branching and grayish-brown or reddish bark with deep longitudinal furrows. While usually spinous, some specimens lack spines. Young branchlets exhibit dense white pubescence and tend to follow a zigzag pattern, with branches spreading erect before becoming flexuous and dull brown-grey.

The fruiting branches persist rather than shed[17].

The leaves are characterized by elliptic to ovate or nearly orbicular laminae. They feature rounded, obtuse, or sub-acute to emarginated apexes, with rounded, occasionally cuneate, largely symmetrical bases. The margins display minute serration, with three prominent nerves extending almost to the apex. The upper surface shows depressed nerves and appears light or dark green and glabrous, while the lower surface typically presents a whitish or buff coloration due to persistent dense hairs, though some specimens show glabrous lower surfaces. Leaves are petiolate (1.1-5.8 mm long) with stipules typically developing into spines, either paired with one hooked and one straight, both hooked, or rarely undeveloped[17].

The flowers possess dorsally tomentose sepals, a disk approximately 3 mm in diameter, and a 2-celled ovary immersed in the disk. They feature two 1 mm long styles, connate for half their length, and emit an acrid odor. The flowers grow in cymes or small axillary clusters, with sessile or shortly pedunculate cymes featuring tomentose peduncles (1-4 mm) and pedicels (2-4 mm at flowering, 3-6 mm at fruiting). The fruit develops as a glabrous globose or oval edible drupe, typically measuring (1-)1.5(-2) cm in diameter, though some oval varieties can reach 5 x 3 cm. The pulp offers both acidic and sweet flavors, with fruit coloration ranging from greenish to yellow or occasionally reddish[17].

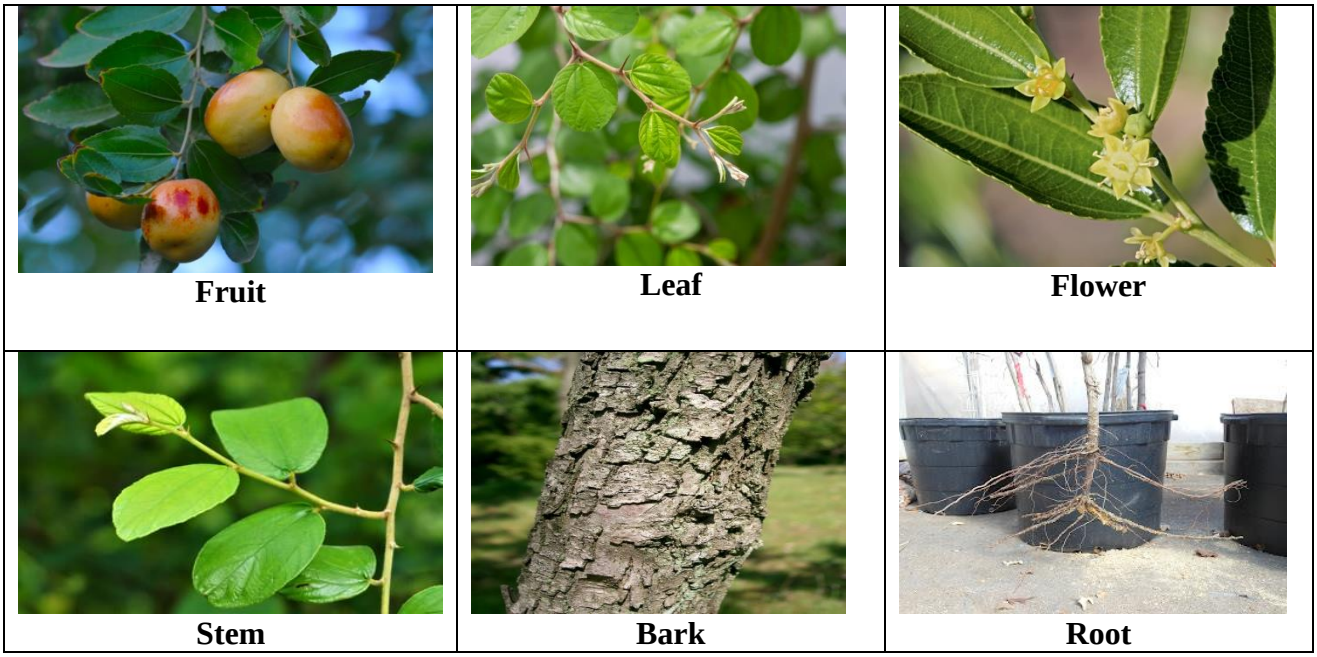


Fig1: Schematic Representation of Different Parts of *Ziziphus jujuba*

The antioxidant activity, measured through DPPH and ABTS radical scavenging, shows a decrease as jujube fruits mature. Green jujube thus presents potential as a source of natural antioxidants (catechin, epicatechin, proanthocyanidin)[18]. Both fresh and dried jujube fruits (*Ziziphus jujuba*) contain phenols and flavonoids that demonstrate hepatoprotective properties through their antioxidant capacity[19].

Research has demonstrated *Z. jujube's* anticancer activities across multiple tumor cell lines[20], including inhibition of HeLa cervical cancer and A549 lung cancer cell growth[21]. Its chloroform fraction shows anticancer activities in human liver cancer cells[22], while the extract reduces viability of HeLa and MAD-MB-468 cells in a concentration-dependent manner[23]. Additionally, *Z. jujube* has shown

effectiveness in delaying colon cancer progression[24].

Chemical Constituents: The major chemical constituents of *Z. jujuba* vary across different plant parts:

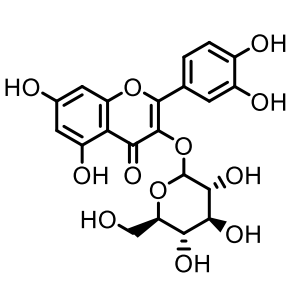
- Fruit: Contains quercetin, catechin, and rutins, with betunilic acid and amphitolic acid showing cytotoxicity against HT-29 colon cancer cell line
- Leaves: Features diglycerol, myristic acid, and palmitic acid
- Seeds: Contains compounds including 7-ethyl-4-decen-6-one, linoleoyl chloride, linoleic acid, and 2,5-octadecadiynoic acid methyl ester, contributing to antimicrobial properties

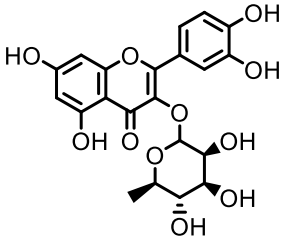
The detailed chemical constituents and their structures are presented in Table 2 and Figure 1.

Table 2: The various chemical constituents present in the different parts of *Z. jujube*

PARTS OF THE PLANT	NAME OF THE CHEMICAL CONSTITUENTS	MOLECULAR FORMULA	MOLECULAR WEIGHT(g/mol)	REFERENCE
FRUIT	A.1) Quercetin-3-glucoside	$C_{21}H_{20}O_{12}$	464.4	[25]
	2) Quercetin-3-rhamnoside	$C_{21}H_{20}O_{11}$	448.4	[25]
	3) Procyanidin B2	$C_{30}H_{26}O_{12}$	578.5	[25]
	4) Quercetin 3-O-rutinoside	$C_{27}H_{30}O_{16}$	610.5	[26]
	5) Quercetin 3-O-β-D-galactoside	$C_{21}H_{20}O_{12}$	464.38	[26]
	6) Kaempferol 3-O-robinobioside	$C_{27}H_{20}O_{12}$	594.5	[47]
	7) Quercetin 3-O-β-D-glucoside	$C_{21}H_{30}O_{15}$	464.4	[27]
	8) Kaempferol 3-rutinoside	$C_{27}H_{30}O_{15}$	594.5	[27]
	9)Quercetin-3-O-alpha-l-arabinopyranosyl-(1->2)-alpha-l-rhamnopyranoside	$C_{26}H_{28}O_{15}$	580.5	[27]
	10) Catechin	$C_{15}H_{14}O_6$	290.27	[28]
	11) Epicatechin	$C_{15}H_{14}O_6$	290.27	[28]
	12) Galacturonic acid	$C_6H_{10}O_7$	194.14	[29]
	13) Xylose	$C_5H_{10}O_5$	150.13	[29]
	14) Galactose	$C_5H_4N_2O_4$	156.1	[29]
	15) Arabinose	$C_5H_{10}O_5$	150.13	[29]
	16) Rhamnose	$C_6H_{12}O_5$	164.16	[29]
	17)Uronic acid	$C_{13}H_{17}BrO_9$	397.17	[30]
	18)Juziphine	$C_{18}H_{21}NO_3$	299.4	[30]
	19) Juzirine	$C_{17}H_{15}NO_3$	281.3	[30]
	20) Norisoboldine	$C_{18}H_{19}NO_4$	313.3	[30]
	21) Isoboldine	$C_{19}H_{21}NO_4$	327.4	[30]
	22) Asimilobine	$C_{17}H_{17}NO_2$	267.32	[30]
	23) Delphinidin-3,5-	$C_{27}H_{30}O_{17}$	626.5	[31]

	diglucoside			
	24) Cyanide ion	CN^-	26.017	[31]
	25) Cyanidin-3,5-diglucoside	$C_{27}H_{31}ClO_{16}$	647	[31]
	26) Delphinidin-3-glucoside	$C_{21}H_{21}ClO_{12}$	500.8	[31]
	27)Pelargonidin-3,5-diglucoside	$C_{27}H_{31}ClO_{15}$	631	[31]
	28) Peonidin-3-glucoside	$C_{22}H_{23}O_{11}^+$	463.4	[31]
	29) Cyanidin-3-glucoside	$C_{21}H_{21}ClO_{11}$	484.8	[31]
	30)Pelargonidin-3-glucoside	$C_{21}H_{21}ClO_{10}$	468.8	[31]
	31) Ceanothic acid	$C_{30}H_{46}O_5$	486.7	[32]
	32)Epiceanothic	$C_{30}H_{46}O_5$	486.7	[32]
	33) Betulinic acid	$C_{30}H_{48}O_3$	456.7	[32]
	34) Oleanolic acid	$C_{30}H_{48}O_3$	456.7	[32]
	35) Ursonic acid	$C_{30}H_{46}O_3$	454.7	[33]
	36)Zizyberanalic acid	$C_{30}H_{46}O_4$	470.7	[33]
	37)3-O-cis-p-coumaroyl maslinic acid	$C_{39}H_{54}O_6$	618.8	[34]
	38)Colubrinic acid	$C_{30}H_{46}O_4$	470.7	[34]
	39)Alphitolic acid	$C_{30}H_{48}O_4$	472.7	[35]
LEAVES	B. 1.Rutin	$C_{27}H_{30}O_{16}$	610.5	[36]
	2. Quercetin-3-o-alpha-l-arabinopyranosyl-(1->2)-alpha-l-rhamnopyranoside	$C_{26}H_{28}O_{15}$	580.5	[37]
	3. Catechin	$C_{15}H_{14}O_6$	290.27	[28]
	4. Diglycerol	$C_6H_{14}O_5$	166.17	[38]
	5.2,3-dihydrobenzofuran	C_8H_8O	120.15	[38]
	6. Palmitic acid	$C_{16}H_{32}O_2$	256.42	[39]
	7. Myristic acid	$C_{14}H_{28}O_2$	228.37	[38]
	8.α-tochopherol	$C_{29}H_{50}O_2$	430.7l	[38]
SEEDS	1) 13-Heptadecyn-1ol	$C_{17}H_{32}O$	252.4	[40]
	2) 7-Ethyl-4-decen-6-one	$C_{12}H_{22}O$	182.30	[41]
	3)Lineoleoyl chloride	$C_{18}H_{31}ClO$	298.9	[41]
	4) Linoleic acid	$C_{18}H_{32}O_2$	280.4	[41]
	5) 2,5-Octadecadiynoic acid, methyl ester	$C_{19}H_{30}O$	290.45	[41]
	7)Palatinol A	$C_{12}H_{14}O_4$	222.24	[41]


Quercetin-3-glucoside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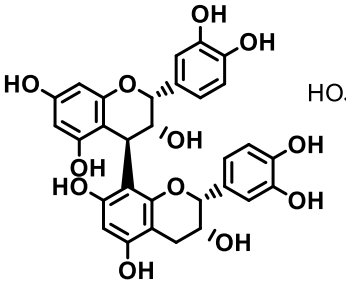
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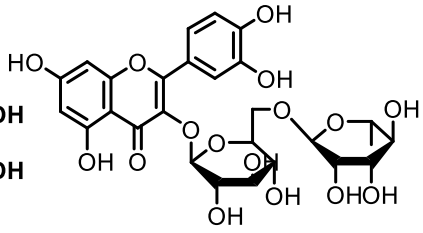
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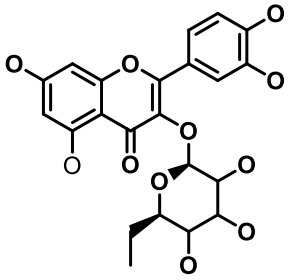
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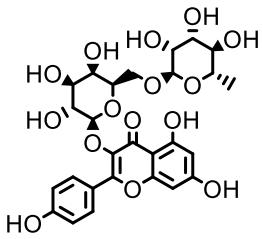
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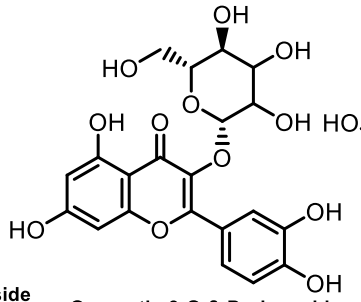
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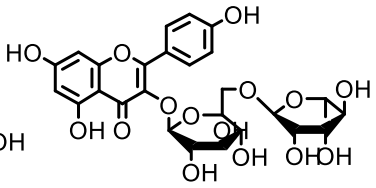
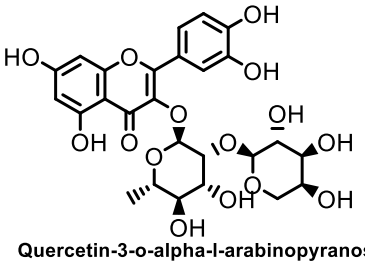

Kaempferol 3-rutinoside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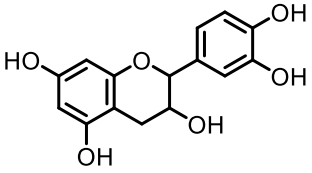
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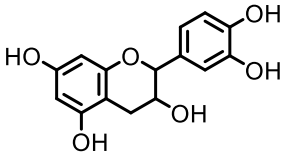
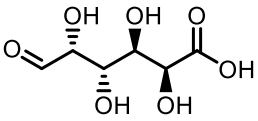

Epicatechin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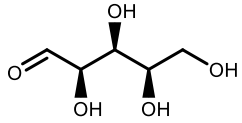
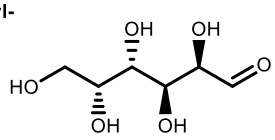

Xylose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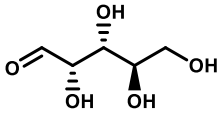
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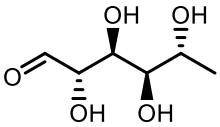
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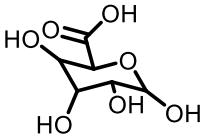
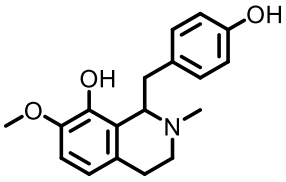

Uronic acid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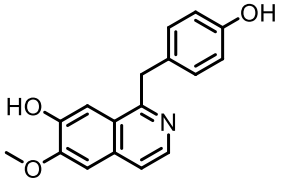
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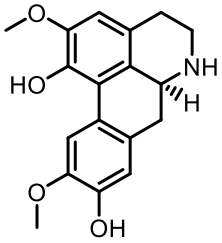
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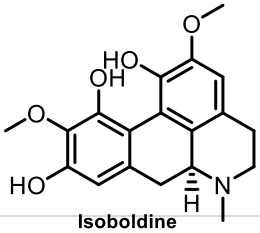
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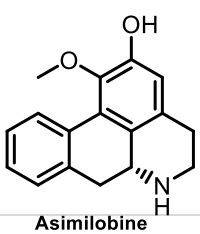
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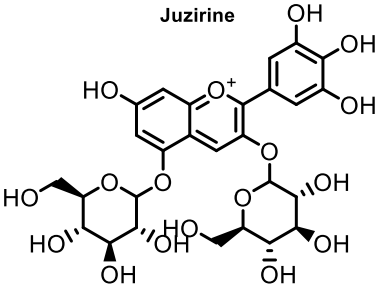
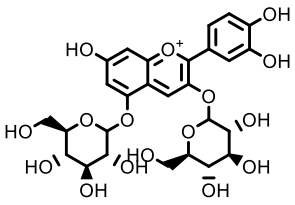

Delphinidin-3,5-diglucoside


Cyanide ion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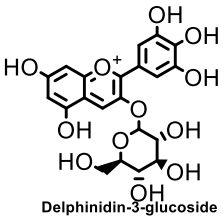
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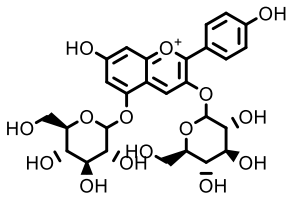
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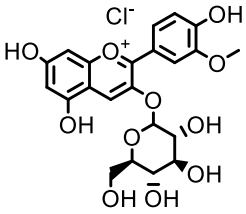
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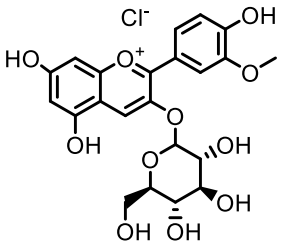
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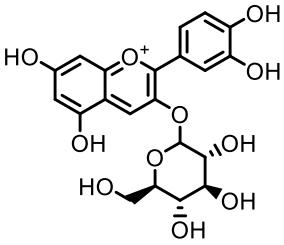
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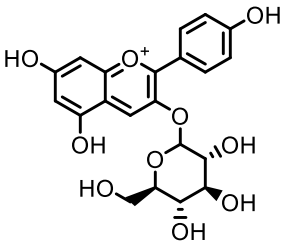
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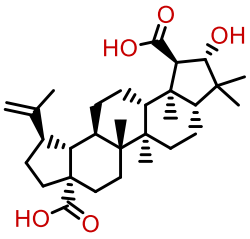
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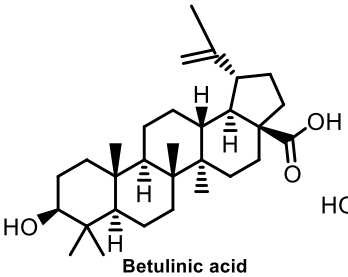
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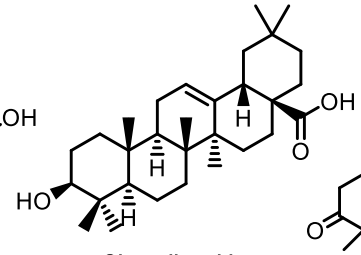
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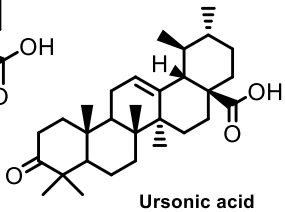
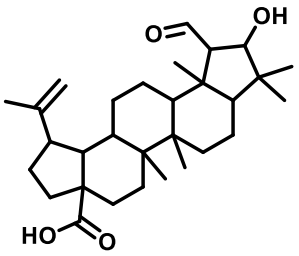

Ursonic acid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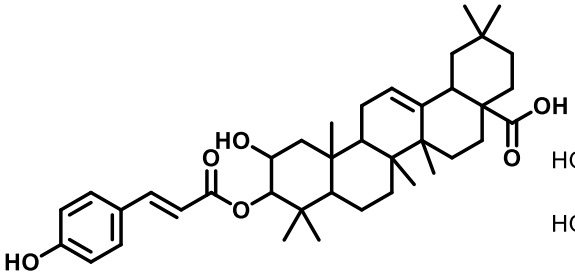
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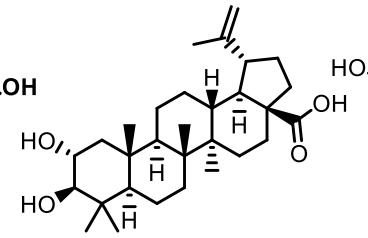
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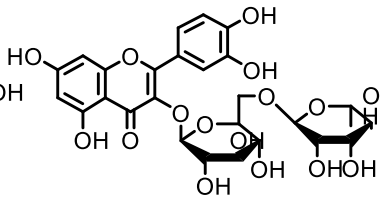
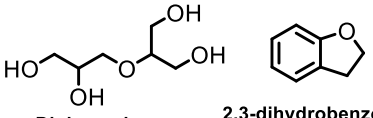
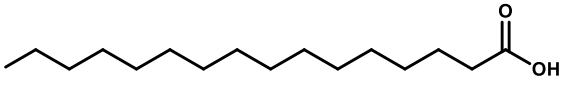

Rutin


Diglycerol

2,3-dihydrobenzofuran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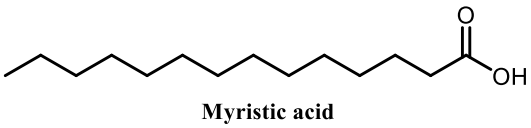
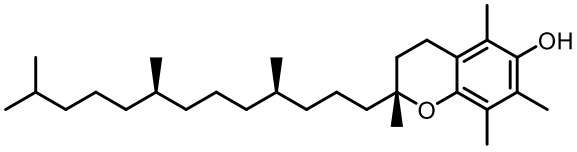
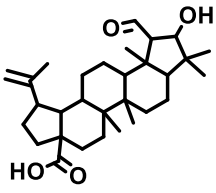

Myristic acid


alpha--tocopherol


Colubrinic acid

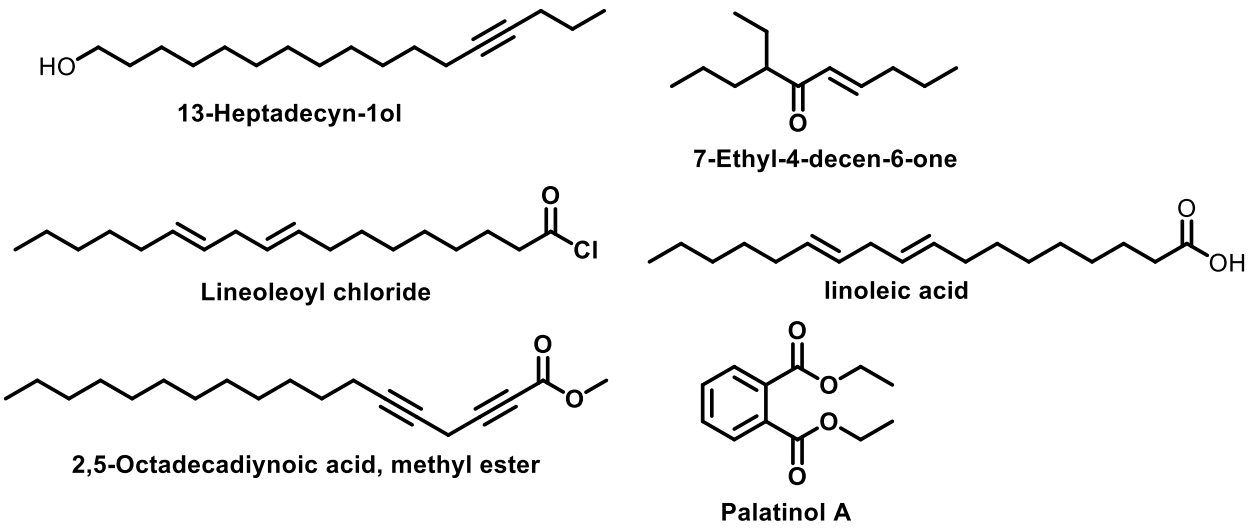


Fig: Chemical components isolated from Ziziphus jujube

B) PHARMACOLOGICAL ACTIVITY

According to Islamic traditional medicine (ITM), *Z. jujuba* fruit functions as an emollient, maturative, and digestive agent, potentially enhancing blood circulation, purifying blood, reducing inflammation, and lowering internal temperature. Modern research has validated various therapeutic properties, including antioxidant, antibacterial, anti-hyperglycaemic, hepatoprotective, and sedative effects[42].

The fruit has historically been used to treat various conditions including sickness, sensations, burns, tuberculosis, thirst, and blood-borne disorders, while also serving as a tonic, digestive aid, laxative, and aphrodisiac[42]. In Indian Ayurvedic medicine, the roots treat headaches, nausea, and coughing[43], while the bark addresses chronic diarrhea and dysentery. The leaves, when boiled, are used for body cleansing before burial and for weight management. In India, powdered leaves and bark serve as traditional wound dressings[44].

Research has demonstrated that all parts of *Z. jujube* possess significant pharmacological and toxicological effects[45-47]. Key therapeutic properties include:

1. Hypnotic-Sedative and Anxiolytic Effects: Seeds and leaves demonstrate central nervous system depression, with Jujuboside A (JuA) showing inhibitory effects on rat hippocampus[48,49]. Sanjoinine A and nuciferine from fruits extend hexobarbital-induced sleeping time.
2. Antineoplastic Properties: Triterpenoic acids, particularly lupane-type triterpenes, show significant cytotoxic activities. The 3-O-p-coumaroylalphitolic acids demonstrate enhanced cytotoxic activity[50]. Betulinic acid exhibits selective toxicity against melanoma cells and shows promise against various carcinomas, inducing apoptosis[51,52].
3. Antimicrobial Activity: Root ethanol extract shows antifungal effects against various Candida and Aspergillus species[53]. Leaf extracts demonstrate antibacterial properties[54], while betulinic acid from stem bark shows anti-HIV-1 activity[55].
4. Antiulcer Properties: Leaf extracts show dose-dependent antiulcer activity through cytoprotective and antisecretory mechanisms[56].

5. Anti-inflammatory Activity: The hydroalcoholic fruit extract reduces edema and granuloma tissue formation, likely through nitric oxide inhibition[57,58].
6. Additional Benefits Include:

- Antiallergic effects through hyaluronidase inhibition[59]
- Permeability enhancement for drug delivery[60]
- Cognitive benefits against Alzheimer's disease through oleamide[61]
- Reversible antifertility properties[62]
- Nephroprotective effects against drug-induced toxicity[63]
- Immunostimulant properties[64]
- Antioxidant activities[65,66]
- Wound healing capabilities[67-69]
- Neuroprotective effects through compounds like quercetin, rutin, and kaempferol[70]

In the research by Pahuja et al. [69], it was discovered that the hydroalcoholic extract of jujube fruit (HEJF) has anti-seizure properties. Rats' tonic hind limb extension and generalized tonic-clonic seizures were both resistant to the anticonvulsant effects of HEJF. According to this study, HEJF exhibited anticonvulsant qualities, lowered oxidative stress and cholinesterase activity, improved memory, and learning, and alleviated epileptics' effects on cognitive impairment [71]. Phenytoin, Phenobarbital, and HEJF when administered together improved their activity but not carbamazepine [72]. MEZJ (a methanolic extract of *Ziziphus jujuba* leaves) was also shown by Panda, et al. [73] to dramatically prevent PTZ-kindled seizures and to reduce oxidative stress brought on by PTZ-kindling, providing a neuroprotective effect on the brain via its antioxidant activity.

The neuroprotective and antiamnesic properties of Z. jujuba aqueous extract on the scopolamine model of AD were demonstrated by Djeuzong et al. in 2021[74]. Animals receiving the aqueous extract were shielded against memory and learning deficits over the long run. The anti-inflammatory, antioxidant, and anti-apoptotic actions associated with the extract may have a role in mediating these benefits, at least in part, according to an analysis of potential mechanisms of action.

Kaempferol 3-O-rutinoside was one among the flavonoids found in jujube that Zhu et al.[75] claimed had neuroprotective properties against oxidative stress and the ability to inhibit A aggregation. According to Gupta and Gupta's [76] research, pretreatment with the HEZJ and silymarin combination improved neuroprotection in the focal cerebral ischemia model by reducing oxidative stress.

Snakin-Z, a new peptide, was isolated from *Ziziphus jujuba* fruits and studied for its cholinesterase inhibitory effect by Zare-Zardini et al. [77]. The findings show that this peptide inhibits AChE and BChE enzyme activity and has an influence on ions' DPPH radical quenching [77]. The studies mentioned above clearly state the neuroprotective action of Z. jujube and it can be used in treating various neurodegenerative diseases.

C) TRADITIONAL USES

Traditionally, the selected plant along with other sub-species is used to treat different ailments[78] Current research indicates that almost all parts and its extracts showed significant pharmacological activity and frequently used as an alternative medicine to treat a range aliments and disorders.[79]

Traditional use of different parts of *Ziziphus jujube*

Fruits: The fruits are the main ingredient which are traditionally used as a digestible, tonic, aphrodisiac, and laxative to treat nausea, burn, sensations, thirst, tuberculosis[81] and blood bone diseases.[82]

Roots: the roots of *Ziziphus jujuba* species in ayurveda system is used to treat coughs, nausea, and headache. [80]

Bark: The bark of the *Ziziphus jujuba* is used to treat chronic dysentery and diarrhea.[80]

Leaves: The leaves of the Ziziphus jujube boiled in water is also used to clean corpse prior to burials. In addition, the leaves can be used to

reduce the weight and combat obesity. the fresh leaves of this species can be used to treat a wounds and urinary infection. When boiled in water it can be used to treat smallpox and chickenpox [81].the fresh leaves of this species can be used to treat a wounds and urinary infection. When boiled in water it can be used to treat smallpox and chickenpox[82]

Seeds: The seed extracts of the selected species can be used to treat eye inflammation and leucorrhoea[83].

However, the Omani community, primarily use the plant as an antifungal agent, cardiotonic, and an antiseptic agent to treat swollen especially joint, acne, shampoo, burns, acute constipation and diarrhea[84][85].

4. METHODOLOGY

A thorough literature survey was conducted on Z. jujube and the outcomes are documented concerning the presence of chemical constituents, pharmacological activity, and traditional uses. Various databases such as Pub Med, Google Scholar, Scopus, Science Direct, Consensus, Research Gate, etc were used for the current review work. The Different methods that are used to confirmed the pharmacological activites are DPPH Assay (2,2-Diphenyl-1-picrylhydrazyl), ABTS Assay (2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)), Enzyme Inhibition Assays, Cell-based Assays, Disk Diffusion Method, Broth Dilution Method, MTT Assay, Flow Cytometry, Colorimetric assay etc.

5. CONCLUSION

Traditional Indian medicine has long relied on natural herbs for healing. Medicinal plants derive their curative properties from various complex chemical substances, particularly secondary metabolites including alkaloids, flavonoids, terpenoids, saponins, and phenolic compounds, which are distributed throughout different plant parts.

Ziziphus jujuba Mill (commonly known as Bor), a member of the Rhamnaceae family, demonstrates an impressive range of traditional and validated medicinal properties. Traditionally used as a tonic and aphrodisiac, it has shown therapeutic potential as a hypnotic-sedative, anxiolytic, anticancer agent (particularly against melanoma cells), antifungal, antibacterial, antiulcer, anti-inflammatory, cognitive enhancer, antispastic, antifertility/contraceptive, hypotensive, antinephritic, cardiotonic, antioxidant, immunostimulant, and wound healing agent.

The remarkable medicinal properties of *Z. jujuba* stem from its diverse phytochemical constituents, each offering unique and multifaceted benefits. The fruit contains two particularly potent compounds - betulinic acid and amphitolic acid - which demonstrate cytotoxicity against HT-29 colon cancer cell lines. The seeds contain several active compounds, including 7-ethyl-4-decen-6-one, linoleoyl chloride, linoleic acid, and 2,5-octadecadiynoic acid methyl ester, contributing to its significant antimicrobial properties.

This comprehensive review highlights the importance of *Ziziphus jujuba* as a premier natural medicinal herb by examining its chemical constituents, pharmacological activities, and traditional applications. Given the plant's demonstrated potency in both *in vitro* and *in vivo* studies, *Ziziphus jujuba* shows considerable promise as a medicinal plant. Further clinical trials are warranted to fully realize its potential for improving human health and well-being.

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