Andrographis paniculata: India's antiviral and immune-boosting answer to rare disease therapeutics


Bhagyashree C. Wagh, Divya Ashok Kulkarni*
Department of Pharmacy Practice,
Shree Chanakya Education Society's Indira College of Pharmacy, Pune-411033
Email: kulkarni.divya13@gmail.com

Abstract
India's phytopharmaceutical industry, built on vast biodiversity and traditional medicinal practices, has spotlighted *Andrographis paniculata* (Kalmegh), known for its potential in rare disease treatment. Traditionally used in Ayurveda and Southeast Asian medicine for ailments like fever, malaria, and diarrhea, *Andrographis paniculata* contains andrographolide—a bioactive compound with anti-inflammatory, antiviral, and immunomodulatory properties. Andrographolide's immune-modulating, anticancer, antibacterial, hepatoprotective, protozoacidal, and antithrombotic effects render it valuable for synthetic pharmaceutical applications, particularly in autoimmune and tropical diseases, as well as cancer therapies. This article explores *Andrographis paniculata's* journey from traditional use to advanced therapeutic applications, emphasizing pharmacological benefits, rare disease potential, and sustainable cultivation. Challenges such as clinical trials, safety, and intellectual property are also considered, with India positioned as a leader in phytopharmaceutical innovation.

Keywords: *Andrographis* paniculata, Phytopharmaceuticals, Andrographolide

1. Introduction

Phytopharmaceuticals, defined as plant-based medicinal products that meet pharmaceutical standards, are an emerging field in India's healthcare and pharmaceutical landscape. With its diverse flora and extensive traditional knowledge, India is uniquely positioned to develop and produce phytopharmaceuticals that address the unmet needs of modern medicine, particularly in the realm of rare diseases (1). Rare diseases, often characterized by limited treatment options and high treatment costs, present significant challenges to healthcare systems (2). Phytopharmaceuticals offer a cost-effective, natural alternative to synthetic drugs, and *Andrographis paniculata* (AP) is a prime candidate in this sector (3).

Given its rich pharmacological profile, *Andrographis* is being studied for its potential to treat conditions ranging from autoimmune disorders to rare infectious diseases (4). India's government has recognized the potential of phytopharmaceuticals and introduced policies to encourage their development and production (5). The Indian Council of Medical Research (ICMR), in collaboration with pharmaceutical companies, is conducting research to bring traditional remedies like *Andrographis* into mainstream therapeutic use (6).

2. *Andrographis paniculata*: From traditional use to synthetic phytopharmaceuticals

Andrographis paniculata, traditionally used for its anti-inflammatory, antipyretic, and hepatoprotective properties, has long been a staple of Ayurvedic and Traditional Chinese Medicine (TCM)(7). However, the plant's transition from a traditional remedy to a modern synthetic phytopharmaceutical involves isolating and synthesizing its bioactive components, primarily andrographolide.

2.1. Botanical profile

Scientific Classification (8):
Kingdom: Plantae
Family: Acanthaceae
Genus: *Andrographis*
Species: A. *paniculata*

2.2. Active phytochemicals

The primary active compound in *Andrographis paniculata* is andrographolide, a diterpenoid lactone that exhibits potent anti-inflammatory, antiviral, and immunomodulatory activities. Other compounds, including neoandrographolide, andrograpanin, and 14-deoxyandrographolide, contribute to the plant's therapeutic effects (9).

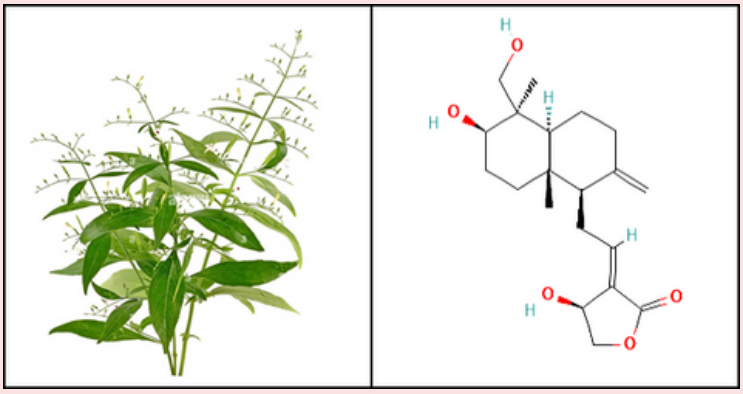

Figure 1. Image of *Andrographis paniculata* plant and chemical structure of andrographolide

2.3. Synthetic derivatives and formulations

To improve the pharmacokinetics of andrographolide, synthetic derivatives are being developed. These derivatives enhance the bioavailability and stability of the compound, making it more effective in treating diseases with chronic or acute inflammatory components. For example, andrographolide nanoparticles have been explored for improved drug delivery and controlled release, particularly in autoimmune and viral diseases (10).

2.4. Bioavailability of andrographolide

Andrographis paniculata, has poor oral bioavailability due to its low aqueous solubility and high lipophilicity**.** This results in limited absorption in the gastrointestinal tract. It is absorbed quickly, reaching maximum concentration in the blood within 1.36 hours, after which it binds extensively to blood proteins and redistributes between tissues. Metabolism of andrographolide occurs mainly in the liver, and its elimination happens through urine and feces**,** with the drug being undetectable after 8 hours (11).

2.5. Pharmacology of andrographolide

Andrographolide works by modulating immune responses through the inhibition of nuclear factor-kappa B (NF-κB), a key regulator of inflammatory cytokines. By downregulating pro-inflammatory cytokines like TNF-α, IL-1β, and IL-6, andrographolide can suppress inflammatory responses, making it a potential therapeutic agent for diseases where inflammation is a primary pathological feature (12).

3. Therapeutic potential of *A. paniculata* in rare autoimmune and viral diseases

3.1 Autoimmune disorders

AP has shown significant potential in treating autoimmune disorders, where the immune system mistakenly attacks healthy tissues. Multiple Sclerosis (MS) and Lupus (SLE) are two rare autoimmune diseases where current treatment options are limited, expensive, and often come with severe side effects. Research indicates that andrographolide's ability to suppress the overactivation of immune cells and inflammatory pathways may offer a new therapeutic avenue for these conditions (13).

In MS, a neurodegenerative autoimmune disorder, andrographolide has been observed to reduce neuronal inflammation and protect the central nervous system from damage. Similarly, in Lupus, andrographolide's immune-modulating properties could help control flares and reduce systemic inflammation, a hallmark of the disease (14).

3.2. Cystic fibrosis

Cystic fibrosis, a rare genetic disorder affecting the lungs and digestive system, is characterized by excessive inflammation and mucus buildup in the respiratory tract. Recent studies suggest that andrographolide could mitigate the inflammatory response in the lungs and improve respiratory function, offering potential relief to cystic fibrosis patients (12).

3.3. Tropical diseases

The antimicrobial and antiviral properties of AP make it a candidate for treating rare tropical diseases, such as Leishmaniasis and Dengue fever. Its antiviral mechanisms, which inhibit viral replication and reduce virus-induced inflammation, could be valuable in addressing these neglected tropical diseases (14).

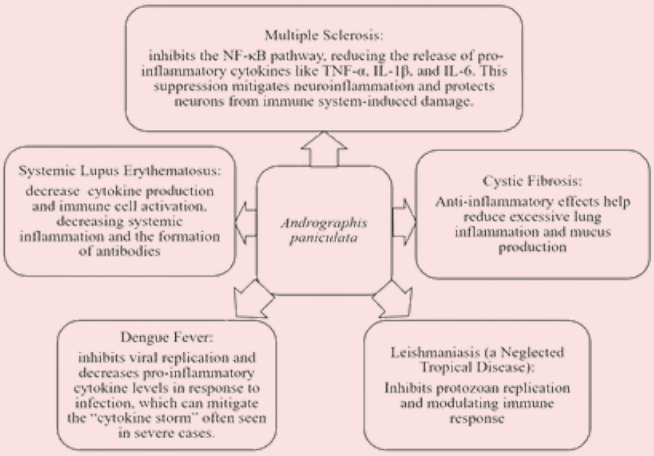

Figure 2. Mechanism of action of *Andrographis paniculata* in various diseases (12-15).

3.4. Cancer therapy

Emerging research also points to the anticancer potential of andrographolide, particularly in inhibiting cancer cell proliferation and inducing apoptosis. These effects are primarily mediated through the suppression of NF-κB signaling and the activation of pro-apoptotic pathways. In addition to targeting multiple pathways to eliminate cancer cells, andrographolide demonstrates a protective effect on normal cells, reducing treatment-induced toxicity-a contrast to its action on cancer cells. This unique profile makes it a promising candidate for further study. Moreover, semi-synthetic analogues of andrographolide have been developed, with some showing significant anti-cancer potential.*Andrographis* may offer an adjunct or alternative therapy for cancers with limited treatment options (15).

Table 1. Key therapeutic mechanisms and clinical applications of *A. paniculata*

S.No.	Action	Mechanism of Action	Biological Target	Clinical Applications	Ref.
1	Antiviral Activity	Inhibits viral entry and replication processes, reduces viral protein synthesis, and interferes with virus maturation stages.	Viral proteases (e.g., 3CLpro in SARS-CoV-2)	SARS-CoV-2, Dengue, Influenza A	(14)
2	Anti-Inflammatory Action	Suppresses NF-κB pathway, reducing pro-inflammatory cytokines (e.g., TNF-α, IL-6, IL-1β) and minimizing immune overactivation.	F-κB, MAPK, cytokine signaling	Inflammatory diseases, Cytokine storm reduction, COVID-19, autoimmune disorders	(13)

3	Immunomodulation	Balances immune responses by modulating Th1/Th2 pathways, reducing cytokine storm.	Immune cells (T-cells, macrophages)	Autoimmune diseases, respiratory infections	(13,14)
4	Antioxidant Activity	Reduces oxidative stress by increasing antioxidant enzyme levels, like glutathione peroxidase, and scavenging free radicals.	Reactive oxygen species (ROS)	Cancer, chronic infections, cardiovascular health	(14,15)
5	Apoptosis Induction in Cancer	Activates caspase-dependent pathways, leading to programmed cell death in tumor cells.	Caspases, Bcl-2 family proteins	Targeted cancer therapy, especially hepatocellular carcinoma	(15)
6	Antibacterial Action	Disrupts bacterial cell wall synthesis and inhibits key bacterial enzymes.	Bacterial enzymes (e.g., β-lactamase)	Respiratory, gastrointestinal, and skin infections	(14)

4. Clinical evidence and pharmacovigilance: ensuring efficacy and safety

Clinical trials are crucial in transitioning AP from a traditional remedy to a scientifically validated treatment for rare diseases. In recent years, there have been several clinical trials evaluating its efficacy in conditions like autoimmune diseases, tropical infections, and even cancer (3). Early-phase trials show promise, particularly in reducing systemic inflammation and modulating immune responses, but larger studies are required to confirm these findings (16).

4.1. Pharmacovigilance and safety

Safety is a paramount concern, especially when treating rare diseases where patients often have complex medical conditions. Pharmacovigilance systems must be put in place to monitor the long-term effects of *Andrographis*-based treatments. While generally considered safe at traditional doses, higher doses or long-term use of andrographolide may cause adverse effects, including gastrointestinal discomfort and allergic reactions. Ensuring proper dosing and formulation will be key to minimizing risks (17).

4.2. Nanotechnology-enhanced drug delivery for *Andrographis paniculata*

Nanotechnology offers innovative solutions to improve the delivery of andrographolide (18). Andrographolide-loaded nanoparticles and liposomal formulations are being researched to enhance drug delivery, improve bioavailability, and target specific tissues. These technologies hold promise for more effective and safer administration of *Andrographis*-derived therapies in clinical settings (19).

5. Sustainable cultivation and large-scale production in India

AP is typically cultivated in tropical and subtropical regions of India. The plant thrives in well-drained soils with sufficient moisture and is primarily grown from seeds. Optimal planting occurs between May and July, with recommended spacing of 30 cm x 15 cm to achieve high density and optimal yield. The aerial parts of the plant, particularly the leaves, are harvested between 110 to 130 days after sowing, as they contain the highest concentration of andrographolide, the bioactive compound responsible for the plant's therapeutic properties (20).

As the demand for AP-based drugs grows, ensuring sustainable cultivation becomes critical. India, where the plant grows abundantly, has the potential to become a global supplier of raw materials for pharmaceutical production. Sustainable farming practices not only protect biodiversity but also ensure that large-scale production can meet the needs of the pharmaceutical industry (21).

The Indian government has already initiated programs to promote the cultivation of medicinal plants, including *Andrographis*, under the National Medicinal Plants Board (NMPB). These initiatives focus on organic farming, soil conservation, and biodiversity protection to support long-term sustainability (22).

6. Economic and ecological importance of *Andrographis paniculata* for India

Large-scale cultivation of AP presents significant economic opportunities for rural communities in India. The economic viability of growing *Andrographis*, combined with its ecological benefits, such as promoting soil health and preventing erosion, makes it an ideal candidate for sustainable agriculture (23).

7. Global market opportunities and India's role in *A. paniculata* leadership

The global phytopharmaceutical market is projected to grow exponentially, driven by the increasing demand for natural and plant-based therapies. India is uniquely positioned to become a global leader in the production and export of*Andrographis*-based products, particularly for rare diseases (21).

7.1. Export potential of *Andrographis paniculata*

Countries facing challenges in treating rare diseases, especially in regions with tropical climates, may benefit from importing *Andrographis*-derived drugs. India's ability to provide high-quality, affordable phytopharmaceuticals could make it a key player in the global healthcare market.

7.2. Intellectual property challenges

Securing intellectual property (IP) rights for synthetic derivatives of andrographolide is crucial for India to maintain a competitive edge in the global market. Although traditional knowledge cannot be patented, the process of isolating, synthesizing, and modifying andrographolide (24).

8. Conclusion

Andrographis paniculata emerges as a compelling candidate for treating rare diseases, holding significant promise on both national and global fronts. India's rich agricultural heritage and advanced pharmaceutical capabilities position it to lead the development of synthetic *Andrographis*-based therapies for orphan drug applications. With its natural antiviral and immune-modulating properties, *Andrographis* could transform the treatment landscape for underserved conditions. By leveraging its therapeutic potential, India can improve global health outcomes and stimulate economic growth through large-scale cultivation and export of these innovative phytopharmaceuticals. Collaborative research efforts will be vital to unlocking the full benefits of this powerful natural remedy.

References

1.Bhatt A. Phytopharmaceuticals: A new drug class regulated in India. PerspectClin Res. 2016;7(2):59–61.

2.Gimenez-Lozano C, Páramo-Rodríguez L, Cavero-Carbonell C, Corpas-Burgos F, López-Maside A, Guardiola-Vilarroig S, et al. Rare Diseases: Needs and Impact for Patients and Families: A Cross-Sectional Study in the Valencian Region, Spain. Int J Environ Res Public Health. 2022 Aug 19;19(16):10366.

3.Intharuksa A, Arunotayanun W, Yooin W, Sirisa-ard P. A Comprehensive Review of Andrographis paniculata (Burm. f.) Nees and Its Constituents as Potential Lead Compounds for COVID-19 Drug Discovery. Molecules. 2022 Jul 13;27(14):4479.

4.Okhuarobo A, EhizogieFalodun J, Erharuyi O, Imieje V, Falodun A, Langer P. Harnessing the medicinal properties of Andrographis paniculata for diseases and beyond: a review of its phytochemistry and pharmacology. Asian Pac J Trop Dis. 2014 Jun;4(3):213–22.

5.Katiyar CK. Phytopharmaceuticals. In: Ghosh D, Mukherjee PK, editors. Natural Medicines [Internet]. 1st ed. Boca Raton : Taylor & Francis, [2019]: CRC Press; 2019 [cited 2024 Oct 24]. p. 223–33. Available from: https://www.taylorfrancis.com/books/9781351741354/chapters/10.1201/9781315187853-12

6.Tandon N, Yadav SS. Contributions of Indian Council of Medical Research (ICMR) in the area of Medicinal plants/Traditional medicine. J Ethnopharmacol. 2017 Feb 2;197:39–45.

7.Jayakumar T, Hsieh CY, Lee JJ, Sheu JR. Experimental and Clinical Pharmacology of Andrographis paniculata and Its Major Bioactive Phytoconstituent Andrographolide. Evid-Based Complement Altern Med ECAM. 2013;2013:846740.

8.Hossain MS, Urbi Z, Sule A, Hafizur Rahman KM. Andrographis paniculata (Burm. f.) Wall. ex Nees: a review of ethnobotany, phytochemistry, and pharmacology. ScientificWorldJournal. 2014;2014:274905.

9.Chao WW, Lin BF. Isolation and identification of bioactive compounds in Andrographis paniculata (Chuanxinlian). Chin Med. 2010 May 13;5:17.

10.Messire G, Rollin P, Gillaizeau I, Berteina-Raboin S. Synthetic Modifications of Andrographolide Targeting New Potential Anticancer Drug Candidates: A Comprehensive Overview. Mol Basel Switz. 2024 Jun 18;29(12):2884.

11.Pandey G, Rao C. Andrographolide: its pharmacology, natural bioavailability and current approaches to increase its content in andrographispaniculata. Int J Complement Altern Med [Internet]. 2018 [cited 2024 Oct 25];11(4). Available from: https://medcraveonline.com/IJCAM/andrographolide-its-pharmacology-natural-bioavailability-and-current-approaches-to-increase-its-content-in-andrographis-paniculata.html

12.Li X, Yuan W, Wu J, Zhen J, Sun Q, Yu M. Andrographolide, a natural anti-inflammatory agent: An Update. Front Pharmacol. 2022;13:920435.

13.Low M, Suresh H, Zhou X, Bhuyan DJ, Alsherbiny MA, Khoo C, et al. The wide spectrum anti-inflammatory activity of andrographolide in comparison to NSAIDs: A promising therapeutic compound against the cytokine storm. Ali A, editor. PLOS ONE. 2024 Jul 17;19(7):e0299965.
14.Hossain S, Urbi Z, Karuniawati H, Mohiuddin RB, MohQrimida A, Allzrag AMM, et al. Andrographis paniculata (Burm. f.) Wall. ex Nees: An Updated Review of Phytochemistry, Antimicrobial Pharmacology, and Clinical Safety and Efficacy. Life. 2021 Apr 16;11(4):348.
15.Varma A, Padh H, Shrivastava N. Andrographolide: a new plant-derived antineoplastic entity on horizon. Evid-Based Complement Altern Med ECAM. 2011;2011:815390.
16.Vetvicka V, Vannucci L. Biological properties of andrographolide, an active ingredient of Andrographis Paniculata: a narrative review. Ann Transl Med. 2021 Jul;9(14):1186.
17.Shang YX, Shen C, Stub T, Zhu SJ, Qiao SY, Li YQ, et al. Adverse Effects of Andrographolide Derivative Medications Compared to the Safe use of Herbal Preparations of Andrographis paniculata: Results of a Systematic Review and Meta-Analysis of Clinical Studies. Front Pharmacol. 2022;13:773282.
18.Pawar A, Rajalakshmi S, Mehta P, Shaikh K, Bothiraja C. Strategies for formulation development of andrographolide. RSC Adv. 2016;6(73):69282–300.
19.Shrivastava S, Kaur CD. Development of andrographolide-loaded solid lipid nanoparticles for lymphatic targeting: Formulation, optimization, characterization, in vitro, and in vivo evaluation. Drug DelivTransl Res. 2023 Feb;13(2):658–74.
20.Hossain MdS, Urbi Z, Sule A, Rahman KMH. Andrographis paniculata (Burm. f.) Wall. ex Nees: A Review of Ethnobotany, Phytochemistry, and Pharmacology. Sci World J. 2014;2014:1–28.
21.Raju S, Das M. Medicinal plants industry in India: Challenges, opportunities and sustainability. Med Plants - Int J PhytomedicinesRelat Ind. 2024;16(1):1–14.
22.Dadhich MK, Sanwal CS, Mahajon B, Vaishya JK, Dutt S, Rath C, et al. Contributions of the National Medicinal Plants Board (NMPB), Ministry of Ayush in the medicinal plants sector - An appraisal. Int J Ayurveda Res. 2024 Apr;5(2):62–75.
23.Himanshu Verma MN. Evaluation of an emerging medicinal crop Kalmegh [Andrographis paniculata (Burm. F.) Wall. Ex. Nees] for commercial cultivation and pharmaceutical & industrial uses: A review. J PharmacognPhytochem. 2019 Mar 6;Vol. 8(4):835–48.
24.Chaudhary A, Singh N. Intellectual property rights and patents in perspective of Ayurveda. Ayu. 2012 Jan;33(1):20–6.