Review Article

Review on A Wild Medicinal Plant: *Ziziphus rugosa*

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ABSTRACT

Ziziphus rugosa is one of the wild plant belongs to the family Rhamnaceae. This plant is traditionally used for the treatment of Diarrhoea, Menorrhagia, Ulcer, Skin disease, Cough, Hypotension. The phytochemical analysis showed the presence of tannins, quinines, phenols, flavonoids, alkaloids, terpenoids, saponins, glycosides, protein, fibre, carbohydrates. Some active chemical constituents isolated and evaluated for their medicinal use. The pharmacological studies revealed that *Ziziphus rugosa* possess antidiabetic, antioxidant, anti-inflammatory, analgesic, anti-cancer, CNS depressant, antimicrobial, antiparasitic, dermatological and many other effects. The results of this exploration showed that, traditional use of *Ziziphus rugosa* plant is to treat various ailments in their area is based on the knowledge of tribal people reside in those regions. The current review will discuss the traditional uses, chemical constituents, pharmacological effects and therapeutic importance of *Ziziphus rugosa*.

Keywords: *Ziziphus rugosa*, Anti-diabetic, Antioxidant, Anti-inflammatory and cytotoxic.

INTRODUCTION

The world health organization (WHO) estimates that 4 billion people, 80 percent of world population presently use herbal medicine for some aspect of primary health care. WHO notes that 119 plants derived pharmaceutical medicines correlated directly with their traditional uses as plant medicines by native cultures.[1]The plant kingdom still holds many species of plant containing substances of medicinal value which have yet to be discovered and large numbers of plants are constantly being screened for their pharmacological value in addition to the already exploited plants. As a result of modern isolation techniques and pharmacological screening procedures new plant drugs usually find their place in modern medicine.[2] Since the time immemorial, our traditional system of medicine and folklore claiming those medicinal plants as whole or their parts are being used in all types of skin diseases successfully including bacterial and fungal. The most of the medicinal preparations now a day's available in the market are either not effective up to the mark or has developed resistance resulting in reoccurrence again. Plant derived drug serve as prototype to develop more effective and less toxic medicines.[3,4]

Ziziphus rugosa is one of the wild plants belongs to the family Rhamnaceae. This is a large family of flowering plants, mostly trees, shrubs, and some vines, commonly called as buckthorn family, included in the order Rosales. *Ziziphus rugosa* Lam. chiefly found in dry deciduous forests. It is a large straggling thorny evergreen straggling spiny shrub or small tree, 3-6 m tall, Leaves are alternate, dark-green, broadly ovate or broadly elliptic, serrate, oblique or subcordate or rounded at the base. The wood of the tree is reddish in color and moderately hard,[5] fruits orange to black, obovoid-globose or subglobose fruit is 9 - 12mm long and 8-10mm wide.[6-7] The Kodava community in the Kodagu region of the Western Ghats eats the raw and ripened fruit for nutritional source traditionally.[8] This plant is host for *Laccifer lacca*, a parasitic scale insect[9] and is food for various wild animals like Elephant and Deer.[10]

Figure 1: *Ziziphus rugosa* plant and its inflorescence.

Table 1: Some of the selected species of genus *Ziziphus* are[11-13]

Ziziphus angolito Standl	*Z. apetala* Hook.f. ex	*Z. attopensis* Pierre
Z. celata	*Z. cotinifolia* Reissek	*Z. fungii* Merr
Z. horrida Roth	*Z. hutchinsonii*	*Z. incurva* Roxb.
Z. mauritiana Lam.	*Z. mexicana* Rose.	*Z. mistol* Griseb.
Z.s montana W.Smith	*Z. mucronata* Willd.	*Z. platyphylla* Reissek
Z. robertsoniana	*Z. rugosa,*	*Z. saeri Pittier*

Common names of *Ziziphus rugosa*[13]

Hindi: churna **Kannada:** Bilichurimullu, Kottemullu **Malayalam:** Malamtutali **Marathi:** Churan, **Sanskrit:** Ghonta **Tamil:** Totari **Telugu:** Gottikampa pindu parighamu **Tulu:** Kottemullu.

Classification: [14]

Kingdom: Plantae

Division: Tracheophytes

Subdivision: Angiosperms

Order: Rosales

Family: Rhamnaceae

Genus: *Ziziphus*

Species: *Ziziphus rugosa*

TRADITIONAL USES

From ethnobotonical and traditional claims the plant parts used by the natives for various ailments. Bark, fruit, leaves, flower and root are used in the preparation of Herbal formulations. In some parts of South India natives use dried stem bark as Astringent, for Mouth ulcer and Diarrhoea, Flower is uses for Menorrhagia[15]. Traditionally natives of Thalamalai Hills, Namakkal District, Tamilnadu[16], Gopalswamy hills of Karnataka, Western Ghats and Coimbatore district of Tamilnadu, used the bark of this plant for the treatment of Ulcer, Skin disease, Cough, diarrhoea, hypotension. [17]

Z. *rugosa* fruit is commonly known as famine edible and even sold by locals. Natives prepare dosa by grinding the ripe fruit. The fruit is described as demulcent in the treatment of throat and broncho-pulmonary irritation and powdered dried fruit and leaves are applied topically in the treatment of boils.[18]. The fruit was also used as coolant and to keep body hydrated used by villages of upper-Ghat (Salkani and Killara) and two of the coastal zone (Murur and Kallabbe) in the central Western Ghats, Karnataka, India. The fruit is used by the rural communities of Tiruchirappalli District, Tamilnadu, South India for wounds and diarrhea.[19]

PHYTOCHEMICAL INVESTIGATION

Preliminary phytochemical investigations reported the presence of various phytoconstituents and the results are given in the table 2.

Isolated Phytochemicals

Phytochemical investigations reported the presence of various isolated phytoconstituents and the results are given in the table 3.

Table 2: The preliminary phytochemical studies.

Fruit	Bark	Leaves	Root
Alkaloids, saponins, flavonoids and glycosides, fibre protein and carbohydrates [20] **Macronutrients:** Nitrogen, potassium, calcium and magnesium **Micronutrients**: Zinc, copper, manganese and iron[21]	Terpenoids, alkaloids, steroids, flavonoids, glycosides and saponins [23]	carbohydrates (monosaccharides, reducing and mixed-reducing sugars), alkaloid, glycosides, steroids, tannins and saponin[22]	Tannins, alkaloids, steroids, saponins, flavonoids, coumarin and terpenoids[25]

Table 3: Isolated compounds reported.

Fruit	Bark	Root
Triterpeniod: Betulinic acid [20]	**Cyclopeptide alkaloids:** Nummularine-P, Sativanine-H and Rugosanine-B **Triterpinoids:** Lupeol and Betunilic acid. **Lignan glycosides**, (6 S,7 R,8 R)-7a-[(b-glucopyranosyl)oxy] lyoniresinol and (þ)-lyoniresinol-3a-O-b-D-glucopyranoside. **Flavonoid glycosides:** Kaempferol-3-O-a-L-rhamnopyranosyl-(1!2)-a-L-rhamnopyranoside and Horridin[33]	**Triterpeniods:** Lupeol, betulin, betulinic aldehyde, betulinic acid, alphitolic acid, euscaphic acid, zizyberenalic acid, and β–sitosterol. **Coumarin:** Scopoletin **Flavonoids:** Kaempferol, afzelin, quercitrin, and (+)-catechin.24

PHARMACOLOGICAL ACTIVITIES

Cytotoxic and anticancer activity

The methanolic extract of Pericarp and seed has proved as good anticancer agent and when tested against human melanoma cells.[20] Pericarp and Seed Extract of *Zizyphus rugosa* Lam. was evaluated for Cytotoxic Activity in terms of lethal effect on the brine shrimp *Artemia nauplii* assay. Degree of lethality was directly proportional to the concentration of the extract. Seed extract showed potent cytotoxicity (LC_{50} of 564.73µg/ml) and thus it was toxic compared to pericarp (LC_{50} of 1000µg/ml) the extracts have shown bioactivity in terms of causing mortality of brine shrimps.[22] The ethanolic extract was found to have good toxicity to Brine Shrimp *Artemia nauplii* compared with the reference anticancer drug vincristine sulphate.[22]

Antimicrobial and insecticidal activity

Methanol extract of *Z. rugosa* fruit pericarp was evaluated for antibacterial activity. The extract exhibited dose dependent inhibition of test bacteria using well plate method. Among bacteria, *E. coli* was found to be more susceptible to extract than *S. aureus* as revealed by wider zones of inhibition.[26] From another study it is inferred that the aqueous pericarp extract of *Z. rugosa* exhibited efficient antibacterial activity against both gram positive and gram negative organisms. The ethanolic extract possesses highest antifungal activity followed by aqueous and hexane against *A. niger*. and *C. albican*.[27]

Ethanolic extract of *Ziziphus rugosa* leaves also exhibited antimicrobial activity, where showed moderate activity against only one bacterium (*Shiggla sonni*) while the standard drug Chloramphenicol showed very good zone of inhibition against all five types (*Salmonella typhi, Staphylococcus aureus, Shiggla sonni, Salmonella paratyphi, Salmonella grb*) of bacteria[18]. Chloroform extract of bark as antimicrobial agent showed significant inhibition against *Staphylococcus aureus* but good inhibition against *Streptococcus pyogens*, *Pseudomonas aerogenes* and *Salmonella typhi*.[28]

The seed methanolic extract was evaluated for Insecticidal activity in terms of Larvicidal effect.on second instar larvae of *A. aegypti.* The larvicidal effect of extract was determined after 24 hours. Dead larvae were identified when they failed to move after probing with a needle in siphon or cervical region. Concentration of 50 mg/ml was effective and produced 100% mortality.[29]

Antioxidant activity

The free radical scavenging activity of methanol seed extract was evaluated. The extract exhibited concentration dependent radical scavenging activity i.e., higher the concentration, more scavenging potential on DPPH method. The extract was able to reduce the stable free radical DPPH to the yellow colored diphenylpicrylhydrazine with an IC_{50} value of 61.88 µg/ml. The scavenging activity was compared with ascorbic acid.[30]

The Ethanolic extract of leaves In DPPH and NO radical scavenging methods for evaluation of its antioxidant activity, IC_{50} was moderately was found satisfactory (179.713µg/ml) compared with the reference ascorbic acid (15.707µg/ml). In LPO (Lipid peroxidation) assay the Leaf fraction extract showed moderate inhibition potential (IC50 402.835µg/ml) in comparison to standard drug BHT (IC50 32.94µg/ml).[22] Active compounds (1–6) were isolated from bark shown in table 3, were evaluated for antioxidant (DPPH) activities, there compound 6 showed the most potent antioxidant activity.[33]

In vivo analgesic activity

The analgesic activity of the methanolic extract of *Z. rugosa* leaves was evaluated using acetic acid-induced writhing method in rat. The extract significantly reduced the number of writhing movements induced by intraperitoneal administration of acetic acid solution. The dose-dependent inhibition of abdominal constrictions by the methanol extract indicates anti-nociceptive potential. The exerted inhibition of writhing was close to the standard non-narcotic analgesic drug, Indomethacin.[30]

Anti-inflammatory activity

The anti-inflammatory activity of aqueous and methanolic extract of *Z. rugosa* on carrageenan-induced paw edema was determined using Wistar rats. The aqueous and Methanolic extracts of root and bark showed significant anti-inflammatory effect in the acute phase of the inflammation process.[31]

CNS Depressant Activity

Methanolic extract of *Z. rugosa* leaves exerted CNS Depressant activity in Open field test and Hole cross test using rats. In open field test the extract was evaluated for decreasing capability of CNS-locomotor activity. The extract significantly decreased the locomotor activity in a dose dependent manner and this effect was evident from the initial observation (0 min) period and continued up to 5th observation period (120min). In Hole cross test the extract showed a decrease in locomotionin the test animals. The number of crossing hole from one chamber to another by rat of the control group remained almost steady to slight decrease from 0 minute to 120 minutes. The extract displayed dose dependent activity and Depression produced was found to be close to that of standard drug, Diazepam.[31]

Anti-diabetic activity:

In vivo alloxan induced diabetic rat model and *invitro* alpha amylase inhibition assay of *Ziziphus rugosa Lam.* bark was selected for determination of its anti-diabetic potential. Two doses of the petroleum ether extract and standard drug Glibenclamide were administered to the diabetic rats. Treated diabetic groups showed statistically significant decrease in blood glucose level which indicates the antidiabetic potential. There was significant decrease in α-amylase, urea and creatinine levels which showed the improvement in pancreas and kidney functions. It also

showed increase in total protein level which maintains the body weight.

In *invitro* method Alpha amylase inhibition assay was performed to assess the antidiabetic property of *Ziziphus rugosa Lam.* bark. It was also found that the IC50 value of the benzene fraction was much closer to the IC50 value of acarbose compared to the other fractions, which indicates that the benzene fraction possesses good antidiabetic property.[32]

The α-glucosidase inhibition of crude ethanol extract obtained from the bark of *Z. rugosa* was assayed and molecular docking studies has been carried out for its anti diabetic activity. Betunilic acid showed the most powerful yeast α-glucosidase inhibitory activity. The molecular docking results highlighted the role of the carboxyl moiety of 2 for yeast a-glucosidase inhibition through H-bonding, and concluded that Lupeol and Betunilic acid emerged as promising molecules for anti-diabetic therapy[32].

CONCLUSION

Plants are natural sources of bioactive compounds to treat various life-threatening diseases. The present review is the first review work on *Ziziphus rugosa* plant to explain the traditional uses, chemical constituents and reported pharmacological activities of this plant.

The review shows the activity of various parts of the plant and its pharmacognostic profile. Extracts and Phytoconstituents isolated from this plant have shown to produce different pharmacological response, which includes antidiabetic, antioxidant, anti-inflammatory, analgesic, cytotoxic, anti-cancer, CNS depressant, antimicrobial, antiparasitic, dermatological and many other effects.

The reported pharmacological activities show that *Ziziphus rugosa* is a promising medicinal plant, could be utilized and further studied for several medical applications because of its effectiveness and safety. Considering all the above medicinal importance of Ziziphus rugosa, it can be concluded that further studies on this plant may helpful for future researchers to explore more medicinal uses.

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