Assessment of the Gastroprotective Potential of Alcoholic Extract of Zanthoxylum armatum in Rats

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ABSTRACT

This study investigates the antiulcer potential of alcoholic extract of Zanthoxylum armatum (AEZA) in rat models. Zanthoxylum armatum (family Rutaceae), traditionally used in the treatment of various gastrointestinal disorders, was evaluated for its gastroprotective effects using established ulcer induction methods: ethanol-induced, pylorus ligation-induced, and indomethacin-induced ulcer models. Ranitidine (50 mg/kg) served as the standard drug while AEZA was administered at doses of 200 mg/kg and 400 mg/kg. The extract significantly reduced ulcer indices across all models in a dose-dependent manner. At 400 mg/kg, AEZA demonstrated 72.6%, 68.3%, and 70.1% ulcer inhibition in ethanol, pylorus ligation, and indomethacin models, respectively. Biochemical analysis revealed that the extract significantly increased gastric mucus secretion, reduced gastric volume, and normalized pH values. Additionally, AEZA treatment significantly decreased pepsin activity and acid output, while elevating mucin levels. Histopathological examinations confirmed reduced mucosal damage and preservation of gastric mucosal architecture in AEZA-treated rats. The findings establish strong evidence for the significant gastroprotective effects of Z. armatum, supporting its traditional use in gastric disorders. The antiulcer activity appears to be mediated through multiple mechanisms including antioxidant activity, mucosal strengthening, and modulation of gastric secretory parameters.

Keywords: Zanthoxylum armatum, antiulcer activity, gastric ulcer, pylorus ligation, ethanol-induced ulcer, indomethacin, gastroprotection

1. INTRODUCTION

1.1 Gastric Ulcers: Prevalence and Challenges

Peptic ulcer disease represents a significant global health concern, affecting approximately 10% of the world population, with gastric ulcers comprising a substantial proportion of these cases [1]. The multifactorial etiology of gastric ulcers involves an imbalance between aggressive factors (gastric acid, pepsin, bile salts, Helicobacter pylori infection, and non-steroidal anti-inflammatory drugs) and defensive factors (mucus-bicarbonate barrier, prostaglandins, and epithelial cell renewal) [2]. Despite advancements in understanding ulcer pathophysiology and the development of various synthetic antiulcer medications, complete management remains challenging due to efficacy limitations, adverse effects, and recurrence rates associated with conventional therapies [3]. These challenges have driven increasing interest in natural product-based interventions with potentially improved safety profiles and multitargeted therapeutic mechanisms.

1.2 Zanthoxylum armatum: Ethnopharmacological Perspectives

Zanthoxylum armatum DC. (Rutaceae), commonly known as "Tejphal" or "Timur," is a medicinal plant widely distributed throughout the Himalayan region of India, Pakistan, Nepal, China, and Taiwan [4]. In traditional medicine systems including Ayurveda,

Siddha, and folk practices across the Indian subcontinent, various parts of Z. armatum have been utilized to treat diverse ailments [5]. The bark, fruits, and seeds are traditionally employed for treating digestive disorders, including dyspepsia, abdominal pain, and gastritis [6]. Phytochemical investigations have revealed that Z. armatum contains numerous bioactive compounds, including alkaloids (particularly benzophenanthridines), phenolics, lignans, coumarins, and terpenoids, many of which exhibit significant pharmacological activities [7]. The documented antimicrobial, anti-inflammatory, antioxidant, and analgesic properties of Z. armatum extracts suggest potential value in gastrointestinal mucosal protection [8].

1.3 Rationale and Objectives of the Study

Despite the traditional use of Z. armatum in treating gastrointestinal disorders, scientific validation of its efficacy, particularly regarding antiulcer activity, remains inadequate. The few preliminary studies investigating Z. armatum's gastroprotective effects have shown promising results but lack comprehensive evaluation across multiple ulcer models with corresponding biochemical and histopathological assessments [9]. Therefore, this study was designed to systematically evaluate the antiulcer potential of alcoholic extract of Z. armatum (AEZA) using complementary experimental models that simulate the various pathophysiological mechanisms of gastric ulceration. Specifically, the study aimed to: (i) assess the gastroprotective effects of AEZA in ethanol-induced, pylorus ligation-induced, and indomethacin-induced ulcer models; (ii) investigate the effects of AEZA on gastric secretory parameters and mucosal defensive factors; (iii) examine the histopathological changes in gastric tissues following AEZA treatment; and (iv) correlate the observed effects with the phytoconstituents present in the extract.

2. LITERATURE SURVEY

Gastric ulcer therapeutics have evolved significantly over the past decade, with traditional antiulcer drugs including antacids, H2 receptor antagonists, proton pump inhibitors (PPIs), and cytoprotective agents forming the cornerstone of conventional treatment [10]. However, the recognition of limitations associated with these approaches, including acid rebound with PPIs and H2 receptor antagonist tolerance, has stimulated exploration of alternative therapeutic strategies [11]. Kumar et al. (2013) reported that despite advances in synthetic antiulcer medications, approximately 30% of patients experience relapse within 12 months of treatment completion, underscoring the need for more effective interventions [12].

The ethnopharmacological approach to ulcer management has gained significant attention, with numerous medicinal plants demonstrating promising antiulcer activities through diverse mechanisms. Ahmad et al. (2013) systematically reviewed 120 plant species with documented antiulcer properties, highlighting their potential advantages including multi-target action, reduced side effects, and cost-effectiveness [13]. Specifically regarding Zanthoxylum species, Negi et al. (2011) documented traditional uses of Z. armatum in treating stomach disorders across various indigenous communities in the Himalayan region [14]. In vitro studies by Singh and Sharma (2012) demonstrated significant antioxidant activity in Z. armatum extracts, showing potential relevance to gastroprotection given the established role of oxidative stress in ulcer pathogenesis [15].

Preliminary investigations into Z. armatum's antiulcer potential have revealed promising results. Barman et al. (2014) reported that aqueous extracts of Z. armatum seeds (250 mg/kg) reduced ethanol-induced ulceration in rats by approximately 58% [16]. Similarly, Chen et al. (2011) demonstrated that certain alkaloids isolated from Z. armatum bark exhibited protective effects against indomethacin-induced gastric damage in mice [17]. However, these studies employed single ulcer models and lacked comprehensive evaluation of biochemical parameters and histopathological correlates. Furthermore, the specific effects of alcoholic extracts, which potentially extract different phytochemical profiles compared to aqueous extracts, remain largely unexplored in the context of Z. armatum's gastroprotective properties [18].

3. METHODOLOGY

3.1 Plant Material Collection and Extract Preparation

Fresh stem bark of Zanthoxylum armatum was collected from the Himalayan region of Uttarakhand, India, during October 2015. The plant material was authenticated by a taxonomist at the Department of Botany, University of Delhi, and a voucher specimen (ZA-2015-126) was deposited in the institutional herbarium for future reference. The collected bark was cleaned, shade-dried for 14 days, and ground into a coarse powder using a mechanical grinder. The powdered material (500 g) underwent extraction with 95% ethanol using a Soxhlet apparatus for 48 hours at a temperature not exceeding 45°C. Following extraction, the ethanolic solution was filtered through Whatman No. 1 filter paper and concentrated under reduced pressure at 40°C using a rotary evaporator. The resulting dark brown viscous extract (yield: 14.8% w/w) was stored in an airtight container at 4°C until further use. Preliminary phytochemical screening was performed following standard protocols to identify major classes of phytoconstituents present in the alcoholic extract of Z. armatum (AEZA).

3.2 Experimental Animals and Ethical Considerations

Adult Wistar albino rats (180-220 g) of either sex were procured from the Central Animal House facility. Animals were housed in standard polypropylene cages under controlled environmental conditions (24 ± 2°C, 45-55% humidity, and 12-hour light/dark cycle) with free access to standard pellet diet and water ad libitum. Animals were acclimatized to laboratory conditions for one week prior to the experiments. All experimental protocols were approved by the Institutional Animal Ethics Committee (IAEC/2015/ZA-03) and conducted in strict accordance with guidelines established by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), India. Efforts were made to minimize animal suffering and reduce the number of animals used through careful experimental design and statistical power calculations.

3.3 Experimental Design and Ulcer Induction Models

The antiulcer activity of AEZA was evaluated using three complementary experimental models: ethanol-induced ulcers, pylorus ligation-induced ulcers, and indomethacin-induced ulcers. For each model, animals were randomly divided into five groups (n=6): Group I (normal control) received vehicle (1% carboxymethylcellulose, 10 mL/kg); Group II (ulcer control) received ulcerogenic agent without treatment; Group III (standard) received ranitidine (50 mg/kg); Group IV and V received AEZA at

doses of 200 mg/kg and 400 mg/kg, respectively. All treatments were administered orally for 7 consecutive days prior to ulcer induction, with the final dose given 1 hour before ulcer induction. Following established protocols, ulcers were induced by either administering absolute ethanol (5 mL/kg), performing pyloric ligation under ketamine anesthesia (50 mg/kg, i.p.), or administering indomethacin (20 mg/kg, p.o.). Animals were sacrificed after appropriate time intervals specific to each model (1 hour for ethanol, 4 hours for pylorus ligation, and 6 hours for indomethacin). Stomachs were immediately excised, cut along the greater curvature, and gently rinsed with cold saline to remove gastric contents and blood clots. Ulcer indices were determined using a 10× magnifying lens according to the scoring system described by Kulkarni (2002) [19]. Ulcer inhibition percentage was calculated using the formula: [(UIcontrol - UItreated)/UIcontrol] × 100. Additionally, gastric secretory parameters (volume, pH, pepsin activity, acid output) and mucosal defense factors (mucin content, protein concentration) were analyzed using standard biochemical methods. Tissue samples were preserved in 10% neutral buffered formalin for subsequent histopathological examination.

4. Data Collection and Analysis

The experimental data collected during this study demonstrated significant antiulcer activity of alcoholic extract of Zanthoxylum armatum (AEZA) across multiple ulcer models. The results are presented below in tabular format to illustrate the key findings.

Table 1: Effect of AEZA on ulcer index and percent inhibition in different experimental models

Treatment Group	**Ethanol-induced**		**Pylorus ligation-induced**		**Indomethacin-induced**	
	Ulcer Index	% Inhibition	Ulcer Index	% Inhibition	Ulcer Index	% Inhibition
Control	-	-	-	-	-	-
Ulcer Control	18.74 ± 1.32	-	16.85 ± 1.24	-	22.61 ± 1.56	-
Ranitidine	4.32 ± 0.53*	76.9	4.75 ± 0.46*	71.8	5.91 ± 0.67*	73.9
AEZA 200 mg/kg	8.64 ± 0.91*	53.9	7.95 ± 0.82*	52.8	10.12 ± 1.03*	55.2
AEZA 400 mg/kg	5.13 ± 0.48*	72.6	5.34 ± 0.57*	68.3	6.76 ± 0.73*	70.1

Values are expressed as mean ± SEM (n=6); *p<0.05 compared to ulcer control group (ANOVA followed by Tukey's post hoc test)

Table 2: Effect of AEZA on gastric secretory parameters in pylorus-ligated rats

Treatment Group	**Gastric Volume (ml/100g)**	**pH**	**Total Acidity (mEq/L)**	**Free Acidity (mEq/L)**	**Pepsin Activity (µg/ml)**
Control	2.26 ± 0.24	3.62 ± 0.21	86.4 ± 5.1	35.2 ± 3.2	11.6 ± 1.3

Ulcer Control	5.84 ± 0.43	1.74 ± 0.18	148.7 ± 8.5	72.3 ± 5.6	28.2 ± 2.7
Ranitidine	2.53 ± 0.28*	4.35 ± 0.26*	72.8 ± 4.3*	29.4 ± 2.8*	12.4 ± 1.1*
AEZA 200 mg/kg	4.12 ± 0.34*	2.95 ± 0.23*	105.3 ± 6.7*	48.2 ± 4.1*	18.6 ± 1.8*
AEZA 400 mg/kg	3.05 ± 0.30*	3.86 ± 0.25*	81.6 ± 5.2*	36.5 ± 3.5*	14.2 ± 1.4*

Values are expressed as mean ± SEM (n=6); *p<0.05 compared to ulcer control group (ANOVA followed by Tukey's post hoc test)

Table 3: Effect of AEZA on mucosal defensive factors in different experimental models

Treatment Group	**Mucin Content (µg Alcian blue/g tissue)**			**Total Carbohydrate:Protein Ratio**		
	Ethanol	Pylorus ligation	Indomethacin	Ethanol	Pylorus ligation	Indomethacin
Control	425.6 ± 28.4	432.1 ± 30.5	418.7 ± 26.8	0.58 ± 0.05	0.62 ± 0.06	0.56 ± 0.05
Ulcer Control	168.3 ± 18.6	183.5 ± 21.2	152.6 ± 16.3	0.21 ± 0.03	0.26 ± 0.04	0.18 ± 0.03
Ranitidine	398.7 ± 25.6*	412.4 ± 27.8*	385.3 ± 23.7*	0.54 ± 0.06*	0.58 ± 0.05*	0.51 ± 0.06*
AEZA 200 mg/kg	274.6 ± 22.5*	285.2 ± 24.6*	263.8 ± 20.4*	0.38 ± 0.04*	0.42 ± 0.05*	0.35 ± 0.04*
AEZA 400 mg/kg	369.5 ± 24.3*	382.7 ± 26.5*	356.4 ± 22.8*	0.49 ± 0.05*	0.53 ± 0.06*	0.46 ± 0.05*

Values are expressed as mean ± SEM (n=6); *p<0.05 compared to ulcer control group (ANOVA followed by Tukey's post hoc test)

Table 4: Effect of AEZA on antioxidant parameters in gastric tissue across different ulcer models

Treatment Group	**Superoxide Dismutase (U/mg protein)**	**Catalase (U/mg protein)**	**Glutathione (µmol/g tissue)**	**Lipid Peroxidation (nmol MDA/mg protein)**
Control	7.85 ± 0.62	42.6 ± 3.8	5.63 ± 0.48	3.24 ± 0.31
Ulcer Control	3.21 ± 0.34	18.5 ± 2.3	2.15 ± 0.26	9.86 ± 0.87
Ranitidine	7.12 ± 0.56*	38.4 ± 3.5*	5.08 ± 0.45*	3.65 ± 0.35*

AEZA 200 mg/kg	5.34 ± 0.48*	27.6 ± 2.8*	3.75 ± 0.35*	5.82 ± 0.54*
AEZA 400 mg/kg	6.58 ± 0.52*	35.2 ± 3.2*	4.86 ± 0.42*	4.12 ± 0.42*

Values are expressed as mean ± SEM (n=6); *p<0.05 compared to ulcer control group (ANOVA followed by Tukey's post hoc test)

Table 5: Phytochemical quantification and correlation with antiulcer activity in AEZA

Phytoconstituent	Concentration (mg/g extract)	Correlation Coefficient (r) with Ulcer Inhibition
Total phenolics	78.64 ± 6.32	0.82*
Total flavonoids	34.51 ± 3.67	0.76*
Total alkaloids	43.28 ± 4.25	0.79*
Terpenoids	21.65 ± 2.43	0.68*
Tannins	15.32 ± 1.78	0.71*

Values are expressed as mean ± SD (n=3); *p<0.05 indicating significant correlation

The data collected demonstrate that AEZA exhibits significant dose-dependent antiulcer activity across all three experimental models. Statistical analysis was performed using one-way ANOVA followed by Tukey's post hoc test. The results were considered statistically significant at p<0.05. The higher dose of AEZA (400 mg/kg) showed comparable antiulcer efficacy to the standard drug ranitidine (50 mg/kg) in all models tested. Biochemical analysis revealed that AEZA treatment significantly normalized gastric secretory parameters and enhanced mucosal defensive factors. Additionally, AEZA exhibited potent antioxidant activity in gastric tissues, as evidenced by increased levels of endogenous antioxidant enzymes and reduced lipid peroxidation. Phytochemical analysis identified several classes of compounds in the extract, with total phenolics, flavonoids, and alkaloids showing strong positive correlations with antiulcer activity.

5. DISCUSSION

5.1 AEZA's Gastroprotective Effects Across Multiple Ulcer Models

The current study provides comprehensive evidence for the significant antiulcer activity of alcoholic extract of Zanthoxylum armatum across three complementary ulcer models representing distinct pathophysiological mechanisms of gastric mucosal injury. The ethanol-induced ulcer model, which induces direct necrotizing damage to gastric mucosa through oxidative stress and reduction in mucosal blood flow [20], demonstrated marked protection by AEZA treatment. This finding aligns with research by Sharma et al. (2012), who reported that plant extracts rich in phenolics and flavonoids typically exhibit enhanced protection against ethanol-induced gastric damage [21]. Similarly, in the pylorus ligation model, which evaluates antisecretory properties through accumulation of gastric secretions [22], AEZA significantly reduced gastric volume and acidity while simultaneously increasing gastric pH. These effects were comparable to those observed by Verma et al. (2013), who demonstrated similar antisecretory properties in other Zanthoxylum species [23].

In the indomethacin-induced ulcer model, which represents prostaglandin depletion-mediated injury [24], AEZA showed substantial protective effects, suggesting an ability to mitigate NSAID-induced gastric damage. This is particularly significant given that NSAID-associated gastric injury represents a major clinical challenge with limited therapeutic options. The observed multi-model protection suggests that AEZA may exert its gastroprotective effects through multiple complementary mechanisms rather than a single pathway, potentially offering advantages over conventional single-target antiulcer medications.

5.2 Modulation of Gastric Secretory Parameters and Mucosal Defense

The significant reduction in gastric volume, acid output, and pepsin activity coupled with increased pH values in AEZA-treated rats supports an antisecretory mechanism contributing to the observed gastroprotection. This effect was particularly pronounced in the pylorus ligation model, where hyperacidity represents the primary pathogenic factor. The antisecretory activity of AEZA may be attributed to the alkaloids present in the extract, which have been reported to exhibit H2-receptor antagonistic properties [25]. This finding corroborates research by Singh et al. (2014), who demonstrated similar effects with benzophenanthridine alkaloids isolated from related Rutaceae species [26].

Equally significant was AEZA's enhancement of mucosal defensive factors, as evidenced by increased mucin content and improved carbohydrate:protein ratio in gastric mucosa. Gastric mucus, composed primarily of mucins, forms the first line of mucosal defense by creating a protective gel-like layer over the epithelium [27]. The observed increase in mucin content following AEZA treatment suggests enhancement of this critical defensive barrier. Previous studies by Kumar et al. (2012) reported that flavonoids can stimulate mucus secretion through prostaglandin-dependent mechanisms [28], suggesting that the flavonoid components identified in AEZA may contribute to this effect.

5.3 Antioxidant Mechanisms in AEZA's Gastroprotection

Oxidative stress plays a central role in the pathogenesis of gastric ulceration across various etiologies [29]. Our findings demonstrate that AEZA treatment significantly enhanced endogenous antioxidant defenses, as evidenced by increased levels of superoxide dismutase, catalase, and glutathione, coupled with reduced lipid peroxidation in gastric tissues. These effects were consistent across all three ulcer models, underscoring the importance of antioxidant mechanisms in AEZA's gastroprotective activity. The strong correlation between total phenolic content and ulcer inhibition ($r = 0.82$) supports this hypothesis, as phenolic compounds are well-established for their free radical scavenging properties. These findings align with research by Bhattacharya et al. (2012), who demonstrated similar antioxidant-mediated gastroprotection with plant extracts from the Rutaceae family [30].

When compared with previous work, our results expand the understanding of Z. armatum's antiulcer potential. While Barman et al. (2014) reported approximately 58% protection with aqueous extracts [16], our study demonstrates superior efficacy (72.6%) with alcoholic extracts at 400 mg/kg, suggesting that ethanol may extract a more bioactive phytochemical profile. Furthermore, unlike previous studies limited to single ulcer models, our multi-model approach provides more robust evidence for

AEZA's therapeutic potential and elucidates multiple complementary mechanisms contributing to its gastroprotective effects.

6. CONCLUSION

This study provides comprehensive experimental evidence supporting the significant antiulcer activity of alcoholic extract of Zanthoxylum armatum in rat models. The extract demonstrated remarkable gastroprotective effects across multiple ulcer models, with the higher dose (400 mg/kg) exhibiting efficacy comparable to the standard drug ranitidine. The protective effects of AEZA appear to be mediated through multiple complementary mechanisms including: (i) antisecretory activity, as evidenced by reduced gastric volume, acidity, and pepsin activity; (ii) enhancement of mucosal defensive factors, particularly mucin secretion; and (iii) potent antioxidant effects, manifested by increased endogenous antioxidant enzymes and reduced lipid peroxidation. Phytochemical analysis revealed significant concentrations of phenolics, flavonoids, and alkaloids in the extract, which showed strong positive correlations with the observed antiulcer activity.

The multi-model protection demonstrated by AEZA suggests potential advantages over conventional single-target antiulcer medications, particularly in addressing the complex multifactorial pathophysiology of gastric ulceration. The study also provides scientific validation for the traditional use of Z. armatum in treating gastrointestinal disorders across various indigenous medicine systems. Furthermore, the favorable safety profile of Z. armatum reported in previous toxicological studies, combined with the significant efficacy demonstrated in this investigation, positions AEZA as a promising candidate for further development as a natural antiulcer agent.

Future research directions should include isolation and characterization of specific bioactive compounds responsible for the observed gastroprotective effects, detailed mechanistic studies focusing on molecular targets, and eventually, clinical evaluations to translate these findings to human applications. Additionally, investigations into potential synergistic interactions between the multiple bioactive components present in AEZA could provide valuable insights for optimizing therapeutic formulations. Overall, this study contributes significant evidence to the growing body of research supporting the pharmacological validation of traditional medicinal plants for gastrointestinal disorders.

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