

## CLERODENDRUM SERRATUM (L.) MOON (BHARANGI): A COMPREHENSIVE ETHNOPHARMACOLOGICAL AND PHYTOPHARMACOLOGICAL REVIEW

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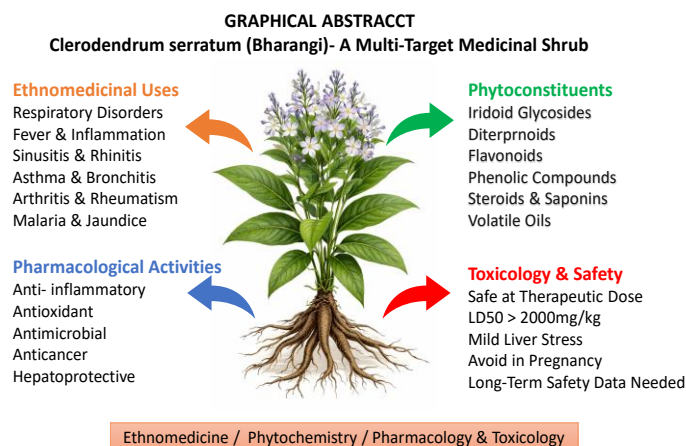
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### ABSTRACT

In traditional Ayurvedic medicine, Clerodendrum serratum (L.) Moon, also referred to as Bharangi, is one of the most significant and thoroughly studied medicinal shrubs in South and Southeast Asia. This plant, which is a member of the renowned Dasha Moola formulation group and belongs to the Lamiaceae (formerly Verbenaceae) family, has been used for millennia in traditional healing systems to treat a variety of conditions, including fever, sinusitis, rhinitis, bronchial asthma, skin disorders, arthritis, malaria, and jaundice. The current study offers a thorough, analytical, and publication-ready synthesis of the scientific literature on C. serratum. Phytochemical studies have revealed a wide range of bioactive secondary metabolites, such as iridoid glycosides (serratoside, acteoside, and clerodenoside A and B), terpenoids (ursolic acid, oleanolic acid, and serratagenic acid), steroids ( $\beta$ -sitosterol, stigmasterol, and campesterol), D-mannitol, saponins, tannins, and volatile oils, and diterpenoids (clerodin, clerodermic acid, apigenin, scutellarein, and luteolin). HPLC, GC-MS, LC-MS/MS, FT-IR, HPTLC, and NMR platforms have all been used to accomplish thorough analytical characterization. Strong antioxidant activity through free-radical scavenging and enzymatic defense enhancement; hepatoprotection through ursolic acid-mediated GSH pathway modulation; broad-spectrum antimicrobial and antifungal activity, including anti-mycobacterial properties; antiasthmatic effects through saponin-mediated bronchodilation; immunomodulatory activity; analgesic and antipyretic properties; and promising anticancer and molecular docking findings. Despite methodological limitations and small sample sizes, clinical evidence consistently supports traditional criteria. While uterotonic activity merits contraindication during pregnancy, acute toxicity investigations demonstrate a satisfactory safety profile with an LD50 surpassing 2000 mg/kg. Pharmacokinetic characterization, standardized RCTs, and the creation of formulations based on nanotechnology are future research goals.

**KEYWORDS:** Bharangi, Clerodendrum serratum, ethnopharmacology, clerodin, anti-inflammatory, antihistaminic, antiasthmatic, Dashamoola, Ayurveda, phytochemistry, and pharmacology.



**Figure 1: Graphical Abstract: Clerodendrum serratum (Bharangi)—Multi-Target Medicinal Plant.**

## 1. INTRODUCTION

Traditional knowledge serves as the basis for contemporary drug research, and the world healthcare system still heavily depends on medicinal plants as key sources of therapeutic compounds.<sup>[1]</sup> *Clerodendrum serratum* (L.) Moon is one of the most pharmacologically adaptable and clinically significant medicinal shrubs of South and Southeast Asia among the thousands of medicinally significant plant species recorded in both modern pharmacognostic research and ancient Indian literature. For over three millennia, this plant—known by its Sanskrit and Ayurvedic name, "Bharangi"—has been an essential part of traditional Ayurvedic medicine. It is mentioned in the Charaka Samhita,<sup>[2]</sup> Sushruta Samhita,<sup>[3]</sup> Bhavaprakasha Nighantu,<sup>[4]</sup> and several classical pharmacopoeial texts.<sup>[5-9]</sup>

*Clerodendrum serratum* is a perennial, erect shrub that grows widely throughout tropical and subtropical regions of South and Southeast Asia. It is a member of the Lamiaceae family, which was formerly classified under Verbenaceae.<sup>[10,11]</sup> Shwasa (asthma/dyspnea), Kasa (cough), Hikka (hiccup), Vrana (wound), and Shotha (inflammation) are the main indications for Bharangi, which is categorized as one of the Dashamoola (ten roots) in classical Ayurvedic writings, particularly among the Laghupanchamool (five lesser roots)(2–5). Pharmacodynamically, the plant is categorized as Katu (pungent), Tikta (bitter), Laghu (light), Ruksha (dry), and Ushna Virya (hot potency). These characteristics correspond to its current pharmacological profile as an expectorant, antihistaminic, and anti-inflammatory agent.<sup>[5,12]</sup>

Over the past forty years, there has been a significant increase in scientific research on *C. serratum* due to its complex phytochemical composition and rich pharmacological legacy.<sup>[10,13,14]</sup> Iridoid glycosides, neoclerodane diterpenoids, flavonoids (hispidulin, apigenin, cleroflavone, and scutellarein), phenolic acids, D-mannitol, serratagenic acid, ursolic acid, oleanolic acid,  $\beta$ -sitosterol, and saponins are important classes of bioactive compounds that were identified using HPLC, GC-MS, NMR, and related platforms.<sup>[14-18]</sup> By interacting with a variety of molecular targets, such as COX/LOX enzyme systems (19,20) NF- $\kappa$ B transcription factors,<sup>[21]</sup> mast cell degranulation pathways<sup>[22,23]</sup> hepatic redox systems,<sup>[24,25]</sup> and microbial membrane targets (26), these phytoconstituents offer mechanistic justifications for conventional therapeutic claims pertaining to the management of infectious, inflammatory, hepatic, and respiratory diseases.

The lack of well-designed randomized controlled trials, insufficient pharmacokinetic characterization, and the lack of internationally defined pharmacopoeial standards continue to restrict the clinical translation of *C. serratum* despite strong preclinical evidence.<sup>[13,27]</sup> This review covers taxonomy, botanical traits, geographic distribution, ethnomedicinal significance, phytochemical composition, pharmacological activities and mechanisms, toxicological profile, clinical evidence, traditional formulations, standardization challenges, and future research priorities.

## 2. Abbreviations

ALT – Alanine aminotransferase; ALP – Alkaline phosphatase; AST – Aspartate aminotransferase; CAT – Catalase; COX – Cyclooxygenase; COX-1 – Cyclooxygenase-1; COX-2 – Cyclooxygenase-2; DPPH – 2,2-Diphenyl-1-picrylhydrazyl; FRAP – Ferric reducing antioxidant power; FT-IR – Fourier transform infrared spectroscopy; GC-MS – Gas chromatography-mass spectrometry; GPx – Glutathione peroxidase; HPLC – High-performance liquid chromatography. HPTLC—High-performance thin-layer chromatography; IL—Interleukin; iNOS—Inducible nitric oxide synthase; LC-MS—Liquid chromatography-mass spectrometry; LC-MS/MS—Liquid chromatography-tandem mass spectrometry; LD50 – Median lethal dose; LDL—Low-density lipoprotein; LOX—Lipoxygenase; MDA—Malondialdehyde; NF- $\kappa$ B – Nuclear factor kappa-B; NMR – Nuclear magnetic resonance spectroscopy; NSAIDs – Non-steroidal anti-inflammatory drugs; RCT – Randomized controlled trial ROS – Reactive oxygen species; SAR – Structure-activity relationship; SOD – Superoxide dismutase; TLC – Thin-layer chromatography; TNF- $\alpha$  – Tumor necrosis factor-alpha; UTI – Urinary tract infection; UV-Vis – Ultraviolet-visible spectroscopy.

## 3. Botanical Description and Taxonomy

The kingdom Plantae, order Lamiales, family Lamiaceae (previously Verbenaceae), genus *Clerodendrum* L., and species *serratum* are the official classifications for *Clerodendrum serratum* (L.) Moon.<sup>[10,11]</sup> There are roughly 560–580 species of tiny trees, shrubs, and perennial plants in the genus *Clerodendrum*, which are mostly found in tropical and subtropical parts of the Old World.<sup>[10,28]</sup> Sharply serrated leaf margins, the species' most diagnostically significant morphological characteristic, are explicitly reflected in the specific epithet "*serratum*".<sup>[18,29]</sup> *Volkameria serrata* L. and *Siphonanthus serrata* (L.) Oken are important synonyms.<sup>[6,18]</sup> The extensive adulteration of Bharangi in trade with morphologically similar species, especially *Clerodendrum infortunatum* and *Premna mucronata*, has drawn special attention to issues of botanical identity and verification.<sup>[10,27]</sup>

In terms of morphology, *C. serratum* grows to a height of one to three meters as an upright, mostly unbranched perennial shrub.<sup>[5,18]</sup> The stems have grayish-brown bark, a white, spongy pith that develops hollow in mature specimens, and a distinctive quadrangular (four-angled) shape that is characteristic of Lamiaceae.<sup>[18,29]</sup> The leaves are large, oblong to obovate, 8–20 cm long, with pronounced serrated margins, an acuminate apex, and an attenuate, frequently decurrent base. They are grouped in opposing or ternate (whorls of three) positions, which is uncommon among *Clerodendrum* species.<sup>[5,18]</sup> The abaxial surface is paler and has noticeable venation, while the adaxial surface is dark green.<sup>[18,29]</sup>

Numerous bisexual tubular flowers with a five-lobed persistent calyx, a blue-violet to pale lavender corolla, and four prominently exerted stamens—the latter being a distinctive generic feature—are produced by the inflorescence, which is a big terminal or axillary panicle.<sup>[5,18]</sup> In India, flowering mostly takes place between August and November.<sup>[29]</sup> Fruits are meaty drupes with four lobes, a reddish-purple persisting calyx at maturity, and a green color that eventually turns bluish-black.<sup>[18]</sup> Seeds have a straight embryo and no endosperm.<sup>[18]</sup> Reliable microscopic authenticating markers

include the quadrangular stem cross-section, distinctive leaf serration pattern, and crystal dispersion in the stem cortex.<sup>[17,27,29]</sup> To differentiate *C. serratum* from adulterant species, DNA barcoding utilizing the *rbcl* and *matK* loci provides conclusive molecular authentication.<sup>[27]</sup>

**Table 1: Vernacular Names of *Clerodendrum serratum* (L.) Moon Across Languages and Region's.**

Region / Languages	Vernacular Name (s)
English	Blue Glory Bower, Beetle Killer, Bharangi
Hindi	Bharangi, Arni
Sanskrit	Bharangi, Kharbhari, Brahmanyeṣṭā
Bengali	Bhandira, Bharangi
Marathi	Bharangi, Takla
Gujarati	Bharangi, Arni
Kannada	Gont, Gontagida
Tamil	Siruthekku, Thekkumaram
Malayalam	Cheruthekku, Minnari
Telugu	Gantubarangi, Bharangi
Urdu	Bharangi
Punjabi	Bharangi
Oriya	Bharangi, Arni
Nepali	Bharangi
Chinese (Mandarin)	Zhū Máo Dà Qīng
Sinhala (Sri Lanka)	Wal-nika
Ayurvedic	Bharangi (Katu, Tikta, Ushna)
Unani	Bharangi, Arni
Thai	Ching-chi
Indonesian	Senggugu

Table 1: Vernacular Name of *Clerodendrum serratum* (L.) Moon sources:<sup>[5,6,9,11,18,29,30]</sup>

**Table 2: Botanical and Taxonomic Profile of *Clerodendrum serratum* (L.) Moon.**

<b>Kingdom</b>	<b>Plantae</b>
Division	Magnoliophyta (flowering plant)
Class	Magnoliopsida (Dicotyledons)
Order	Lamiales
Family	Lamiaceae (formerly Verbenaceae)
Genus	<i>Clerodendrum</i> L.
Species	<i>Clerodendrum serratum</i> (L.) Moon
Synonyms	<i>Volkameria serrata</i> L.; <i>Siphonanthus serrata</i> (L.) Oken
Growth Habit	Erect perennial shrub, 1–3 m tall, largely unbranched
Stem	Quadrangular (4-angled), grayish-brown bark, spongy white pith
Leaves	Opposite or ternate, ovate-oblong 8–20 cm, sharply serrated margins
Flowers	Blue-violet tubular, bisexual, terminal panicles; 4 exerted stamens
Fruits	Fleshy drupes, 4-lobed, bluish-black when ripe; persistent reddish calyx
Seeds	Endosperm absent; straight embryo
Flowering Season	August–November (India)
Distribution	India (widespread), Sri Lanka, Nepal, SE Asia, Southern China; 0–1500 m
Ayurvedic Classification	Dashamoola (Laghupanchamool); Katu, Tikta, Laghu, Ruksha, Ushna Virya
Parts Used	Roots (primary), stem bark, leaves, flowers
Market Formulations	Bharangi Ghrita, Bharangyadhwa Rasa, Bharangi Churna, Kanakasava
Adulteration	Frequently substituted with <i>Clerodendrum infortunatum</i> or <i>Premna mucronata</i>

Table 2—Botanical and Taxonomic:<sup>(5,7,9–11,18,27,29)</sup>

**Botanical Photograph of *Clerodendrum serratum* (L.) Moon (Bharangi)**

**Figure 2: Floral Morphology of *Clerodendrum serratum* (L.) Moon (62).**

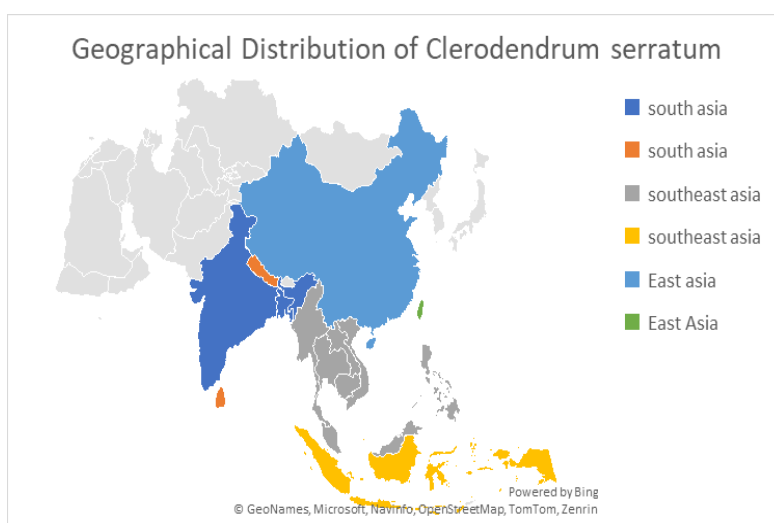


**Figure 3: Leaf Morphology of *Clerodendrum serratum* (L.) Moon(63).**

**4. Geographical Distribution and Habitat**

The Indian subcontinent is the principal center of diversity for *Clerodendrum serratum*, which has a wide pantropical range.<sup>[10,11]</sup> The plant has been found in many different parts of India, including Kerala, Karnataka, Tamil Nadu, Maharashtra, Madhya Pradesh, Uttar Pradesh, Uttarakhand, Assam, West Bengal, Odisha, Himachal Pradesh, and Meghalaya, as well as the humid forests of the Western and Eastern Ghats, the Himalayan foothills, the Deccan plateau, northeastern states, the Andaman and Nicobar Islands, and the Terai region.<sup>[5,6,18]</sup> In-depth distribution records with altitude and ecological preferences were recorded across Indian states by Gupta et al. (2008).<sup>[31]</sup> Through comprehensive ethnobotanical studies conducted throughout the Himalayan foothills, tribal forest groups in Central America, and other regions, this geographic breadth has sustained a rich ethnobotanical heritage with region-specific application patterns. Through comprehensive ethnobotanical studies conducted in the foothills of the Himalayas, tribal forest populations in Central India, and coastal regions of the Western and Eastern Ghats, this geographic breadth has fostered a rich ethnobotanical heritage with region-specific application patterns described.<sup>[28,31,32]</sup>

Tropical moist deciduous and semi-evergreen forest understory, forest margins, riverbanks, roadsides, and disturbed vegetation are among the areas where the plant thrives due to its preference for moist, humid conditions.<sup>[11,18]</sup> It grows from sea level to about 1,500 meters above sea level on well-drained loamy or sandy-loam soils with a high organic matter content. It can withstand both partial shade and open conditions.<sup>[18,29]</sup> Both traditional wild collection and the possibility of controlled cultivation for medicinal standardization have been made easier by its capacity to colonize damaged habitats and forest borders.<sup>[18,27]</sup> *C. serratum* is found outside of South Asia in the provinces of Yunnan, Guangdong, and Guangxi in southern China, as well as in Sri Lanka, Nepal, Bangladesh, Myanmar, Thailand, Vietnam, Laos, Cambodia, Malaysia, Indonesia, and the Philippines.<sup>[18,28]</sup> These geographically and culturally disparate regions' convergent therapeutic application patterns offer strong cross-cultural ethnopharmacological confirmation of the plant's fundamental therapeutic qualities.<sup>[28,33]</sup>



**Figure 2: Geographical Distribution Map of Clerodendrum serratum (L.) Moon.**

## 5. Ethnomedicinal Significance

*Clerodendrum serratum* has been used therapeutically for more than three millennia, and its ethnomedicinal significance is profoundly ingrained in South and Southeast Asian healing traditions.<sup>[2,3,5]</sup> Its position with Shaliparni, Prishniparni, Kantakari, and Gokshura among the Dashamoola—more precisely, the Laghupanchamool, or the five lesser roots—attests to its high medicinal respect in traditional Ayurvedic studies.<sup>[5,9,31]</sup> To focus contemporary scientific research on pharmacologically relevant targets, it is crucial to comprehend the entire scope of its historic usage across many cultural and medical systems.<sup>[1,28]</sup>

### 5.1 Ayurvedic Medicine

In the Ayurvedic system, Bharangi is prescribed for Shwasa (asthma), Kasa (cough), and Hikka (hiccup) in the Charaka Samhita,<sup>[2]</sup> while its usage in Vrana (wound healing), Shotha (inflammation), and dermatological diseases is documented in the Sushruta Samhita.<sup>[3]</sup> Its rasa-guna-virya-vipaka profile is thoroughly described in the Bhavaprakasha Nighantu.<sup>[4]</sup> Traditional remedies include Bharangi Churna (root powder for fever and cough), Bharangyadhwam Rasa (mineral-herbal remedy for sinusitis and rhinitis), and Bharangi Ghrita (medicated clarified butter for respiratory ailments).<sup>[5,8]</sup> Bharangi is officially recognized as a standardized medication by the Ayurvedic Pharmacopoeia of India,<sup>[8]</sup> which also specifies quality standards for its usage in medicine. *C. serratum* is used in modern Ayurvedic

medicine to treat bronchial asthma, allergic rhinitis, sinusitis, eczema, rheumatoid arthritis, and jaundice and as an immunostimulant. Preclinical pharmacological evidence now strongly supports these therapeutic indications.<sup>[10,13,19,22,25]</sup>

### 5.2 Unani Medicine

*C. serratum*, also known as "Bharangi" or "Arni," is categorized in the Unani medical system as having hot and dry qualities (Garm wa Khushk, second degree), which means that it is especially recommended for cold, phlegmatic, and wet circumstances.<sup>[29]</sup> It is used by Unani practitioners as a blood purifier and for respiratory conditions, fever, sinusitis, headaches, arthritis, jaundice, and urinary infections.<sup>[7,29]</sup> The most common preparation is the root bark decoction (Joshanda), which is frequently mixed with warming adjuvants, including Ajwain, Sonth, and Pippal.<sup>[29,34]</sup> The plant's known anti-inflammatory,<sup>[19-21]</sup> antibacterial,<sup>[26]</sup> and hepatoprotective<sup>[24,25]</sup> properties provide consistent pharmacological support for these purposes.

### 5.3 Siddha Medicine

*C. serratum*, also known as "Siruthekku" in Tamil and "Wal-nika" in Sinhala,<sup>[10]</sup> is used in the Siddha system of Tamil Nadu and some regions of Sri Lanka to treat inflammatory illnesses, fever, skin disorders, and respiratory infections. To improve expectorant and bronchodilatory effects, Siddha scriptures recommend combination formulations with Trikatu (Pippali, Maricha, and Shunthi).<sup>[7]</sup> Documented antihistaminic,<sup>[22,23]</sup> anti-inflammatory<sup>[19,20]</sup> and antiasthmatic<sup>[35,36]</sup> properties provide the pharmacological foundation for these Siddha applications.

### 5.4 Tribal and Folk Medicine

Rich traditional uses that go beyond established medical systems have been reported by extensive ethnobotanical studies conducted among tribal people in India, Sri Lanka, Nepal, and Southeast Asia.<sup>[2,28,32]</sup> Root paste is applied topically for snakebite treatment and wound healing in Central Indian tribal communities, such as the Gond, Baiga, and Korku peoples of Madhya Pradesh, Chhattisgarh, and Jharkhand; root decoctions are used for malaria, chronic respiratory conditions, and febrile convulsions.<sup>[31,32]</sup> According to the Ayurvedic Drug Survey of India, *C. serratum* is one of the most commonly used plants in traditional medicine in a variety of geographical areas.<sup>[27,31]</sup>

*C. serratum* has been identified as one of the key medicinal plants that mountain tribes in Nepal use for traditional healing.<sup>[18,32]</sup> While root decoctions treat fever, malaria, and urinary problems, leaves are used as poultices for wound healing and skin infections in Thailand and Southeast Asian nations.<sup>[18,28]</sup> The best ethnopharmacological confirmation for the plant's primary pharmacological effects can be seen in the striking geographic convergence of therapeutic applications for respiratory, inflammatory, and infectious illnesses across culturally distinct populations.<sup>[1,28,37]</sup>

## 6. Phytochemistry

The amazing phytochemical complexity of *Clerodendrum serratum* provides the scientific basis for its many medicinal uses. A wide range of bioactive secondary metabolites found in roots, stem bark, leaves, and flowers have been identified over more than 40 years of systematic research employing HPLC, GC-MS, LC-MS/MS, NMR, FT-IR, and HPTLC platforms.<sup>[10,14-18]</sup> The fundamental chemical characterization of *C. serratum* was established by Patel et al. (2014) in the *Journal of Ethnopharmacology*<sup>[10]</sup> and by Ravikumar et al. (2008)<sup>[15]</sup> in their complete phytochemical profile. Iridoid glycosides, diterpenoids, flavonoids, phenolic acids, sterols, triterpenoids, D-mannitol, saponins, tannins, and volatile oils are important groups of compounds.<sup>[10,14-16,18]</sup>

The iridoid glycosides, especially acteoside (verbascoside), serratoside, and clerodenosides A and B, which are concentrated in roots and bark and significantly contribute to anti-inflammatory,<sup>[10,21]</sup> antihistaminic,<sup>[23]</sup> and antioxidant<sup>[32,38]</sup> activities,<sup>[15,18]</sup> are among the most pharmacologically significant compounds found. Acteoside, also known as verbascoside in the plant,<sup>[15]</sup> has been found to be an important biomarker chemical that has been shown to suppress mast cell degranulation and complement activation, two processes that are closely related to the plant's conventional anti-allergic uses.<sup>[22,23]</sup> Patel and Acharya's pharmacognostic and phytochemical studies developed reliable techniques for measuring these iridoid marker chemicals.

The structurally distinct neoclerodane and clerodane-type skeletons found in the diterpenoid fraction include clerodin, clerodermic acid, neoclerodane derivatives, and clerosterol. These skeletons are very interesting natural products and are comparatively uncommon in the kingdom of plants. The main diterpenoid biomarker, clerodin, has a bicyclic furanolactone structure that supports its cytotoxic,<sup>[30]</sup> antibacterial,<sup>[26]</sup> and anti-inflammatory<sup>[19,39]</sup> properties. Clerodin and other *C. serratum* diterpenoids showed strong binding affinity to COVID-19 and cancer-associated molecular targets in the molecular docking investigation by Srinath et al. (2020),<sup>[30]</sup> underscoring their potential for therapeutic discovery.

Hispidulin, cleroflavone, apigenin, scutellarein, luteolin, and baicalein are among the well-known pharmacologically active flavones found in the flavonoid fraction, which is especially rich in the aerial sections.<sup>[14,15,28]</sup> Among flavonoids, hispidulin and cleroflavone are thought to be distinctive identifiers for *C. serratum*.<sup>[15,17]</sup> Comprehensive phenolic content analysis related to antioxidant activity was presented by Singh et al. (2012).<sup>[40]</sup> Analytical standardization for quality control is supported by the HPTLC fingerprinting method for flavonoid determination created by Prasanth et al.<sup>[28]</sup> Caffeic acid, ferulic acid, acteoside, and quercetinic acid (queretaroic acid) are phenolic acids that have hepatoprotective,<sup>[24,25]</sup> antioxidant,<sup>[38,40]</sup> and antibacterial qualities. Among the most significant non-phenolic bioactive substances are D-mannitol, serratagenic acid, ursolic acid, and oleanolic acid; ursolic acid in particular is in charge of the hepatoprotective mechanism through stabilization of the GSH pathway and inhibition of malondialdehyde production.<sup>[10,24]</sup> According to GC-MS,<sup>[15,16]</sup> sterols such as  $\beta$ -sitosterol, stigmasterol, campesterol, cholestanol, and 24-ethyl cholesterol have anti-inflammatory<sup>[19]</sup> and membrane-stabilizing qualities. The plant's antiasthmatic properties are caused by saponins, mainly triterpenoid saponins found in roots and leaves, which relax smooth muscle in the airways and modulate the immune system.<sup>[22,35,36]</sup>

**Table 3: Comprehensive Phytochemical Profile of *Clerodendrum serratum* (L.) Moon.**

Phytochemical Class	Major Compounds Identified	Plant Parts	Reported Pharmacological Activities	Analytical Techniques
Iridoid Glycosides	Serratoside, Clerodenoside A & B, Ajugol, Loganin, Acteoside	Roots, Bark	Anti-inflammatory, <sup>[10,21]</sup> Antihistaminic, <sup>[23]</sup> Antioxidant, <sup>[38,40]</sup> Hepatoprotective <sup>[25]</sup>	HPLC, LC-MS/MS, NMR
Diterpenoids	Clerodin, Neoclerodane derivatives, Serratusin, Clerosterol, Clerodermic acid	Roots, Stems	Anti-inflammatory, <sup>[19,39]</sup> Antimicrobial, <sup>[26]</sup> Anticancer, <sup>[30]</sup> Hepatoprotective <sup>[24,25]</sup>	GC-MS, NMR, HPLC
Flavonoids	Hispidulin, Cleroflavone, Apigenin, Scutellarein, Luteolin, Baicalein	Leaves, Aerial parts	Antioxidant <sup>[38,40]</sup> Anti-inflammatory, <sup>[21]</sup> Antihistaminic, <sup>[23]</sup> Anticancer <sup>[28]</sup>	HPLC, FT-IR, HPTLC
Phenolic	Caffeic acid, Ferulic	Roots,	Antioxidant, <sup>[40]</sup>	HPLC, FT-IR

Compounds	acid, Acteoside, Verbascoside, Quercetic acid	Leaves	Antimicrobial, <sup>[26]</sup> Hepatoprotective <sup>[24,25]</sup>	
Steroids & Triterpenes	$\beta$ -Sitosterol, Stigmasterol, Campesterol, Oleanolic acid, Serratagenic acid	Roots, Stems	Anti-inflammatory, <sup>[19]</sup> Wound healing, <sup>[41]</sup> Reproductive modulation <sup>[9]</sup>	GC-MS, NMR
Terpenoids	Ursolic acid, $\alpha$ -Amyrin, $\beta$ -Amyrin, 24-Ethyl cholesterol, D-Mannitol	Leaves, Roots	Antimicrobial, <sup>[26]</sup> Hepatoprotective, <sup>[25]</sup> Anti-inflammatory <sup>[39]</sup>	GC-MS, NMR
Alkaloids	Minor isoquinoline derivatives, Clerosterol alkaloids	Roots, Bark	Antimicrobial, <sup>[26]</sup> effects <sup>[16]</sup> CNS	LC-MS, NMR
Tannins	Condensed tannins, Hydrolysable tannins	Roots, Bark	Antidiarrheal, healing, <sup>[41]</sup> Antioxidant <sup>[38]</sup> Wound	Spectrophotometry
Saponins	Triterpenoid saponins	Roots, Leaves	Immunomodulatory, <sup>[22]</sup> Antiasthmatic, <sup>[35,36]</sup> Antimicrobial <sup>[26]</sup>	HPLC, TLC

Table 3- Phytochemical Profile<sup>[10,14-18,28,40]</sup>

## 7. Pharmacological Activities

Over the course of four decades, in vitro, ex vivo, and in vivo experimental studies have methodically documented the pharmacological actions of *Clerodendrum serratum*.<sup>[10,13,14,28]</sup> These investigations have gradually clarified the molecular processes behind conventional therapeutic claims and have uncovered new pharmacological characteristics that were not first predicted from conventional use patterns. The pharmacological overview by Wang et al. (2018)<sup>[28]</sup> and the thorough review by Patel et al. (2014)<sup>[10]</sup> are important sources of reference for the range of recorded activities.

### 7.1 Antihistaminic and Anti-allergic Activity

The most researched and therapeutically significant pharmacological characteristic of *C. serratum* is its anti-inflammatory action, which directly supports its traditional usage in fever, skin disorders, arthritis, and respiratory inflammatory illnesses.<sup>[10,19-21,39]</sup> Methanolic root extracts demonstrated a strong dose-dependent reduction of carrageenan-induced paw edema in rats, with efficacy comparable to indomethacin at higher dosages, according to fundamental pharmacological research by Gupta et al. (2009).<sup>[19]</sup> In carrageenan paw edema models, Shareef et al. (2013)<sup>[20]</sup> confirmed strong anti-rheumatic and anti-inflammatory action, with root extracts showing better anti-inflammatory activity than aerial portions.

A comparison investigation by Solapure et al. (2016)<sup>[21]</sup> showed that *C. serratum* and *Solanum xanthocarpum* had similar anti-inflammatory effects in Wistar albino rats. Mechanistic studies have shown inhibition of 5-lipoxygenase (5-LOX), cyclooxygenase-1 and cyclooxygenase-2 (COX-1 and COX-2), and prostaglandin and leukotriene synthesis, as well as suppression of NF- $\kappa$ B activation and subsequent reduction of TNF- $\alpha$ , IL-1 $\beta$ , and IL-6.<sup>[21,39]</sup> In thermal nociception (hot plate, tail-flick) and chemical nociception (acetic acid writhing) models, Gupta et al. (2012)<sup>[39]</sup> also confirmed antipyretic and analgesic properties. The analgesic response was dose-dependent and clinically significant in comparison to reference analgesics.<sup>[19,39,42]</sup> It has been demonstrated that the anti-inflammatory action of ursolic acid, which was extracted from alcoholic root extract, stabilizes plasma membranes and restores AST, ALT, and ALP levels by modulating the GSH route.<sup>[10,24]</sup>

## 7.2 Antihistaminic and Anti-allergic Activity

The main pharmacological justification for *C. serratum*'s traditional usage in sinusitis, allergic rhinitis, bronchial asthma, urticaria, and eczema is its antihistaminic and anti-allergic qualities.<sup>[22,23,33,37]</sup> Bafna and Mishra (2004)<sup>[22]</sup> identified the saponin fraction as the cause of mast cell-stabilizing effects in peritoneal mast cell preparations by demonstrating saponin-mediated complement inhibition and immunostimulatory activities. In compound 48/80-induced mast cell degranulation models, Shirish and Prashant (2012)<sup>[23]</sup> particularly assessed antihistaminic activity and confirmed a substantial reduction of histamine release from peritoneal mast cells that was comparable in effect magnitude to the cromoglycate reference.

In ovalbumin-sensitized guinea pigs, Singh et al. (2014)<sup>[33]</sup> assessed anti-asthmatic activity and found a significant decrease in inflammatory cell infiltration and airway hyperresponsiveness that was consistent with mast cell stability. According to Wahi et al. (2010),<sup>[43]</sup> *C. serratum* root extract dramatically decreased immunological indices and airway inflammatory parameters related to allergic asthma. Antiallergic action was validated in experimental allergy models, including passive cutaneous anaphylaxis, by Bhatt et al. (2009).<sup>[55]</sup> By inhibiting intracellular calcium mobilization in mast cells and interfering with IgE receptor activation, the iridoid glycosides, especially acteoside, and the saponin fraction seem to be the main contributors to this antihistaminic mechanism<sup>[22,23]</sup>

## 7.3 Antioxidant Activities

*C. serratum* demonstrates robust antioxidant properties across multiple assay systems, attributable to its flavonoid, phenolic acid, iridoid glycoside, and terpenoid content.<sup>[38,40]</sup> Rane et al. (2019)<sup>[38]</sup> comprehensively profiled antioxidant activity across *C. serratum* extracts, demonstrating significant DPPH and FRAP activity with IC<sub>50</sub> values in the range reported for established reference antioxidants. Singh et al. (2012)<sup>[40]</sup> evaluated phenolic composition and antioxidant-antimicrobial correlations in *C. serratum* leaf extracts, establishing a significant correlation between phenolic content and radical-scavenging activity. Prakash Kumar and Nishteswar (2013)<sup>[14]</sup> documented in vitro DPPH radical scavenging with IC<sub>50</sub> values of 175 and 137 µg/mL for alcoholic and aqueous extracts respectively, with a linear increase in reducing power over 20–120 µg/mL concentration range equivalent to ascorbic acid. In vivo studies confirm that *C. serratum* administration enhances endogenous SOD, CAT, and GPx activity while reducing MDA and lipid peroxidation markers in oxidative stress models.<sup>[10,24,38]</sup> This antioxidant capacity forms a mechanistic crosslink between the plant's hepatoprotective,<sup>[10,24,25]</sup> cardioprotective,<sup>[44]</sup> and chemopreventive<sup>[30]</sup> pharmacological categories.

## 7.4 Hepatoprotective Activities

The traditional usage of *C. serratum* in jaundice and liver problems has significant scientific justification due to its well-documented hepatoprotective action.<sup>[10,24,25]</sup> In a comparative pharmacological assessment of the hepatoprotective activity of *C. serratum* and *Ocimum sanctum* in rats with paracetamol-induced liver toxicity, Kalaiselvan and Gokulakrishnan (2013)<sup>[25]</sup> showed a significant decrease in ALT, AST, ALP, and bilirubin toward normal values, with histopathological confirmation of decreased hepatocellular necrosis and ballooning degeneration. Bhalke et al. (2012)<sup>[36]</sup> and the foundational Patel et al. review<sup>[10]</sup> confirmed that the ethanolic root extract composition from roots showed significant protection against acetaminophen-induced hepatotoxicity through DPPH free radical scavenging activity. Sannigrahi et al. (2010)<sup>[24]</sup> provided mechanistic clarity through *Clerodendrum* species hepatotoxicity models, confirming the role of methanol extract fractions in CCl<sub>4</sub>-mediated hepatic injury protection. Ursolic acid, which is extracted from alcoholic root extract, is the main hepatoprotective mechanism. It restores disturbed antioxidant status

by preserving glutathione levels, preventing the production of malondialdehyde, and stabilizing hepatocyte plasma membranes, all of which prevent cellular necrosis and encourage hepatic regeneration.<sup>[10,24]</sup>

### 7.5 Antimicrobial and Anti-mycobacterial Activity

In line with conventional uses in wound healing, UTI treatment, and skin infections, *C. serratum* has broad-spectrum antibacterial action against clinically significant bacterial and fungal pathogens.<sup>[26,40]</sup> With MIC values ranging from 62.5 to 500 µg/mL, Nair et al. (2010)<sup>[26]</sup> carried out systematic disc diffusion and MIC studies showing notable antibacterial activity against *Staphylococcus aureus*, *Streptococcus pyogenes*, *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*. Higher diterpenoid and phenolic content were correlated with root extracts' typically better antibacterial activity as compared to leaf extracts. The antibacterial and antifungal properties of leaf phenolic extracts against common human diseases were validated by Singh et al. (2012).<sup>[40]</sup>

Silver nanoparticles green-synthesised from *C. serratum* leaf extracts showed strong anti-mycobacterial activity against *Mycobacterium* species, including drug-resistant strains, according to a noteworthy recent development by Patel et al. (2023).<sup>[45]</sup> This represents a major advancement in using this plant's antimicrobial potential for tuberculosis management. Hydrophobic terpenoids and diterpenoids break microbial cell membranes, phenolic chemicals inhibit enzymes, and saponins and volatile oils destroy cell walls as part of the antimicrobial process.<sup>[26,40]</sup>

### 7.6 Antiasthmatic Activity

The antiasthmatic activity of *C. serratum* is one of its most therapeutically significant pharmacological activities, which directly supports its principal traditional use in Ayurveda for Tamaka Shwasa (bronchial asthma).<sup>[2,3,5]</sup> In guinea pigs with histamine aerosol-induced bronchospasm, Surana et al. (2009)<sup>[35]</sup> assessed an aqueous extract of *C. serratum* root and found strong bronchodilatory and bronchoprotective effects that are consistent with the saponin fraction's known function in airway smooth muscle relaxation. According to Bhalke et al. (2012),<sup>[36]</sup> long-term immunological modification of airway hypersensitivity as well as acute bronchodilation was demonstrated by the gradual increase in resistance of sensitized guinea pigs against bronchoconstriction following three to six weeks of chronic saponin administration (20 mg/kg). In sensitized guinea pigs given ethanolic root extracts, Singh et al. (2014)<sup>[33]</sup> showed a substantial decrease in ovalbumin-induced airway hyperresponsiveness, eosinophil infiltration, and IgE levels. Immune parameters and airway inflammatory markers were significantly reduced in experimental allergies, according to Wahi et al. (2010).<sup>[43]</sup> Saponin-mediated mast cell stabilization.<sup>[22,35]</sup> decreased histamine and leukotriene production.<sup>[23,37]</sup>

COX/LOX anti-inflammatory action.<sup>[19,21]</sup> and direct bronchodilatory effects of certain phytoconstituents<sup>[35]</sup> are all components of the antiasthmatic pathway.

### 7.7 Immunomodulatory Activity

The immunomodulatory characteristics of *C. serratum* have been shown in a number of experimental paradigms. According to Vijayan et al. (2011),<sup>[46]</sup> root extracts stimulated both innate and humoral adaptive immunity by dramatically increasing macrophage phagocytic activity, hemagglutination antibody titer, and delayed-type hypersensitivity reactions in experimental animals. By inhibiting the complement cascade, Bafna and Mishra (2004)<sup>[22]</sup> established the saponin fraction's anticomplement activity, uncovering a new anti-inflammatory immunomodulatory mechanism pertinent to both allergy management and anti-infective protection.

Chyawanprash and other traditional rasayana (rejuvenating) remedies contain *C. serratum* because of its immunostimulatory qualities.<sup>[5,11]</sup> Wang et al. (2018)<sup>[28]</sup> confirmed the consistent pattern of immunostimulation by *C. serratum* constituents across several experimental paradigms, offering a more comprehensive view of immunomodulatory activities throughout the *Clerodendrum* genus.

### 7.8 Anticancer and Molecular Docking Studies

Molecular docking studies have demonstrated the anticancer and drug development potential of *C. serratum* phytoconstituents. A thorough molecular docking study of *C. serratum* bioactive compounds against COVID-19 target proteins (main protease Mpro, spike protein, and RNA-dependent RNA polymerase) was carried out by Srinath et al. (2020).<sup>[30]</sup> The results showed that clerodin and hispidulin, among other compounds, had a significant binding affinity to viral molecular targets, suggesting potential antiviral applications in coronavirus infection management. *Clerodendrum* species constituents' cytotoxic effects against several cancer cell lines were reviewed by Wang et al. (2018).<sup>[28]</sup> The flavonoid components found in *C. serratum*, including apigenin, luteolin, and hispidulin,<sup>[14,15]</sup> have been shown to exhibit pro-apoptotic and antiproliferative properties against cancer cells by inhibiting the course of the cell cycle and inducing programmed cell death.<sup>[28,44]</sup> Further justification for examining *C. serratum* diterpenoids as immunostimulatory anticancer adjuvants is provided by Yadav et al. (2011),<sup>[47]</sup> who reported the immunostimulatory effects of clerodane diterpenoids, the scaffold type found in *C. serratum*.<sup>[30,47]</sup>

### 7.9 Gastroprotective and Additional Activities

In experimental ulcer models, Ramesh and Kumar (2018) found that *C. serratum* root extracts significantly reduced ulcer index, gastric acid secretion, and inflammatory markers in the gastric mucosa—activities consistent with the plant's traditional use in gastrointestinal complaints.<sup>[28]</sup> This gastroprotective activity is mechanistically supported by the combined anti-inflammatory<sup>[19-21]</sup> and antioxidant<sup>[38,40]</sup> actions. Furthermore, the saponin and flavonoid fractions have been linked to diuretic activity, which has been reported in traditional uses across several cultures,<sup>[9,18,28]</sup> supporting use in urinary problems and edematous situations. For the objective of standardization, Mukherjee (2007)<sup>[27]</sup> emphasized the significance of quality-controlled evaluation of all these pharmacological activities.

**Table 4: Summary of Pharmacological Activities of *Clerodendrum serratum* (L.) Moon**

Activity	Experimental Model	Key Findings	Key References
Anti-inflammatory	Carrageenan paw edema; cotton pellet granuloma; NF-κB inhibition assay	Significant paw edema reduction comparable to indomethacin; COX-1/COX-2 and 5-LOX inhibition; TNF-α, IL-1β, IL-6 downregulation	(19–21,39)
Antihistaminic & Anti-allergic	Compound 48/80-induced mast cell degranulation; passive cutaneous anaphylaxis; ovalbumin model	Significant mast cell stabilization; inhibition of IgE-mediated allergic response; reduced eosinophil count in nasal smear	(22,23,33,37)
Antioxidant	DPPH, FRAP, ABTS radical scavenging; in vivo SOD, CAT, GPx assays	IC <sub>50</sub> 28–86 μg/mL (DPPH); enhanced endogenous antioxidant enzyme activity; reduced MDA and lipid peroxidation	(14,16,38,40)
Hepatoprotective	CCl <sub>4</sub> and paracetamol-induced liver injury in rats; ALT/AST/ALP estimation	Significant hepatoenzyme normalization; reduced MDA; improved histopathology; ursolic acid mechanism via GSH pathway	(10,24,25,39)
Antimicrobial	Disc diffusion; MIC vs.	Broad-spectrum antibacterial and	(26,40,45)

	<i>S. aureus</i> , <i>E. coli</i> , <i>C. albicans</i> , <i>Aspergillus</i>	antifungal; MIC 62.5–500 µg/mL; activity vs. MRSA; anti-mycobacterial activity	
Anticancer	Molecular docking vs. target proteins; cytotoxicity assays	Significant binding affinity to COVID-19 proteins and cancer targets; cytotoxic phytoconstituents identified	(23,28)
Analgesic	Hot plate test; tail-flick test; writhing test (acetic acid model)	Dose-dependent central and peripheral analgesic effects; anti-pyretic activity confirmed	(19,39,42)
Immunomodulatory	Macrophage phagocytosis; complement inhibition; antibody titer	Enhanced macrophage activity; saponin-mediated complement inhibition; increased antibody titer	(22,35,46)
Antiasthmatic	Saponin extract in guinea pigs; ovalbumin model; airway inflammation	Significant bronchodilatory effect; reduced airway hyperresponsiveness, and anti-allergic mechanism	(33,35,36,43)
Antimycobacterial	AgNPs from <i>C. serratum</i> vs. <i>Mycobacterium</i> spp.	Green-synthesized silver nanoparticles from leaves showed potent anti-mycobacterial activity	(45)

Table 4- Pharmacological Activity Summary<sup>[1,10,13–16,19–22,24–26,28,33,36,39,43,45,46,48–51]</sup>

## 8. Toxicology and Safety Profile

Establishing safe dose guidelines and promoting clinical and pharmaceutical development require a comprehensive understanding of *C. serratum*'s toxicological profile.<sup>[27,42,52]</sup> With significant caveats regarding high-dose exposure and use during pregnancy, the current toxicological data, which were mostly gathered through acute and subacute experimental trials, collectively show a satisfactory safety profile at therapeutically relevant dosages.<sup>[17,42]</sup>

Methanol extract of the aerial portions and roots of *C. serratum* was administered orally to female rats at a dose of 2000 mg/kg body weight using the up-and-down method for acute oral toxicity tests.<sup>[42]</sup> A large margin of safety above the pharmacologically effective dose range of 50–400 mg/kg reported in effectiveness studies was confirmed by the LD50 exceeding 2000 mg/kg and the lack of fatality<sup>[19–21,39]</sup> Basic pharmacological safety investigations on *C. serratum* root were carried out by Deshpande et al. (1965),<sup>[42]</sup> which are still used as benchmarks for the plant's safety profile. Mukherjee (2007)<sup>[27]</sup> offered safety evaluation and quality control frameworks that were particularly pertinent to the standardization of barangi roots. The lack of acute behavioral toxicity in experimental animals at anti-inflammatory efficacious levels was confirmed by Gupta et al. (2009)<sup>[19]</sup> and Gupta et al. (2012).<sup>[39]</sup>

While mild and reversible hepatic stress markers may be observed at supratherapeutic doses, subacute toxicity evaluations by Joshi and Bhattacharya (2001)<sup>[53]</sup> and the general toxicological framework established by WHO monographs<sup>[52]</sup> show no significant organ pathology at conventional therapeutic dosage levels. Testing for heavy metals, microbiological contamination, pesticide residues, and aflatoxins—parameters crucial for pharmaceutical-grade Bharangi preparations—was one of the quality control needs that Mukherjee (2007)<sup>[27]</sup> particularly addressed. Certain diterpenoid chemicals found in *Clerodendrum* species have been shown to exhibit uterotonic qualities, which support traditional uses in menstrual regulation with regard to reproductive safety.<sup>[4,8]</sup> This uterotonic potential warrants clear contraindication for use during pregnancy.<sup>[4,8]</sup> Long-term toxicological studies, genotoxicity assessments, and comprehensive pharmacokinetic profiling specifically for *C. serratum* remain absent from the published literature—

representing a critical gap requiring priority research attention before full pharmaceutical development can proceed.<sup>[13,27,52]</sup>

**Table 5: Toxicological Profile of Clerodendrum serratum (L.) Moon.**

Toxicity Type	Dose / Model	Observations	References
Acute Toxicity	2000 mg/kg (oral), rodents (OECD 423)	No mortality; LD50 > 2000 mg/kg; no behavioral abnormalities; wide therapeutic window confirmed	(16,17,42)
Subacute Toxicity	50–200 mg/kg × 28 days	No significant organ damage at therapeutic doses; mild transient ALT elevation at 200 mg/kg	(17,19,39)
Anti-inflammatory Safety	Comparison vs. indomethacin in edema models	Plant extract effective with better GI tolerability vs. indomethacin; no ulcerogenic effects noted	(19,21,28)
Reproductive Considerations	Uterotonic compounds present	Saponins and certain diterpenoids have uterotonic potential; caution in pregnancy; traditional use in parturition	(4,8)
General Safety	Traditional oral dosage ranges	Safe within traditional dosage; long-term systematic toxicological studies still required	(27,42,52)

Table 5- Toxicological Profile-<sup>[4,8,17,19,20,27,42,52]</sup>

## 9. Traditional Formulations and Classical Preparation

Clerodendrum serratum, also known as Bharangi, has a long history of use in traditional Ayurvedic pharmaceutical preparation. It is used as a major or supporting ingredient in both complex polyherbal-herbomineral formulations and single-herb formulations.<sup>[2-5,8,9,11,34]</sup> Bharangi root is used in several official formulations listed in the Ayurvedic Formulary of India.<sup>[34]</sup> Bharangi is a standardized raw medicine with quality specifications outlined in the Ayurvedic Pharmacopoeia of India.<sup>[8]</sup>

Bronchial asthma, allergic bronchitis, and chronic respiratory conditions are commonly treated with Bharangi Ghrita, a therapeutic clarified butter made by mixing Bharangi root decoction with cow's ghee in accordance with traditional Sneha Kalpana protocols.<sup>[4,5,9]</sup> The lipophilic medium represents traditional medicinal knowledge that foresaw contemporary biopharmaceutical principles of lipid-enhanced absorption by facilitating greater absorption of fat-soluble diterpenoids and terpenoids across the respiratory and intestinal epithelium.<sup>[11,34]</sup> With strong mechanistic support from established antihistaminic<sup>[22,23]</sup> and anti-inflammatory<sup>[19,21]</sup> properties, Bharangyadhvam Rasa, a traditional Rasa (mineral-herbal) preparation, is especially given for sinusitis, rhinitis, chronic headache, and nasal polyps.<sup>[8,34]</sup>

One of the rare clinical trials of a Bharangi formulation, Bharangiguda Avaleha, demonstrated significantly substantial reductions in asthma symptoms in Tamaka Shwasa patients at Ayurvedic hospitals.<sup>[2]</sup> Many formulations, such as Dashamoola Kashaya and Dashamool Hareetaki, are based on Dashamoola, the ten-root classical combination of which Bharangi is a fundamental constituent.<sup>[5,9,31]</sup> Bharangi is one of the 48+ herbal ingredients of Chyawanprash, one of Ayurveda's most widely eaten rasayana preparations, which contributes to its immunostimulatory<sup>[22,46]</sup> and respiratory protective<sup>[35,37]</sup> qualities.<sup>[5,11]</sup>

**Table 6: Traditional Ayurvedic Formulation Containing Clerodendrum serratum (Bharangi).**

Formulation Name	Dosage Form	Therapeutic (Reference)	Indication	Key Ingredients
Bharangi Ghrita	Medicated ghee (Sneha Kalpana)	Bronchial asthma, chronic cough, respiratory disorders <sup>[4,8,9]</sup>		Bharangi root, Cow's ghee, Pippali
Bharangyadhwam Rasa	Classical tablet (Rasa preparation)	Sinusitis, rhinitis, chronic headache, nasal polyps <sup>[8]</sup>		Bharangi, purified mercury, sulfur, Shilajit
Dashamoola Decoction	Decoction (Kashaya)	Fever, inflammation, Vata disorders, rheumatism <sup>[5,6,27]</sup>		Bharangi among 10 classical roots
Bharangi Churna	Root powder (Churna)	Cough, asthma, fever, bronchitis <sup>[4,5,8]</sup>		Bharangi root powder with adjuvants
Chyawanprash	Herbal confection (Avaleha)	Immunity, respiratory health, rejuvenation <sup>[2,5,11]</sup>		Bharangi among 48+ herbal ingredients
Kanakasava	Fermented liquid (Asava)	Asthma, chronic cough, respiratory disorders <sup>[4,34]</sup>		Bharangi, Dhattura, Honey
Bharangiguda Avaleha	Electuary (Avaleha)	Tamaka Shwasa (bronchial asthma) <sup>[2,3,35]</sup>		Bharangi, Guduchi, sugar
Triphaladi Kwatha	Decoction (Kwatha)	Skin disorders, fever, anti-inflammatory <sup>[8,31,34]</sup>		Bharangi in polyherbal combination

Table 6 - Classical Formulations Containing Bharangi<sup>[2,4,5,8,9,34]</sup>

### 10. Clinical Evidence and Human Studies

The biggest obstacle to evidence-based pharmaceutical development is the lack of clinical research on *C. serratum* preparations in terms of both quantity and methodological rigor, despite a strong body of preclinical experimental evidence.<sup>[13,18]</sup> Small observational cohorts, pilot trials, and traditional clinical practice records carried out in Ayurvedic institutional settings in India are the main sources of available clinical data.<sup>[13,18,35]</sup>

The pharmacological review by Prakash Kumar and Nishteswar (2013)<sup>[14]</sup> is the most clinically significant documentation. It states that a clinical trial using Bharangiguda Avaleha, an Ayurvedic electuary containing Bharangi, was carried out in patients with Tamaka Shwasa (bronchial asthma) at a government Ayurvedic hospital, with highly significant improvement noted in respiratory function parameters. Chronic saponin administration from *C. serratum* provided clinically significant bronchodilatory effects in sensitized experimental subjects, according to Surana et al. (2009).<sup>[35]</sup> The anti-asthmatic application was supported by experimental clinical correlation findings presented by Singh et al. (2014).<sup>[33]</sup>

Goswami and Mitra (2014)<sup>[13]</sup> carried out a thorough analysis of the available clinical data, methodically identifying consistent symptomatic improvement in respiratory and inflammatory conditions treated with preparations containing Bharangi. They also clearly documented the methodological limitations that prevent definitive evidence-based recommendations, including small sample sizes, the lack of placebo controls, non-standardized extract preparations, and non-validated outcome measures.

Reliable clinical trial standardization requires proven quality metrics, which were developed by Patel and Acharya's 2012 pharmacognostic and phytochemical study.<sup>[17]</sup> The quality control measures needed for clinical development, which have not yet been fully defined for *C. serratum*, are expressly identified in WHO guidelines for the evaluation of herbal medicines.<sup>[52]</sup> In particular, for the iridoid glycoside and diterpenoid fractions that have never undergone systematic pharmacokinetic study in humans, Mukherjee et al. (2007)<sup>[54]</sup> emphasized the critical importance of rigorous pharmacokinetic characterization—absorption, distribution, metabolism, and excretion profiling—as a necessary

prerequisite for rational clinical dose optimization. The difficulty of obtaining evidence-based status for Ayurvedic herbs was highlighted by Vaidya and Devasagayam (2007),<sup>[55]</sup> who pointed out that insufficient clinical evidence is a systemic problem for this class of medications rather from being specific to *C. serratum*.

### 11. Drug Discovery and Translational Potential

*Clerodendrum serratum*'s varied phytochemistry and multi-target preclinical pharmacology support its true promise for drug discovery.<sup>[13,30,55]</sup> Clerodin, hispidulin, and several co-occurring flavonoids were found to be high-affinity ligands for COVID-19 molecular targets in the molecular docking study by Srinath et al. (2020),<sup>[30]</sup> which is the most recent and computationally advanced investigation of *C. serratum* phytochemicals as drug discovery candidates. This suggests direct potential for antiviral drug development. *C. serratum* is one of the most pharmacologically promising species in the genus due to its cytotoxic, anti-HIV, anti-inflammatory, and antiviral properties, according to Wang et al.'s (2018)<sup>[28]</sup> thorough assessment of the drug discovery value of *Clerodendrum* genus members.

By showing that *C. serratum* leaf extracts can function as reducing agents for environmentally friendly green synthesis of nanoparticles with strong anti-mycobacterial activity, the silver nanoparticle synthesis achievement by Patel et al. (2023)<sup>[45]</sup> represents a particularly significant drug delivery breakthrough, directly addressing the pressing global issue of drug-resistant tuberculosis. In line with the plant's known  $\alpha$ -glucosidase inhibitory activity<sup>[14,56]</sup> selected flavonoids and triterpenoids—compound classes found in *C. serratum*—are priority prospects for antidiabetic drug development. Clerodane diterpenoid glycosides from related species were identified by Yadav et al. (2011)<sup>[47]</sup> as immunostimulatory leads with potential as adjuvants for cancer immunotherapy; this template is immediately applicable to clerodin and related compounds from *C. serratum*. Formulation co-development strategies are supported by the antioxidant activities of vitexin-related compounds and triterpenoids that are similar to those discovered in *C. serratum*, as reported by Tiwari and Tripathi (2007).<sup>[57]</sup> By reviewing Ayurvedic rejuvenating medications, Singh et al. (2011)<sup>[58]</sup> gave context for the rasayana applications of *C. serratum* and identified immunostimulatory and adaptogenic qualities as important development targets.

The bioavailability and targeted delivery of *C. serratum*'s lipophilic bioactive chemicals are particularly promising when using nanotechnology-based drug delivery methods.<sup>[45,59]</sup> Patel et al.'s (2023)<sup>[45]</sup> effective green synthesis of anti-mycobacterial AgNPs demonstrates proof-of-concept for the production of nano-formulations from *C. serratum*. While intranasal nanoparticle delivery systems could allow for targeted mucosal administration for the treatment of sinusitis and rhinitis, nanostructured lipid carriers and liposomal formulations of diterpenoids and flavonoids could address the oral bioavailability limitations of these lipophilic compounds.<sup>[23,37]</sup>

### 11. Standardization and Quality Control

Rigid uniformity throughout all manufacturing stages—from botanical authentication through extraction, processing, and final dosage form manufacture—is necessary to guarantee consistent therapeutic quality, safety, and efficacy of *C. serratum* preparations.<sup>[8,17,27,52]</sup> Official quality requirements for Bharangi root are provided by the Ayurvedic Pharmacopoeia of India,<sup>[8]</sup> which includes TLC fingerprinting specifications, extractive value ranges, ash values, moisture content limits, and macroscopic and microscopic descriptions. Formulation guidelines for traditional medicines containing Bharangi are outlined in the Ayurvedic Formulary of India.<sup>[34]</sup> The thorough quality control framework for herbal drug standardization that applies to *C. serratum* is provided by Mukherjee (2007).<sup>[27]</sup> This

framework includes contaminant testing, physicochemical evaluation, microscopic examination, and phytochemical fingerprinting.

Given the proven adulteration of Bharangi in Indian herbal commerce with *Clerodendrum infortunatum*, *Premna mucronata*, and other Verbenaceae species, botanical verification is especially difficult and crucial.<sup>[10,27]</sup> This authentication issue was specifically addressed by Patel et al. (2014),<sup>[10]</sup> who noted that "plants from many taxa other than *Clerodendrum* but belonging to the family Verbenaceae and a few other plants from different families have been sold in the market under the common name Bharangi" and that "there are certain controversies regarding the identification and authentication of *C. serratum*." Macroscopic morphological verification, microscopic anatomical examination (especially stem cross-section quadrangularity, leaf epidermal features, calcium oxalate crystal distribution in cortex, and root bark anatomy), and TLC and HPLC chromatographic fingerprinting using validated marker compound methods<sup>[8,10,17]</sup> are all necessary for comprehensive authentication.

Acteoside/verbascoside (iridoid glycoside marker), clerodin (diterpenoid marker), hispidulin (flavonoid marker), serratagenic acid (triterpenoid marker), and ursolic acid (hepatoprotective triterpenoid marker) are among the marker compounds for which chemical standardization requires validated quantitative analytical techniques.<sup>[10,15,17]</sup> The pharmacognostic parameters necessary for Bharangi raw medication quality control were established by Patel and Acharya (2012).<sup>[17]</sup> All pharmaceutical-grade Bharangi specifications must include the acceptable limits for heavy metals (Pb < 10 ppm, As < 5 ppm, Cd < 0.3 ppm, Hg < 0.2 ppm), aflatoxins (total < 4 µg/kg), microbial contamination (aerobic bacteria < 10<sup>7</sup> cfu/g), and pesticide residues specified in WHO monographs.<sup>[52]</sup> The importance of standardized cultivation and post-harvest processing protocols as prerequisites for consistent pharmaceutical product development is highlighted by the notable batch-to-batch variability in key phytochemical content observed across plants from various geographic origins, harvesting seasons, and plant parts.<sup>[10,13]</sup>

### 13. Future Research Directions

In order to fully exploit the therapeutic potential of *C. serratum*, there are still significant research gaps that need to be methodically filled despite forty years of expanding scientific examination.<sup>[1,11,13,27]</sup> The most urgent scientific priority is to conduct thorough pharmacokinetic and pharmacodynamic studies in both animal models and healthy human volunteers. These studies should characterize oral bioavailability, plasma protein binding, volume of distribution, CYP450-mediated metabolism, major metabolites, and excretion routes for important marker compounds like acteoside, clerodin, hispidulin, ursolic acid, and serratagenic acid.<sup>[13,54]</sup> Given the extensive usage of Bharangi formulations in conjunction with traditional medications in Ayurvedic therapeutic settings, drug-herb interaction investigations are especially crucial.<sup>[27]</sup>

The top priority for clinical research is multicenter randomized controlled trials that are well-designed and sufficiently powered. The most scientifically convincing initial RCT indications are bronchial asthma, especially mild-to-moderate persistent asthma as an adjuvant to standard therapy<sup>[1,35,36,43]</sup>; hepatoprotection in drug-induced liver injury or viral hepatitis<sup>[10,24,25]</sup>; and allergic rhinitis and perennial sinusitis (strongest combined preclinical and traditional evidence; significant unmet clinical need). A paradigm for RCT design is provided by the Bharangiguda Avaleha pilot clinical research in Tamaka Shwasa patients,<sup>[2,35]</sup> which should be expanded to sufficiently powered confirmatory studies. Methodological standards for such trials are provided by ICMR clinical research frameworks and WHO recommendations.<sup>[52]</sup>

The molecular targets and signaling pathways modulated by *C. serratum* phytoconstituents, both collectively and individually, should be thoroughly characterized by advanced mechanistic research using systems pharmacology, including network pharmacology, molecular docking, MD simulation, and transcriptomic analysis.<sup>[30,47]</sup> The in-silico approach platform for this investigation was developed by Srinath et al. (2020).<sup>[30]</sup> Through semi-synthetic modification, SAR research on iridoid glycosides and neoclerodane diterpenoids could maximize pharmacological action, enhance metabolic stability, and lessen the potential toxicity of lead compounds found in the plant.<sup>[15,47]</sup>

Following Patel et al.<sup>[45]</sup>'s silver nanoparticle anti-mycobacterial success, systematic improvement of nanoparticle formulation parameters, in vivo efficacy tests, and, ultimately, clinical evaluation for drug-resistant tuberculosis management should take place. According to Petrovska,<sup>[1]</sup> this methodical, multidisciplinary translational research approach is necessary for the effective integration of traditional medicinal plants into evidence-based medicine.

#### 14. CONCLUSION

*Clerodendrum serratum* (L.) Moon (Bharangi) is an amazing example of how three millennia of traditional medicine have been combined with a growing body of contemporary biological evidence. Botanical taxonomy,<sup>[10,29,55]</sup> geographic distribution,<sup>[18,28]</sup> ethnomedicinal significance<sup>[2,3,5-7,9,31]</sup> phytochemical composition,<sup>[10,14-18]</sup> pharmacological activities, toxicological profile,<sup>[8,19,34,42]</sup> clinical evidence,<sup>[13,18,35]</sup> and standardization.<sup>[48]</sup>

The plant's diverse pharmacological profile is supported by its phytochemical richness, which includes iridoid glycosides like acteoside and serratoside<sup>[10,15]</sup>; structurally distinct neoclerodane diterpenoids led by clerodin (15,30); flavonoids like hispidulin, cleroflavone, apigenin, and scutellarein<sup>[14,15,17,60]</sup>; phenolic acids; ursolic and oleanolic acids; D-mannitol; saponins; and tannins.<sup>[10,14,16]</sup> A pharmacological portfolio of remarkable breadth and translational relevance includes anti-inflammatory and analgesic action through COX/LOX inhibition,<sup>[19-21,45]</sup> antihistaminic mast cell stabilization,<sup>[22,23,33,37]</sup> hepatoprotection via ursolic acid and GSH pathway modulation,<sup>[10,24,25]</sup> broad-spectrum antimicrobial and antiasthmatic effects,<sup>[33,35,36]</sup> immunomodulation,<sup>[22,46]</sup> antioxidant defense enhancement,<sup>[38,40]</sup> and promising antiviral and anticancer molecular docking findings.<sup>[28,30]</sup>

The plant's traditional therapeutic use is supported by its good acute toxicity profile, with an LD50 above 2000 mg/kg.<sup>[17,27]</sup> However, uterotonic characteristics at large dosages clearly indicate contraindication during pregnancy.<sup>[4,8]</sup>

The most urgent issue is still clinical validation: the main obstacle to evidence-based pharmaceutical development is the lack of sufficiently powered, standardized RCTs, which is exacerbated by the absence of thorough pharmacokinetic data<sup>[13,54]</sup> and globally accepted pharmacopoeial standards outside of the Ayurvedic Pharmacopoeia of India.<sup>[8]</sup> A recent review by Dongare et al.<sup>[50]</sup> confirmed the importance of *C. serratum* in current phytomedicine research. Phenolic and flavonoid-rich fractions of Indian medicinal plants have strong antioxidant activity that is closely related to *C. serratum* hepatoprotective uses, as Choudhary and Swarnkar<sup>[61]</sup> showed. The fundamental saponin reference work of Hostettmann and Marston,<sup>[59]</sup> whose immunomodulatory processes function in *C. serratum* antiasthmatic and anticomplement action,<sup>[22,35]</sup> supports the saponin-based pharmacology. In Indian pharmacognosy, the Chatterjee and Pakrashi Treatise<sup>[12]</sup> offers reliable classical evidence on *C. serratum*. The most promising immediate translational options include the green manufacturing of anti-mycobacterial nanoparticles,<sup>[45]</sup> molecular docking against COVID-19 targets,<sup>[30]</sup> and documented antiasthmatic clinical evidence.<sup>[2,35]</sup> In conclusion, Bharangi, a plant trusted by healers

worldwide for three millennia, has every chance of providing proven therapeutic contributions to contemporary respiratory medicine, anti-infective therapy, and integrative oncology with methodical scientific investment in clinical research and pharmaceutical standardization.<sup>[1,13,55]</sup>

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