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Phytochemical Composition and Therapeutic Potential of Timur (Zanthoxylum armatum)

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ABSTRACT

Zanthoxylum armatum DC., commonly known as Timur, is a medicinally and culturally significant plant indigenous to the Himalayan region. Traditionally utilized in Ayurveda, Unani, and various ethnic systems of medicine, the plant has been extensively valued for its culinary use and its therapeutic applications in treating dental disorders, digestive complaints, inflammation, and infections. This chapter provides a comprehensive review of the phytochemical diversity and pharmacological potential of Z. armatum. The plant is rich in bioactive constituents including alkaloids (e.g., berberine, chelerythrine), flavonoids, terpenoids, glycosides, phenolics, tannins, and essential oils containing compounds such as linalool, limonene, and β-caryophyllene. Scientific studies have demonstrated its broad-spectrum antimicrobial, antioxidant, anti-inflammatory, antidiabetic, hypolipidemic, and gastroprotective properties. In addition, emerging evidence supports its roles in immunomodulation, neuroprotection, and potential anticancer activity. Traditional and modern dosage practices are discussed along with considerations for safety, toxicity, and regulatory aspects. Despite its therapeutic promise, gaps remain in clinical validation, standardization, and toxicity profiling. The chapter emphasizes the need for integrated research efforts to fully harness the nutraceutical and pharmaceutical potential of Z. armatum while promoting its sustainable utilization and conservation.

Keywords: *Zanthoxylum armatum, Ayurveda, Flavnoids, antidiabetic, hypolipidemic..*

1. Introduction

Zanthoxylum armatum DC., commonly known as Timur in Hindi, Toothache tree, or Prickly ash, is a deciduous, spiny shrub or small tree belonging to the Rutaceae family. It is valued both for its culinary spice and its medicinal applications. The dried fruits are aromatic and pungent, used traditionally to treat dental and gastrointestinal disorders, and the seeds are often used in making traditional spice blends. It can grow up to 6 meters tall. It has spiny branches, pinnate leaves with aromatic glands, and small greenish-yellow unisexual flowers. The fruits are reddish-brown capsules that split open at maturity, releasing shiny black seeds. It belongs to:

- **Kingdom:** Plantae
- **Order:** Sapindales
- **Family:** Rutaceae
- **Genus:** Zanthoxylum
- **Species:** *Z. armatum* DC.

This species is often confused with other *Zanthoxylum* species such as *Z. alatum* and *Z. bungeanum*, but it can be distinguished by its leaf morphology and fruit characteristics.

Timur is native to the Indian subcontinent, particularly the Himalayan belt, including India (Uttarakhand, Himachal Pradesh, Sikkim), Nepal, Bhutan, and parts of China and Southeast Asia. It typically grows in the wild at elevations of 900 to 2,500 meters above sea level in subtropical and temperate forests.

In Ayurveda, Timur is used to treat conditions like toothache, indigestion, fever, asthma, and rheumatism. The bark and seeds are known for their antibacterial, analgesic, and anthelmintic properties. The fruits are traditionally chewed to relieve dental pain—hence the name "toothache tree." In **Nepali and Indian cuisine,** the dried fruit is an important spice, imparting a **citrusy, numbing flavor,** often used in chutneys, pickles, and local spice blends like *timur ko chhop*.

Despite its rich ethnomedicinal background, *Zanthoxylum armatum* remains **underexplored scientifically**, particularly in terms of **standardized phytochemical profiling** and **evidence-based pharmacological studies**. The objective of this review is to:

- Consolidate the current knowledge on its **phytochemical constituents** (e.g., essential oils, alkaloids, flavonoids)
- Analyze and document its **therapeutic potential** (antioxidant, antimicrobial, anti-inflammatory, etc.)
- Identify research **gaps** and highlight future prospects for its use in **drug development**, **nutraceuticals**, and **sustainable herbal medicine**.

2. Phytochemical Composition

Phytochemicals are naturally occurring chemical compounds in plants that contribute to their medicinal, ecological, and pharmacological properties. Zanthoxylum armatum, a shrub or small tree from the Rutaceae family, is widely distributed in the Himalayan region and is valued in traditional medicine for its diverse bioactive compounds. Its phytochemical profile includes alkaloids, flavonoids, terpenoids, phenolics, glycosides, lignans, tannins, and essential oils, each with distinct therapeutic potential.

2.1 Major Phytoconstituents The major classes of phytoconstituents in Z. armatum are responsible for its pharmacological activities, including antimicrobial, antioxidant, anti-inflammatory, antidiabetic, and anticancer effects. Below is a detailed breakdown of each class, including their chemical nature, biological activities, and significance.

2.1.1 Alkaloids (e.g., Berberine, Chelerythrine)

- **Chemical Nature**: Alkaloids are nitrogen-containing organic compounds, typically heterocyclic, known for their bitter taste and potent bioactivity. In *Z. armatum*, berberine (an isoquinoline alkaloid) and chelerythrine (a benzophenanthridine alkaloid) are prominent.
- **Distribution**: Found primarily in the seeds and bark, with lower concentrations in leaves.
- **Biological Activities**:

a) **Berberine**: Exhibits antimicrobial activity against bacteria (e.g., *Staphylococcus aureus*), fungi, and protozoa. It disrupts microbial cell membranes and inhibits DNA replication. Berberine is also studied for its antidiabetic effects, as it enhances insulin sensitivity and regulates glucose metabolism. Its anticancer properties involve inducing apoptosis and inhibiting tumor cell proliferation.

b) **Chelerythrine**: Known for its anti-inflammatory and antimicrobial effects, chelerythrine inhibits protein kinase C, a key enzyme in inflammatory pathways. It also shows cytotoxic activity against cancer cells.

c) **Antioxidant Properties**: Both alkaloids neutralize reactive oxygen species (ROS), reducing oxidative stress.

- **Therapeutic Potential**: These alkaloids support the traditional use of *Z. armatum* in treating infections, diabetes, and inflammatory conditions. Berberine's broad-spectrum activity makes it a candidate for developing natural antimicrobial agents. Bisht et al. (2010) highlight the pharmacological versatility of these alkaloids, emphasizing their role in the plant's ethnomedicinal applications.

2.1.2 Flavonoids (e.g., Quercetin, Kaempferol, Rutin)

- **Chemical Nature**: Flavonoids are polyphenolic compounds with a C6-C3-C6 carbon skeleton, known for their antioxidant and anti-inflammatory properties.

- **Distribution**: Abundant in fruits, leaves, and bark, with varying concentrations depending on the plant part and environmental factors.

- **Biological Activities**:

a) **Quercetin**: A potent antioxidant that scavenges free radicals, preventing lipid peroxidation and cellular damage. It also exhibits anti-inflammatory effects by inhibiting pro-inflammatory cytokines (e.g., TNF-α).
b) **Kaempferol**: Shows anticancer activity by inducing apoptosis in cancer cells and inhibiting angiogenesis. It also has antimicrobial and neuroprotective effects.
c) **Rutin**: Enhances vascular health by strengthening capillaries and reducing inflammation. It also contributes to antioxidant defense.

- **Therapeutic Potential**: Flavonoids are key to *Z. armatum*'s ability to combat oxidative stress-related diseases, such as cardiovascular disorders and cancer. Their presence supports the plant's use in traditional remedies for fever, inflammation, and skin disorders. Manandhar (2002) notes that flavonoids contribute significantly to the plant's antioxidant potential, aligning with its ethnobotanical uses in Nepal.

2.1.3 Terpenoids (Monoterpenes, Sesquiterpenes)

- **Chemical Nature**: Terpenoids are isoprene-derived hydrocarbons, classified by the number of isoprene units (e.g., monoterpenes with 2 units, sesquiterpenes with 3 units). They are major components of essential oils.
- **Distribution**: Predominantly found in fruits and seeds, especially in essential oils.

- **Key Compounds**:

a) **Monoterpenes**: Limonene (citrus-like aroma, anti-inflammatory, anticancer), linalool (floral scent, sedative, antibacterial), α-pinene (pine-like aroma, antimicrobial).
b) **Sesquiterpenes**: β-caryophyllene (spicy aroma, anti-inflammatory, analgesic).

- **Biological Activities**:

a) Anti-inflammatory effects via inhibition of cyclooxygenase (COX) and lipoxygenase (LOX) pathways.
b) Antimicrobial activity against pathogens like *Escherichia coli* and *Candida albicans.*
c) Insect-repellent properties, protecting the plant from herbivores and pests.

- **Therapeutic Potential**: Terpenoids contribute to the plant's use in aromatherapy, as natural flavoring agents, and in treating infections and inflammation. Their volatile nature makes them ideal for topical and inhalation therapies. Singh et al. (2008) demonstrate the antibacterial efficacy of *Z. armatum* essential oils, attributing it to terpenoids like limonene and linalool.

2.1.4 Phenolics (e.g., Gallic Acid, Ferulic Acid)

- **Chemical Nature**: Phenolics are aromatic compounds with hydroxyl groups, ranging from simple phenols to complex polyphenols.
- **Distribution**: Found in bark, leaves, and fruits, with higher concentrations in bark.
- **Biological Activities**:

a) **Gallic Acid**: A strong antioxidant that chelates metal ions and scavenges ROS, preventing oxidative damage. It also exhibits anti-carcinogenic and anti-aging properties.
b) **Ferulic Acid**: Protects against UV-induced skin damage and has anti-inflammatory effects by modulating nuclear factor-kappa B (NF-κB) pathways.

- **Therapeutic Potential**: Phenolics underpin the plant's traditional use in wound healing, anti-aging remedies, and gastrointestinal treatments. Their ability to protect against oxidative stress makes them valuable in preventing chronic diseases. Rana and Avijit (2012) confirm the high antioxidant activity of *Z. armatum* leaf extracts, driven by phenolic compounds.

2.1.5 Glycosides

- **Chemical Nature**: Glycosides are compounds where a sugar moiety is bonded to a non-sugar (aglycone) component, such as flavonoids or phenolics.
- **Distribution**: Present in leaves and fruits, though less studied in *Z. armatum* compared to other *Zanthoxylum* species.
- **Biological Activities**:

a) Cardioprotective effects, potentially by regulating cardiac ion channels.
b) Anti-inflammatory activity through modulation of immune responses.

- **Therapeutic Potential**: While specific glycosides in *Z. armatum* are under-researched, their presence in related species suggests potential in cardiovascular and anti-inflammatory therapies. Sharma et al. (2011) indicate that glycosides contribute to the pharmacological profile of *Z. armatum*, but further studies are needed for detailed characterization.

2.1.6 Lignans and Tannins

- **Chemical Nature**:

a) **Lignans**: Phenylpropanoid dimers with antioxidant and anti-inflammatory properties.
b) **Tannins**: Polyphenolic compounds, either condensed (proanthocyanidins) or hydrolyzable, known for their astringent properties.

- **Distribution**: Lignans and tannins are concentrated in the bark and fruits.

- **Biological Activities**:

a) Antioxidant effects by neutralizing free radicals.
b) Anti-inflammatory and antimicrobial properties, supporting oral and gastrointestinal health.
c) Astringent effects, useful in treating diarrhea and wounds.

- **Therapeutic Potential**: These compounds explain the plant's traditional use in dental care (e.g., toothache relief) and gastrointestinal disorders (e.g., dysentery). Tannins also contribute to the plant's defense against pathogens and herbivores. Raut and Gaikwad (2006) highlight the role of tannins in oral health, aligning with *Z. armatum*'s use in traditional dentistry.

2.2 Essential Oil Composition : The essential oils of *Z. armatum*, primarily extracted from fruits, are a rich source of volatile compounds with significant pharmacological and industrial applications. Below is a detailed exploration of their composition, extraction methods, and analytical techniques.

2.2.1 Chemical Profiling

- **Major Constituents**:

a) **Linalool (Monoterpene Alcohol)**: Contributes a floral aroma and has mild sedative effects, making it useful in aromatherapy. Its antibacterial activity targets Gram-positive bacteria.
b) **Limonene (Monoterpene)**: Imparts a citrus-like scent and exhibits anti-inflammatory and anticancer properties by inhibiting tumor cell growth and reducing inflammation.
c) **Sabinene (Monoterpene)**: Adds a woody, spicy note and shows antimicrobial and antioxidant activities, enhancing the oil's preservative potential.
d) **β-Caryophyllene (Sesquiterpene)**: Known for its spicy aroma, it acts as an anti-inflammatory and analgesic by binding to cannabinoid receptors (CB2).

- **Quantitative Composition**: The relative abundance of these compounds varies depending on geographical location, season, and extraction method. For example, linalool may constitute 20–40% of the oil, while limonene ranges from 10–30%.
- **Applications**:

a) **Pharmaceutical**: Antimicrobial and anti-inflammatory properties make the oils suitable for topical ointments and infection treatments.
b) **Food Industry**: Used as natural flavoring agents due to their pleasant aroma and antimicrobial effects.

c) **Aromatherapy**: The sedative and calming effects of linalool support mental health applications. Pandey et al. (2011) report that the essential oil from Uttarakhand samples is rich in linalool and limonene, with strong antimicrobial activity

2.2.2 Methods of Extraction and Analysis

- **Extraction Methods**:

a) **Hydrodistillation**: The most common method for extracting essential oils from *Z. armatum* fruits. Plant material is boiled in water, and the volatile oils are collected via steam condensation. This method preserves the integrity of volatile compounds.

b) **Soxhlet Extraction**: Used for extracting non-volatile and alcohol-soluble fractions, such as flavonoids and phenolics, from leaves and bark. It involves repeated solvent (e.g., ethanol) percolation through the plant material.

- **Analytical Techniques**:

a) **Gas Chromatography-Mass Spectrometry (GC-MS)**: The gold standard for profiling essential oils. GC separates volatile compounds based on their volatility, while MS identifies them by their mass-to-charge ratio. This technique quantifies compounds like linalool and limonene and detects trace constituents.

b) **High-Performance Liquid Chromatography (HPLC)**: Used for analyzing non-volatile compounds, such as flavonoids (quercetin, rutin) and phenolic acids (gallic acid). HPLC separates compounds based on their interaction with a stationary phase and detects them using UV or fluorescence detectors.

- **Significance**: These methods ensure accurate identification and quantification of bioactive compounds, facilitating standardization of herbal products and quality control in pharmaceutical applications. Singh et al. (2006) used GC-MS to confirm the dominance of monoterpenes in *Z. armatum* essential oils, correlating their composition with antimicrobial efficacy.

2.3 Variation Across Plant Parts

The phytochemical profile of *Z. armatum* varies significantly across its fruits, seeds, bark, and leaves, influencing their specific medicinal applications. This variation arises from differences in biosynthetic pathways, environmental adaptations, and ecological roles of each plant part.

2.3.1 Fruit vs. Seed vs. Bark vs. Leaves

- **Fruits**:

a) **Phytochemicals**: Rich in essential oils (monoterpenes like linalool, limonene, sabinene; sesquiterpenes like β-caryophyllene) and flavonoids (quercetin, rutin).

b) **Applications**: Used in gastrointestinal remedies (e.g., for indigestion, flatulence) due to their carminative and antimicrobial properties. The volatile oils also make fruits valuable in aromatherapy and as flavoring agents.

Figure 1: Timru Seeds

Figure 2: Timru Fruit with leaves

(Source : Red Chief Earth)

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- **Seeds**:

a) **Phytochemicals**: Contain fixed oils (non-volatile lipids) and alkaloids (berberine, chelerythrine).
b) **Applications**: Traditionally used for their antimicrobial and antidiabetic effects. Seeds are less volatile than fruits but contribute to systemic pharmacological actions.

- **Bark**:

a) **Phytochemicals**: High in tannins, alkaloids (berberine), and phenolics (gallic acid, ferulic acid).
b) **Applications**: Employed in dental care (e.g., toothache relief, gum infections) due to its astringent and antimicrobial properties. Bark extracts are also used for wound healing and anti-inflammatory treatments.

Figure 3 : Timur Bark

Figure 4: Timur Leaves (Source: Plant Ayurveda)

- **Leaves**:

a) **Phytochemicals**: Contain moderate levels of flavonoids, glycosides, and chlorophyll derivatives, with lower concentrations of essential oils.
b) **Applications**: Used in traditional remedies for fever, skin disorders, and inflammation. Leaves are less potent than fruits or bark but are valued for their antioxidant properties.

- **Ecological Context**: The variation reflects the plant's adaptation to its environment. For example, fruits and seeds produce volatile terpenoids to deter herbivores and attract dispersers, while bark's tannins for pathogen defense.

Comparative Analysis of Phytochemical Content

- **Quantitative Differences**:

a) **Total Phenolic Content**: Highest in bark and leaves due to their role in defense against oxidative stress. Spectrophotometric assays (e.g., Folin-Ciocalteu method) show bark extracts with phenolic levels up to 50–100 mg gallic acid equivalents per kg.
b) **Volatile Terpenoids**: Most concentrated in fruits (up to 2–5% essential oil yield), with GC-MS revealing 70–90% monoterpenes. Seeds have trace amounts, while bark and leaves contain minimal volatile oils.
c) **Alkaloids**: Predominantly in seeds and bark, quantified via HPLC or UV spectroscopy. Berberine content may range from 0.1–0.5% in bark extracts.

- **Qualitative Differences**:

a) Chromatographic methods (GC-MS, HPLC) reveal distinct profiles: fruits are dominated by terpenoids, while bark and leaves show phenolic and flavonoid peaks.
b) **Environmental Influence**: Factors like altitude, climate, and soil affect phytochemical content. For instance, fruits from higher altitudes may have higher terpenoid levels due to stress-induced biosynthesis.

- **Therapeutic Implications**: The variation allows targeted use of plant parts. For example, fruit-based preparations are ideal for digestive issues, while bark is preferred for oral health. Nautiyal et al. (2002) and Rana et al. (2014) confirm these variations, linking them to the plant's ecological and medicinal applications.

3. Therapeutic and Pharmacological Properties

Zanthoxylum armatum exhibits a wide range of pharmacological activities due to its diverse phytochemical profile, including alkaloids, flavonoids, terpenoids, phenolics, and essential oils. These activities have been validated through in vitro, in vivo, and traditional use studies, making the plant a promising candidate for both traditional and modern therapeutic applications.

3.1 Antimicrobial Activity: *Z. armatum* demonstrates broad-spectrum antimicrobial activity against bacteria, fungi, and some viruses, attributed to its rich content of terpenes (e.g., linalool, limonene) and alkaloids (e.g., berberine, chelerythrine). Extracts from fruits, bark, and leaves are effective against both Gram-positive and Gram-negative bacteria, as well as fungal pathogens.

- **Target Pathogens**:

a) **Bacteria**: *Staphylococcus aureus* (causes skin infections), *Escherichia coli* (gastrointestinal infections), *Pseudomonas aeruginosa* (opportunistic infections), and *Salmonella typhi* (typhoid fever).
b) **Fungi**: *Candida albicans* (causes oral and vaginal thrush) and *Aspergillus niger* (associated with respiratory and food spoilage issues).
c) **Viruses**: Limited studies suggest antiviral potential, though specific viral targets are less documented.

- **Mechanisms**:

a) **Terpenes**: Disrupt microbial cell membranes, leading to leakage of cellular contents and cell death. For example, linalool and limonene increase membrane permeability in bacteria.
b) **Alkaloids**: Berberine inhibits bacterial DNA replication and protein synthesis, while chelerythrine disrupts microbial enzyme activity. Both compounds exhibit bactericidal and fungicidal effects.

- **Experimental Evidence**:

a) **In Vitro Studies**: Methods like agar well diffusion, minimum inhibitory concentration (MIC), and minimum bactericidal concentration (MBC) confirm the efficacy of *Z. armatum* extracts. For instance, essential oils show MIC values as low as 0.1–0.5 mg/mL against *S. aureus* and *E. coli*.
b) **In Vivo Studies**: Animal models demonstrate reduced bacterial loads in infected tissues after treatment with Timur extracts, supporting their therapeutic potential.

- **Applications**: The antimicrobial properties justify the plant's traditional use in treating infections (e.g., skin infections, diarrhea) and its potential in developing natural preservatives or antimicrobial drugs. Singh et al. (2007) found that acetone extracts and essential oils from *Z. armatum* fruits exhibit strong antifungal activity against *A. niger* and antibacterial activity against *S. aureus*, with terpenes as the primary active components.

3.2 Antioxidant Potential: *Z. armatum* extracts, particularly from leaves and bark, exhibit potent antioxidant activity, neutralizing free radicals and reducing oxidative stress. This is driven by phenolic compounds (e.g., gallic acid, ferulic acid) and flavonoids (e.g., quercetin, rutin).

- **Mechanisms**:

a) **Free Radical Scavenging**: Phenolics and flavonoids donate electrons to stabilize reactive oxygen species (ROS), such as superoxide anions and hydroxyl radicals, preventing cellular damage.
b) **Assays**: In vitro tests like DPPH (2,2-diphenyl-1-picrylhydrazyl) and ABTS (2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)) show high radical scavenging activity. For example, leaf extracts may exhibit DPPH inhibition comparable to standard antioxidants like ascorbic acid.
c) **Enzyme Inhibition**: Flavonoids inhibit pro-oxidant enzymes (e.g., xanthine oxidase), reducing ROS production.

- **Therapeutic Implications**:

a) Protects against oxidative stress-related conditions, such as cardiovascular diseases, neurodegenerative disorders (e.g., Alzheimer's), and aging.

b) Supports traditional uses for skin health and wound healing, where oxidative stress delays recovery.

- **Experimental Evidence**: Ethanolic leaf extracts show IC50 values (concentration required to inhibit 50% of radicals) in the range of 20–50 µg/mL in DPPH assays, indicating strong antioxidant potential. Rana and Avijit (2012) report that *Z. armatum* leaf extracts have high phenolic content, correlating with their ability to scavenge DPPH and ABTS radicals, supporting their role in preventing oxidative damage.

3.3 Anti-inflammatory and Analgesic Properties: *Z. armatum* exhibits significant anti-inflammatory and analgesic effects, mediated by alkaloids (berberine, chelerythrine) and terpenes (β-caryophyllene, limonene). These properties align with its traditional use for toothache, joint pain, and muscular spasms.

- **Mechanisms**:

a) **Anti-inflammatory**: Inhibits pro-inflammatory mediators, such as cyclooxygenase-2 (COX-2), lipoxygenase (LOX), and cytokines (e.g., TNF-α, IL-6). β-Caryophyllene binds to cannabinoid receptors (CB2), reducing inflammation.

b) **Analgesic**: Alkaloids and terpenes modulate nociceptive pathways, possibly by inhibiting pain signaling in the central nervous system or reducing peripheral inflammation.

- **Experimental Evidence**:

a) **Carrageenan-Induced Paw Edema**: A rat model shows that *Z. armatum* extracts reduce paw swelling by 40–60% within 4 hours, comparable to standard drugs like ibuprofen.

b) **Analgesic Tests**: Hot plate and tail-flick tests in rodents demonstrate prolonged pain latency with Timur extracts, indicating central and peripheral analgesic effects.

- **Applications**: Supports the plant's use in treating inflammatory conditions (e.g., arthritis) and pain-related disorders. Its topical application in balms for joint pain is particularly relevant. Bisht and Purohit (2010) highlight that the anti-inflammatory and analgesic effects of *Z. armatum* are due to synergistic actions of alkaloids and terpenes, validating its traditional use in pain relief.

3.4 Antidiabetic and Hypolipidemic Effects: *Z. armatum* shows promise in managing diabetes and dyslipidemia, primarily through flavonoids (quercetin, rutin) and saponins found in fruits and seeds.

- **Mechanisms**:

a) **Antidiabetic**: Inhibits α-glucosidase, an enzyme that breaks down carbohydrates into glucose, reducing postprandial blood glucose spikes. Flavonoids also enhance insulin sensitivity and protect pancreatic β-cells from oxidative damage.

b) **Hypolipidemic**: Lowers triglycerides and low-density lipoprotein (LDL) cholesterol by modulating lipid metabolism pathways, possibly via activation of peroxisome proliferator-activated receptors (PPARs).

- **Experimental Evidence**:

a) **Streptozotocin-Induced Diabetes**: In rat models, fruit and seed extracts reduce fasting blood glucose by 20–30% and improve lipid profiles (e.g., 15–25% reduction in triglycerides).

b) **In Vitro Studies**: Extracts inhibit α-glucosidase with IC50 values comparable to acarbose, a standard antidiabetic drug.

- **Applications**: Supports traditional uses for metabolic disorders and suggests potential for developing natural antidiabetic agents. Sharma et al. (2011) emphasize the role of flavonoids in *Z. armatum*'s antidiabetic and hypolipidemic effects, highlighting its potential in managing type 2 diabetes.

3.5 Gastroprotective and Anthelmintic Activity: The bark and fruits of *Z. armatum* are used traditionally for digestive issues, including flatulence, indigestion, and intestinal worms. These effects are mediated by alkaloids, tannins, and essential oils.

- **Gastroprotective Mechanisms**:

a) Inhibits gastric acid secretion, reducing ulcer formation.

b) Strengthens the gastric mucosal barrier via tannins' astringent properties, which promote tissue repair.

c) Exhibits antimicrobial activity against *Helicobacter pylori*, a key ulcer-causing pathogen.

- **Anthelmintic Mechanisms**:

a) Alkaloids (e.g., berberine) paralyze helminths (e.g., *Pheretima posthuma*) by disrupting their neuromuscular function.
b) Essential oils enhance anthelmintic activity by penetrating worm cuticles.

- **Experimental Evidence**:

a) **Antiulcer Studies**: Rat models of ethanol-induced ulcers show reduced ulcer indices with *Z. armatum* extracts, comparable to omeprazole.
b) **Anthelmintic Tests**: In vitro studies demonstrate paralysis and death of worms within 1–2 hours of exposure to fruit extracts.

- **Applications**: Validates the plant's use in treating gastrointestinal disorders and parasitic infections, with potential for developing natural antiulcer and anthelmintic drugs. Ghimire et al. (2015) confirm the gastroprotective and anthelmintic effects, attributing them to the synergistic action of alkaloids and tannins.

3.6 Other Reported Activities

- **Immunomodulatory**:

a) **Mechanism**: Timur extracts stimulate immune cell proliferation (e.g., T-lymphocytes) and modulate cytokine production, enhancing innate and adaptive immunity.
b) **Potential**: Could be used to boost immunity in infections or immunocompromised conditions.

- **Cytotoxic/Anticancer**:

a) **Mechanism**: Alkaloids (berberine) and flavonoids (quercetin) induce apoptosis in cancer cell lines (e.g., HepG2 liver cancer, MCF-7 breast cancer) by activating caspase pathways and inhibiting cell proliferation.
b) **Evidence**: In vitro studies show cytotoxicity with IC50 values of 50–100 μg/mL, though clinical translation requires further research.

- **Antidepressant/Neuroprotective**:

a) **Mechanism**: Essential oils (linalool) and alkaloids exhibit anxiolytic and antidepressant effects, possibly by modulating GABA or serotonin pathways in the central nervous system.
b) **Evidence**: Rodent models (e.g., forced swim test) show reduced immobility time, indicating antidepressant potential. Kumar and Chaurasia (2016) highlight these emerging activities, suggesting *Z. armatum* as a candidate for novel therapeutic applications in immunology, oncology, and neurology.

4. Traditional and Modern Medicinal Applications

Z.armatum has a rich history in traditional medicine and is increasingly incorporated into modern herbal formulations due to its validated pharmacological properties.

4.1 Applications in Traditional Systems

- **Ayurveda**:

a) Used to balance *Kapha* (phlegm) and *Vata* (air) doshas, which are associated with respiratory and neurological imbalances.
b) Indications: Cough, asthma, toothache, dyspepsia (indigestion).
c) Preparations: Fruit powder, decoctions, or pastes for oral and topical use.

- **Unani**:

a) Considered a stimulant and stomachic agent, promoting digestion and appetite.
b) Used for gastrointestinal disorders and as a tonic for general vitality.

- **Traditional Chinese Medicine (TCM)**:

a) Closely related *Zanthoxylum* species (e.g., *Z. bungeanum*) are used for pain relief (e.g., neuralgia) and digestive stimulation.
b) *Z. armatum* shares similar applications, particularly in pain management. Warrier et al. (1994) document the widespread use of *Z. armatum* in Indian traditional systems, emphasizing its role in respiratory and digestive health.

4.2 Herbal Formulations and Commercial Products

- **Products**:

a) **Tooth Powders**: Bark extracts, rich in tannins and alkaloids, are used in herbal tooth powders for their antimicrobial and astringent effects, aiding in gum health and toothache relief.

b) **Digestive Tablets**: Fruit extracts are incorporated into tablets for indigestion and flatulence, leveraging their carminative and antiulcer properties.

c) **Pain-Relieving Balms**: Essential oils are used in balms for joint pain, muscle spasms, and neuralgia, due to their analgesic and anti-inflammatory effects.

d) **Anti-Worm Formulations**: Fruit and seed extracts are included in anthelmintic preparations for intestinal parasites.

e) **Ayurvedic Oils**: Used for rheumatoid arthritis and neuralgia, combining *Z. armatum* with other herbs for synergistic effects. Joshi (2008) notes the commercial use of *Z. armatum* essential oils in antimicrobial and pain-relieving products, highlighting their industrial potential.

4.3 Dosage Forms and Routes of Administration

- **Traditional Forms**:

a) **Powdered Fruit**: Taken orally (1–3 g/day) for digestive issues or as a spice in culinary preparations.

b) **Paste or Decoction**: Applied topically for wounds, toothaches, or skin infections.

c) **Essential Oil**: Used topically for pain relief or inhaled for aromatherapy.

- **Modern Forms**:

a) **Capsules**: Standardized extracts for controlled dosing in antidiabetic or antioxidant applications.

b) **Tinctures**: Alcohol-based extracts for oral or topical use.

c) **Essential Oil Blends**: Combined with carrier oils for massage or aromatherapy. Rai (2016) documents the ethnomedicinal use of *Z. armatum* in Eastern Nepal, emphasizing its versatility in both traditional and modern dosage forms.

5. Toxicological Profile and Safety Evaluation

While *Z. armatum* shows significant therapeutic potential, its safety profile is critical for its widespread use. Toxicological studies provide preliminary insights, but gaps remain.

5.1 Acute and Chronic Toxicity Studies

- **Acute Toxicity**:

a) Aqueous and ethanol extracts of *Z. armatum* are safe in rats at doses up to 2000 mg/kg body weight, with no observed mortality or behavioral changes.

b) Parameters like body weight, liver function (ALT, AST), and kidney function (creatinine) remain unaffected.

- **Subchronic Toxicity**:

a) Repeated dosing (e.g., 28 days) shows no significant organ toxicity (liver, kidney, heart) or histopathological changes in rodents.

b) Hematological parameters (e.g., RBC, WBC counts) remain within normal ranges. Upadhyay et al. (2011) confirm the low toxicity of *Z. armatum* extracts, supporting their safety for short-term use.

5.2 Safe Dosage Range

- **Traditional Dosing**: Powdered fruit is typically used at 1–3 g/day for adults, adjusted based on the condition (e.g., digestive issues, pain relief). (Rai and Bhujel., 2016)
- **Modern Dosing**: Standardized extracts require dosing based on alkaloid or flavonoid content, typically 100–500 mg/day for capsules or tinctures Ghimire et al., 2015)
- **Precautions**:

a) **Pregnancy**: Limited data suggest avoiding high doses due to potential uterine stimulation by alkaloids.

b) **Gastric Sensitivity**: High doses may cause gastrointestinal irritation in sensitive individuals, due to tannins' astringent nature. Dosing should be tailored to extract potency and patient profile, with monitoring for adverse effects.

6. Conclusion

Timur, is a botanically and pharmacologically significant plant native to the Himalayan region, with deep roots in traditional medicinal systems such as Ayurveda, Unani, and various indigenous folk practices. Its dual role as a culinary spice and therapeutic agent highlights its ethnobotanical richness and multifunctional applications.

Timur contains a wide array of phytochemicals, including alkaloids (e.g., berberine, chelerythrine), flavonoids, terpenoids, glycosides, tannins, phenolics, and essential oils rich in monoterpenes and sesquiterpenes. These constituents are responsible for its documented biological activities, such as antimicrobial, antioxidant, anti-inflammatory, antidiabetic, hypolipidemic, and gastroprotective effects. Traditional uses for treating toothaches, digestive issues, respiratory ailments, and infections are increasingly supported by scientific studies involving in vitro assays, animal models, and phytochemical profiling techniques like GC-MS and HPLC.

Modern pharmacological investigations have further revealed the plant's potential in immunomodulation, cytotoxicity against cancer cell lines, and possible neuroprotective and antidepressant effects. Despite these promising attributes, significant research gaps remain, particularly in areas such as clinical validation, chronic toxicity studies, dosage standardization, and regulatory assessment.

In conclusion, *Zanthoxylum armatum* is a compelling candidate for development as a natural therapeutic agent and functional ingredient. Its traditional legacy, coupled with emerging scientific validation, positions it as a valuable plant for both pharmaceutical innovation and community-based conservation strategies.

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