

Ziziphus xylopyrus (Retz.) Wild.: A plant of enormous biomedical potential

Mohammad Hashim Mansoori^{1,2}, Charanjit Kaur³, Mahesh Kumar Gupta²,
Manish Vyas⁴, Vijay Mishra^{5*}

¹Department of Medicinal Chemistry, Adina Institute of Pharmaceutical Sciences, Sagar, Madhya Pradesh, India, ²Department of Pharmacy, Oriental University, Indore, Madhya Pradesh, India, ³Department of Pharmaceutical Chemistry, School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, Punjab, India, ⁴Department of Ayurveda, School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, Punjab, India, ⁵Department of Pharmaceutics, School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, Punjab, India

Abstract

In the current scenario, demand for the herbal products is growing exponentially worldwide. Herbal medicine is becoming an integral part of both traditional and modern system of medicines for the treatment of various ailments and diseases. A number of plant materials are under research for exploiting their potential medicinal values, and *Ziziphus xylopyrus* (Retz.) Wild. is one of them. The main phytoconstituents of this plant include quercetin, quercitrin, kaempferol, kaempferol-4'-methylether, and cyclopeptide alkaloids amphibine-H and nummularine-K, which show a variety of biomedical applications. The present review sheds light on the botanical profile, phytoconstituents, traditional and ethnomedicinal uses as well as different pharmacological activities of *Z. xylopyrus* plant.

Key words: Antioxidant, herbal medicine, phytoconstituents, quercetin, zizyphus

INTRODUCTION

Traditional medicine, which is based on theories, beliefs, and personal experiences, is a pool of knowledge skills and practices that are being used by various cultures for maintaining health and preventing, diagnosing, improving, and treating both physical and psychological illnesses.^[1] The affordability and accessibility of the medicinal plants have made them an important part of many people's life worldwide.^[2] Many herbs and roots are used in the Kingdom of Saudi Arabia by common people for various ailments.^[3]

BOTANICAL PROFILE OF *ZIZIPHUS XYLOPYRUS*

It is universally known as Jujab. *Z. xylopyrus* is a huge, sprawling shrub, having height 6–10 m, with undeveloped shoots and rusty tomentose. The fresh branches possess two spines, first one is straight and second one is curved having swollen nodes at the leaf scars [Figure 1].^[4,5]

Taxonomy of *Z. xylopyrus*

The taxonomy of *Z. xylopyrus* plant can be summarized as Kingdom - Plantae, Phylum - Magnoliophyta, Subphylum - Euphyllophytina, Class - Magnoliopsida, Subclass - Rosidae, Order - Rhamnales, Family - Rhamnaceae, Genus - *Ziziphus*, and Species - *xylopyrus*.^[6]

Occurrence and Distribution

It is a perennial shrub with immense medicinal potential and is dispersed all over Pakistan, China, Northwestern, Central, and South India as well as Uttar Pradesh and Bihar.^[7]

Address for correspondence:

Dr. Vijay Mishra, Department of Pharmaceutics, School of Pharmaceutical Sciences, Lovely Professional University, Phagwara – 144 411, Punjab, India.
E-mail: vijaymishra2@gmail.com

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Description of Plant Parts

Fruits

Z. xylopyrus fruit is a rounded or globular-shaped drupaceous berry having 1.2–1.8 cm diameter, dark brown colored, and possesses astringent taste. The pericarp of the fruit is hard, and endocarp is stony in nature. The fruit has 3 cells with wrinkles on its surface. The round concave depression with a diameter up to 2 mm is left at the point of separation of stalk. The seed of the plant is long (5–8 mm).^[4,5,8]

Leaves

Green leaves of *Z. xylopyrus* possess pungent taste and slight aromatic odor. They possess alternate arrangement with glabrous surface having rounded symmetrical oblique base and obtuse apex. Leaves are about 2–7 cm long and have serrulate margin with pinnate venation.^[9]

Flowers

Z. xylopyrus flowers are tiny, yellowish white, or yellow colored, compactly juvenile, ovoid buds, 3–4 mm long pedicels. Calyx lobes, 2–2.5 mm long, are turned upside down to the central. It has hair and projection free interior with juvenile exterior. There are 5 egg-shaped, flat with narrow base petals of 1.5–2 mm long. It has 5 fused sepals with diameter of $2.5-3 \times 1.5$ mm. There are 5 discoid stamens with 10–60 lobes, which are rarely glabrous and 5-lobed.^[10]

ETHANOMEDICINAL USES OF *Z. XYLOPYRUS*

It is recommended in periodontitis and for the investigation of production and development of ovum.^[11,12] The sticks obtained from its bark are beneficial for cleaning of teeth and also possess the property of contracting the body tissues to reduce secretions of body fluids.^[13,14] In India, for the management of cough, fresh stem bark of this plant is masticated with one or two peppers (*Piper nigrum*), and to relieve chest pain associated with cough, paste of bark and leaf powder is applied on the chest.^[15] It is used as a sedative in Turkey for medicinal purpose.^[16]

The black dye used for dyeing leather is obtained from barks and fruits of this plant.^[17] This plant has been reported to be useful in case of patient suffered from snake bite, obesity, fever, diabetes, digestive disorders, insomnia, and diarrhea and hence commonly used in Ayurvedic and conventional medicine.^[18-24]

Z. xylopyrus possesses a number of bioactivities including analgesic,^[25] antimicrobial,^[26] antioxidant,^[27] antidiarrheal,^[28] anti-inflammatory,^[25] antiulcer,^[27] antidepressant,^[29] antisteroidogenic effect,^[30] and wound healing.^[31]



Figure 1: *Ziziphus xylopyrus* (Retz.) Wild., (a) plant and (b) leaves

TRADITIONAL USES OF *Z. XYLOPYRUS*

As per Jain *et al.*, when a woman took a decoction of this plant root early in the morning for a week, the sterility developed.^[11] Bhattacharjee has detailed about relief from chest pain in patient with cough and cold with roasted seed powder's paste.^[32] According to Ayyarna and Ignacimuthu, snake bite can be treated with the hot paste made from a mixture of leaves of *Z. xylopyrus* and *Terminalia bellerica* and stem bark of *Murraya koenigii*.^[33] As per Patil and Bhaskar, leucodermal patches can be cured by the application of paste on the external surface prepared from leaves of *Z. xylopyrus* and flowers of *Datura innoxia*.^[34]

Reddy *et al.* have reported that diseases such as anthrax, trypanosomiasis, and ephemeral fever are prominent in the Eastern Ghats of Andhra Pradesh (India) and can be treated with mixture of powdered roots of this plant and bark obtained from stem of *Erythroxylum monogynum*, *Pterocarpus marsupium*, *Calotropis gigantea*, and chilies when dried and administered internally with water for 2–3 days once daily, it helps in the treatment of mentioned diseases in the Lambadas tribes of the Eastern Ghats of Andhra Pradesh (India).^[35] Jagtap *et al.* have described the use of pulverized fresh fruits of *Z. xylopyrus* in urinary problems when administered 2 times daily.^[16] According to Dash and Pandhy, root bark and fruits of this plant are beneficial in case of patient suffering from diarrhea.^[13] As per Karuppusamy, in Paliyan tribes of Sirumalai hills of Southern India, the fruit triturate of *Z. xylopyrus* in combination with milk proved useful in diabetes when taken continuously for 5 days.^[36] Reddy *et al.* have conveyed that stomach indigestion can be treated with powder mixture of *Z. xylopyrus* fruit and pinch of ginger when taken orally 3 times daily.^[20]

Tetali *et al.* informed that, for the treatment of diarrhea, with one cup of water or boiled milk or tea, 15 ml of seed powder of this plant is useful if administered 3 times daily orally for 2 days.^[37] Kadavul and Dixit described the use of leaves and stems of *Z. xylopyrus* in tropical forests of the Eastern Ghats of India for the management of headache, hysteria, and fox bite.^[38] According to Meena and Rao, for the treatment of bristles and pyorrhea, *Z. xylopyrus* roots are valuable and

are used to investigate oogenesis in Meena Community of Rajasthan.^[12]

Rajendar *et al.* detailed about Eturnagaram Mandal of Warangal district of Andhra Pradesh, India, that they have used water concentrate of *Z. xylopyrus* bark to cure the skin rashes.^[39] As per Jain *et al.*, the pigment recovered from the fruits of this plant has been utilized for leather production by treatment and processing of animal hides by Bheel tribes of Guna District of Madhya Pradesh.^[21] Naidu and Khasim have stated about the use of the leaf paste of this plant and latex of *Ipomea carnea* for the treatment of pimples or boils and its use by the people of the Eastern Ghats of Andhra Pradesh.^[14] Lalitha *et al.* tested the treatment of indigestion with infusion of this plant prepared from bark powder (stem) when taken orally before meals in the morning in single dose for 3 consecutive days.^[40]

Rao and Sunitha described about the utility of tablets manufactured from the powder of stem bark of this plant in cases of cholera.^[41] As per Kumari *et al.*, the blend of bark powder of root of whole plant of *Viscum articulatum*, *Anogeissus latifolia*, *Acacia catechu*, and *Z. xylopyrus* is useful in patients suffering from piles and hemorrhage from nose and mouth.^[42]

PHYTOCONSTITUENT PROFILE OF *Z. XYLOPYRUS*

It has been found that leaves of this plant contain quercitrin and quercetin. The plant bark has oleanic acid, 7,3,4-trihydroxyflavan-3,4-diol, and tannins (7.2%).^[5] The plant also possesses xylopyrine-A and B (new 13-membered cyclopeptide alkaloids).^[43] The phytochemical screening of its leaf extract with different solvents has revealed the existence of carbohydrates, steroids, alkaloids, glycosides, saponins, sterol, flavonoids, phenolic compounds, and triterpenoids.^[9,29,44]

Numerous alkaloids (cyclopeptide) segregated from this plant are remarkably present in family Rhamnaceae. About 81 distinct alkaloids (cyclopeptide) have been disclosed from various species of this plant including seven (15-membered), 39 (14-membered), and 35 (13-membered) ring cyclopeptides.^[45] The different phytocompounds found in various parts of this plant are revealed in Table 1.

Numerous workers have separated phytoconstituents from this plant. In this regard, Devi *et al.* have achieved the isolation of cyclopeptide alkaloids, i.e. nummularie-K and amphibine-H from *Z. xylopyra* stem bark.^[46] Singh *et al.* have segregated xylopyrine-A and B (new 13-membered cyclopeptide alkaloids) from it and the structures of these alkaloids are elucidated using spectral and chemical techniques.^[43] Pandey *et al.* have separated two already existing alkaloids, i.e. sativanine-H and nummularine-P along with a novel 14-membered ring cyclopeptide alkaloid xylopyrine-F from *Z. xylopyrus* root bark.^[47]

Pandey *et al.* have also isolated scutianine-C along with xylopyrine-C (a new 14-membered cyclopeptide alkaloid) from the root bark of this plant.^[48] In the preceding studies, Pandey *et al.* have segregated xylopyrine-H and G (two novel cyclopeptide alkaloids) from the bark of this plant.^[49]

Washid and Ammeta have separated various phytoconstituents from ethanolic leaf extract of the plant using chromatographic techniques such as thin-layer chromatography.^[50] Jain *et al.* have accomplished the phytochemical examinations on different leaf extracts of the plant and revealed the existence of flavonoids, tannins, carbohydrates, gum, and mucilage.^[9] Gautam *et al.* analyzed the methanolic leaf extract of the plant through phytochemical techniques and specified the occurrence of flavonoids, tannins, carbohydrates, saponins, mucilage, and gum.^[51]

Sharma *et al.* have executed the phytochemical examinations on ethanolic leaf extract of the plant and realized the occurrence of saponins, carbohydrates, flavonoids, alkaloid, tannins, steroids, and terpenoids.^[52]

PHARMACOLOGICAL ACTIVITIES OF *Z. XYLOPYRUS*

Z. xylopyrus shows various pharmacological activities, which are represented in Figure 2.

Antifungal Activity

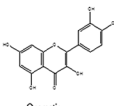
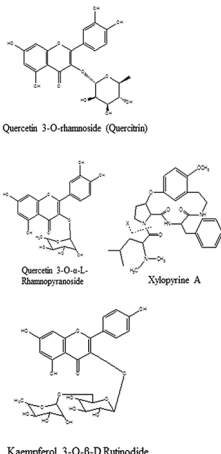
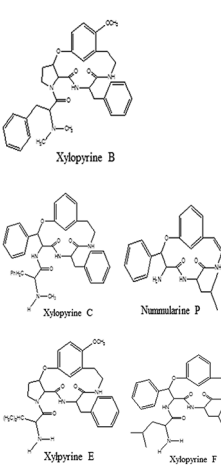
Activity of phytocompounds isolated from the extracts prepared from leaf and fruit against fungi has given a potential lead to control the diseases that affect plants and can be a good substitute for chemical alternatives. Numerous studies have stressed the value of plants and phytocompounds to constrain various fungal infectious agents.^[53-60] Raghavendra *et al.* assessed the extract prepared from leaf and fruit of this plant for its activity against fungi using poisoned food technique that is one of the extensive methods adopted for assessing the antifungal activity of plant extracts. In this technique, authors noticed that the diameter of the colony made by treated fungi was reduced in poisoned plates in comparison to control by plant extract. Among the extracts of different parts of plant, leaf extracts revealed greater inhibition in comparison to extract prepared from fruit.^[17]

Antioxidant Activity

2,2-Diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity

The scavenging action of the extract prepared from leaf and fruit of this plant using DPPH assay was testified. Various concentrations of extracts were compared with the standard DPPH radical solution for color fading at 517 nm. The salvage DPPH radicals depended on the concentration. Among various

Table 1: Phytochemical constituents present in different parts of *Z. xylopyrus*

Plant part	Phytoconstituents	Chemical structures	References
Fruits	Reducing sugars, l-leucocyanidin, oleanolic acid, 3,3,4-tri-O-methyl-ellagic acid, carotene, Vitamin C, citric acid, and sucrose	 Quercetin	[4,10]
Root bark	Kaempferol and kaempferol-4'-methyl ether, cyclopeptide alkaloids - Xylopyrine A, B, C, D, E, F, G, and H, sativanine-H, and nummularine-p	 Quercetin 3-O-α-L-Rhamnoside (Quercitrin) Xylopyrine A Kaempferol 3-O-β-D-Rutinoidide	[43,47-49]
Flowers	5,7,3',4'-tetra hydroxy-3-O-α-L-rhamnosyl flavone: Quercitrin, E-4-hydroxy cinnamic acid, p-coumaric acid, E-4-hydroxy-3-methoxycinnamic acid, ferulic acid, hyperoside, 5,7,3',4'-tetrahydroxy 3-O-P-D-galactosyl, rutin, kaempferol, and 3-O-rutinoside	 Xylopyrine B Xylopyrine C Nummularine P Xylopyrine E Xylopyrine F	[29]
Stem bark	Oleanolic acid, d-7,3',4'trihydroxyfavan 3,4-diol, Tannins, Nummularine- K Cyclopeptide alkaloids: Amphibine H		[29,46]
Seeds	Insoluble mixed fatty acids: Myristic, Unsaponifiable matter: sterol; oleic acid and linoleic		[62]
Leaves	Quercitrin and Quercetin		[7]

Z. xylopyrus: *Ziziphus xylopyrus*

extracts, the leaf extract showed stronger scavenging potential ($IC_{50} = 31.73 \mu\text{g/ml}$) then fruit extract ($IC_{50} = 36.79 \mu\text{g/ml}$). However, ascorbic acid revealed significant scavenging of DPPH radicals ($IC_{50} = 6.17 \mu\text{g/ml}$). Thus, it was concluded that the extracts of *Z. xylopyrus* owed reducing character and acted as an effective free radical scavengers.^[17]

ABTS radical scavenging activity

Raghavendra *et al.* figured out the effectiveness of extracts prepared from leaf and fruit of this plant to trap ABTS radicals. Both leaf and fruit extracts were able to trap ABTS

radicals depending on the concentration. Leaf extract showed potent scavenging action ($IC_{50} = 4.61 \mu\text{g/ml}$) in comparison to fruit extract ($IC_{50} = 8.37 \mu\text{g/ml}$). Ascorbic acid displayed robust salvaging activity ($IC_{50} = 3.05 \mu\text{g/ml}$) in comparison to different extracts. Then, it was concluded that extracts of this plant bear reducing activity and thus are powerful scavengers of free radicals.^[17]

Ferric reducing activity

Chung *et al.* investigated the extracts prepared from leaf and fruit of this plant for reducing activity of ferric ion. Authors

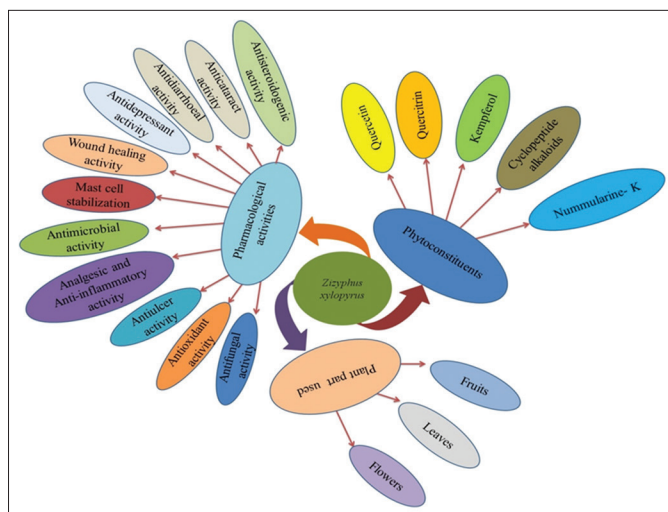


Figure 2: Pharmacological activities, plant part used, and phytoconstituents of *Ziziphus xylopyrus*

observed increased absorbance of reaction mixtures having increased concentration of extracts which revealed the reducing character of the extracts. The activity of leaf extract was more than extracts prepared from other parts of the plant. However, ascorbic acid showed higher reduction potential. Thus, extracts of this plant could act as donors of electrons, ceasing chain reactions of the radicals, and display reducing power.^[61]

Antilulcer Activity

Sharma *et al.* induced gastric ulcer using hydrochloric acid (HCL)/ethanol. Authors used ranitidine as positive control and assessed the antilulcer potential of ethanolic extract, ethyl acetate fraction, and precipitated aqueous fraction of *Z. xylopyrus* leaves. Among all extracts, aqueous fraction with precipitation exhibited a substantial decrease in ulcer index, because of its antioxidant potential.^[27]

Analgesic and Anti-inflammatory Activity

Mishra *et al.* have examined the anti-inflammatory and analgesic potential of methanolic and chloroform extracts of *Z. xylopyrus* stem. The investigations evidenced about substantial anti-inflammatory and analgesic potential of the methanolic extract.^[25]

Antimicrobial Activity

Karuppusamy and Rajasekaran investigated the antibacterial potential of the aqueous extract of *Z. xylopyrus* seeds against *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Escherichia coli*, and *Bacillus subtilis* using hemocytometric and colorimetric assays along with microtiter plate. Authors revealed that the seed extract displayed no activity against bacteria.^[62]

Mast Cell Stabilization

Jena *et al.* examined 9-day-old fertilized chick eggs *in vitro* to determine the wound healing potential of ethanolic extract of stem bark of the plant using chorioallantoic membrane model. An angiogenic activity was witnessed in fertilized chick eggs given with extract in comparison to control, depending on the dose.^[63]

Wound Healing Activity

Jain *et al.* estimated the wound curing activity of ethanolic leaf extract of the plant in rats using incision and excision wound models. It was observed that pre-treatment with ethanol extract resulted in prominent decreases in the epithelization period, lesion area, and improved breaking strength in incision wound model and improved percentage of lesion contraction in case of excision wound model.^[31] When the linear incision and excision wound model was used with framycetin sulfate cream (positive control), the ointment prepared from the ethanolic extract showed wound healing activity with a substantial dose-dependent wound contraction and tensile strength in comparison to positive control group.^[63]

Antidepressant Activity

Sharma *et al.* assessed the potential of precipitated fraction and ethyl acetate fraction of defatted ethanolic extract of the leaves of this plant against depression utilizing tail suspension test and forced swimming test with imipramine HCL as a positive control. In each model, precipitated fraction appreciably decreased the time of immobility greater than the ethyl acetate and ethanol extract in comparison to positive control. Authors proposed that the flavonoid glycosides can be responsible for the antidepressant activity of *Z. xylopyrus* through entrance into the brain tissues by the metabolic reactions, shielding functions of the brain from CNS perturbations and finally causing an effect against depression.^[29]

Antidiarrheal Activity

Singhal and Senthil Kumar provided clear evidence regarding antidiarrheal potential of orally administered ethanolic and aqueous extract of fruit at dose 200 mg/kg body weight. The results were 51.85% and 89.88% for aqueous and ethanolic extracts, respectively, in comparison to the standard drug, diphenoxylate (5 mg/kg) with 93.80% protection ($P < 0.001$).^[28]

Anticataract Activity

Kumar *et al.* testified the efficacy of methanolic extract prepared from its fruit on glucose-induced cataract. Goat

eye lens were distributed to four groups, and artificial aqueous humor with different glucose concentration was used for incubation, in different groups such as Group I lenses - 5.5 mM (normal control), Group II lenses - 55 mM (toxic control), and Group III and IV lenses - 55 mM with 50 and 100 µg/ml, respectively. The entire lenses were exposed to photographic estimation for opacity. The same procedure was adopted for chick lens also. The grades of opacity were 0, +, ++, and +++ in individual group, respectively. The extract at 100 µg/ml displayed effective prevention on *in vitro* glucose-induced cataract.^[64]

Antisteroidogenic Activity

Dhanapal *et al.* have assessed onset of reproductive maturity (antisteroidogenic action) of the ethanolic extract prepared from its leaves on the ovary and the ovarian steroidogenesis in pre-pubertal female mice. Remarkable delay in sexual maturation proportional was noticed and verified by a change in the vaginal opening and arrival of first estrus. Moreover, an increased level of protein contents, the ovarian cholesterol, and ascorbic acid were evidenced in a dose-dependent manner while the extract appreciably reduced the weight of the uterus and the ovary and glucose-6-phosphate dehydrogenase and $\Delta 5\text{-}3\beta$ -hydroxysteroid dehydrogenase activities. The antisteroidogenic action on pre-pubertal female mice with prior treatment might be because of inhibited ovarian steroidogenesis and interruption in puberty.^[30]

CONCLUSION AND FUTURE PERSPECTIVE

The demand of the time is the development of safe and effective drugs from herbal origin. Keeping this point of view, the blending of traditional knowledge with advanced experimental methodologies for determining the efficacy and safety of *Z. xylopyrus*-based herbal drugs is required. It virtues further work toward the isolation and characterization of phytoconstituents obtained from this plant.

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