

Zanthoxylum armatum (Timru): A detailed study of chemical constituents and significant biological properties

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ABSTRACT

Zanthoxylum armatum also known as Timru and toothache tree. This is a sub deciduous aromatic, branched, scandent, or erect shrub or a small tree that grows to 6–7 meter in height and belongs to the Rutaceous family. This plant is common in the hot valleys of the Himalayas from Jammu to Bhutan, Nepal, and Pakistan. It covers a considerable portion of Orissa and Andhra Pradesh in India This plant is considered as a divine plant in contiguous areas. The seeds contain many important phytoconstituents and essential oils which contribute to its biological activities including larvicidal, anti-inflammatory, analgesic, antinociceptive, antioxidant, antibiotic, hepatoprotective, ant plasmodial, cytotoxic, antiproliferative, anthelmintic, antiviral and antifungal. It contains alkaloids, essential oil, resins, sterols, triterpenes, glycosides, saponins, tannins and flavonoids. Because of its Significant medicinal properties and excessive increase in demand has put this plant in the category of endangered plants. This review paper focuses on the different biological activities, chemical constituents, pharmacological and medicinal properties of zanthoxylum armatum plant.

Keywords: *Zanthoxylum armatum*, Phytochemistry, traditional uses, pharmacological activity.

INTRODUCTION

Zanthoxylum armatum is also known as the toothache tree, Nepal Piper and Indian prickly bush it is common in the north east India and also known as Tejpal in Hindi, Tejowati in Sanskrit, Timur in Nepali and Mukthrub in Manipuri, it is prevalent in north east India. different parts of *Z. armatum* plant, including the fruits, stem, leaves, and bark, have been used in various indigenous medical systems to treat gastric problems, fever, and appetizer. It works well to treat toothaches, irritation, and stomach aches. Due to its pharmacological benefits, *Zanthoxylum armatum* is in high demand on both the domestic and global markets. Around 1,748 distinct types of medicinal plants can be found in the Indian Himalayan region. It is a big spiky shrub or small tree.[1]

Due to its exceptional therapeutic efficacy, *Z. armatum* (family: Rutaceae) is regarded as a significant medicinal plant. Many *Z.* species are traditionally used as medicinal plants in managing various health conditions. Secondary metabolites isolated from parts of plant species in this genus have demonstrated several pharmacological activities, such as antioxidant, analgesic, anti-inflammatory activities, and modulatory effects against obesity, dementia, and diabetes [2,3] The fruit part of the plant may use to purify the water. Also used as insect repellent. The wood of this plant may be very heavier and stronger than it is used for walking sticks. *Z. armatum* also gives and showed work against antioxidants [4] antinociceptive, antifungal [5] anti-inflammatory, hepatoprotective [6] pesticides, anthelmintic, antiproliferative [7] etc

COMMON NAME

Sanskrit: Tumburu, dhiva, grandhalu

Hindi: Dharmar, tejphal, Nepali Dhaniya, Timru

Bengali: Gaira, tambal

Oriya: Tundopoda

Taxonomic classification [8]

Botanical name: *Zanthoxylum armatum*

Kingdom: Plantae

Family: Rutaceae

Sub kingdom: Viridaplantae

Domain: Eukaryote

Phylum: Tracheophyta

Sub phylum: Euphyllophytina

Infra phylum: Radiatopses

Class: Magnoliopsida

Sub class: Rosidae

Super order: Rutanae

Order: Spindale

Genus: *Zanthoxylum*

DISTRIBUTION

Zanthoxylum armatum trees are widely dispersed around the world.

Zanthoxylum armatum is also grown in nations including China, Japan, Korea, Taiwan, Bangladesh, Bhutan, Nepal, Pakistan, Laos, Myanmar, Thailand, Vietnam, and Indonesia. There are numerous kinds of the tree in the Indian states of Andhra Pradesh, Jammu & Kashmir, Assam, Manipur, Meghalaya, Nagaland, Orissa, and Uttar Pradesh [9]. *Zanthoxylum armatum* is mostly found in North-East India and is distributed throughout India from Jammu and Kashmir to Bhutan at an altitude of about 2500 m. The species' primary habitats include wastelands, mountains, valleys, and forests.[10]

DESCRIPTION

Zanthoxylum armatum is a small tree having large spiny shrubs. The Leaves are distinctively trifoliolate with the leaf-stalk winged. Leaflets are stalk less, 2.0-7.5 × 1.0-1.7 cm, elliptic to ovate-lance like, entirely to slightly toothed, sharp tipped, base sometimes oblique. Minute yellow flowers arise in leaf axils. Flowers have 6-8 acute sepals. Petals are absent. Male flowers have 68 stamens and large anthers because of which the flowers look yellow. Female flowers have 1-3 celled ovaries, pale red, splitting into two when ripe. Seeds are round 3 mm in diameter shining black colour (11) Fruits have purplish red colour and have a round 4 mm diameter. Flowers having growth April to May and fruits may appears in tree all over the year (12)



Traditional uses of zanthoxylum armatum

The traditional uses of *Zanthoxylum* species as food and in medicinal practices are highlighted in this section. Pastes prepared from *Z.* species are used in South Africa and Kenya to relieve wound pain and speed up the healing process. (13,14) *Z.* species like *Z. zanthoxyloides* are used to treat sickle cell anaemia, rheumatism, urinary tract infection, and venereal diseases. (15)

Fruits and seeds are usually used as a condiment and spice in momos, chowmien, biscuits, thukpa, sweetened cakes etc. The fruit part of the plant may be used to purify the water. Also used as insect repellent. The wood of this plant may be much heavier and stronger than it is used for walking sticks. *Z. armatum* also contains essential oils and is also known as an ornamental plant (16) They are also used as an insect repellent agent. The natives of North America crush the bark and apply on their gums for relief hence it is known as the toothache tree. It is used in China and India as a snake bite remedy (17) The traditional uses of *Z. armatum* are listed in Table

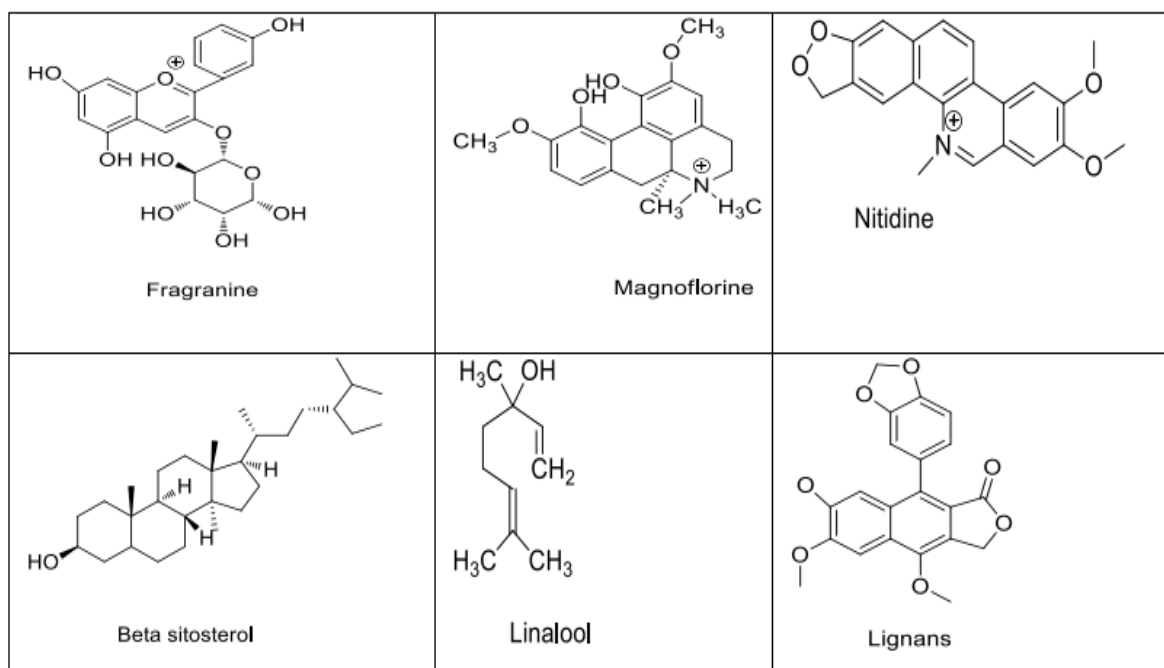
SLno	Country	Part of plant	Traditional uses	References
1	India	Seeds and bark Aerial parts	fever, dyspepsia, cholera. insecticidal	18
2	Japan	Seed	Git problem and depression	19
3	Nepal	Fruit Berries Bark Fruits	Decoction is used for abdominal pain Carminative, antispasmodic, anti-rheumatic cholera, diabetes and asthma diarrhoea, dysentery and stomach-ache	20
4	Pakistan	Fruit	Spice and condiment Powder of its dried fruit along with <i>Mentha longifolia</i> Twigs are used as toothbrush during gum problems and toothache	21
5	China	Aerial part	As infusion in vinegar is used to expel bugs or worms infecting ear. Scabies is treated by the plant using a lotion applied to the skin	22

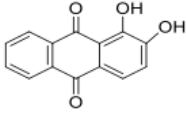
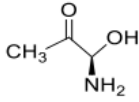
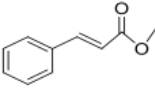
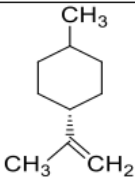

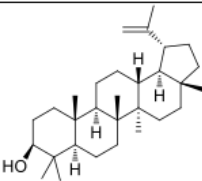
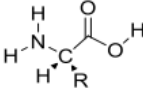
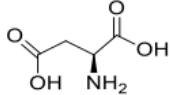
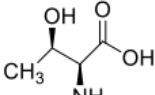
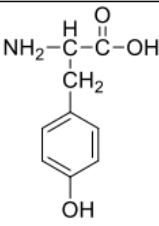
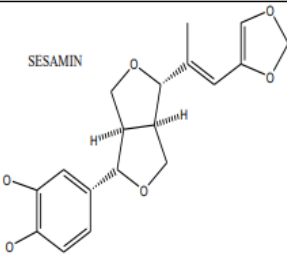
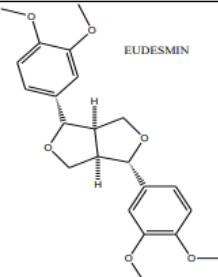
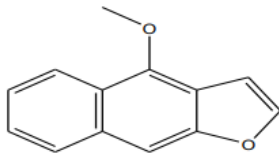
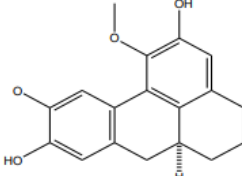
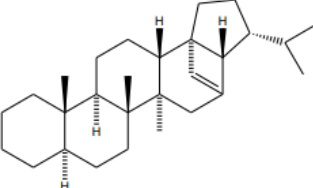
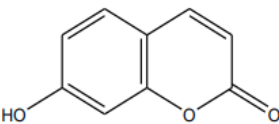
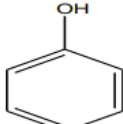
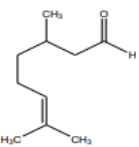
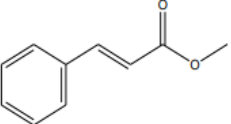
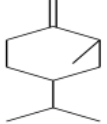
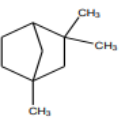
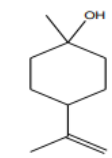

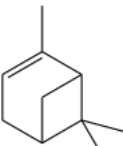
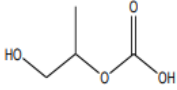
Chemical composition

The alkaloids found in the plant *Zanthoxylum armatum* include g-fagarine, b-fagarine, magnoflorine, nitidine, chelerythrine, and tambatarine. It also contains linalool, beta-sitosterol, tamblin, tambulating, aramatamide, lignans, asarinin and fragesin Bark of plant contains yellow crystalline compounds named as berberine (23) Many chemical studies are done which introduced the isolation of further two new phenolic compounds 3-3',4'-dimethoxyflavone-5-β-d-xylopyranoside along with the five known compounds, 1-methoxy-1,6,3-anthraquinone,

1-hydroxy- 6,13-anthraquinone, 2-hydroxybenzoic acid, 2-hydroxy-4-methoxybenzoic acid and stigmasta-5-en-3 β -deglucopyranoside, on the basis of spectral data and chemical analyses(24) Two new phenolic glycoside, 2-methoxy-4-hydroxyphenyl-1-O- α -L-rhamnopyranosyl-(1 \rightarrow 6)- β -D-glucopyranoside and threo-3-methoxy-5-hydroxyphenylpropanetriol-8-O- β -D-glucopyranoside were isolated from the stems of *Zanthoxylum armatum*(25)

Along with other ingredients including arginine, aspartic and glutamic acid, glycine, histidine, threonine, tyrosine, and others, it contains alkaloids, flavonoids, saponin, steroids, terpenes, phenols, carbohydrates, proteins, and essential oil. (26) From the bark of this plant armatamide which is an amide is identified. Seed part of this plant consists of hydroxycinnamic acid and other volatile compounds (27). Stem and root part of the plant consists of beta-amyrin, beta-sitosterol, lasarinin and L-plananin and zanthobungeneanine. Methylcinnamate, limonene, carvone, linalool, palmitic acid, p-cymene are some other compounds present in *Zanthoxylum armatum* (28) On the other hand, the aerial section of the plant contains sitosterol and pinoresinol diethyl ether. Linalyl acetate, phenols, methyl-n-nonyl ketone, sesquiterpenes hydrocarbon, tricosane, citronellal, 1,8-lineole, and limonene are among the compounds found in the oil extracted from *Zanthoxylum armatum* (29) Important active ingredients found in the plant *Zanthoxylum armatum* include lignin, alkaloids, coumarin, benzenoids, amino acids, phenols, and flavonoids (30,31) And many more derivatives are found in the research (32)



 <p>Lisarinin</p>	 <p>Alanine</p>	 <p>Methyl cinnamate</p>	
 <p>Limonene</p>	 <p>Palmitic acid</p>	 <p>Lupeol</p>	
 <p>Amino acid</p>	 <p>Aspartic acid</p>	 <p>Threonine</p>	
 <p>Tyrosine</p>	 <p>SESAMIN</p>	 <p>EUDESMIN</p>	
<p>DICTAMINE</p> 	<p>XANTHOPLANINE</p> 	<p>TRITERPENE</p> 	
<p>UMBELLIFERONE</p> 	<p>PHENOLS</p> 	<p>CITRONELLAL</p> 	
<p>CINNAMATE</p> 	<p>SABINENE</p> 	<p>1,8-CINEOLE</p> 	
<p>BETA-TERPINEOL</p> 	<p>2-TRIDECANONE</p> 	<p>ALPHA-PINENE</p> 	<p>BETHANECHOL</p> 

Pharmacology

Anti-inflammatory activities

SINGH *et al* (34) enquired the methanolic and chloroform extracts of leaves and bark of *Zanthoxylum armatum*. T-butylamine and benzoxazole, 2-(isobutyl amino) were identified as the major constituents in bark methanolic and bark chloroform extracts respectively. The total flavonoids, Ortho dihydric phenols and phenolic contents were also quantified in the extracts. Result showed that the that *Zanthoxylum armatum* DC. May be used as herbal antioxidant, food preservative, natural anti-inflammatory drug and natural bactericidal, besides generation of data base for judicious exploitation in future

Anti-inflammatory and antioxidant properties of steam bark from *Zanthoxylum armatum* were investigated. The DPPH free radical method was used to measure the antioxidant activity in vitro and the in vivo anti-inflammatory activity in Wister rats using carrageenan-induced paw edoema (35)

Anti-diabetic activity

Rats that were given 60 mg/kg of streptozotocin to produce diabetes were used to test the anti-diabetic properties of a hydro-methanolic extract of the bark of *Zanthoxylum armatum*. The typical reference medication was glibenacmide (5 mg/kg). For 21 days, oral administration of *Zanthoxylum armatum* hydro methanolic extract (200 and 400 mg/kg) led to a significant rise in HDLP and a significant decrease in blood glucose, total cholesterol, triglycerides, LDL, and VLDL. (36)

Antioxidant Activity

Z. armatum leaf extract shown strong antioxidant activity in in-vivo studies. The administration of the extract (100, 200 mg/kg b.w.) dramatically increased the treated animals' levels of antioxidant enzymes (SOD, CAT, and GSH). The levels of SOD, CAT, and GSH increased significantly ($p < 0.05$ and $p < 0.01$ at each dose), while the level of lipid peroxidation decreased in a dose-dependent manner. (37)

Hepatoprotective Activity

According to research, the plant *Zanthoxylum armatum* has hepatoprotective effect against carbon tetrachloride, which damages the liver, and it can help restore normalcy by raising the number of hepatic enzymes. Additionally, it lessens the marker enzyme leakage and guards against membrane fragility in hepatocytes. And thus, said that this plant aids in shielding the hepatocytes' plasma membrane (38)

Antifungal Activities

Ram et al (39) evaluated the acetone and methanol extract of bark and leaf of *Zanthoxylum armatum*. According to antibacterial results, acetone extracts inhibited *Salmonella typhi* (16.67 mm) in the case of the bark and *Shigella dysenteriae* (16.67 mm) in the case of the leaf better than methanol extracts did against *Escherichia coli* (20.33 mm in the case of the bark and 18.67 mm in the case of the leaf). From the present investigation, it has been concluded that both acetone and methanol extracts of bark possess significant antibacterial potential. Methanol extracts of both the plant parts exhibited considerable antioxidant and antibacterial activity.

PATHAK et al (2021) evaluated and extracted essential oil and methanol extract of the fruit of *Zanthoxylum armatum* DC. The methanol extract showed the presence of alkaloids, flavonoids, glycosides, polyphenols, terpenoids, volatile oils, tannins, and saponins. Result showed that the methanol extract was found to be effective against gram-positive bacteria only. Both oil and extract showed moderate antifungal activity against bacterial strain (40).

Antimicrobial activities

Nooreen et al (41) Using the well diffusion method, the antibacterial activity of extracts of *Zanthoxylum armatum* bark in methanol, acetone, and chloroform was investigated. The acetone extract showed the highest zone of inhibition (42.3 mm) against *S. aureus*, while the methanolic extract showed the second-highest zone of inhibition (28.7 mm) against *S. aureus*. The chloroform extract exhibited the highest activity (28.3 mm) against *P. vulgaris*.

Bark extracts in methanol and acetone shown greater effectiveness against *S. aureus* and chloroform extract against *P. vulgaris*. Activities could demonstrate the impact on microorganisms. *Bacillus subtilis* has a minimum bactericidal concentration and a zone of inhibition. The fungicidal effects of the oil composition against *Alternaria brassicicola* may also be evident. (42)

Antidepressant activity

We have investigated the antidepressant properties of several *Z. armatum* extracts in our laboratory. To determine which component functions as an antidepressant most effectively, a bioassay guided fraction was conducted. Its hydroalcoholic extract trailed the hexane extract in potency across a range of depression models, including the tail suspension test in mice and the forced swimming paradigm in rats and mice. Studies on behaviour, biochemistry, and molecular biology have demonstrated that the plant's seed has strong antidepressant effects (43).

Alam et al. (44) performed MTT, neutral red uptake (NRU), and DAPI stain assays to test the anticancer effects of methanol extract and crude saponins from the fruit, bark, and leaves of *Z. armatum* on colorectal (Caco-2) and breast (MDA-MB-468 and MCF-7) cancer cell lines. In comparison to Actinomycin-D (4 μ M), which demonstrated a growth inhibition of 65.40(\pm 4.29) %, the effect of saponins from fruit, bark, and leaves (Zf. Sa, Zb. Sa, and Zl. Sa) against Caco-2 cell lines inhibited the growth of Caco-2 by 53.16 (\pm 3.31) %, 66.43 (\pm 3.24), and 45.96 (\pm 10.67), respectively. Recently, saponins have become popular as chemotherapeutic agents in clinical settings.

When tested against colon cancer cells, saponins can stop tumour cell growth by causing apoptosis through signalling pathways without changing the normal architecture of the colon.

Yadav et al (45) examine the anti-depressant potential of *Zanthoxylum armatum* seed extract using Swiss albino mice in forced swim and tail suspension tests the research revealed that there was strong antidepressant action in the *Zanthoxylum armatum* extract. The mean and standard error of the mean were calculated using Microsoft Excel, and the one-way ANOVA and turkey multiple comparison test were used to analyse the data

Barkatullah et al (46) did in-vitro and in-vivo pharmacological screening of *Zanthoxylum armatum* and used crude ethanolic and n-hexane extract of the leaves (ZLE, ZLH) and fruits (ZLE, ZLH) of this plant for evaluation of phytotoxic and cytotoxic potential. Phytotoxicity and cytotoxicity were found to be dose dependant and showed maximum efficiency at 1000µg/ml. This study demonstrates that crude saponins and extract from leaves, bark and fruit of *Zanthoxylum armatum* exert cytotoxic effect on cancer cell lines involving apoptosis.

Antispasmodic Effect

Mice treated with *Z. armatum* crude extract (100 and 300 mg/kg; p.o.) demonstrated 20% and 60% protection against castor oil-induced diarrhoea, respectively, and had similar efficacy to the standard medication Loperamide (10 mg/kg). (47) In a different study, the essential oil of *Z. armatum* leaves was tested for potential anti-diarrheal properties on spontaneously contracted smooth muscle of the isolated rabbit jejunum as well as muscle constricted due to potassium chloride. At a dose of 10 mg/ml, the volatile oil's spasmolytic impact reached 100% of its peak at 0.03 mg/ml. The tensed muscle was eased by the extracts, which may have been caused by sarcoplasmic reticulum calcium channel blockage (48)

Antibacterial activity

IRSAD et al (49) investigated the antibacterial and antioxidant activities of three different extracts (acetone, methanol, and n-hexane) of *Zanthoxylum armatum* fruits and leaves the results of the present study showed fluctuation among different extracts. The acetonic and methanolic extract showed an excellent antibacterial effect, while n-hexane extract exhibited a minimum antibacterial effect against tested bacterial pathogens. In the extract, the methanol leaf extract had the highest inhibition rate against *K. pneumoniae* (20.51±0.93 mm), and the methanol extract had the lowest inhibition rate against *S. typhimurium* (12.01±0.93 mm)

Antitumor Activity

Z. armatum possesses anticancer properties as well. By exhibiting a monoterpenoleupol that demonstrates the medicinal and chemoprotective actions, the fruits and leaves may demonstrate their anticancer properties (50)

CONCLUSION

Zanthoxylum armatum is one of the important medicinal plants having a wide array of household, commercial and ethno-medicinal applications. The fruits, leaves, seeds and stem bark are used in head-ache, fever, toothache, tonsillitis, diarrhoea, dysentery, altitude sickness. The fruits contain essential oil that possesses antiseptic, disinfectant properties so it has its wide application in pharmaceuticals and flavouring industries. The main constituents of the essential oil are limonene and linalool s. In many studies, drug-sensitive strains of infectious agents and cancer cells were used to assess bioactivity. Hence, future research should target the activity of *Z.* species against drug-resistant species or strains. This is important because one of the ultimate goals of new drug development is to curb drug resistance. Furthermore, several *Z.* species phytochemicals with strong bioactivities against infectious microorganisms, especially against drug-resistant strains of malarial parasites, viruses and other microbes, as well as drug-resistant cancer cells should be subjected to clinical trials as potential natural alternatives to synthetic drugs. In addition, since many studies were conducted in vitro, there is a dearth of information on the intestinal transport, biostability, bio accessibility, and bioavailability of many of the active compounds. Additional research is needed to clarify the specific chemical compounds responsible for the promising biological activities of some of the plant extracts as well as the bioactivity and mechanisms of action of some of the isolated compounds. Future research should also confirm bioactivities and safety of the compounds in vivo using animal models and humans. Finally, researchers should endeavour to mimic the traditional methods used in preparation of the plant extract to ensure the preservation of the bioactive principles of interest. In this review, suggesting for further potential biological applications of *Zanthoxylum armatum*. Many active components have been identified from the plant that might be developed into novel drugs. Therefore, further emphasis.

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