

## Review Article

### *Zizyphus oenoplia* Mill: A review on Pharmacological aspects

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Received: 11 February 2016

Revised: 25 March 2016

Accepted: 28 March 2016

#### Abstract

**Objective:** Herbal medicine is the oldest medical practice known to man. Since the dawn of mankind, various plant resources are used to cure different diseases and also for a long and healthy life. This review focuses on the detailed phytochemical composition, medicinal uses, along with pharmacological properties of different parts of this multipurpose tree. The ancient knowledge of plant based medicine has transferred from generations to generations and accumulated as ethno-pharmacological knowledge among different ethnic groups. India is the spanning bed of traditional phytomedicinal system where Ayurveda was born out of the knowledge of traditional medicine. In various other countries of South-Eastern Asia, South America, and in Arabian countries, still today, a great number of people rely primarily on phytomedicines for the treatment of diseases. In the complementary and alternative medicinal systems, *Zizyphus oenoplia* is one such plant which is well-known for its therapeutic efficiency in different diseases globally. **Conclusion:** In the present time, the pharmaceutical companies are concentrating more toward the plant based traditional medicines to avoid the side-effects and resistance against synthetic drugs. *Zizyphus oenoplia* has proved its efficiency in different disease models by various researchers. Therefore, this review comprehensively covers the medicinal and pharmacological activities of different parts of the plant *Zizyphus oenoplia*.

**Keywords:** Ethnopharmacology, herbal medicine, *Zizyphus oenoplia*

#### Introduction

Traditional medicine is a main part of the cultural heritage of a society and it has developed in accordance with the lifestyle and ancient practices of the society. During practical experiences of herbal remedies the therapeutic results of the various traditional medicinal systems around the world. Indian, Chinese, and Arabian traditional medicinal systems are highly developed (Akerlee et al., 1996). Traditional Indian medicinal systems have reached to various other countries such as Malaysia and America. According to a WHO report, around 80% of the world's population primarily relies on traditional medicines. *Zizyphus oenoplia* an important shrub, often found throughout the hotter parts of India, Ceylon, Tropical Asia and Australia (Pullaiah et al., 2002). Ayurveda (the knowledge for long life),

originated in India in the mid-second millennium BCE, known as the Vedic period. Susruta Samhita and Charaka Samhita is the core of the Ayurvedic medicinal systems which have describe the therapeutic usage of thousands of plants. One such plant mentioned in Ayurveda. *Zizyphus oenoplia* Mill. (Family-Rhamnaceae) commonly well known as makai in hindi and Jackal Jujube in english, is a straggling shrub distributed all over the hotter regions of Pakistan, Sri Lanka, India, Malaysia, and Tropical Asia (Pullaiah et al., 2002). Hosne et al., (2008), investigated taxonomic studies of six species of *Zizyphus* Mill., viz. *Z. funiculosa* Buch. Ex Lowson, *Z. glabrata* Heyne ex Roth, *Z. mauritiana* Lam., *Z. oenoplia* (L.) Mill., *Z. rugosa* Lam., and *Z. xylopyrus* (Retz.) Willd. occurring in the flora of Bangladesh has been given. It is distributed from Indian subcontinent through southern China and South East Asia to northern Australia (Jadhav et al., 2011; Indian Pharmacopoeia, 1996). The flowers are green, in sub sessile axillary cymes. The fruits are containing a single seed having globose drupe, black and shiny when ripe (Hosne et al., 2008). It is one of the folk herbal medicine has some

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major pharmacological properties as blood purifier, abdominal pain killer, febrifuge etc. It is frequently used in Uttar Pradesh (India) for liver diseases (Pundir et al., 2009; Jadhav et al., 2011). The roots of the plant possess antiulcer and antioxidant, anthelmintic (Majumder et al., 2011; Jadhav et al., 2012), antiplasmodial (Suksamrarn et al., 2005) angiogenic potential (Mahapatra et al., 2011), antidenaturation and antibacterial activity (Ramalingam et al., 2010), wound healing activity (Kuppast et al., 2012), hepatoprotective potential against antitubercular drugs induced hepatotoxicity (Rao et al., 2012) and as an ingredient in the preparation of stomach ache pills among the Munda tribe (Singh and Panda, 2005). *Z. oenoplia* plant is widely used in Ayurveda for the treatment of various diseases, such as ulcer, Stomach ache, obesity, asthma and it has an astringent, digestive, antiseptic, hepatoprotective, wound healing and diuretic property (Suryakant et al., 2011; Rao et al., 2012; Pullaiah et al., 2002). *Ziziphus* plants are traditionally used as medicine for the treatment of various diseases such as digestive disorders, urinary troubles, diabetes, skin infections, diarrhea, fever, bronchitis, liver complaints, anaemia, etc (Mishra and Bhatia, 2014) and also used as astringent, bitter tonic, anthelmintic, digestive and antiseptic, used in hyperacidity and healing of wounds (WHO/PHARM/92.559/rev).

*Z. oenoplia* reveals the presence of alkaloid, flavonoids, phenolic content and terpenoid which may be responsible for its medicinal efficacy. The plant also contains heavy metal and inorganic elements within the permissible limits. Furthermore phytochemical study required to isolate and characterize the active principles of *Ziziphus oenoplia* (Eswari et al., 2013). Chemical investigation of *Z. oenoplia* has shown the presence of cyclopeptide alkaloids such as Ziziphine (Suksmrarn et al., 2005). It is reported that the leaves of *Z. oenoplia* have phenolic content, heavy metal and inorganic elements, which is determined by official method. The results obtained shows that the extracts contain medicinally important bioactive constituents and also heavy metals present in the plant extracts were within the permissible limits. This justifies its use in the traditional medicine for the treatment of different diseases such as ulcer, asthma, dysentery and fever (Lalitha et al., 2013). The root bark of *Z. oenoplia* chloroform extract identified three new compounds by spectral analysis and stereo chemical assignments with reference to other related compounds of known stereochemistry. In continuation of the search for bioactive substances of new structural type we found that the chloroform extract from the root bark of *Z. oenoplia* consists of a new compound Hydroxy carboxylic acid (Prabhavathi et al., 2015).

## Ethnomedicinal uses

The ethanobotanicals has a long folkloric uses for the treatment of various diseases. The plant produces cyclopeptide alkaloids known as ziziphines and has major biomedical applications. In India, the roots are used in Ayurvedic medicine. The Konkani peoples of Maharashtra uses leaves as a dressing for wounds (Suksmrarn et al., 2005). In Burma, the stem barks are used as a mouthwash for sore throats, dysentery, and for inflammation of the uterus. Research in Thailand has found that extracts of ziziphine from *Z. oenoplia* var. *brunoniana* show antiplasmodial in vitro activity against the malaria parasite *Plasmodium falciparum*. Therefore the researchers continue looking for more effective and safer hypoglycemic agents from natural source. This is new era of imperative topic for active research.

A survey of literature on *Zizyphus jujuba* linn. revealed a few pharmacological reports on the plant like antioxidant and antilisterial effect (Kritikar and Basu et al., 1994). It contains three flavones-Cglucosides-6"-sinapoylspinosin, 6"-feruloylspinin and 6-"p-coumaroylspinosin. The leaves and stems of genus *zizyphus* contain saponins 3-o-[2- $\alpha$ -L-fucopyrnosyl-3-o- $\beta$ -Dglucopyranosyl- $\alpha$ -L-arabinopyranosyl] jujubogenin. Abdel-Zaher et al., (2005), reported the butanol extracts of *zizyphus jujuba* leaves improved the oral glucose tolerance and potentiated glucose induced insulin release in type 2 diabetic rats (Abdel-Zaher et al., 2005). In previous study we investigated the effects of *Z. oenoplia* mill stem in type 2 diabetes model against alloxan induced diabetic rats to ascertain the folkloric claims of local healers (Shukla et al., 2011).

## Pharmacological activities

### Antibacterial activity

Dhunmati et al., (2013) studied that evaluation of antibacterial and antifungal activity of the roots of *Ziziphus oenoplia* (Linn) Mill, (Rhamnaceae), *in-vitro* antidenaturation and antibacterial activities of *Ziziphus oenoplia* (Ramalingam et al., 2010). The antibacterial activities of *Z. oenoplia* components were tested against wound pathogens, including *Staphylococcus epidermidis*, methicillin-resistant *Staphylococcus aureus*, multidrug-resistant (MDR), *Escherichia coli*, *Streptococcus pyogenes*, *Pseudomonas aeruginosa* and MDR *Acinetobacter baumannii* against skin infections. This antibacterial property leads to support the use of traditional medicine in the treatment of bacterial skin infections (David, 2010). *Ziziphus* plants (Rhamnaceae) possess

potent antibacterial activity with various bioactive compounds already recognized for medicinal importance (Sameera et al., 2015).

#### **Antimicrobial Activity**

Sharmin et al., (2014) investigated the antimicrobial activities of some Bangladeshi medicinal plants and evaluated of the antimicrobial activities of two *Ziziphus* species (*Ziziphus mauritiana* L. and *Ziziphus spinachristi* L.) on some microbial pathogens (Abalaka et al., 2010). Eswari et al. (2013) observed that aqueous extract of *Z. oenoplia* contains alkaloids, flavonoids, amino acids, tannins. (Tambekar et al., 2013) investigated that *Z. oenoplia* act against some enteric bacteria (*Escherichia coli*, *Staphylococcus aureus*, *Salmonella typhi*, *Salmonella enterica*, *Enterobacter aerogenes*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Klebsiella pneumonia*), *in-vitro* by agar disc diffusion technique. It was reported that ethanol and methanol extract of *Ziziphus oenoplia* showed activity against *P. vulgaris* and *Enterobacter aerogenes* respectively. Investigated root part of *Z. oenoplia* was extracted with ethyl acetate, 90% ethanol and water using soxhlet apparatus. These crude extracts were subjected to investigation for anti-denaturation study and antibacterial study by using a method designed by William's et al and agar ditch diffusion method respectively. Phytochemical analysis reported the presence of carbohydrates, alkaloids, phenolic compounds, tannins and saponins. All the extracts of *Zizyphus oenoplia* protected Bovine Serum Albumin (BSA) from denaturation more than 97% at 1µg/ml concentration. Only ethanolic extract showed activity against *Staphylococcus aureus* (Ramalingam et al., 2010).

#### **Wound healing activity**

Kuppast et al., (2012) studied the wound healing activity of aqueous and alcoholic extracts of fruits of *Z. oenoplia*, and reported that activity was found in alcoholic followed by aqueous extracts when compared to control. From the study it was concluded that alcoholic followed by aqueous extracts were found to posses significant wound healing activity. The results were compared with the Framycetin sulphate cream as reference standard drug.

#### **Anthelmintic activity**

Majumder et al., (2011) have been studied the *in-vitro* anthelmintic activity of *Z. oenoplia* Mill root extracts. Jadhav et al., (2012) also been studied the preliminary phytochemical analysis and anthelmintic activity of *Z. oenoplia* Mill.

#### **Antiplasmodial**

The anti plasmodial activity of the hydroalcoholic extract of *Ziziphus mauritiana* seed against *Plasmodium berghei* in Swiss albino mice was reported (Mishra et al., 2014).

#### **Antioxidant activity**

Ethanol and aqueous extract of *Z. oenoplia* posses significant antioxidant activity, which has greater utility as therapeutic agent in preventing oxidative stress related degenerative diseases (Suryakant et al., 2012). Further in future it is necessary to identify & isolate the possible active phytoconstituents responsible for the antioxidant activity and study its pharmacological activity

#### **Antihepatotoxicity activity**

Pundir et al., (2009) was investigated the herbal hepatoprotective formulations in Lucknow, india, and studied ethanolic extract of *Z. oenoplia* (L.) Mill roots against antitubercular drugs induced hepatotoxicity in experimental models (Rao et al., 2012). The hepatoprotective activity of ethyl acetate fraction of *Z. oenoplia* roots (ZO) against paracetamol induced liver damage in albino rats was investigated and ethyl acetate fraction found an effective hepatoprotective action against paracetamol-induced hepatic injure in rats (Rao et al., 2015). Investigation of herbal formulation containing *Z. oenoplia* and others screened for hypatoprotective effect compared to formulations present in market (Singh et al., 2005).

#### **Antiulcer activity**

Jadhav et al., (2011) has been studied the anti ulcer activity of *Z. oenoplia* (L.) Mill roots in rats. *Z. oenoplia* roots were extracted with ethanol and antiulcer activity was investigated using Pyloric ligation test in rats. Results of the study suggested that antiulcer activity of *Z. oenoplia* is significant in alcoholic extract at a dose of 300mg/kg. Chloroform and aqueous fraction doesn't produce significant effect at a dose of 300mg/kg.

#### **Antiplasmodial Activity**

Suksamrarn et al., (2005) was isolated new antiplasmodial cyclopeptide alkaloids from *Z. oenoplia*. The roots of Thai *Z. oenoplia* extracted by using ethyl acetate and isolated four new 13-membered cyclopeptide alkaloids of the 5 type, ziziphine N–Q. Ziziphine N and Q exhibited significant antiplasmodial activity against the parasite *Plasmodium falciparum* with the inhibitory concentration IC<sub>50</sub> values of 3.92 and 3.5 µg/mL, respectively. Ziziphine N and Q also reported week antimycobacterial activity against *Mycobacterium tuberculosis* with MIC value of 200µg/mL.

#### **Anticancer activity**

A number of promising agents such as combrestatin, betulinic acid and silvesterol are natural plant derived compounds and played an important role in the treatment of various diseases (Kaur et al., 2011). Researchers investigated that Betulinic acid was isolated from *Zizyphus*

species, e.g. *Zizyphus mauritiana*, *Zizyphus rugosa* and *Z. oenoplia* and displayed selective cytotoxicity against human melanoma cell lines (Cichewitz et al., 2004). Mahapatra et al., (2011) has been investigated antiangiogenic potential of ethanolic extract of *Z. oenoplia* root screened by the chick chorioallantoic membrane (CAM) model in 9 days old fertilized chick eggs. The ethanolic extract was found to increase the number of capillaries on the treated CAM surfaces from 9 days old fertilized chick eggs. These results suggested that the ethanolic extract of *Z. oenoplia* root possesses significant angiogenic potential, which may be beneficial in the wound healing activity.

#### Hypolipidemic activity

Hypolipidemic activity of *Z. oenoplia* by measurement of various biochemical parameters such as total cholesterol, triglycerides, LDL, VLDL, atherogenic index (AI), LDL-C/HDL-C ratio and HDL cholesterol were studied (Eswari et al., 2013). Atherogenic index was used to determine the atherogenic potential of the drugs. Ethanolic extract at two dose levels (250 mg/kg and 500mg/kg) were showed significant hypolipidemic activity ( $p < 0.01$ ) by reduction in the level of serum cholesterol, triglyceride, LDL, VLDL, AI, LDL-C/HDL-C ratio and increase in HDL level as compared to cholesterol control groups. Hypolipidemic and antiatherosclerotic property of *Z. oenoplia* may be due the presence of alkaloids and flavonoids compounds. *Z. oenoplia* significantly decreases the cholesterol, triglyceride, VLDL-C, LDL-C, atherogenic index and a significantly increase in HDL-C in serum. These results were further substantiated with histopathological results. Ethanolic extract of *Z. oenoplia* significantly suppressed the elevated levels of AI and LDL-C/HDL-C ratio showing the beneficial effect of this plant in preventing atherosclerosis incidence.

#### Analgesic and anti-nociceptive activity

In previous studies, we were reported the analgesic effect on the tail flick model and found comparable with morphine sulfate in dose dependent manner (Shukla et al., 2016). Anti nociceptive effect of extract in formalin-induced paw licking model, *Z. oenoplis* was found significantly in the early phase at 100 and 200 mg/kg p.o. and comparable to the Diclofenac sodium (25mg/kg) group. It was found effective in both type non-narcotic and narcotic nociception models. The activity can be concluded due to presence of alkaloids and terpenoids in hydroalcoholic extract of *Z. oenoplia*.

#### Conclusion

*Z. oenoplia* plant is widely used in Ayurveda for the treatment of various diseases, such as ulcer, Stomach ache, obesity, asthma and it has an astringent, digestive, antiseptic, hepatoprotective, wound healing and diuretic property. It is traditionally used as

medicine for the treatment of various diseases such as digestive disorders, urinary troubles, diabetes, skin infections, diarrhea, fever, bronchitis, liver complaints, anaemia, etc. *Z. oenoplia* reveals the presence of alkaloid, flavonoids, phenolic content and terpenoid which could attribute to the medicinal efficacy. It consists of a new compound Hydroxy carboxylic acid. It is reported that the leaves of *Z. oenoplia* have phenolic content, heavy metal and inorganic elements. Chemical investigation of *Z. oenoplia* plant has shown the presence of cyclopeptide alkaloids such as Ziziphine.

#### References

- Abdel-Zaher AO, Salim SY, Assaf MH, Abdel-Hady RH. 2005. Teucrium Polium Antidiabetic activity and toxicity of *Zizyphus spina-christi* leaves. Journal of Ethnopharmacology, 101(1-3):129-138.
- Akerlee O. 1996. WHO guidelines for the assessment of the herbal medicines. Fitoterapia, 63:99-110.
- Cichewitz RH, Kouzi SA. 2004. Chemistry, biological activity, and chemotherapeutic potential of betulinic acid for the prevention and treatment of cancer and HIV infection. Medicinal Research Review 24: 90-114.
- David B. 2010. *In-vitro* anti-denaturation and antibacterial activities of *Zizyphus oenoplia*. Scholars Research Library Der Pharmacia Letter, 2(1): 87-93
- Dhummati K, Kousalya M, Jaison D, Yaseen AM. 2013. Evaluation of antibacterial and antifungal activity of the roots of *Zizyphus oenoplia* (Linn) Mill, (Rhamnaceae). World Journal of Pharmacy and Pharmaceutical Sciences, 2: 546-553.
- Eswari LM, Bharathi VR, Jayshree N. 2013. Hypolipidemic Activity on Ethanolic Extract of Leaves of *Zizyphus oenoplia* (L) Mill. Gard. International Journal of Pharmaceutical & Biological Archives, 4(1): 136-141.
- Eswari LM, Bharathi VR, Jayshree N. 2013. Preliminary Phytochemical Screening and Heavy Metal Analysis of Leaf Extracts of *Zizyphus oenoplia* (L) Mill. Gard International Journal of Pharmaceutical Sciences and Drug Research, 5(1): 38-40
- Hosne Are, Hassan Abdul Md, Khanam Mahbuba. 2008. Taxonomic study of the genus *Zizyphus* Mill. (Rhamnaceae) of Bangladesh. Bangladesh Journal of Plant Taxonomy, 15 (1): 47-61.
- Indian Pharmacopoeia. 1996. Government of India, Ministry of health and family welfare, controller of publication 4th ed, New Delhi, 4(ii)A, 53-54.
- Jadhav SA, Chavan SD, Jadhav DP. 2012. Preliminary Phytochemical and Anthelmintic activity of *Zizyphus*

- oenoplia* (L.) Mill. Journal of Chemical and Pharmaceutical Research, 2(3): 543-545.
- Jadhav SA, Chavan SD. 2012. In vitro antioxidant activity of *Ziziphus oenoplia* (L.) Mill Root extract. International Journal of Pharmaceutical Science, 4(4): 586-588.
- Jadhav SA, Prassanna SM. 2011. Evaluation of antiulcer activity of *Ziziphus oenoplia* (L.) Mill roots in rats. Asian Journal of Pharmaceutical Clinical Research, 1(1): 92-95.
- Kaur R, Kapoor K, Kaur H. 2011. Plants as a source of anticancer agents Scholars Research Library Journal of Natural Product and Plant Resource, 1(1): 119-124.
- Kirtikar KR, Basu BD. 1991. Indian Medicinal Plants, 2nd Edition, 1:295-296.
- Kuppast IJ, KV. 2012. Satish kumar wound healing activity of aqueous and alcoholic extracts of fruits of *Ziziphus oenoplia*. International Journal of Chemical Science, 10(2): 1021-1027.
- Mahapatra SS, Mohanta S, Satyaranjan, Nayak KA. 2011. Preliminary investigation of the angiogenic potential of *Ziziphus oenoplia* root ethanolic extract using the chorioallantoic membrane model. Science Asia, 37: 72-74.
- Majumder P. 2011. In vitro anthelmintic activity of *Ziziphus oenoplia* (L.) Mill root extracts – a promising ethnomedicinal plant. International Journal of Research Review Pharma Applied Science, 1(4): 334-340.
- Mishra T, Bhatia A. 2014. Antiplasmodial effects of the aqueous ethanolic seed extract of *Ziziphus mauritiana* against *Plasmodium berghei* in Swiss albino mice. International Journal of Pharmacological Research, 4(3): 111-116.
- Prabhavathi S, Vijayalakshmi S. 2015. New hydroxy carboxylic acid from the root bark of *Ziziphus oenoplia*. Journal of Pharmacognosy and Phytochemistry, 3(6): 150-152.
- Pullaiah T. 2002. Medicinal Plants in Andhra Pradesh. Illustrated Edn, Daya books 406-407.
- Pundir R, Singh G, Pandey AA, Saraf SA. 2009. Demand of herbal hepatoprotective formulations in Lucknow-A Survey. The Pharma Research, 1: 23-33.
- Ramalingam R, Madhavi BB, Nath AR, Duganath N, Sri UE, Banji D. 2010. In-vitro antitubercular and antibacterial activities of *Ziziphus oenoplia*. Scholars Research Library, Der Pharmacia Lettre, 2(1): 87-93.
- Rao V, Rawat AKS, Singh Anil P. 2012. Hepato protective potential of Ethanolic extract of *Ziziphus oenoplia* (L) Mill roots against antitubercular drugs induced hepato toxicity in experimental models. Asian Pacific Journal of Tropical Medicine, 283-288.
- Sameera, NS, Mandakini, BP. 2015 Investigations into the antibacterial activity of *Ziziphus mauritiana* Lam. and *Ziziphus xylopyra* (Retz.) Willd. International Food Research Journal, 22(2): 849-853
- Shukla A, Bukhariya V, Mehta J, Bajaj J, Charde R, Charde M, Gandhare B. 2011. Herbal Remedies for Diabetes: An Overview International Journal of Biomedical and Advance Research, 2(1): 57-68.
- Shukla A, Garg S, Garg A, Mourya P, Jain CP. 2016. Investigations on hydroalcoholic extract of *Ziziphus oenoplia* for analgesic and anti-nociceptive activity Asian Journal of Pharmacy and Pharmacology, 2(1): 15-18.
- Singh A, Kumar R, Gupta SS, Singh S, Rao CHV. 2015. Hepatoprotective Potential of *Ziziphus oenoplia* (L.) Mill Roots against Paracetamol Induced Hepatotoxicity in Rats. American Journal of Phytomedicine and Clinical Therapeutics, 3(01): 064-078.
- Singh MP, Panda H. 2005. Medicinal herbs with their formulations, vol 1. Delhi: Daya Publishing House, 97-100.
- Suksamrarn S, Suwannapoch N, Aunchai N, Kuno M, Ratananukul P, Haritakun R. 2005 *Ziziphine* N, O, P and Q, new antiplasmodial cyclopeptide alkaloids from *Ziziphus oenoplia* var. *brunoniana*. Tetrahedron, 61: 1175-1180.
- Suryakant A, Jadhav, Prassanna SM. 2011. Evaluation of antiulcer activity of *Ziziphus oenoplia* (L) Mill root in rats. Asian Journal of Pharmaceutical Clinical Research, 4(1): 92-95.
- Tambekar DH, Tiwari BK, Shirsat SD, Jaitalkar DS. 2013. Antimicrobial potential and Phytochemical analysis of medicinal plants from lonar lake. International Journal of Lifescience Biotechnology and Pharmaceutival Research, 2(3): 203-2011.
- The WHO Expert Committee on Diabetes mellitus, Technical Report Series, 1980.
- WHO/PHARM/92.559/rev.1 Quality control method for medicinal plant materials, Geneva: organization mondiale, dela sante, Geneva, 1992, 9, 22-34.