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A COMPREHENSIVE REVIEW ON KOKILAKSHA: BRIDGING TRADITIONAL KNOWLEDGE AND MODERN MOLECULAR UNDERSTANDING OF INFLAMMATION

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ABSTRACT

Hygrophila auriculata (syn. *Asteracantha longifolia*) commonly known as Kokilaksha is described in Ayurveda as a shothahara dravya (anti-inflammatory agent) along with diuretic, hepatoprotective, and aphrodisiac properties. Its pharmacological potential is attributed to diverse phytoconstituents including terpenoids, sterols, flavonoids, and phenolic acids. Scientific validation of these compounds is essential to bridge Ayurvedic claims with modern pharmacology. Phytochemical data of *H. auriculata* were retrieved from the IMPPAT (Indian Medicinal Plants, Phytochemistry and Therapeutics) database. Each entry was identified with its unique IMPHY code and linked to PubChem Compound Identifier (CID). A literature survey was subsequently performed to validate the anti-inflammatory potential of these compounds using experimental and review-based evidence. Data were compiled into a consolidated table highlighting plant part, compound identity, and reported pharmacological activity. IMPPAT screening identified multiple bioactives such as lupeol, betulin, β-sitosterol, stigmasterol, lupenone, apigenin derivatives, nicotinic acid, and fatty acids like oleic and linoleic acid and they exhibit potent anti-inflammatory and immunomodulatory effects through NF-κB and COX pathway inhibition. Apigenin-7-O-glucuronide and cosmosiin demonstrated suppression of inflammatory mediators in cellular and animal models. Betulin showed COX-modulating properties, while oleic and linoleic acids contributed to immune regulation. Ascorbic acid provided indirect anti-inflammatory effects via antioxidant activity. The integration of IMPPAT data with published pharmacological evidence validates the traditional use of Kokilaksha as an anti-inflammatory drug. This database-driven and literature-supported approach highlights its phytoconstituents as promising leads for anti-inflammatory drug discovery. The findings reinforce the relevance of Ayurvedic herbs in modern therapeutics and provide a rational basis for further *in silico, in vitro,* and *in vivo* studies

Keywords: Anti-inflammatory activity, apigenin, Ayurveda, β-sitosterol, betulin, drug discovery, IMPPAT database, Kokilaksha, lupeol, phytoconstituents, stigmasterol

INTRODUCTION

Inflammation is a fundamental biological response aimed at protecting the body against infections, toxins, and injury. While acute inflammation is beneficial, uncontrolled or chronic inflammation is associated with various pathological conditions, including arthritis, cardiovascular diseases, neurodegeneration, and metabolic disorders. Current anti-inflammatory drugs, such as non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, provide symptomatic relief but are often limited by adverse effects during long-term use. This highlights the need for safer, plant-based alternatives that offer effective modulation of inflammatory pathways.[1] Ayurveda, the traditional system of Indian medicine, has long emphasized the therapeutic use of medicinal plants for inflammation. *Hygrophila auriculata* (syn. *Asteracantha longifolia*, commonly known as Kokilaksha) is a well-documented herb classified as shothahara dravya (anti-inflammatory agent). In addition, it is traditionally recognized for its diuretic, hepatoprotective, and aphrodisiac properties.[2] Phytochemical studies on *H. auriculata* have reported the presence of diverse secondary metabolites, including alkaloids, terpenoids, sterols, flavonoids, phenolic acids, and fatty acids, many of which are associated with anti-inflammatory and antioxidant activities.[3] With the advancement of phytochemical informatics, resources such as the IMPPAT (Indian Medicinal Plants, Phytochemistry and Therapeutics) database provide a systematic catalogue of phytoconstituents with therapeutic potential. Integrating IMPPAT-derived phytochemicals with experimental evidence offers a rational approach to validate the pharmacological basis of Ayurvedic claims.[4] The present work compiles phytoconstituents of *H. auriculata* from IMPPAT and corroborates their anti-inflammatory potential through a structured literature review. By mapping traditional knowledge with modern evidence, this study aims to reaffirm Kokilaksha's role as a promising source of natural anti-inflammatory agents and establish a framework for future drug discovery research

Data Source and Retrieval

Phytochemical information of *Hygrophila auriculata* (Kokilaksha) was retrieved from the IMPPAT (Indian Medicinal Plants, Phytochemistry and Therapeutics) database (https://cb.imsc.res.in/imppat). IMPPAT is a curated resource that provides unique identifiers (IMPHY codes), plant part associations, and references to phytoconstituents from Indian medicinal plants. All phytochemicals reported for different plant parts of *H. auriculata* (roots, leaves, seeds, flowers, and whole plant) were compiled.

Phytochemical Identification and Standardization
Each phytochemical obtained from IMPPAT was cross-verified with PubChem (https://pubchem.ncbi.nlm.nih.gov/) to retrieve PubChem Compound Identifiers (CID), molecular structure, and relevant pharmacological notes. This step ensured standardization of compound identity and eliminated redundancy across synonyms.

Evidence-Based Validation of Anti-Inflammatory Activity
A comprehensive literature search was conducted using PubMed, Scopus, ScienceDirect, and Google Scholar databases. The keywords used included "compound name + anti-inflammatory activity", "compound name + COX inhibition", and "compound name + NF-κB modulation". Experimental studies, reviews, and clinical reports that validated the anti-inflammatory potential of the identified phytochemicals were included.

Data Compilation
All validated phytochemicals were tabulated with details including IMPPAT ID, compound name, plant part, PubChem CID and supporting evidence of anti-inflammatory activity. The flow diagram illustrates the sequential steps adopted in this study. Phytochemicals of *Hygrophila auriculata* were initially retrieved from the IMPPAT database, followed by cross-verification with PubChem for structural and identification details. Subsequently, a systematic literature survey was conducted to validate the anti-inflammatory activity of the retrieved compounds. The final evidence was organized into a consolidated table, linking each phytochemical with its IMPPAT ID, PubChem CID, plant part and documented pharmacological evidence.

Phytochemical identification
Phytochemical profiling of *Hygrophila auriculata* (Kokilaksha) using the IMPPAT database yielded a diverse set of secondary metabolites distributed across various plant parts including roots, seeds, leaves, flowers, and the whole plant. The table lists the compound name, plant part of origin, IMPPAT ID, PubChem CID, and reported evidence of pharmacological activity. "–" indicates that no PubChem CID or direct evidence was available for the compound. A total of 31unique phytoconstituents were identified, each represented by an IMPPAT identifier. (IMPHY code). (Table 1) Through cross-linking with PubChem, literature evidence, and activity reports, IMPPAT enables validation of traditional claims of Kokilaksha by highlighting anti-inflammatory, antioxidant, hepatoprotective, and immunomodulatory phytoconstituents.

Kokilaksha
Ayurveda describes Kokilaksha *(Asteracantha longifolia Nees*, syn. *Hygrophila auriculata* T. Anders.) as a versatile medicinal plant with diuretic, aphrodisiac, hepatoprotective, and anti-inflammatory actions. Classical Ayurvedic texts provide detailed descriptions of the pharmacological properties (karma*)* of *Asteracantha longifolia* (Kokilaksha). Various Nighantu and Samhita sources highlight its diuretic (Mutra-janana), aphrodisiac (Vrishya), galactagogue (Stanyajanana), tonic (Balya), and other therapeutic actions. Table 2 compiles these references from authoritative Ayurvedic texts including Bhavaprakasha Nighantu, Raja Nighantu, Nighantu Ratnakara, Kaiyyadeva Nighantu, Vangasena, and Harita Samhita.

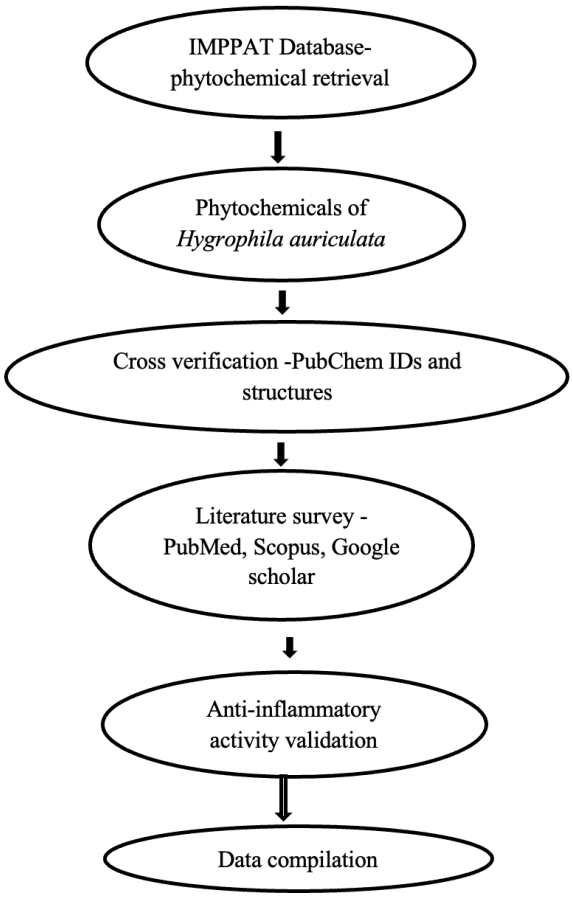

Figure 1: Methodology diagram

Table 1: Phytochemicals identified from *Hygrophila auriculata* (Kokilaksha) retrieved from the IMPPAT database

Indian medicinal plant	Plant part	IMPPAT Phytochemical identifier	Phytochemical name
Hygrophila auriculata	Flower	IMPHY011710	Apigenin-7-o-glucuronide
Hygrophila auriculata	Flower	IMPHY012719	Cosmosiin
Hygrophila auriculata	Leaf	IMPHY007357	Nicotinic acid
Hygrophila auriculata	Root	IMPHY004271	Betulin
Hygrophila auriculata	Root	IMPHY007080	3-Methylnonacosane
Hygrophila auriculata	Root	IMPHY011471	Lupenone
Hygrophila auriculata	Root	IMPHY012473	Lupeol
Hygrophila auriculata	Root	IMPHY014836	beta-Sitosterol
Hygrophila auriculata	Root	IMPHY014842	Stigmasterol
Hygrophila auriculata	Seed	IMPHY004271	Betulin
Hygrophila auriculata	Seed	IMPHY004631	Stearic acid
Hygrophila auriculata	Seed	IMPHY007327	Palmitic acid
Hygrophila auriculata	Seed	IMPHY007357	Nicotinic acid
Hygrophila auriculata	Seed	IMPHY011797	Oleic acid
Hygrophila auriculata	Seed	IMPHY012029	Sterol
Hygrophila auriculata	Seed	IMPHY014990	Linoleic acid
Hygrophila auriculata	Seed	IMPHY015116	D-Xylose
Hygrophila auriculata	whole plant	IMPHY002074	Isoflavone glycoside
Hygrophila auriculata	whole plant	IMPHY009413	Triacontane
Hygrophila auriculata	whole plant	IMPHY014842	Stigmasterol
Hygrophila auriculata	whole plant	IMPHY004271	Betulin
Hygrophila auriculata	whole plant	IMPHY004631	Stearic acid
Hygrophila auriculata	whole plant	IMPHY006362	Ascorbic acid
Hygrophila auriculata	whole plant	IMPHY007080	3-Methylnonacosane
Hygrophila auriculata	whole plant	IMPHY007327	Palmitic acid
Hygrophila auriculata	whole plant	IMPHY011797	Oleic acid
Hygrophila auriculata	whole plant	IMPHY012473	Lupeol
Hygrophila auriculata	whole plant	IMPHY013730	Rizolipase
Hygrophila auriculata	whole plant	IMPHY014842	Stigmasterol
Hygrophila auriculata	whole plant	IMPHY014990	Linoleic acid
Hygrophila auriculata	whole plant	IMPHY015116	D-Xylose

Table 2: Classical Ayurvedic references on *Asteracantha longifolia (*Kokilaksha*)* and their described karmas (functions)

Nighantu / Samhita	Karma (Action)
Bhavaprakasha Nighantu[5]	Mutra-janana (Diuretic), Shukra-shodhana (Detoxifies semen/sperms), Stanya-janana (Galactagogue), Santarpana (Gratifying), Balya (Tonic), Vrishya (Aphrodisiac)
Raja Nighantu[6]	Veeryavardhaka (Increases sperm count), Balakaraka (Tonic), Ruchivardhaka (Improves hunger), Santarpankaraka (Gratifying)
Madanapala Nighantu[7]	Vrishya (Aphrodisiac), Grahaka (Prevents excretion of stool), Garbhasthapaka (Helps in fertilization), Malastambhakara (Prevents expulsion of stool), Shothapaha (Reduces swelling), Shoolapaha (Analgesic), Vishapaha (Reduces toxicity), KaphaVatakara (Increases Vata and Kapha)
Kaiyyadeva Nighantu[8]	Shukrajanana (Increases sperm count)
Hareetakyadi Nighantu[9] Sodhala Nighantu[10]	Vrishya (Aphrodisiac)

General Phytochemical Profile

Preliminary phytochemical investigations of Kokilaksha across roots, leaves, aerial parts, and seeds have consistently revealed a wide spectrum of secondary metabolites including alkaloids, glycosides, steroids, terpenoids, saponins, tannins, flavonoids and phenolic compounds. [11,12]

a) Terpenoids and Sterols

The most extensively studied phytochemicals are triterpenoids and phytosterols such as lupeol, betulin, β-sitosterol, and stigmasterol. [12]

- Lupeol is a pentacyclic triterpene known for its anti-inflammatory hepatoprotective, and nephroprotective effects. Studies on root extracts have shown lupeol to be a major marker compound, quantified using HPTLC and HPLC methods.
- Stigmasterol and β-sitosterol exhibit hypocholesterolemic, antioxidant, and anti-inflammatory activities, being reported from both root and leaf fractions. [13]
- Betulin has been identified as a minor constituent, contributing to antioxidant and antimicrobial effects.[13]

b) Phenolics and Flavonoids

- Kokilakṣha contains abundant phenolic acids (gallic acid, caffeic acid) and flavonoids[15](quercetin, luteolin, apigenin derivatives). [14]
- Gallic acid has strong antioxidant, hepatoprotective, and anti-diabetic properties. Quercetin is a well-characterized flavonoid with broad-spectrum pharmacological roles in inflammation, diabetes, and cardiovascular health.[16]

Validated HPTLC methods have quantified gallic acid and quercetin as quality-control markers in root and leaf extracts.[17] For consistency in pharmacological studies, HPTLC and HPLC marker quantification has been standardized for lupeol, stigmasterol, β-sitosterol, betulin, gallic acid, and quercetin[12] Leaf extracts are comparatively higher in β-sitosterol and flavonoids[12]. Standardization through these markers ensures reproducibility in therapeutic applications and provides a chemical basis for classical formulations like Kokilakṣhaka niryuham.

c) Other Phytoconstituents
Phytochemical analysis has also revealed the presence of alkaloids with reported hepatoprotective action.[18] Fatty acids such as palmitic and linoleic acid identified by GC-MS, contributing to nutritive and antioxidant potential. [19]

Modern Understanding of Inflammatory Mechanisms
Several molecular pathways are responsible for managing inflammation. These pathways either amplify or suppress the inflammatory responses. Major among them is:

Nuclear Factor kappa B (NF-κB) Pathway
One of the key transcription factors in inflammation. Activated by TNF-α, IL-1, or microbial products, it upregulates inflammatory genes. It is activated through TLRs and cytokine receptors, leading to the degradation of IκB inhibitors. This allows NF-κB to translocate into the nucleus and activate transcription of inflammatory genes such as TNFα, IL-1β, and IL-6 [20,21]

JAK-STAT Pathway
Involved in the signaling of many cytokines. Activated by cytokines such as interferons and interleukins, the JAK/STAT pathway transmits extracellular signals to the nucleus, influencing cell proliferation, differentiation, and cytokine production. This pathway is particularly active in autoimmune diseases. [22]

MAPK Pathways
The Mitogen-Activated Protein Kinase (MAPK) pathway involves a series of kinases— ERK, JNK, and p38—that regulate gene expression in response to stress signals and inflammatory stimuli. This pathway enhances cytokine release, leukocyte activation, and tissue remodeling. [23]

Inflammasomes
Inflammasomes are intracellular complexes (e.g., NLRP3) that sense microbial infections or cellular stress. Once activated, they promote the cleavage of pro-caspase-1 into active caspase-1, which processes pro-IL-1β and pro-IL-18 into their active forms, intensifying the inflammatory response. [24]

Arachidonic Acid Pathway in Inflammation
The arachidonic acid pathway is central to the production of lipid-based inflammatory mediators. Upon cellular activation, phospholipase A2 releases arachidonic acid from membrane phospholipids. It is then metabolized via two primary enzymatic pathways. [25]

Cyclooxygenase (COX) Pathway
Produces prostaglandins and thromboxanes. The COX-2 isoform is inducible and upregulated during inflammation, leading to the synthesis of PGE2 and other prostanoids that contribute to pain, fever, and edema. [26]

Lipoxygenase (LOX) Pathway
Generates leukotrienes, such as LTB4, that increase chemotaxis and vascular permeability, particularly important in allergic and asthmatic reactions. This pathway plays a pivotal role in chronic inflammatory diseases and is a therapeutic agent. [26]

Table 3: IMPPAT-derived phytochemicals of *Hygrophila auriculata* and their validated anti-inflammatory activities

IMPPAT ID	Compound Name	Plant Part	PubChem CID	Evidence (Activity Proof)
IMPHY012029	Sterol (generic)	Aerial/Seed	–	General plant sterols reported with anti-inflammatory effects[27]
IMPHY011710	Apigenin-7-O-glucuronide	Flower	44257800	Apigenin derivatives reduce LPS-induced inflammation in vitro.[28]
IMPHY012719	Cosmosiin (Apigenin-7-glucoside)	Flower	5280704	Apigenin-7-glucoside shows anti-inflammatory effects in colitis and macrophage models.[29]
IMPHY007357	Nicotinic acid (Niacin)	Leaf/Seed	938	Niacin activates GPR109A, producing anti-inflammatory effects (reviews & experiments).[30]
IMPHY004271	Betulin	Root/Seed	72326	Betulin and betulinic acid show anti-inflammatory and COX-modulating effects.[31]
IMPHY007080	3-Methylnonacosane	Root	85691	Reported as volatile alkane in phytochemical surveys; limited direct activity reports.
IMPHY011471	Lupenone	Root	92158	Lupane triterpenoid with documented anti-inflammatory potential.[32]
IMPHY012473	Lupeol	Root/Whole plant	259846	Well-documented anti-inflammatory, antioxidant, and wound-healing activities.[32]
IMPHY014836	β-Sitosterol	Root	222284	Strong anti-inflammatory, immunomodulatory effects.[33]
IMPHY014842	Stigmasterol	Root/Whole plant	5280794	Anti-inflammatory, anti-osteoarthritic, NF-κB and NLRP3 pathway inhibition.[34]
IMPHY004631	Stearic acid	Seed	5281	Fatty acid, context-dependent; sometimes neutral/pro-inflammatory.[35]
IMPHY007327	Palmitic acid	Seed	985	Saturated fatty acid; generally pro-inflammatory in excess.[35]
IMPHY011797	Oleic acid	Seed	445639	Widely studied anti-inflammatory and immune-modulatory effects.[36]
IMPHY014990	Linoleic acid	Seed	–	Polyunsaturated fatty acid; dietary studies link to immune modulation[36]
IMPHY015116	D-Xylose	Seed	135191	Monosaccharide, reported in phytochemical surveys; limited direct activity.[37]
IMPHY002074	Isoflavone glycoside (generic)	Whole plant	–	Isoflavone glycosides widely reported with antioxidant/anti-inflammatory effects.[38]
IMPHY009413	Triacontane	Whole plant	12535	Long-chain alkane, reported in phytochemical surveys; limited activity data.[39]
IMPHY006362	Ascorbic acid (Vitamin C)	Whole plant	54670067	Antioxidant; reduces inflammation indirectly via ROS scavenging.

Integration of IMPPAT Phytochemicals and Literature Evidence

The retrieved compounds included terpenoids (lupeol, lupenone, betulin), sterols (β-sitosterol, stigmasterol, generic sterols), flavonoids (apigenin-7-O-glucuronide, cosmosiin), phenolics (ascorbic acid), alkaloid-related metabolites (nicotinic acid), fatty acids (oleic, linoleic, palmitic, stearic), carbohydrates (D-xylose), and hydrocarbons (triacontane, 3-methylnonacosane). After identifying the phytoconstituents of *Hygrophila auriculata* (Kokilaksha) from the IMPPAT (Indian Medicinal Plants, Phytochemistry and Therapeutics) database, a focused literature survey was carried out to substantiate their reported biological activities. Each phytochemical retrieved from IMPPAT was cross-referenced with PubChem CID and published evidence, particularly emphasizing anti-inflammatory relevance. Each phytochemical was further validated through published literature evidence for its anti-inflammatory activity, including in *vitro, in vivo,* or review-based reports. The following table (Table 3) consolidates this information, linking Kokilaksha's phytochemicals to their experimentally validated pharmacological actions. This approach not only reaffirms the Ayurvedic claim of Kokilaksha as a Shothahara dravya (anti-inflammatory drug) but also strengthens the scientific rationale for its therapeutic applications.

DISCUSSION

The present review integrates traditional Ayurvedic knowledge with modern phytochemical evidence, providing a comprehensive perspective on the anti-inflammatory potential of *Hygrophila auriculata* (Kokilaksha). Classical Ayurvedic texts recognize Kokilaksha as a shothahara dravya (anti-inflammatory agent) with additional therapeutic properties such as diuretic, hepatoprotective, and aphrodisiac effects. These traditional claims are supported by the diverse spectrum of secondary metabolites identified across roots, leaves, seeds, flowers, and whole plant parts. Phytochemical profiling using the IMPPAT database revealed a repertoire of 31 unique phytoconstituents, including terpenoids, sterols, flavonoids, phenolics, fatty acids, monosaccharides, and hydrocarbons.

Terpenoids and sterols such as lupeol, lupenone, betulin, β-sitosterol, and stigmasterol emerged as major anti-inflammatory agents. Lupeol has been extensively studied for its ability to modulate NF-κB and COX pathways, antioxidant capacity, and wound-healing properties, corroborating its potential as a multi-target anti-inflammatory compound. Similarly, β-sitosterol and stigmasterol exert immunomodulatory effects, suppressing pro-inflammatory cytokines, inhibiting NF-κB and NLRP3 pathways, and reducing oxidative stress. Betulin and lupenone contribute additionally through COX modulation and general anti-inflammatory actions. Collectively, these triterpenoids and sterols reinforce the rationale for root and leaf fractions being used in classical formulations.

Flavonoids and phenolic acids such as apigenin-7-O-glucuronide, cosmosiin, and ascorbic acid provide complementary anti-inflammatory and antioxidant effects. Apigenin derivatives attenuate LPS-induced inflammatory signaling in vitro and in vivo, reducing cytokine expression and oxidative stress in macrophages and colitis models. Ascorbic acid, though not directly anti-inflammatory, mitigates ROS-mediated activation of NF-κB and MAPK pathways, thereby exerting an indirect anti-inflammatory effect. Isoflavone glycosides, D-xylose, and other phenolic compounds further contribute to antioxidant defense and immune regulation, emphasizing the synergistic nature of plant constituents in modulating inflammation.

Fatty acids identified, including oleic and linoleic acid, are known to influence inflammatory signaling by modulating lipid mediators and immune cell function. Oleic acid exhibits robust anti-inflammatory effects, while linoleic acid serves as a precursor for both pro- and anti-inflammatory eicosanoids, depending on context. In contrast, saturated fatty acids such as palmitic acid may promote inflammation in excess, suggesting that the therapeutic balance of fatty acids in plant extracts is crucial.

The integration of IMPPAT database mining with literature validation provides a systematic framework to map the molecular basis of Ayurvedic claims. Unlike traditional documentation, this approach enables identification of specific bioactive phytochemicals, their plant part distribution, and molecular targets. By linking traditional descriptions with modern molecular pathways, such as NF-κB, MAPK, JAK-STAT, inflammasomes, and COX/LOX signaling, this study underscores the multi-target pharmacology of Kokilaksha and its potential relevance in managing chronic inflammatory conditions.

Furthermore, the compiled table of phytochemicals serves as a resource for future experimental work, including in silico docking, in vitro bioassays, and in vivo models. It highlights both well-characterized compounds (e.g., lupeol, β-sitosterol, stigmasterol) and less-studied molecules (e.g., D-xylose, triacontane), providing opportunities for novel pharmacological investigations. This database-driven strategy emphasizes a rational, evidence-based approach to herbal drug discovery, bridging classical Ayurveda and contemporary biomedical science.

CONCLUSION

This review consolidates the traditional knowledge with modern molecular understanding of *Hygrophila auriculata* (Kokilaksha*),* demonstrating its broad-spectrum anti-inflammatory potential. By systematically mining the IMPPAT database and validating compounds through published literature, the study identifies key phytochemicals—including terpenoids, sterols, flavonoids, phenolics, fatty acids, and glycosides—that modulate multiple inflammatory pathways. Terpenoids and sterols (lupeol, lupenone, betulin, β-sitosterol, stigmasterol) are major anti-inflammatory constituents targeting NF-κB, COX, and NLRP3 pathways. Flavonoids and phenolics (apigenin derivatives, cosmosiin, ascorbic acid) complement anti-inflammatory activity through ROS scavenging, cytokine suppression, and antioxidant effects. Fatty acids contribute to immune modulation, with oleic and linoleic acids promoting anti-inflammatory responses and palmitic acid requiring cautious interpretation. Integration of traditional Ayurvedic descriptions with modern molecular evidence provides a compelling rationale for its therapeutic application and validates its inclusion in anti-inflammatory formulations. This approach demonstrates that efficacy of Kokilaksha is not solely dependent on individual compounds but on the synergistic action of multiple phytoconstituents, aligning with the holistic principles of Ayurveda. The findings underscore its potential as a source for novel anti-inflammatory drug leads and support further in silico, in vitro, and in vivo research to explore mechanistic insights and therapeutic applications. Ultimately, this review bridges the gap between ancient herbal wisdom and modern pharmacology, reinforcing the value of traditional medicinal plants in contemporary drug discovery and inflammatory disease management.

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