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A PHYTO PHARMACOLOGICAL REVIEW ON TRADITIONAL MEDICINAL PLANT *ZIZIPHUS RUGOSA* LAM

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ABSTRACT: *Ziziphus rugosea* member of *Rhamnaceae* family, is found in the deciduous and semi-evergreen forests of Western Ghats, India. It is commonly known as suran in Hindi. chunukoli in Urdu, badara in Sanskrit, and toran in Marathi. *Z. rugosa* is traditionally used in the treatment of skin diseases, mouth ulcers, dropsy, boils, diarrhea, tachycardia, syphilis, miscarriage, misconception, flatulence, hysteria, And as astringent. It has been investigated foranti-diabetic, anti-inflammatory, α-glucosidase inhibitory, cytotoxic, antioxidant, antibacterial, anthelmintic, analgesic, and insecticidal activities. It is reported to contain diverse classes of secondary metabolites like alkaloids, flavonoids, glycosides, saponins, triterpenoids, tannins and phenolics. Several constituents are reported from different parts of this plant cyclopeptide alkaloids (rugosanin-A, amphibine-D, rugosanin-B, sativanin-H, nummularine-P), pentacyclic triterpenoids (2-α-hydroxyursolic acid, oleanalic acid, alphitolic acid, betulinaldehyde, betulin, betulinic acid, lupeol), flavonoids (kaempferol, quercetin, myricetin, apigenin, apigenin-7-o-glucoside, kaempferol-4-methylether, kaempferol-3-o-rhamnoside, luteolin, luteolin -7-o-glucoside), dihydroxy benzoic acid (vanilic acid), quinoline (isoquinoline). The present review is an attempt to connect the traditional use of *Z. rugosa* to its phytochemistry and pharmacology, thereby opening up new avenues in the therapeutic utility of this traditional medicinal plant.

INTRODUCTION: India contains more than 45,000 plant species and is the largest producer of medicinal plants; hence it is called the 'Botanical garden of world' [1]. These medicinal plants play a vital role in the development of potent therapeutic agents across the world and are immensely used traditionally [2]. *Ziziphus rugose*, a member of *Rhamnaceae* family, is found in the deciduous and semi-evergreen forests of Western Ghats, India. This plant is also found in China, India, Jammu and Kashmir, Laos, Thailand, Sri Lanka, Java, Peninsular, Malaysia, Singapore, Vietnam and amans, Nicobars, Myanmar, Nepal, Pakistan, and Bangladesh.

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The taxonomical features of *Ziziphus rugosa* include Kingdome Plantae; Clade Angiosperm; Clade Eudicots; Clade Rosids; Order Rosales;

family *Rhamnaceae*; Genus *Ziziphus*; Species *Ziziphus rogosa*; Binomial name *Ziziphus rugosa* lam. The morphology of this plant comprises **Fig. 1** of subcordate leaves, paniculate flowers, reddish and moderately hardwood and small seed fruit. An exhaustive literature survey indicates that the bark is traditionally used as an astringent. And antidiarrhoeal agent, the flowers are used in menorrhagia, stem and fruits are hypotensive. Phytochemical reports indicate the presence of flavonoids, alkaloids, steroids, saponins, glycosides and triterpenoids class of secondary metabolites. The bark of *Z. rugosa* is reported to contain vanillic acid, betuline, betulinic acid, kaempferol, quercetin, myricetin, apigenin and apigenin-7-O-glucoside. It is reported to contain N-formyl cyclopeptide alkaloids that exhibit antibacterial and antifungal activity [3].

FIG. 1: *ZIZIPHUS RUGOSA* PLANT

Ethnomedicinal Uses of *Zizyphus rugosa*: The Kodava community of Kodagu region of the Western Ghats traditionally eat the endocarp of *Z. Rugosa fruits in raw and ripe form as a nutrional* source [4]. This plant is food for animals such as elephants and deer [5]. The fruit of this plant is a habitat for bee farming in Uttar Kannada district [6]. The fruit is locally used to treat tumors and as a sedative, hepatoprotective, blood purifier and cardiotonic in the districts of Sylhet and Moulvibazar [7] and in the treatment of rheumatism [8]. In India, the decoction of the bark is used to heal wounds and in the treatment of diarrhea. A combination of leaves and flowers is used in menorrhagia [9, 10]. *Z. rugosa* is reported to be used in the treatment of skin diseases, mouth ulcer, dropsy, boils, diarrhea, tachycardia, syphilis, miscarriage, misconception, flatulence, hysteria, and as an astringent [11, 12]

TABLE 1: PHYTOCHEMISTRY OF *ZIZIPHUS RUGOSA*

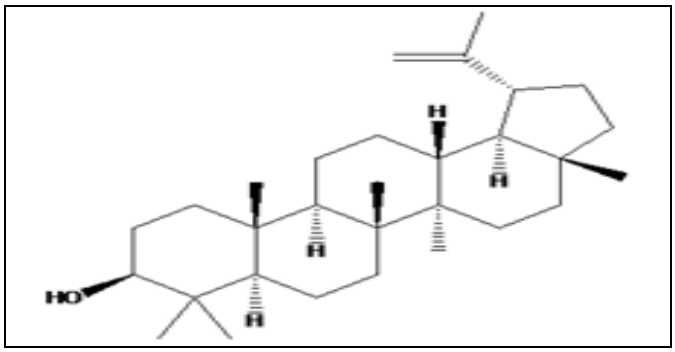
Plant Part of *Z. rugosa*	Phytoconstituents
Stem Bark	Amphibine-D, Isoquinoline, N-Nonacosane, Octacosanol, Saponins, Terpenoids and Steroids [14]
Root bark	Vanilic acid, Betulin, Betulinic acid, Kaempferol, Quercetin, Myricetin, Apigenin, Apigenin-7-o-glucoside, N-formyl cyclopeptide alkaloid, Triterpinsaponine, Lupeol, Betulinaldehyde, Sativanine-H, Nummularine-P, Rugosanine-A, Rugosanine-B, Oleanalic acid, Zizyphoside, Alphitolic acid, 2- α- Hydroxyurolic acid, Kaempferol-3-o-rhamnoside, Quercetine-3-o-rhamnoside, Flavone glycoside, Cyclopeptide alkaloids [3, 14, 13]
Fruit	Alkaloids, Flavonoids & Phenols [25]
Leaves	Carbohydrate , Alkaloids, Flavonoids , Glycosides, Steroids, Tannins, Saponins [15, 21]

Phytochemistry of *Zizyphus rugosa*: A considerable amount of research work is reported on the chemical constituents of *Ziziphus rugosa* indicating the presence of cyclopeptide alkaloids, tannins, flavonoids, steroids, saponins, terpenoids and glycosides. Phytochemical study of the root bark indicated the presence of cyclopeptide alkaloids (sativanine-H, nummularine-P, rogosanine-A, rugosanine-B), pentacyclic triterpenoids (betulinic acid, betulinaldehyde, oleanilic acid, alphitolic acid, 2- α-Hydroxyursolic acid, lupeol), flavonoids (kaempferol, quercetin-3-o-rhamnoside, myricetin-3-o-rhamnoside,quercetin, apigeni-7-o-glucoside, apigenin, kaempferol), dihydroxybenoic acid (vanilic acid) in addition, the root bark also contains rugoside, zizyphoside, ß-sitosterol and ß - sitosterolglycoside. The stem bark is reported to contain amphibine-D, N-

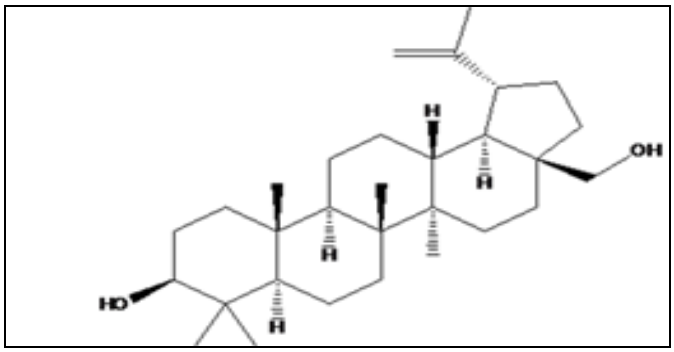
Nonacosaneoctacosanol and flavone glycosides [13], [3, 14]. The leaves are reported to contain carbohydrates, alkaloids, glycosides, flavonoids, steroids, tannins and saponins [15]. The fruits contain alkaloids, flavonoids and phenolics [16]. **Table 1** depicts the phytoconstituents reported in this plant. This review is an effort to collate data on the secondary metabolites of this plant and illustrate the diverse pharmacological activities associated with them, and anticipates opening new avenues for in-depth research on this plant as a source of medicinal agents.

Triterpenoids: Eight triterpenoids have been isolated from the root bark of *Z. rugosa*. Theseincludes lupeol, betuline, betulinic acid, betulinic aldehyde, alphitolic acid, euscaphic acid, zizybeenalic acid and ß-sitosterol. They were evaluated for potential *in-vitro* cytotoxic activity on KB (Human epidermoid carcinoma) and HeLa (Human Cervical Carcinoma) cell lines using MTT assay of these, betuline and zizyberenalic acid showed moderate activity on KB and HeLa cell lines with IC_{50} of 10.0 µg/mL, 5.5 µg/mL and 9.5, 13.0 µg/mL respectively.

Betulinic acid showed modest cytotoxic activity on HeLa cell line with IC_{50} of 10.0 µg/mL; standard adriamycin showed IC_{50} of 0.018 µg/mL on both the cell lines [11]. Lupeol and betulinic acid are reported to have α- glucosidase inhibitory activity [17]. Lupeol, betuline, betulinaldehyde and betulinic acid are also reported to exhibit antibacterial activity [18].



LUPEOL



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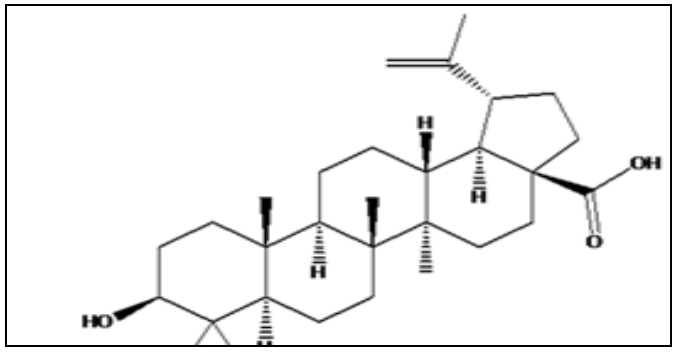
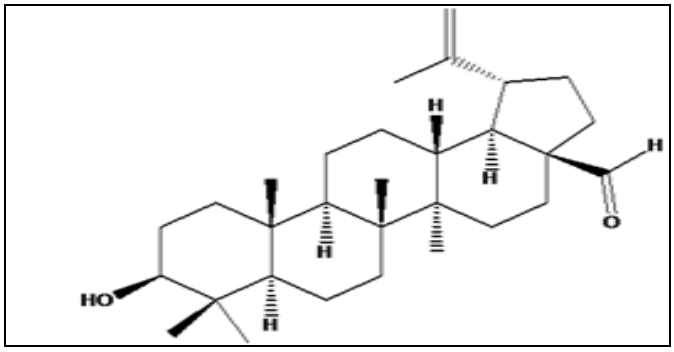


BETULINIC ACID



BETULINALDEHYDE

Cyclopeptide Alkaloids: The cyclopeptide Alkaloids such as Rugosanin-B -B, Sativanin-H, Nummularine-P isolated from the bark of *Z. rugosa* are reported to possess antifungal activity [3].

Triterponoid Saponines: The triterpene saponin Rugoside- Isolated from the bark of *Z. rugosais* reported to have CNS depressant, tranquilizing and analgesic activity [19, 3].

Pharmacological Activity of *Zziphus rugosa*: This traditional medicinal plant is reported to exhibit a diverse spectrum of pharmacological activities.

Analgesic Activity: Yadav *et al.,* 2010 evaluated the chloroform, ethyl acetate, methanol, and aqueous extracts of the root bark for potential analgesic activity. of these, the aqueous extract showed a significant dose-dependent analgesic activity at 50, 100 and 200 mg/kg mice. The methanol extract was better than the chloroform and ethyl acetate extract. The analgesic activity is

attributed to the presence of flavonoids in the aqueous and methanol extracts of the root bark [12]. In another study, Mohammad *et al.*, 2016 evaluated the methanol extract of the leaves for in vivo analgesic activity using acetic acid-induced writhing method using rats. The methanol extract showed 55.20% inhibition in comparison to 51.87 % inhibition exhibited by the standard Indomethacin used in this study [20].

Antibacterial Activity: Kekuda *et a*l., 2011 evaluated the methanol extract of the fruit pericarp for potential antibacterial activity on *Staphylococcus aureus* MTCC- 902 and *Escherichia coli* MCC-405 using the agar well diffusion method with chloramphenicol (1 mg/ml) as the standard and 10% DMSO as vehicle control. The methanol extract exhibited a good dose-dependent antibacterial activity against both *E. coli* and *S. aureus* **Table 2** [21].

TABLE 2: ANTIBACTERIAL ACTIVITY OF THE METHANOL EXTRACT OF *Z. RUGOSA* FRUIT PERICARP

Treatment	Concentration	Zone of Inhibition in mm	
		E. coli	***S.aureus***
Methanol extract	5mg/ml	14	11
	10mg/ml	22	16
	25mg/ml	24	20
	50mg/ml	26	24
Chloramphenicol	1mg/ml	28	27
Control (DMSO)	10%	-	-

TABLE 3: ANTIBACTERIAL ACTIVITY OF *Z. RUGOSA* LEAF AND BARK

Part	Extract	Minimum Inhibitory concentration (mg/mL)	
		E. coli	***S.aureus***
Leaf	Methanol	2.5	2.5
	Chloroform	5	2.5
	Hexane	5	5
Bark	Methanol	10	2.5
	Chloroform	25	2.5
	Hexane	25	5

Kumar *et al.*, 2009 evaluated the methanol, chloroform, and hexane extracts of the leaves and bark of this plant for antibacterial activity against *Staphylococcus aureus* and *Escherichia coli* using the nutrient broth assay. The leaf extract was found to inhibit the test bacteria at a lower concentration than the bark extract. The methanol extract was more potent than the chloroform and hexane extracts. The methanol and chloroform extracts of leaves and bark inhibited *S. aureus* at 2.5 mg/ml, whereas hexane extract inhibited at 5 mg/ml **Table 3** [22]. Another study by Hossain *et al.*, 2013 evaluated the ethanol extract of the leaves for antibacterial activity using the disc diffusion method on *Escherichia coli*, *Bacillus subtilis*, *Staphylococcus aureus*, *S. epidermidis*, *Pseudomonas aeruginosa*, and *Proteusvulgaris* using chloramphenicol] (50 µg/ disc) as the reference standard. The ethanol extract showed moderate activity against (Shigglasonni) in comparison to chloramphenicol on all the test strains **Table 4** [15].

TABLE 4: ANTIBACTERIAL ACTIVITY OF *Z. RUGOSA* LEAF EXTRACT

Test organism	Zone of Inhibition (mm)	
	Chloramphenicol	Leaf extract
Salmonella typhi	1	Nil
Staphylococcus aureus	25.5	Nil
Shigglasonni	28.5	8
Salmonella paratyphi	13	Nil
Salmonella grb	7	Nil

Antidiabetic Activity: Mohammad *et al.*, 2013 studied the effect of oral administration of petroleum ether, chloroform, and ethyl acetate extracts (200 mg/kg, 400 mg/kg) of *Ziziphus rugosa* Lam. for a period of 14 days on blood glucose level in alloxan-induced diabetic rats. The oral administration of these three extracts for 14 days resulted in a significant reduction in blood glucose level and also prevented body weight loss in diabetic rats. The *in-vitro* study was performed by α-amylase inhibition assay using bioassay-guided fractionation where satisfactory IC^{50} values were obtained for the bioassay-guided fractions of petroleum ether 1, 2 and 3 and were comparable with IC_{50} value of the positive control acarbose [23].

Anthelmintic Activity: Krishnamurthy *et al.*, 2007 evaluated the chloroform, petroleum ether, and ethanol extracts of unripe fruits of *Ziziphus rugosa* for anthelmintic activity on adult Indian earthworm, Pheretimapostuma. The paralysis time and death of Pheretimapostuma were determined for the test extracts at concentrations 25, 50 and 100 mg/ml using albendazole (2mg/ml) as the standard. The test extracts showed paralysis death of worms in a shorter time as compared to standard albendazole. of the test extracts, petroleum ether

extract was reported to be more active. The extracts petroleum ether and ethanol extract in the concentration of 25 mg/ml showed an equal time of paralyzing time. The increase in various concentrations of extract did not show the difference in time of paralysis and the death of worm. It was observed that the fruit extract of *Ziziphus rugosa* showed very less anthelmintic activity as compared to standard drug albendazole [16].

Anti-inflammatory Activity: Yadav *et al.,* 2010 evaluated the aqueous and methanol extracts of the root bark for anti-inflammatory activity on carrageenan-induced paw edema using wistar rats. The development of edema induced by carrageenan corresponds to the events in the acute phase of inflammation, mediated by histamine, bradykinin and prostaglandins produced under an effect of cyclooxygenase.

The aqueous and methanol extract of *Ziziphus rugosa* compared against aspirin and piroxicam. of these, the water and methanol extract of *Ziziphus rugosa* showed significant anti-inflammatory effect compared to NSAIDs product in the acute phase of inflammation process [12].

Antioxidant Activity: Hossain *et al.,* 2013 evaluated the ethanol extract of the leaves for antioxidant effect using DPPH radical scavenging assay, NO radical scavenging assay, LPO (Lipid Per oxidation) and by CUPRAC assays. The extract exhibited dose dependent scavenging of DPPH radicals and exhibit activity as like standard ascorbic acid with IC_{50} 179.713 µg/ml, 15.707 µg/ml. In NO radical scavenging assay extract and ascorbic acid showed inhibition at IC_{50} 769.909 µg/ml and 82.642 µg/ml.

In the LPO (Lipid Per oxidation) assay, extract possesses moderate inhibition at IC_{50} 402.835 µg/ml and standard BHT showed IC_{50} at 32.94 µg/ml. Whereas, In the CUPRAC assay extract found to possess low antioxidant activity [15]. The methanol extract of the fruit pericarp also exhibited antioxidant activity evaluated by Kekuda *et., al* 2011. The extract was found to be less active than standard drug ascorbic acid with IC_{50} 61.88 µg/ml and 15.707 µg/ml [24]. Sichaem *et., al* 2017 evaluated the ethanol extract of the bark for potential antioxidant activity. The results indicated that the extract exhibits potent antioxidant activity compared to standard ascorbic acid [21].

CNS Depressant Activity: Mohammad *et al.,* 2016 evaluated the methanol extract of the leaves for CNS depressant activity on rats using the open field test and Hole cross test. In the Open field test by Gupta *et al.* 1971, the extract showed activity decreasing in a dose-dependent manner. The effect was evident from initial observations from 0 min to last observation 120 min. The Hole cross test was another method described by Takagi *et al.*1971 implemented for this study. Where extract showed a decrease in locomotion in test animals. The depression produced at 500 mg/kg body weight was lower than that of standard drug diazepam [24].

Cytotoxic Activity: Hossain *et al.,* 2013 evaluated the ethanol extract of the leaves for cytotoxic activity using Brine Shrimp lethality bioassay (BSLA). In this bioassay, the ethanol extract of leaves showed good activity. The extract showed LC_{50} at 212.402 µg/ml and standard at 2.47 µg/ml. This concentration-dependent increment in percent mortality of Brine Shrimp Naupli produced by leaf extract of *Ziziphus rugosa* indicates the presence of cytotoxic principle [15].

Insecticidal Activity: Mallikarjun *et al.,* 2011 evaluated the methanolic extract of the seeds of this plant for insecticidal activity. In this study, the larvicidal effect of crude methanol extract was determined in terms of causing mortality of larvae. The death of larvae was observed within a short period of time and thus it is concluded that the crude extract could be used to control mosquito vectors and diseases transmitted by them. This study reported the presence of phytoconstituents such as saponins and flavonoids which might be responsible for the observed mortality in larvae. The methanol extract resulted in 100 % mortality at 50 mg/ml [21].

A-Glucosidase Inhibitory Activity: Sichaem *et al.,* 2017 evaluated the ethanol extract of the bark of this plant for α- glucosidase inhibitory activity. The compounds such SAS lupeol, betunilic acid, (6 S,7 R,8 R)-7a-[(b-glucopyranosyl) oxy] lyoniresinol, (þ)-lyoniresinol- 3a-O-b-D-gluco pyranoside, kaempferol-3-O-a-L-rhamnopyranosyl-

(1-2)-a-L-rhamnopyranoside and horridin, isolated from the ethanol extract of bark which was evaluated and results were compared with Acarbose. The results indicated that compound 2, Such as betulinic acid exhibited potential inhibitory activity against yeast α- glucosidase [17].

CONCLUSION: The extensive literature survey revealed that the plant *Ziziphus. rugosa* possesses attractive medicinal activities. This review illustrates the ethnomedicinal uses, phytochemistry, and reported pharmacological activities of this plant and is an attempt to correlate traditional uses of *Ziziphus rugosa* to its phytochemistry and pharmacological activities.

This plant has been evaluated for various pharmacological activities such as antifungal, antibacterial, antioxidant, anti-inflammatory, analgesic, anticancer, insecticidal, and anthelmintic activity. The lupeol, betulinic acid, and N- formyl cyclopeptide alkaloids are *Ziziphus rugosa's* most widely reported chemical constituents.

The traditional and ethnomedicinal uses depict that this plant is very effective and safe for diverse medicinal uses supported by a long traditional use by the local population in several countries. The most bioactive extracts of *Ziziphus rugosa* can be fractionated to identify new constituents, and based on the nature of constituents; they can be screened for new biological activities opening up new avenues for more intensive research on *Z. rugosa*.

In addition, there is a huge scope to conduct molecular biology studies to understand the mechanism of action of the extracts and Constituents thereof to substantiate the research portfolio of this traditional medicinal plant.

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