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Unlocking the pharmacological potential of *Zanthoxylum rhetsa*: A multifaceted medicinal plant

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Abstract
The multifaceted pharmacological potential of *Zanthoxylum rhetsa* is increasingly recognized in the scientific community. This article elucidates the profound antioxidant, antibacterial, anti-inflammatory, and anticancer properties of *Z. rhetsa*, presenting a strong case for its application in therapeutics. The antioxidant capacity of *Z. rhetsa* seed oil is showcased through studies employing the DPPH assay, with results comparable to that of established antioxidants like α-tocopherol. Moreover, extracts from different parts of the plant have demonstrated superior antioxidant activities when juxtaposed with synthetic antioxidants such as BHT and PG. The exploration of its antibacterial effects reveals efficacy against various pathogenic bacteria, highlighting its potential to combat antibiotic resistance. The anti-inflammatory properties of *Z. rhetsa* are also well-documented, with evidence of significant inhibition of inflammatory mediators in macrophages. Furthermore, its anticancer effects have been observed across various cell lines, with components such as flavonoids and limonoids playing a critical role in inducing apoptosis and inhibiting angiogenesis. These promising *in vitro* results support the potential of *Z. rhetsa* as a natural source for the development of new pharmaceutical agents. However, the translation of these findings into clinical practice necessitates further research on the bioactive compounds' mechanisms of action, safety, and efficacy in human models. The current article synthesizes these various strands of research, accentuating the importance of *Z. rhetsa* in the development of future therapeutic agents.

Keywords: *Zanthoxylum rhetsa*, pharmacological property, antibacterial activity, cytotoxic activity, medicinal plant

Introduction
Zanthoxylum is one of the largest Genus of Rutaceae family which includes shrubs and small to large trees which have spiny bole and branches (Gentry, 1993) [1]. The other character of *Zanthoxylum* species is that they possess thorny leaves. They are characterized by sharp thorns on either the stem or leaves. According to Hooker (1875) [2] around 12 species of *Zanthoxylum* are found in India out of which 6 species are confined to Himalayan regions. Plants of genus *Zanthoxylum* are mentioned in various cultures and customs for their medicinal or therapeutical properties (Kharshiing, 2012) [3]. They not only serve for medicinal purposes but also for various sources of foods, wood, edible oils, raw materials for industries. The genus *Zanthoxylum* have also been recognised for number of antimicrobial activities, antiproliferative, allelopathic activities, anti-inflammatory activities, antioxidant (Kumar and Muller, 1999; Xia et al, 2011) [4, 5]. *Zanthoxylum* species are traditionally used for a variety of ailments in addition to oral diseases. In India the leaves are used for fever, indigestion and bronchitis. In Manipur (India), seed oil is used to treat hair loss and bark powder is used to treat toothache. This application is believed to be beneficial for the elderly and those suffering from gum pain and other oral ailments. In parenthesis is the oral anesthetic effect thought to be caused by hydroxyl-α-sanshool, an alkylamide present in *Zanthoxylum* species. Studies have shown that extracts of the leaves of the seeds have potential as anthelmintic agents. It was found to have significant antilarval activity comparable to marketed drugs (Olila and Opuda-Asibo 2002) [7].

Zanthoxylum rhetsa (Roxb) DC, commonly called Indian prickly ash, one of the important medicinal tree species is commonly found in shaded moist localities of tropical regions of India, Bangladesh, Sri Lanka, Indonesia, Malaysia, Vietnam and China (Thu *et al.*, 2010) [8]. In India, it is one of the important non wood forest products (NWFP) of North East India and Karnataka.

The young shoots and leaves are consumed as vegetables, and also used as spices because of which it has a high demand among people of North East India especially by the different tribes of Arunachal Pradesh (Payum *et al.*, 2013) [9]. It have also been reported that this species are been used by South Asian countries as food, for example: Northern Thai people use the fruit as a spice, and an appetizer especially in pork salad and curry (Wongkattiya, 2018) [10]. The fruits are also edible and is widely used in traditional medicine for their analgesic, anticonvulsant, anti-inflammatory and antitumor properties. The fruits are used as a spice in both fresh and dried form due to its typical woody lemon scent and pungent aromatic taste. Keeping in view, the pharmacological importance the present article was formulated to review the pharmacological potential of *Zanthoxylum rhetsa*.

Pharmacological properties of *Zanthoxylum rhetsa*

Antioxidant activities

A plethora of phytochemicals in medicinal flora are identified to possess antioxidative capabilities. The antioxidant activity of *Z. rhetsa* has been extensively studied through *in vitro* assays, particularly focusing on the free radical scavenging ability of its seed oil. A pivotal study conducted by Theeramunkong *et al.* (2018) [11] utilized a customized DPPH (1,1-diphenyl-2-picrylhydrazyl) assay to assess this activity, demonstrating that the oil, at a concentration of 1200 µg/ml, displayed significant radical scavenging efficiency comparable to α-tocopherol, a well-known antioxidant. Furthermore, the efficacy of different plant parts of *Z. rhetsa* has also been explored. The seed, seed coat, and fruit extracts showed a dose-dependent increase in radical scavenging activity when assayed through the DPPH method. These plant extracts revealed greater antioxidant activities when compared to synthetic benchmarks like butylated hydroxytoluene (BHT) and propyl gallate (PG), suggesting the potential for *Z. rhetsa* as a natural alternative to these synthetic compounds (Theeramunkong *et al.*, 2018) [11]. An additional study by Tuz-Zohora *et al.* (2019) [12] expanded on this understanding by evaluating the antioxidant properties of different solvent fractions from the crude methanolic extracts of *Z. rhetsa* root bark. Alongside, two isolated quinolone alkaloids-8-methoxy-N-methylflindersine and zanthodioline were tested. The aqueous (AQ) fraction was found to possess the most potent antioxidant activity, while significant activities were also reported for the carbon tetrachloride (CTC) and chloroform (CF) fractions. These findings underscore the promising potential of *Z. rhetsa* as a source of natural antioxidants, which could be exploited for therapeutic applications against oxidative stress-related pathologies.

Antibacterial activity

With the rise of antibiotic resistance, there has been an increased interest in natural products with antibacterial properties. This has directed scientific attention towards *Zanthoxylum rhetsa* and its phytochemical components, which have been reported to possess significant antibacterial activity. The antibacterial properties of *Zanthoxylum rhetsa* can be attributed to its diverse phytochemical composition. It contains various bioactive compounds such as alkaloids, flavonoids, terpenoids, and essential oils (Rahman et al, 2008) [13]. Alkaloids from the fruit have been found to inhibit bacterial growth, while essential oils have shown efficacy against a spectrum of gram-positive and gram-negative bacteria. Recent studies have examined the antibacterial activity of *Zanthoxylum rhetsa* extracts against a variety of pathogenic bacteria. For instance, extracts from the bark have exhibited significant inhibitory effects on *Sarcina lutea*, *Staphylococcus aureus*, *Salmonella paratyphi-A*, *Shigella dysenteriae*, *Shigella boydii* and *Shigella sonnei* (Tuz-Zohora *et al.* 2019) [12]. The mechanism of action is believed to be associated with the disruption of bacterial cell wall synthesis and protein function, although more research is needed to elucidate the precise biochemical pathways. An exciting aspect of *Zanthoxylum rhetsa* is its potential to enhance the efficacy of conventional antibiotics. A novel amide, designated as zanthorhetsamide have been extracted from the root and stem bark of *Zanthoxylum rhetsa* that possess potent antibacterial action against methicillin-resistant *Staphylococcus aureus* SK1, as well as exhibit moderate efficacy against *Escherichia coli* TISTR 780, with minimum inhibitory concentration (MIC) values recorded at 8 µg/mL and 16 µg/mL, respectively (Cholpisut *et al.* 2012) [14].

Anti-inflammatory activity

Phytochemical analyses have revealed that *Z. rhetsa* is rich in alkaloids, flavonoids, terpenoids, and coumarins (Kumar *et al.*, 2019) [15]. Among these, the alkaloids, particularly the amides, have shown significant anti-inflammatory activity. The anti-inflammatory activity of *Z. rhetsa* has been linked to the inhibition of inflammatory mediators via LPS-induced NO, TNF-*α*, and PGE2 in RAW264.7 macrophages (Nguyen Van Hieu *et al.* 2020; Imphat *et al.* 2021) [18, 16]. The *in vitro* examination of the anti-inflammatory properties of *Zanthoxylum rhetsa* (Roxb.) stem via assays involving protein denaturation and the Human Red Blood Cell (HRBC) membrane stabilization method indicated that the stem extract of *Z. rhetsa* manifested notable anti-inflammatory effects (Parthiban *et al.* 2017) [17]. Complementary to this, the evaluation of anti-inflammatory potential through the suppression of nitric oxide (NO) production in lipopolysaccharide (LPS)-stimulated RAW 264.7 macrophage cells through the application of *Z. rhetsa* essential oil revealed a substantial reduction in NO synthesis, with an IC50 value of 16.42 ng/mL (Nguyen Van Hieu *et al.* 2020) [18]. These studies collectively suggest that *Z. rhetsa* has pronounced anti-inflammatory properties, offering promising therapeutic avenues for the management of inflammation.

Anti-cancerous property

Cancer continues to be a leading cause of mortality worldwide, driving the exploration for new anticancer agents from natural sources. *Zanthoxylum rhetsa*, a member of the Rutaceae family, has gained attention due to its rich repository of bioactive compounds, such as alkaloids, flavonoids, limonoids, and coumarins (Balunas & Kinghorn, 2005) [19]. The traditional use of *Z. rhetsa* in treating ailments, including inflammation and gastrointestinal disorders, has prompted researchers to explore its efficacy against cancer cells. The anticancer properties of *Z. rhetsa* can be largely ascribed to its complex phytochemical composition. Flavonoids, which are ubiquitous in the *Zanthoxylum* genus, exhibit anti-proliferative effects by inducing apoptosis and inhibiting angiogenesis (Middleton *et al.*, 2000) [20]. These compounds operate synergistically, enhancing the plant's overall anticancer potential. The *in vitro* studies have shown that *Z. rhetsa* DC. stem bark and root bark extract exhibit

potential effect against human stomach-cancer cell lines, SCL, SCL-6, SCL-3706, SCL-9, Kato-3, and NUGC-4 (Ahsan *et al.*, 2014) [21]. *Zanthoxylum rhetsa* bark and the compound kobusin, derived from the same source exhibit pronounced cytotoxic response in B16-F10 melanoma cells (Santhanam *et al.*, 2016). The petroleum ether extract from the stem bark of *Zanthoxylum rhetsa* also possess cytotoxic effects (Ahsan 2000) [22]. The green silver nanoparticles (AgNPs) synthesized utilizing the seed coat extract of *Z. rhetsa* demonstrated substantial anti-cancer activity against A549 lung cancer cell lines (Nayaka *et al.*, 2020) [18]. The study on *Z. rhetsa* leaf extract also suggested an anti-leukemic potential, although the specific mechanisms underlying the observed cytotoxic effects were not fully elucidated. These findings provide a promising outlook for *Z. rhetsa* as a candidate for developing new anticancer drugs. Despite the promising anticancer properties, the clinical application of *Z. rhetsa* is still in its infancy. Future research should focus on the isolation and characterization of individual compounds from *Z. rhetsa*, evaluating their efficacy, specificity, and safety profiles in preclinical and clinical settings. Furthermore, understanding the molecular mechanisms underlying the anticancer effects of *Z. rhetsa* will be crucial for its development as a therapeutic agent.

Conclusion

The *Zanthoxylum* genus, particularly *Zanthoxylum rhetsa*, emerges as a significant repository of pharmacologically active compounds. Its utilization in folk medicine and its versatility in addressing diverse health conditions highlight its vast therapeutic range. The genus offers notable antioxidant, antibacterial, anti-inflammatory, and anti-cancer benefits, which establish a solid foundation for further scientific exploration and potential pharmaceutical innovation. These bioactive constituents could serve as viable alternatives to synthetic medications, especially in the fight against drug-resistant diseases. *Zanthoxylum rhetsa* is also deeply woven into the socio-economic and cultural tapestry of many Asian regions, where it is valued not just for its medicinal properties but also as a dietary element and a spice. This underscores the importance of preserving both the species and its natural environment for the future. The transition from traditional usage to scientific endorsement and medical use of *Z. rhetsa* is still underway, hindered by the lack of clinical evidence. The promising results from laboratory and animal studies beckon for comprehensive clinical evaluations to validate the safety and therapeutic efficacy in human populations. Advancing our understanding through detailed pharmacokinetic and pharmacodynamic research, along with robust clinical trials, will be crucial steps in integrating *Zanthoxylum rhetsa* into the realm of recognized medical treatments. If traditional insights are amalgamated with contemporary scientific research, *Zanthoxylum rhetsa* may pave the way for a new generation of natural therapeutic agents.

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