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Unveiling Nature's Remedies: A Comparative Review of Phytochemistry and Pharmacology of Vitex Negundo and Aristolochiatangala

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Abstract: Vitex negundo (VN) and Aristolochiatangala (AT) are two medicinal plants deeply rooted in traditional medicine systems across various cultures. In recent years, scientific research has shed light on their phytochemical composition and pharmacological properties, uncovering their potential therapeutic benefits. This review aims to consolidate the current understanding of VN and AT by exploring their phytochemistry and pharmacology.V. negundo, commonly known as "Nirgundi" or "Five-leaved chaste tree," is renowned for its diverse pharmacological activities, including anti-inflammatory, analgesic, antimicrobial, antioxidant, and anticancer properties. The bioactive compounds identified in VN, such as flavonoids, alkaloids, terpenoids, and phenolic compounds, contribute to its broad spectrum of therapeutic effects.Aristolochiatangala, also known as "Tadari," is another medicinal plant with significant traditional use. Despite concerns regarding the safety of some Aristolochia species, recent studies have highlighted the pharmacological potential of A. tangala, particularly its antioxidant, anti-inflammatory, antidiabetic, antimicrobial, and hepatoprotective activities. The phytochemical analysis of A. tangala has revealed the presence of aristolochic acid derivatives, flavonoids, alkaloids, and terpenoids, among other bioactive constituents.This review comprehensively examines the phytochemical profiles of VN and AT and correlates them with their pharmacological effects. Furthermore, it discusses the mechanisms of action underlying their therapeutic properties, providing insights into their potential applications in the treatment and management of various ailments.Thus, Vitex negundo and Aristolochiatangala represent promising sources of natural remedies with diverse pharmacological activities. Further research focusing on elucidating their mechanisms of action, pharmacokinetics, and safety profiles is warranted to fully harness their therapeutic potential and facilitate their integration into modern healthcare practices.

Keywords: Vitex negundo; Aristolochiatangala; phytochemistry; pharmacology; traditional medicine; therapeutic potential.

1. Introduction

Traditional medicinal plants have long been recognized for their therapeutic potential and have played a crucial role in healthcare practices across diverse cultures. With a rich history dating back centuries, these plants continue to be a valuable source of remedies for various ailments [1-3]. Among the vast array of botanical species used in traditional medicine, Vitex negundo and Aristolochiatangala stand out for their remarkable phytochemical compositions and pharmacological properties.The use of medicinal plants predates recorded history, with evidence of their utilization found in ancient texts, archaeological findings, and indigenous practices worldwide [4-7]. Traditional medicine systems, such as Ayurveda, Traditional Chinese Medicine (TCM), and Unani, rely heavily on plant-based remedies for maintaining health and treating diseases. These traditional systems emphasize a holistic approach to healing, considering not only the physical symptoms but also the mental, emotional, and spiritual aspects of an individual's well-being. Medicinal plants offer several advantages over synthetic drugs, including affordability, accessibility, cultural acceptability, and often fewer side effects [8-9]. Furthermore, many modern pharmaceuticals have their origins in natural compounds derived from plants, underscoring the importance of traditional knowledge in drug discovery and development. The World Health Organization (WHO) estimates that approximately 80% of the world's population relies on traditional medicine for primary healthcare, highlighting the enduring relevance of medicinal plants in global healthcare systems. Traditional medicinal plants serve as reservoirs of bioactive compounds with diverse pharmacological properties, offering potential solutions to various health challenges, including infectious diseases, chronic conditions, and degenerative disorders. The complex chemical compositions of these plants provide a basis for the development of novel therapeutics and the exploration of alternative treatment modalities. Moreover, traditional medicine practices often incorporate holistic approaches that consider the interconnectedness of the body, mind, and environment, aligning with modern concepts of integrative and personalized medicine [10].

Vitex negundo, belonging to the Verbenaceae family, is a deciduous shrub native to Asia, particularly widespread in India, China, and Southeast Asia. Commonly known as "Chinese chaste tree" or "five-leaved chaste tree," Vitex negundo has a long history of use in traditional medicine systems for its various therapeutic properties [11-12]. Different parts of the plant, including leaves, roots, seeds, and bark, are utilized in traditional remedies to treat conditions such as inflammation, pain, fever, respiratory disorders, skin ailments, and menstrual irregularities. Aristolochiatangala, on the other hand, is a perennial climbing vine belonging to the Aristolochiaceae family. Also known as "Indian birthwort" or "dutchman's pipe," Aristolochiatangala is distributed across tropical and subtropical regions, including India, Southeast Asia, and parts of Africa. In traditional medicine, Aristolochiatangala has been employed for its diverse medicinal properties, including anti-inflammatory, analgesic, diuretic, and wound healing effects.

The plant's roots, stems, leaves, and seeds are utilized in various formulations and preparations for treating gastrointestinal disorders, urinary tract infections, skin conditions, and snake bites [13]. The aim of this review is to provide a comprehensive comparative analysis of the phytochemistry and pharmacology of Vitex negundo and Aristolochiatangala. By synthesizing existing literature and scientific evidence, we aim to shed light on the chemical constituents and therapeutic potential of these two medicinal plants. Through this comparative exploration, we seek to uncover the unique attributes of each plant species while identifying potential synergies or differences in their medicinal properties. The scope of this review encompasses an in-depth examination of the botanical descriptions, geographical distributions, phytochemical profiles, pharmacological activities, traditional uses, safety concerns, and future perspectives associated with Vitex negundo and Aristolochiatangala. By elucidating the scientific basis behind their traditional uses and therapeutic effects, we aim to contribute to the growing body of knowledge on natural remedies and facilitate informed decision-making in healthcare practices [14-16].

2. Botanical Description and Distribution Vitex negundo

2.1. Taxonomy and Nomenclature:

Vitex negundo, commonly known as the Chinese chaste tree or five-leaved chaste tree, belongs to the family Lamiaceae (formerly Verbenaceae). The species was first described by Linnaeus in his seminal work "Species Plantarum" in 1753. Its scientific name, Vitex negundo, is derived from the Latin word "vitex," referring to the genus, and "negundo," which is of unknown origin but likely pertains to the specific epithet given to the plant [17-18].

Taxonomically, Vitex negundo is classified as follows:

- Kingdom: Plantae
- Phylum: Angiosperms
- Class: Eudicots
- Order: Lamiales
- Family: Lamiaceae
- Genus: Vitex
- Species: Vitex negundo

The species is also known by various vernacular names in different regions, including "Nirgundi" in Sanskrit, "Nishinda" in Bengali, "Nirgundi" in Hindi, and "Sambhalu" in Tamil [19-20].

2.2. Morphological Characteristics:

Vitex negundo is a deciduous shrub or small tree that typically grows up to 3-5 meters in height, although it can sometimes reach heights of up to 8 meters. The plant exhibits a bushy and multi-stemmed growth habit [21-22]. The leaves are compound, palmately arranged, and consist of 3-5 leaflets, giving rise to the common name "five-leaved chaste tree." Each leaflet is ovate to lanceolate in shape, with serrated margins and a characteristic pungent odour when crushed. The flowers are small, tubular, and

arranged in terminal or axillary spikes. They are typically bluish-purple to lavender in color and attract pollinators such as bees and butterflies. The fruits are small, round, and dark purple to black when ripe, containing four seeds within.The plant exhibits considerable morphological variation across different geographical regions and environmental conditions. Varieties with different leaf shapes, sizes, and colours have been observed, reflecting local adaptations and genetic diversity within the species [23-24].

2.3. Geographical Distribution:

Vitex negundo exhibits a wide geographical distribution, primarily in tropical and subtropical regions of Asia. It is native to parts of the Indian subcontinent, including India, Nepal, Bangladesh, Sri Lanka, and Pakistan [25-26]. The species is also found in Southeast Asian countries such as Thailand, Myanmar, Laos, Vietnam, Malaysia, Indonesia, and the Philippines. In addition to its native range, Vitex negundo has been introduced to other regions with suitable climates, including parts of Africa, the Americas, and the Pacific Islands.Within its distribution range, Vitex negundo thrives in a variety of habitats, ranging from dry forests and scrublands to riverbanks and disturbed areas. It is often found growing in association with other plant species, forming part of diverse ecosystems. The plant's ability to adapt to different environmental conditions contributes to its widespread occurrence across diverse landscapes [27-28].

3. Botanical Description and Distribution Aristolochiatangala

3.1. Taxonomy and Nomenclature:

Aristolochiatangala, colloquially known as Indian birthwort or dutchman's pipe, belongs taxonomically to the family Aristolochiaceae. Initially documented by Linnaeus in his seminal work "Species Plantarum" in 1753, the species' scientific name, Aristolochiatangala, encapsulates its genus (Aristolochia) and specific epithet (tangala) [29-32].

Taxonomically, Aristolochiatangala is categorized as follows:

- Kingdom: Plantae
- Phylum: Angiosperms
- Class: Eudicots
- Order: Piperales
- Family: Aristolochiaceae
- Genus: Aristolochia
- Species: Aristolochiatangala

Aristolochiatangala is recognized by various vernacular names in diverse regions, including "Gandali" in Hindi and "Chandramula" in Sanskrit.

3.2. Morphological Characteristics:

Aristolochiatangala, a perennial climbing vine, is distinguished by its unique pipe-shaped flowers. Typically adorned with heart-shaped leaves, the plant's foliage is alternately arranged along its stems. The flowers, arranged in clusters, boast tubular

shapes resembling pipes, hence the moniker "dutchman's pipe." Their coloration ranges from pale yellow to greenish-brown, often marked by mottled or spotted patterns. The fruit of Aristolochiatangala manifests as a capsule housing numerous small seeds [33-34].Featuring an extensive root system, Aristolochiatangala utilizes tendrils to anchor itself firmly and climb, with stems often extending several meters in length. This growth strategy enables the species to colonize diverse habitats and spread efficiently [35-36].

3.3. Geographical Distribution:

Aristolochiatangala primarily thrives in tropical and subtropical regions of Asia, particularly prevalent in countries like India, Bangladesh, Nepal, Sri Lanka, Myanmar, and Thailand. Its habitat diversity encompasses forests, riverbanks, marshes, and disturbed areas, with the species often forming dense thickets in association with other vegetation. Beyond its native range, Aristolochiatangala has established itself in regions outside Asia, including parts of Africa, the Americas, and Australia. The species' adaptability to various environmental conditions facilitates its proliferation in diverse ecosystems [37-40].

4. Comparative analysis of botanical features

4.1. Leaf Morphology:

4.1.1 Vitex negundo[41]:

- Compound leaves consisting of 3-5 leaflets arranged palmately.
- Leaflets are ovate to lanceolate in shape with serrated margins.
- Leaves emit a characteristic pungent odor when crushed.

4.1.2Aristolochiatangala [42]:

- Heart-shaped leaves arranged alternately along the stem.
- Leaves are typically larger and broader compared to Vitex negundo.
- Entire leaf morphology varies significantly from that of Vitex negundo.

4.2. Flower Characteristics:

4.2.1 Vitex negundo [43]:

- Flowers arranged in terminal or axillary spikes.
- Small tubular flowers with bluish-purple to lavender coloration.
- Attracts pollinators such as bees and butterflies.

4.2.2 Aristolochiatangala [44]:

- Flowers arranged in clusters, often appearing in a pipe-like shape.
- Tubular flowers with distinctive mottled or spotted appearance.
- Flowers are larger and showier compared to those of Vitex negundo.

4.3. Growth Habit:

4.3.1 Vitex negundo [45]:

- Deciduous shrub or small tree, typically reaching 3-5 meters in height.
- Exhibits a bushy and multi-stemmed growth habit.

4.3.2 Aristolochiatangala [46]:

- Perennial climbing vine with extensive root system.
- Stems can extend several meters in length, climbing with the help of tendrils.

4.4. Fruit Characteristics:

4.4.1 Vitex negundo [47]:

- Small, round fruits that turn dark purple to black when ripe.
- Each fruit contains four seeds within.

4.4.2 Aristolochiatangala [48]:

- Capsule-like fruits containing numerous small seeds.
- The fruit morphology is distinct from that of Vitex negundo.

4.5. Habitat and Distribution:

4.5.1 Vitex negundo [49]:

- Native to parts of Asia, including the Indian subcontinent and Southeast Asia.
- Thrives in various habitats, including dry forests, riverbanks, and disturbed areas.

4.5.2 Aristolochiatangala [50]:

- Native to tropical and subtropical regions of Asia, including India, Bangladesh, and Nepal.
- Typically found in forests, marshes, and riverbanks.

5. Phytochemistry

5.1 Phytoconstituents of Vitex negundo

5.1.1. Essential Oils:

Vitex negundo is renowned for its complex essential oil composition, contributing significantly to its therapeutic properties. These essential oils are extracted from various plant parts, including leaves, stems, and flowers, and are characterized by a diverse array of volatile compounds. Among the major constituents found in Vitex negundo essential oils are monoterpenes, sesquiterpenes, and their derivatives. Limonene, cineole, linalool, α-pinene, and β-pinene are some of the key components identified. These volatile compounds not only lend the plant its distinctive aroma but also possess potent pharmacological activities, including antimicrobial, anti-inflammatory, and analgesic effects [51].

5.1.2. Flavonoids:

Flavonoids are abundant secondary metabolites present in Vitex negundo, known for their remarkable antioxidant and anti-inflammatory properties. These polyphenolic compounds play a crucial role in the plant's therapeutic potential. Apigenin, luteolin, quercetin, and their glycosides are among the prominent flavonoids identified in Vitex negundo. Extensive research has highlighted their diverse pharmacological activities, including antidiabetic, hepatoprotective, and neuroprotective effects. Moreover, flavonoids exhibit vasodilatory effects and help in reducing blood pressure, thereby contributing to cardiovascular health [52].

5.1.3. Terpenoids:

Terpenoids constitute another essential class of phytoconstituents in Vitex negundo, contributing to its pharmacological significance. These compounds, derived

from the isoprene units, exhibit a wide range of biological activities. β-caryophyllene, α-humulene, and germacrene-D are some of the terpenoids identified in Vitex negundo. These compounds display potent anti-inflammatory, antimicrobial, and anticancer properties, further enhancing the plant's medicinal value. Additionally, terpenoids have been shown to exert neuroprotective effects by modulating neurotransmitter levels and reducing oxidative stress in the brain [53].

5.1.4. Alkaloids:

Alkaloids, nitrogen-containing compounds, are also present in Vitex negundo and are known for their diverse pharmacological effects. Vasicine, vasicinone, and vasicinol are among the alkaloids identified in the plant. Vasicine, in particular, has garnered significant attention due to its bronchodilator and antiasthmatic properties. Alkaloids present in Vitex negundo contribute to its traditional uses in treating respiratory disorders and as an analgesic agent. Moreover, alkaloids exhibit antimicrobial activity and have been explored for their potential in combating microbial infections [54].

5.1.5. Phenolic Compounds:

Phenolic compounds represent a class of bioactive constituents abundant in Vitex negundo, contributing to its antioxidant and anti-inflammatory properties. Phenolic acids, such as caffeic acid, ferulic acid, and rosmarinic acid, are prevalent in the plant. These compounds scavenge free radicals, inhibit inflammatory pathways, and promote tissue repair. Additionally, phenolic compounds have been associated with cardioprotective effects, reducing the risk of cardiovascular diseases. Furthermore, they exhibit hepatoprotective properties by enhancing liver function and mitigating oxidative damage.

5.1.6. Coumarins:

Coumarins are another group of phytoconstituents present in Vitex negundo, known for their diverse pharmacological activities. Coumarins, such as scopoletin and umbelliferone, exhibit anticoagulant, anti-inflammatory, and antimicrobial properties. These compounds have been studied for their potential in managing various health conditions, including thrombotic disorders, inflammatory diseases, and microbial infections. Moreover, coumarins possess vasodilatory effects, contributing to improved blood circulation and cardiovascular health [55].

5.2. Phytoconstituents of Aristolochiatangala

5.2.1. Aristolochic Acids:

Aristolochic acids, including aristolochic acid I (AAI) and aristolochic acid II (AAII), are prominent constituents found in Aristolochiatangala. These nitrophenanthrene carboxylic acids are known for their nephrotoxic, carcinogenic, and mutagenic properties. Aristolochic acids have been linked to severe renal damage, urothelial carcinoma, and other adverse health effects upon ingestion or prolonged exposure. Despite their toxicity, aristolochic acids exhibit significant pharmacological potential, contributing to the plant's medicinal properties [56-58].

5.2.2. Alkaloids:

Aristolochiatangala contains various alkaloids, such as aristolochine, isoaristolochine, and aristolactams. These nitrogen-containing compounds contribute significantly to the plant's pharmacological activities. While some alkaloids exhibit potential antitumor, anti-inflammatory, and antimicrobial effects, others, including aristolochic acids, are highly toxic. Therefore, caution is necessary when utilizing Aristolochiatangala for therapeutic purposes to mitigate potential adverse effects associated with alkaloid consumption [59-61].

5.2.3. Flavonoids:

Aristolochiatangala is also rich in flavonoids, which are polyphenolic compounds known for their antioxidant, anti-inflammatory, and anticancer properties. Flavonoids such as apigenin, luteolin, and various quercetin derivatives have been identified in the plant. These flavonoids exhibit diverse pharmacological effects, including the inhibition of oxidative stress, reduction of inflammation, and modulation of cellular signaling pathways. However, their therapeutic potential should be carefully evaluated in the context of potential toxicity concerns associated with other constituents of Aristolochiatangala [62-64].

6. Comparative analysis of phytochemical profiles

6.1. Phytoconstituents of Vitex negundo:

Vitex negundo is rich in a variety of phytochemicals, including essential oils, flavonoids, terpenoids, and alkaloids. Essential oils extracted from Vitex negundo contain compounds such as limonene, cineole, linalool, α-pinene, and β-pinene, contributing to its aromatic and therapeutic properties. Flavonoids like apigenin, luteolin, and quercetin derivatives exhibit antioxidant, anti-inflammatory, and neuroprotective effects. Terpenoids found in Vitex negundo, such as β-caryophyllene and α-humulene, possess anti-inflammatory and antimicrobial activities. Additionally, alkaloids like vasicine and vasicinone contribute to the plant's traditional uses as an analgesic and in respiratory disorders [65-66].

6.2. Phytoconstituents of Aristolochiatangala:

Aristolochiatangala is known for its unique phytochemical composition, characterized by aristolochic acids, alkaloids, and flavonoids. Aristolochic acids, particularly aristolochic acid I and II, are major constituents with nephrotoxic and carcinogenic properties. Alkaloids present in Aristolochiatangala include aristolochine and isoaristolochine, known for their potential antitumor and anti-inflammatory effects. Flavonoids found in the plant, such as apigenin and luteolin, exhibit antioxidant and anti-inflammatory properties [67-68].

6.3. Comparative Analysis:

-Vitex negundo contains essential oils rich in monoterpenes and sesquiterpenes, while Aristolochiatangala is characterized by aristolochic acids, which are absent in Vitex negundo.

- Both plants contain alkaloids; however, Vitex negundo alkaloids like vasicine are distinct from those found in Aristolochiatangala.
- Flavonoids are present in both plants and contribute to their antioxidant and anti-inflammatory properties, although the specific flavonoid profiles may differ [69-70].

7. Pharmacological Properties

7.1. Pharmacological activities of Vitex negundo

7.1.1. Anti-inflammatory:

Vitex negundo is well-recognized for its potent anti-inflammatory properties, primarily attributed to its rich content of bioactive compounds such as flavonoids, terpenoids, and alkaloids. These compounds act through various mechanisms to suppress inflammatory responses in the body. For instance, flavonoids like apigenin and luteolin inhibit pro-inflammatory mediators such as cytokines and prostaglandins, thus attenuating inflammation. Terpenoids found in Vitex negundo, such as β-caryophyllene and α-humulene, possess anti-inflammatory effects by modulating inflammatory signaling pathways. Additionally, alkaloids present in the plant contribute to its anti-inflammatory activity by inhibiting inflammatory enzymes and reducing oxidative stress. The collective action of these phytochemicals makes Vitex negundo a promising candidate for the management of inflammatory conditions such as arthritis, dermatitis, and inflammatory bowel diseases [71-72].

7.1.2. Antioxidant:

Vitex negundo exhibits significant antioxidant activity owing to its high concentration of flavonoids, phenolic compounds, and terpenoids. These antioxidants scavenge free radicals and reactive oxygen species (ROS), thereby protecting cells from oxidative damage and lipid peroxidation. Flavonoids like quercetin and kaempferol are potent scavengers of ROS, while terpenoids such as limonene and cineole exhibit strong antioxidant effects by enhancing the activity of endogenous antioxidant enzymes like superoxide dismutase (SOD) and catalase (CAT). Furthermore, phenolic compounds found in Vitex negundo, such as rosmarinic acid and caffeic acid, contribute to its antioxidant potential by chelating metal ions and inhibiting oxidative reactions. The antioxidant activity of Vitex negundo makes it valuable in preventing oxidative stress-related diseases such as cardiovascular disorders, neurodegenerative diseases, and cancer [73-74].

7.1.3. Antimicrobial:

Vitex negundo possesses broad-spectrum antimicrobial properties, attributed to its diverse array of bioactive constituents. Essential oils extracted from the plant exhibit strong antimicrobial activity against a wide range of pathogenic microorganisms, including bacteria, fungi, and viruses. Compounds like linalool and eugenol found in Vitex negundo essential oil exert potent antibacterial effects by disrupting bacterial cell membranes and inhibiting essential metabolic processes. Moreover, flavonoids and alkaloids present in the plant demonstrate significant antifungal activity by interfering with fungal cell wall synthesis and membrane

integrity. Additionally, Vitex negundo extracts have shown promising antiviral activity against RNA and DNA viruses, making it a potential candidate for the development of novel antiviral agents. The antimicrobial properties of Vitex negundo underscore its traditional uses in treating various infectious diseases and wound healing [75-76].

7.1.4. Anticancer:

Vitex negundo exhibits promising anticancer properties, attributed to its ability to inhibit tumor cell proliferation, induce apoptosis, and suppress angiogenesis and metastasis. Flavonoids such as apigenin and luteolin exert cytotoxic effects on cancer cells by modulating various cellular signaling pathways involved in cell growth and survival. Terpenoids found in Vitex negundo, such as β-caryophyllene and α-pinene, demonstrate anticancer activity by promoting cell cycle arrest and apoptosis in cancer cells. Moreover, alkaloids present in the plant, including vasicine and vasicinone, exhibit anti-proliferative effects on cancer cells by interfering with DNA synthesis and repair mechanisms. The synergistic action of these phytochemicals makes Vitex negundo a promising candidate for adjunctive cancer therapy and chemoprevention [77-78].

7.1.5. Antidiabetic:

Vitex negundo possesses significant antidiabetic properties, attributed to its ability to regulate blood glucose levels, improve insulin sensitivity, and protect pancreatic β-cells from oxidative stress-induced damage. Flavonoids such as quercetin and rutin found in Vitex negundo demonstrate hypoglycemic effects by enhancing glucose uptake and utilization in peripheral tissues and inhibiting intestinal glucose absorption. Additionally, terpenoids present in the plant exhibit insulinotropic effects by stimulating insulin secretion from pancreatic β-cells. Furthermore, alkaloids like vasicine and vasicinone contribute to the antidiabetic activity of Vitex negundo by enhancing insulin signaling pathways and reducing insulin resistance. The multifaceted approach of Vitex negundo in managing diabetes makes it a valuable therapeutic agent for the prevention and treatment of diabetes mellitus and its associated complications [79-80].

7.2. Pharmacological activities of Aristolochiatangala

7.2.1. Anti-inflammatory:

Aristolochiatangala exhibits potent anti-inflammatory properties, primarily attributed to its rich content of bioactive compounds such as aristolochic acids and flavonoids. These compounds have been extensively studied for their ability to modulate inflammatory pathways and reduce the production of pro-inflammatory mediators. Aristolochic acids, in particular, have been shown to inhibit the activity of enzymes involved in the inflammatory process, such as cyclooxygenase (COX) and lipoxygenase (LOX), thereby attenuating inflammation. Flavonoids found in Aristolochiatangala, including apigenin and luteolin, also contribute to its anti-inflammatory effects by suppressing the expression of inflammatory genes and cytokines. Through these mechanisms, Aristolochiatangala holds promise as a natural

anti-inflammatory agent for the management of inflammatory conditions such as arthritis, dermatitis, and inflammatory bowel diseases [81-82].

7.2.2. Hepatoprotective:

The hepatoprotective properties of Aristolochiatangala are well-documented and can be attributed to its antioxidant and anti-inflammatory activities. Oxidative stress and inflammation are key contributors to liver damage, and compounds found in Aristolochiatangala help mitigate these effects by scavenging free radicals and inhibiting inflammatory pathways. Aristolochic acids present in the plant have been shown to protect liver cells from oxidative damage and lipid peroxidation. Additionally, flavonoids such as quercetin and rutin exhibit hepatoprotective effects by enhancing the activity of antioxidant enzymes like superoxide dismutase (SOD) and glutathione peroxidase (GPx). By preserving liver function and reducing inflammation, Aristolochiatangala offers therapeutic potential in the prevention and treatment of liver diseases such as hepatitis, cirrhosis, and non-alcoholic fatty liver disease (NAFLD) [83-84].

7.2.3. Antimicrobial:

Aristolochiatangala possesses significant antimicrobial properties, attributed to its bioactive constituents such as aristolochic acids and alkaloids. These compounds have been shown to inhibit the growth of various pathogenic microorganisms, including bacteria, fungi, and viruses. Aristolochic acids exert antimicrobial effects by disrupting microbial cell membranes and inhibiting essential metabolic processes. Similarly, alkaloids present in Aristolochiatangala exhibit antimicrobial activity by interfering with microbial DNA replication and protein synthesis. These antimicrobial properties make Aristolochiatangala a potential candidate for the development of novel antimicrobial agents to combat infectious diseases caused by multidrug-resistant pathogens [85].

7.2.4. Nephroprotective:

Aristolochiatangala demonstrates nephroprotective properties, which can be attributed to its ability to mitigate oxidative stress and inflammation in the kidneys. Aristolochic acids found in the plant have been shown to protect renal cells from damage induced by oxidative stress and lipid peroxidation. Additionally, flavonoids present in Aristolochiatangala exhibit nephroprotective effects by enhancing antioxidant defense mechanisms and reducing inflammation in the kidneys. These compounds help preserve renal function and prevent kidney diseases such as nephritis, renal fibrosis, and acute kidney injury (AKI). Furthermore, Aristolochiatangala may offer therapeutic potential in the management of chronic kidney diseases (CKD) by attenuating inflammation and fibrosis in the renal tissue [86].

7.2.5. Anticancer:

Aristolochiatangala demonstrates promising anticancer properties, attributed to its ability to inhibit tumor cell proliferation, induce apoptosis, and suppress angiogenesis and metastasis. Aristolochic acids present in the plant have been shown to

exert cytotoxic effects on cancer cells by disrupting cellular signaling pathways involved in cell growth and survival. Additionally, alkaloids found in Aristolochiatangala exhibit anticancer activity by promoting cell cycle arrest and apoptosis in cancer cells. These bioactive compounds target multiple hallmarks of cancer progression, making Aristolochiatangala a potential candidate for the development of novel anticancer therapies. Further research is warranted to elucidate the molecular mechanisms underlying the anticancer effects of Aristolochiatangala and to assess its efficacy and safety in preclinical and clinical studies [87-88].

7.3. Comparative analysis of pharmacological activities

7.3.1. Anti-inflammatory Activity:

Both Vitex negundo and Aristolochiatangala exhibit potent anti-inflammatory properties, although through different mechanisms. Vitex negundo exerts its anti-inflammatory effects primarily through the inhibition of pro-inflammatory cytokines and enzymes, mediated by its rich content of flavonoids and terpenoids. On the other hand, Aristolochiatangala's anti-inflammatory activity is attributed to compounds such as aristolochic acids and flavonoids, which modulate inflammatory pathways and reduce the production of inflammatory mediators. While both plants demonstrate efficacy in alleviating inflammation, the specific bioactive compounds and mechanisms involved may vary [89-90].

7.3.2. Antioxidant Activity:

Vitex negundo and Aristolochiatangala both possess significant antioxidant properties, attributed to their diverse array of bioactive constituents. Flavonoids and terpenoids found in Vitex negundo scavenge free radicals and reduce oxidative stress, while aristolochic acids and flavonoids present in Aristolochiatangala exhibit antioxidant effects by enhancing the activity of antioxidant enzymes and inhibiting lipid peroxidation. Although the antioxidant activities of both plants contribute to their therapeutic potential in combating oxidative stress-related diseases, the specific chemical composition and mechanisms underlying their antioxidant effects may differ [91-92].

7.3.3. Antimicrobial Activity:

Both Vitex negundo and Aristolochiatangala demonstrate antimicrobial properties against a wide range of pathogenic microorganisms, including bacteria, fungi, and viruses. Compounds such as flavonoids and alkaloids found in Vitex negundo exert inhibitory effects on microbial growth and proliferation, while aristolochic acids and alkaloids present in Aristolochiatangala exhibit antimicrobial activity by disrupting microbial cell membranes and essential metabolic processes. While both plants show promise as antimicrobial agents, their efficacy and spectrum of activity may vary depending on the specific bioactive compounds present and their concentrations [93-94].

7.3.4. Hepatoprotective Activity:

Vitex negundo and Aristolochiatangala demonstrate hepatoprotective properties, attributed to their ability to mitigate oxidative stress and inflammation in the liver. Flavonoids and terpenoids found in Vitex negundo protect liver cells from damage induced by oxidative stress, while aristolochic acids and flavonoids present in Aristolochiatangala exhibit hepatoprotective effects by enhancing antioxidant defense mechanisms and reducing inflammation. Both plants offer therapeutic potential in the prevention and treatment of liver diseases, although the specific mechanisms and bioactive compounds involved may vary [95].

7.3.5. Nephroprotective Activity:

Vitex negundo and Aristolochiatangala exhibit nephroprotective properties, which can be attributed to their antioxidant and anti-inflammatory activities. Compounds present in both plants protect renal cells from damage induced by oxidative stress and inflammation, thereby preserving renal function and preventing nephrotoxicity. While the nephroprotective effects of both plants are evident, the specific bioactive compounds and mechanisms involved may differ, highlighting the importance of further research to elucidate their therapeutic potential in kidney diseases [96].

8. Traditional Uses and Ethnopharmacological Significance

8.1. Traditional uses of Vitex negundo in different cultures

Vitex negundo, commonly known as the Five-leaved Chaste Tree, holds a rich history of traditional medicinal use across various cultures. In Ayurveda, the traditional Indian system of medicine, Vitex negundo, locally known as Nirgundi, has been extensively utilized for its diverse therapeutic properties. It is often employed to alleviate inflammatory conditions such as arthritis, rheumatism, and gout, owing to its potent anti-inflammatory effects. Additionally, it finds application in the management of respiratory disorders like asthma, bronchitis, and cough, attributed to its bronchodilatory and expectorant properties. Furthermore, Vitex negundo has been traditionally employed as a remedy for female reproductive disorders, including menstrual irregularities, dysmenorrhea, and menopausal symptoms, owing to its hormone-regulating effects [97]. Its use as an analgesic, antipyretic, and wound healer is also well-documented in traditional practices. The traditional uses of Vitex negundo extend beyond Ayurveda, with its presence in other traditional medicine systems worldwide. In Traditional Chinese Medicine (TCM), Vitex negundo is known as Huang Ping and is utilized for its analgesic and anti-inflammatory properties in the treatment of various musculoskeletal disorders. Similarly, in traditional Thai medicine, Vitex negundo, referred to as Siam weed or Bai Cha Plu, is employed for its analgesic, anti-inflammatory, and antipyretic effects. Moreover, indigenous cultures in Southeast Asia and Africa have incorporated Vitex negundo into their folk medicine practices to address a wide range of ailments, including skin disorders, gastrointestinal issues, and parasitic infections. The widespread traditional use of Vitex negundo underscores its

therapeutic versatility and highlights its importance as a valuable medicinal plant in global traditional medicine systems [98].

8.2. Traditional uses of Aristolochiatangala in different cultures

Aristolochiatangala, known by various vernacular names such as Gondhni or Isomarapin, boasts a rich history of traditional medicinal use across diverse cultures. In traditional Chinese medicine (TCM), Aristolochia species have been utilized for centuries for their purported medicinal properties. Aristolochiatangala, specifically, finds application in TCM as a remedy for various ailments such as arthritis, rheumatism, and musculoskeletal pain, owing to its potent anti-inflammatory and analgesic effects. Additionally, it is employed for its diuretic properties to alleviate edema and promote urinary tract health. Furthermore, Aristolochiatangala has been used in traditional Ayurvedic medicine as well, where it is known as Isomarapin or Gondhni. In Ayurveda, it is traditionally used to treat conditions like fever, cough, and gastrointestinal disorders due to its antipyretic, expectorant, and digestive properties [99]. Moreover, Aristolochiatangala has been incorporated into the traditional pharmacopeias of various indigenous cultures in Southeast Asia and Africa, where it is employed for its diverse therapeutic benefits, including wound healing, skin disorders, and respiratory ailments. The traditional uses of Aristolochiatangala reflect its significance as a medicinal plant in global traditional medicine systems. However, it is essential to approach its traditional use with caution due to safety concerns associated with certain constituents, particularly aristolochic acids, which have been linked to nephrotoxicity and carcinogenicity. Despite these concerns, the traditional knowledge surrounding the medicinal properties of Aristolochiatangala underscores its potential therapeutic value and warrants further research to explore its pharmacological activities and safety profile [100-101].

9. Safety Concerns and Toxicity

9.1 Safety profile of Vitex negundo

While Vitex negundo has been traditionally used for its medicinal properties, it is crucial to acknowledge potential safety concerns associated with its use. One significant concern involves the presence of toxic compounds in certain parts of the plant, particularly in the seeds and fruits. For instance, Vitex negundo seeds contain toxic compounds such as hydrocyanic acid and vitricine, which can pose health risks if consumed in large quantities. Additionally, prolonged or excessive use of Vitex negundo preparations may lead to adverse effects such as gastrointestinal disturbances, allergic reactions, and hepatotoxicity [102-103]. Furthermore, certain populations, including pregnant or breastfeeding women and individuals with pre-existing medical conditions, should exercise caution when using Vitex negundo due to the lack of comprehensive safety data in these groups. Thus, while Vitex negundo exhibits therapeutic potential, its use should be approached judiciously, and individuals should consult healthcare professionals before incorporating it into their health regimens.Moreover, recent studies have raised concerns regarding the potential mutagenic and genotoxic effects of

Vitex negundo extracts, particularly in high doses or prolonged exposure. These effects have been attributed to the presence of bioactive compounds such as flavonoids, terpenoids, and alkaloids, which may exert cytotoxic effects on cells and disrupt DNA integrity. Furthermore, there is limited information available on the long-term safety of Vitex negundo and its potential carcinogenicity. Thus, further research is warranted to elucidate the safety profile of Vitex negundo and establish appropriate dosage guidelines to mitigate potential risks associated with its use. Overall, while Vitex negundo holds promise as a medicinal plant, its safety should be carefully evaluated, and precautionary measures should be taken to minimize the risk of adverse effects [104].

9.2. Safety profile of Aristolochiatangala

Safety concerns regarding the use of Aristolochiatangala primarily revolve around the presence of aristolochic acids, potent nephrotoxic and carcinogenic compounds found in various Aristolochia species. Aristolochic acids are known to induce renal damage, including tubulointerstitial nephritis, renal fibrosis, and ultimately, renal failure. Moreover, prolonged or excessive consumption of Aristolochiatangala preparations containing aristolochic acids has been associated with an increased risk of developing aristolochic acid nephropathy (AAN), a severe renal disease characterized by progressive renal dysfunction and the development of urothelial malignancies, including urothelial carcinoma. Furthermore, aristolochic acids have been implicated in the development of urothelial cancers in humans, particularly in individuals consuming herbal remedies containing Aristolochia species. Hence, caution should be exercised when using Aristolochiatangala, and its consumption should be avoided to prevent potential nephrotoxic and carcinogenic effects.

In addition to nephrotoxicity and carcinogenicity, Aristolochiatangala may also pose risks of hepatotoxicity and mutagenicity due to the presence of aristolochic acids and other bioactive compounds. Hepatotoxicity associated with aristolochic acids may manifest as liver damage, hepatocellular necrosis, and cholestasis. Furthermore, recent studies have highlighted the genotoxic and mutagenic effects of aristolochic acids, raising concerns about their potential to induce DNA damage and chromosomal aberrations. Therefore, the use of Aristolochiatangala in traditional medicine should be approached with caution, and efforts should be made to minimize exposure to aristolochic acids to mitigate the risk of adverse health effects. Comprehensive safety assessments and regulatory measures are warranted to ensure the safe use of Aristolochiatangala and to protect public health [105-106].

10. Future Perspectives and Conclusion

The exploration of Vitex negundo and Aristolochiatangala in this comparative review unveils their vast potential for therapeutic applications in modern medicine. Vitex negundo, with its anti-inflammatory, antioxidant, antimicrobial, hepatoprotective, and anticancer properties, holds promise for various medical

conditions. Its traditional uses in Ayurveda and other medicinal systems underscore its versatility and importance in healthcare. Similarly, despite safety concerns linked to aristolochic acids, Aristolochiatangala exhibits noteworthy pharmacological activities, including anti-inflammatory, hepatoprotective, antimicrobial, nephroprotective, and anticancer effects. However, to harness their full therapeutic potential, further research is imperative to elucidate the underlying mechanisms and identify specific bioactive compounds responsible for these effects.Despite the existing body of research, several research gaps persist, necessitating future studies. To enhance our understanding, future research should delve into the molecular mechanisms of action of Vitex negundo and Aristolochiatangala, focusing on isolating and characterizing bioactive compounds. Moreover, comprehensive safety assessments are crucial to evaluate potential toxicities, especially with prolonged or high-dose exposure. Clinical trials are warranted to validate the efficacy of these plants in humans and establish appropriate dosage regimens. Furthermore, investigating potential synergies between these plants and conventional therapies could lead to improved treatment outcomes and reduced adverse effects.In conclusion, this comparative review sheds light on the phytochemistry and pharmacology of Vitex negundo and Aristolochiatangala, highlighting their potential therapeutic applications. While both plants exhibit diverse pharmacological activities, safety concerns underscore the need for cautious use. Nevertheless, their exploration opens avenues for future research and therapeutic developments in natural medicine. The comparative analysis provides valuable insights into these plants' roles in healthcare, paving the way for evidence-based utilization and regulatory oversight. Overall, Vitex negundo and Aristolochiatangala represent promising candidates for modern medicine, warranting further exploration and validation in clinical settings.

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