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A comprehensive review of *Zanthoxylum armatum*: Phytochemistry, pharmacological activities, and therapeutic potential

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Abstract
The deciduous shrub or small tree *Zanthoxylum armatum*, is also called Timur or Indian rattan pepper, It is a member of the Rutaceae family. It is found all over Asia, but especially in the temperate and subtropical Himalayan regions, such as China, India, Nepal, and Bhutan. In traditional medicine, cooking, and as a source of essential oils, the plant is highly valued. According to phytochemical studies, *Zanthoxylum armatum* contains a wide range of bioactive substances, such as terpenoids, alkaloids, flavonoids, and essential oils, all of which support its varied pharmacological properties. These consist of analgesic, antimicrobial, anti-inflammatory, antioxidant, and antidiabetic qualities. Its essential oil, which contains compounds like citronellol, limonene, and linalool, is used extensively in traditional medicine and perfumery. In Ayurveda, Unani, and traditional medicine, the plant's seeds, bark, and leaves are frequently used to treat ailments like digestive problems, toothaches, and skin diseases. Recent research has also demonstrated its potential as a natural pesticide and in the fight against diseases linked to a certain lifestyle. In order to highlight *Zanthoxylum armatum*'s therapeutic potential and the room for further study in pharmacognosy, drug development, and sustainable cultivation methods, this review attempts to compile the ethnobotanical, phytochemical, and pharmacological insights into the plant.

Keywords: *Zanthoxylum armatum*, phytochemicals, pharmacological activities, traditional medicine, herbal medicine, antimicrobial, antioxidant, anti-inflammatory, rutaceae family

Introduction
Medicinal plants, also known as herbs, are plants that have therapeutic properties and have been used for human health and well-being since ancient times. These plants are primarily used to make Ayurvedic medicine, but over time, other pharmaceutical industries began using them to make herbal preparations as well [1]. In Indian ethnobotany, there are 2532 plant species, many of which have medicinal properties. Phytochemicals, which are abundant in plants, protect the body from a variety of illnesses, including oxidative stress and microbial infection [2]. Herbal medicine is widely used by different communities all over the globes as it is simple, cheap, and has fewer side effects compare to medicine of synthetic origin. Today, almost 30% of the pharmaceutical preparation are based on plants and it is highly observable that most developed countries import their raw materials of therapeutically important plants from developing countries [3, 4]. Often referred to as the Toothache tree, Nepal pepper, or Indian prickly ash, *Zanthoxylum armatum* DC is an important member of the Rutaceace family of medicinal plants. This plant is known locally as Mukthrubi (Manipuri), Tejphal (Hindi), Tejowati (Sanskrit), and Timur (Nepal).It can be found all over India, from Kashmir to Bhutan, at elevations of up to 2,500 meters. Additionally, it can be found in northeastern India. At elevations between 1,300 and 1,500 meters, The majority of China, Taiwan, Nepal, the Philippines, Malaysia, Pakistan, and Japan are also home to it. The species usually lives in the understory of mixed forests, wasteland, and mountain valleys and thickets [5, 15]. Zanthoxylum (Rutaceae) is an apocarpous genus of deciduous aromatic shrubs and trees [16]. The Greek term "xanthon xylon," which translates to "yellow wood," is where the name came from [17]. In the Rutaceae family, Zanthoxylum is the second largest genus with 225 species [18]. The genus is mostly found in the Americas, Africa, and the Himalayas, as well as Central, South, Southeast, and East Asia [19, 20]. The genus's plants are a great source of culinary, high-value woods (satinwood), edible fruits, and oils [21]. *Zanthoxylum armatum*

DC, commonly known as the "Timur or Toothache tree,". It is a valuable medicinal plant valued for its economic, cultural, and aromatic qualities [22]. *Zanthoxylum armatum* is a small tree or deciduous shrub that grows best in black, well-drained alluvial soil. The Eastern Ghats in Orissa and Andhra Pradesh (1,200 m), the warmer Himalayan valleys from Jammu and Kashmir to Assam and Khasi (1,000 to 2,100 m amsl), and the lesser Himalayan regions in northeastern India, including Naga Hills, Meghalaya, Mizoram, and Manipur, have all been observed to have it [23, 24, 25]. It is synonymous with *Z. alatum* [26]. *Z. alatum* was subsequently referred to as *Z. armatum* and *Z. planispinum* in earlier research; however, Flora Hupehensis considers both species to be separate [27]. Numerous chemical compounds, including lignins, alkaloids, flavonoids, coumarins, phenols, and terpenoids, are found in this plant. These compounds are responsible for a wide range of biological activities, such as hepato-protective, antiviral, antioxidant, antimicrobial, and insecticidal/larvicidal effects, according to numerous pharmacological studies. Over the past 20 years, the high demand for *Zanthoxylum armatum* in both domestic and foreign markets has resulted in an increase in the plant's market price [28].

Nomenclature of *Zanthoxylum armatum*: [29]

Kingdom	Plantae
Subkingdom	Viridaeplantae
Phylum	Tracheophyta
Subphylum	Euphyllophytina
Class	Magnoliopsida
Subclass	Rosidae

Fig 1: Plant of *Zanthoxylum armatum*

Vernacular Names: [29]

English Name	Prickly Ash
Nepali	Timur, Nepali peeper
Oriya name	Tundopoda
Bengali name	Gaira, Tambul
Manipuri	Mukthrubi

Morphological characteristics *Zanthoxylum armatum*

A small tree or prickly shrub that grows up to six meters in height. Two stipular prickles are present at the base of the glabrous leaves, narrowly winged petiole, and they are 4-20 cm long, imparipinnate, aromatic, and pungent. The undersides of each pair of leaflets, which range from two to six, are glabrous. The plant can be recognized by its dense foliage, prickly trunk and branches, small red, subglobose fruits, shrubby habit, and strong, aromatic flavour [30].

Phytochemical constituents

It has been shown that *Zanthoxylum armatum* essential oil contains a large number of alkaloids, flavonoids, flavonal glycosides, lignins, phenolics, sterols, terpenoids, fatty acids, alkenicacids, amino acids, numerous aromatic and volatile chemicals, and many other substances in good concentrations. [31] Analysis using gas chromatography-mass spectrometry (GC-MS) shows that there are 22 distinct components in seed essential oil [32].

Traditional Uses

The indigenous medical system makes extensive use of *Zanthoxylum armatum*'s bark, fruits, and seeds as an anthelmintic, stomachal, and carminative. The fruit and seeds are used as an aromatic tonic for fever and dyspepsia. An extract of the fruits is believed to successfully evict round worms. The fruits' deodorant, disinfecting, and antiseptic qualities make them useful for dental issues, and their lotion is used to treat sores. They also serve as a deterrent to houseflies [33]. Its stomachic, carminative, and anthelmintic qualities make it valuable in the traditional health system. Zuroor-e-Qula, a powdered polyherbal Unani formulation with antibacterial and anti-inflammatory qualities, contains timur seeds as a major ingredient [34]. In traditional cooking, the fruits are used as flavorings and spices and the younger twigs are used as tooth brushes. Traditionally, the bark has been used to make dye [35, 36].

Pharmacological activities

Antioxidant activity

The methanol and essential oil extracts of leaves have the capacity to chelate Fe2+ ions, reduce power, and scavenge 2,20-diphenyl-1-picrylhydrazyl (DPPH) [37] Antioxidant properties are demonstrated by an ethanolic extract of *Zanthoxylum armatum* stem bark. Wistar rats' paw edema caused by carrageenan was utilized to measure antioxidant activity *in vivo*, while the DPPH free radical technique was employed to measure antioxidant activity *in vitro*. The plant extract demonstrated significant antioxidant activity [38]. Additionally, the fruit and stem bark ethanol extracts have the capacity to chelate Fe2+ ions and scavenge 2, 20-diphenyl-1-picrylhydrazyl (DPPH) [39, 40]. conducted an in-vivo antioxidant test on male Wister Albino rats using a methanol extract of *Zanthoxylum armatum* leaves. The extract was given orally to the test animals at doses of 100 and 200 mg/kg body weight, while the positive control group received standard vitamin E and the normal control group received distilled water. The test animals were given a 1:1 CCl4 and olive oil mixture for two days after the five-day period. In contrast to normal animals, the EAT-bearing control group showed an increase in lipid peroxidation levels, while the normal control groups showed a significant decrease ($P < 0.01$) in SOD, CAT, and GSH activities. The antioxidant enzymes SOD, CAT, and GSH were considerably more active in the treated animals after the extract was administered. Treatment at these doses significantly increased SOD and CAT levels ($P < 0.05$ and $P < 0.01$) as well as GSH levels, even while the lipid peroxidation level decreased at 100 mg/kg ($P < 0.05$) and 200 mg/kg ($P < 0.01$), respectively [41].

Antispasmodic activity

The *in vivo* spasmolytic effects of *Zanthoxylum armatum* crude extract were investigated in relation to castor oil-induced diarrhea in mice. Animals given the extract as a pretreatment showed 60% protection against diarrhea at 1000

mg/kg and 20% protection at 300 mg/kg. A positive control was Loperamide (10 mg/kg) [42]. In a different experiment, the essential oil of *Zanthoxylum armatum* leaves was assessed for a potential antidiarrheal effect on the isolated rabbit jejunum's spontaneously contracted smooth muscle and that induced by potassium chloride. The oil's spasmolytic effect began at 0.03 mg/mL and reached 100% at a dose of 10 mg/mL. The extracts caused the contracted muscle to relax, indicating that this plant may work by either blocking the calcium channel or preventing the sarcoplasmic reticulum from releasing stored calcium [43]. Both spontaneous and high K+-induced contractions were induced by crude extract of *Zanthoxylum armatum*, causing the isolated rabbit jejunum to relax in a concentration-dependent manner. The findings indicate that *Zanthoxylum armatum's* spasmolytic properties, which may be mediated by a Ca++ antagonistic mechanism, provide the pharmacologic foundation for its therapeutic usage in gastrointestinal, pulmonary, and cardiovascular problems [44, 45].

Anti-inflammatory activity

A coumarin called bergapten, which was isolated from the plant, demonstrated a concentration-dependent, substantial reduction of the production of pro-inflammatory cytokines, specifically TNF-a and IL-6, when PBMCS were activated with lipopolysaccharide [42]. Additionally, it is well known that linalyl acetate and linalool have inflammatory properties. [46] After four hours of treatment, the degree of inhibition at a dose of 250 mg/kg was 19.12%. As a positive control, ibuprofen (10 mg/kg body weight) was employed. Additionally, fruit extract blocked the carrageenan that caused the Wister rats' paws to expand [47]. The presence of lignan components facilitates its analgesic activity [48].

Antibacterial activity

Ethanolic and nhexane extracts of the leaves, fruits, and bark of *Zanthoxylum armatum* were tested *in vitro* for their antibacterial activity against a number of bacterial strains, including Micrococcus luteus, Escherichia coli, Staphylococcus aureus, *Pasteurella multocida*, Pseudomonas aeruginosa, Bacillus subtilis, and *Streptococcus viridans*, using the agar well diffusion method [49, 50]. The primary flavonoid, 3,5-diacetyltambulin, isolated from *Z. armatum*, significantly inhibited both Gram positive (Bacillus subtilis, B. megaterium, and Staphylococcus aureus) and Gram negative (*Escherichia coli, Shigella dysenteriae, S. sonnei, S. flexneri, Pseudomonus aeruginosa,* and *Salmonella typhi*) [51, 52].

Antitumor activity

Z. armatum may be used as an anticancer drug due to its cytotoxicity in crude leaf and fruit extract [53]. It contains a monoterpene called luteol, which is used as a chemopreventive and therapeutic agent to treat inflammation and cancer.

Antifungal activity

The essential oil extracted from *Zanthoxylum armatum* leaves demonstrated exceptional anti-mycotic properties in an *in vitro* test against a variety of fungal strains, including Aspergillus flavus, *Fusarium solani* [54], Candida glabrata, *Microsporum canis*, Candida albicans, and *Trichophyton longifilis*. At a concentration of 125 µg/mL, the highest percentage inhibition of mycelial growth was observed against Aspergillus flavus (55.33 ±) and Candida albicans (66.67 ± 0.57%). and *Fusarium solani* (46.33 ± 0.33. DMSO was used as the negative control and miconazole as the positive control [55, 56, 57].

Larvicidal activity

The essential oil from the seeds of *Zanthoxylum armatum* DC (Rutaceae) is used to fight three mosquito species: Aedes aegypti, Anopheles stephensi, and Culex quinquefasciatus [58, 59]. At least 28 compounds were found in the essential oil study, mostly monoterpenes and oxygenated monoterpenes. Three different mosquito species' larvae were vulnerable to the composition of essential oils [60, 61]. Furthermore, Tiwary examined the *in vitro* larvicidal effects of the essential oil of *Zanthoxylum armatum* seeds against three mosquito species: *Culex quinquefasciatus*, Aedes aegypti, and Anopheles stephensi. The study employed the following test doses: 200, 150, 100, 50, 25, and 10 ppm. The most sensitive species was determined to be *Culex quinquefasciatus*, with LC50 and LC95 values of 49 and 146 ppm, respectively. Following with LC50 values ranging from 54 to 58 ppm were Aedes aegypti and *Anopheles stephensi*. As a positive control, temephos, a chemical larvicide commonly used to inhibit mosquito larvae, was used at concentrations between 0.005 and 0.1 ppm [62].

Antiviral activity

The *in vitro* antiviral activity of methanolic extracts of *Zanthoxylum armatum* fruits (concentrations of 100, 50, 25, 12.5 and 6.25 mg/mL) against influenza virus A (100, 50, 25, 12.5 mg/mL) and Herpes simplex virus type 1 (HSV-1) in the systems HSV-1/Vero cells and influenza virus A/MDCK cells has been evaluated using the dye uptake assay. The extracts showed suppression of HSV-1/Vero cells and Influenza A/MDCK cells, with CC50 values > 100 mg/mL and 36 mg/mL, respectively [63, 64]. The aqueous extract of the leaves was found to inhibit both Plasmodium berghei and Giardia lamblia [65].

Insecticidal activity

Using the direct contact method with filter paper (90 mm diameter), the insecticidal activity of the ethanolic extract and different fractions was assessed against *Trogoderma granarium*, *Rhyzopertha dominica*, and *Callosobruchus analis*. The most commonly used insecticidal agent was permethrin (235.71 mg/cm2) [66].

Hepatoprotective activity

When mice are given its ethanolic leaf extract, their livers are protected from the hepatotoxicity and inflammation caused by CCl4 [67, 68]. Through increasing the amount of antioxidant enzyme and regulating serum enzymatic levels. Mice's livers were able to develop a defense mechanism against CCl4 hepatotoxicity thanks to the bark extract. The ethanolic extract of *Zanthoxylum armatum* showed a hepatoprotective effect against carbon tetrachloride-induced liver injury by restoring the increased levels of hepatic enzymes to normal. The ethanolic extract of *Zanthoxylum armatum* can condition the hepatocytes, preventing membrane fragility and lowering the leakage of the marker enzymes into the circulation, in contrast to silymarin, which has been demonstrated to have a protective impact on the hepatocytes' plasma membrane [69, 70].

Conclusion

Numerous medical uses of *Zanthoxylum armatum* have shown its antimicrobial, insecticidal, anti-inflammatory, and analgesic properties. The plant's potential as an

anticarcinogenic agent is not well understood, so further research may be necessary to show off its potential uses. Thus, the plant has shown promise for further research and possesses a potent pharmacological action. Numerous biological activities, such as antioxidant, hepatoprotective, larvicidal, antimicrobial, and antiviral qualities, have been connected to alkaloids, flavonoids, terpenoids, phenols, coumarins, and other chemical compounds present in different plant parts. As this study demonstrates, several *in vitro* and *in vivo* ethno-pharmacological investigations have validated the different traditional ethno-medicinal practices, pointing to further possible biological applications for *Zanthoxylum armatum*. The latest recent information about *Zanthoxylum armatum* may be found in the review above. Strong antibacterial, antifungal, and anthelmintic properties were demonstrated by *Z. armatum* essential oils. All of the essential oils that are derived from the seeds of *Zanthoxylum armatum* have antibacterial properties and are used to treat microbiological illnesses. Strong antibacterial, antifungal, and anthelmintic properties were demonstrated by the essential oils of *Zanthoxylum armatum*. This plant has important therapeutic applications for all parts of it.

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