Pharmacognosy Reviews, 2025; 19(38):148-153.
www.phcogrev.com

Review Article

Nothapodytes nimmoniana: Untapped Potential

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ABSTRACT

The tree species *Nothapodytes nimmoniana* or *Nothapodytes foetida* or *Mappia foetida* of family Icacinaceae commonly known as Ghanera or narakya is of research interest among plant scientist as it contains third most demanding anticancer compound camptothecin and 9-Methoxy camptothecin mainly used for treatment of cervical, breast cancer and few lymphomas. Due to extensive overharvesting to meet market demand of camptothecin, it is now red-listed as per IUCN. More than a 20% decline is reported in *N. nimmoniana* population in the last decade alone. Conservation efforts are underway, including metabolic engineering of plant cells to boost camptothecin production, aiming to reduce pressure on wild populations. This article provides an overview of pharmacognosy, phytochemistry, pharmacology and biotechnology aspects of *Nothapodytes nimmoniana* J. Graham.

Keywords: Camptothecin, Plant tissue culture, Anticancer, Conservation.

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Received: 11-04-2025;
Revised: 09-06-2025;
Accepted: 25-08-2025.

INTRODUCTION

Nothapodytes nimmoniana (Graham) Mabb. (*Synonym-Mappia oblonga, Nothapodytes foetida, Mappia tomentosa, Mappia foetida, Mappia ovate*) is one of the potent medicinal plants and it is known for its anticancer property. This plant is known by different names like Ghenera and Narkya.[1]

It is generally known as stinking tree belonging to the family Icacinaceae and is naturally distributed in Western Ghats, Eastern states of India particularly found in Goa, Karnataka, Kerala, Maharashtra, Tamil Nadu, Jammu and Kashmir.[2]

The anti-cancer compound camptothecin, 9 methoxy camptothecin and its derivatives are used as third promising alkaloids in the treatment of cancer. This plant also possess pharmacological activities such as antioxidant, immunomodulatory, anti-HIV, anti-malarial, antimicrobial, and anti-inflammatory. It is also used to cure psychic disorders, skin disease, tuberculosis, diabetes, jaundice and hypertension.[3]

The ever-increasing worldwide market of topotecan, irinotecan, belotecan, and trastuzumab deruxtecan (semi synthetic camptothecin analogues) has currently reached 1000 million US dollars, which represents approximately 1 ton of CPT raw material.[1-3]

Pharmacognosy

It is a small tree, 3-8 m tall. Leaves are simple and alternate shown in Figure 1. Flowers are bisexual, foul smelling, creamy yellow, in terminal pubescent corymbose cymes or panicles. Fruit is a drupe, ellipsoid, blackish-purple and seeds are glabrous. The trees flower during July-August and ripened fruits are available by November-December.[4,5]

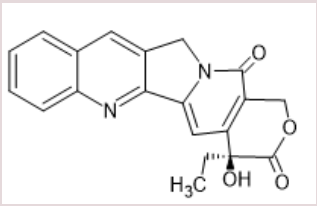
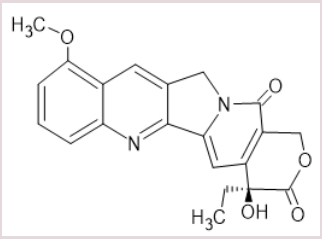
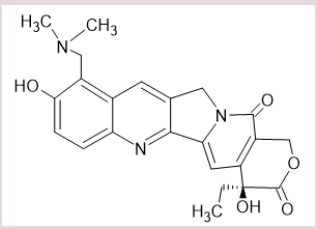
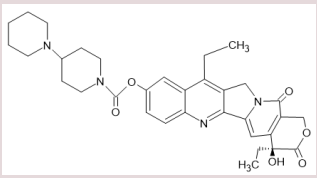
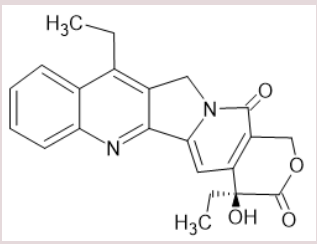
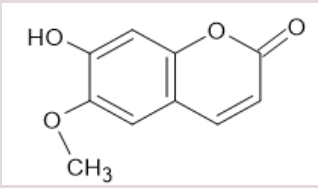
Characters	Leaf	Stem	Root	Bark
Color	Green when Fresh and brown black on drying	Yellow-brown when fresh and dark brown on drying	light yellow when fresh and brownish on drying	Grey color
Odor and Taste	Unpleasant, Sweet	Unpleasant, Sweet	Unpleasant, Sweet	Unpleasant, Sweet
Size	Leaf length 8-25cm, Width 3-15 cm	Stem length up to 10 m and width 25 cm	Length 82-110 cm and width 15 – 30 cm	Approx 5 mm width
Shape	Ovate, elliptical oblong	Cylindrical, rough and fibrous	Cylindrical rough and fibrous	Flat, Soft

Microscopy

Transverse section of *N. nimmoniana* leaf were shown in Figure 2 contain upper and lower epidermis cells were large, thin walled, uniseriate, uniform, hexagonal or polygonal both side of leaf the center of leaf contains vascular bundle, xylem elements and isolated strands of fibers in the phloem layer bundle sheath was absent and larger single layer parenchymatous cells present, also contain trichomes, epidermal region, and vascular elements.

DOI: 10.5530/phrev.20250010

Table 1: Chemical structures of chemicals obtained from *N. nimmoniana*.

Sl. No.	Chemicals	Structure
1	Campothecin	
The concentration of CPT in both stems and roots is significantly higher than that found in fruits and leaves.		
2	9-methoxy camptothecin	
Semisynthetic derivatives		
3	Topotecan	
4	Irinotecan	
5	Acetyl camptothecin	
6	Scopoletin	

Transvers section of *N. nimmoniana* stem shown in Figure 3 shows single layered heavily cuticularized epidermis. The cortex is also differentiated into sclerenchyma, chlorenchyma and parenchyma.[1-5]

Phytochemistry

N. nimmoniana plant is a rich source of the potent alkaloid Camptothecin (CPT), 9-methoxy camptothecin and minor alkaloids mappicine. It also contains scopoletin, sitosterol, stigmasterol and fatty acids shown in Table 1.[5,6]

Pharmacology

In addition to its potent anticancer properties, *N. nimmoniana* exhibits antimicrobial and antioxidant activities, attributed to its rich content of phenolics and flavonoids. These properties underscore the plant's potential for broader therapeutic applications.

Antioxidant activity[7]	DPPH (1,1-diphenyl-2-picryl hydrazine), ABTS+ (2,2'-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid), Ferrous iron chelating ability, Reducing power.	Methanol extracts of leaf and stem showed antioxidant potential to varying degrees.
Antimicrobial activity[8,9]	Petroleum ether, chloroform and methanol extracts of leaf and stem.	Methanol fractions of leaf and stem were found to be most effective against the entire tested organism.
Anti-inflammatory activity[10]	Carrageenan - induced hind paw edema method.	Anti-inflammatory activity of ethanolic extract was found to be more effective.
Antitumor/ Cytotoxic activity[11-15]	Methanol extract of bark and root.	Promising against breast and cervical cell lines.

Biotechnology

N. nimmoniana plant is regarded to be endangered due to huge global demand and overexploitation. Thus, unplanned deforestation, reduced seed germination rate, high market cost and unavailability of economically feasible process of production of camptothecin has motivated researchers to work on plant tissue culture aspects of this plant.

Researchers from IIT Madras and IIT Mandi developed a genome-scale metabolic model (NothaGEM iSM1809) for *N. nimmoniana*. This model identified key enzymes, such as strictosidine synthase and geraniol 10-hydroxylase, whose overexpression could boost CPT synthesis. Experimental

Figure 1: Morphology of plant, a) whole plant, b) stem of plant.

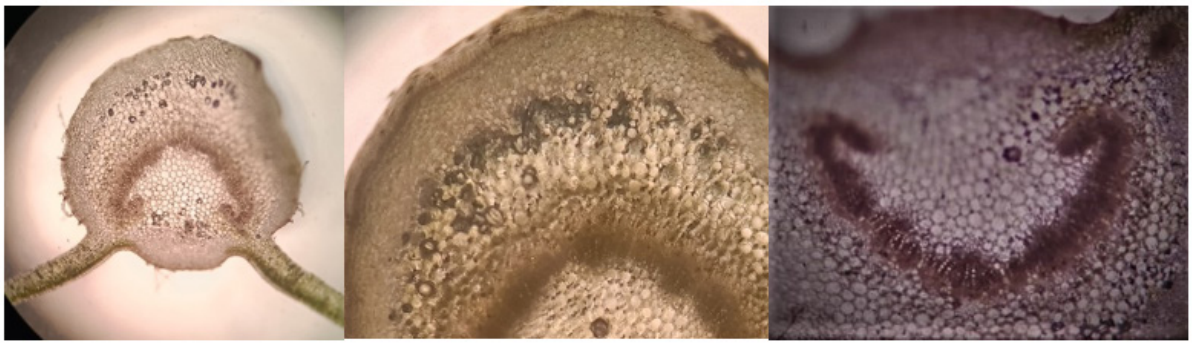


Figure 2: Transverse section of Leaf.

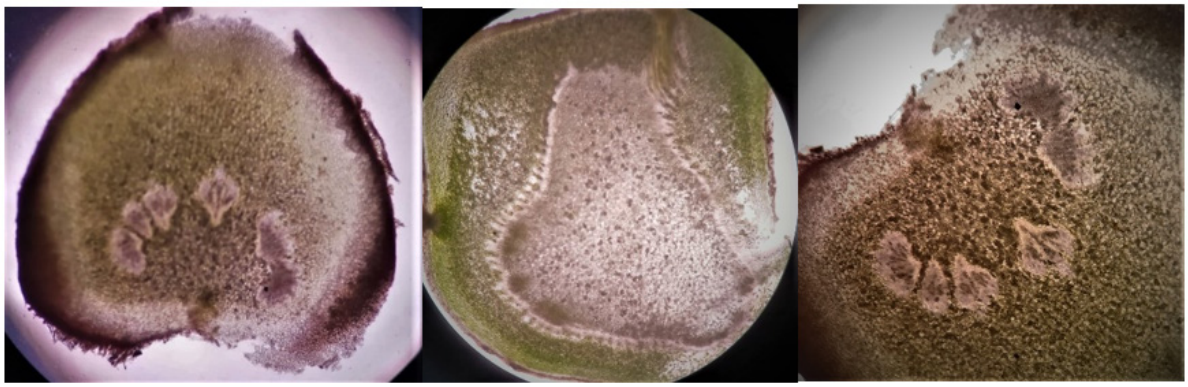


Figure 3: Transverse section of Stem.

Table 2: *In vitro* propagation of *N. nimmoniana* by different techniques.

Part used for callus Production	Medium	Hormone	Duration for Callus induction	References
Nodal explants of shoot	Murashige & Skoog with sucrose and agar	2 mg/L of 2,4-dichloro phenoxy acetic acid	3-4 week	[16]
Hypocotyl leaf	Basal media	1 and 2 mg/L TDZ and 0.5 mg/L 2,4-D.	3-4 week	[17]
Leaf and Stem	Murashige and Skoog	N^6-benzylaminopurine and naphthalene acetic acid (2.0+1.0 mg L^{-1}). $CaCl_2$ elicitor at 25 mM	4 weeks	[18]
Nodal explants derived from regenerated shoots	L2 Medium	BAP (0.5 mg/L) + NAA (1 mg/L) + 2,4-D (1 mg/L).	4 weeks	[19]
Seed embryos	Murashige and Skoog	2,4-dichlorophenoxy acetic acid (2,4-D)+ 2benzylaminopurine (BAP)	3-4 weeks	[20]
Leaf Explants	Murashige and Skoog	TDZ (1mg/L)	1 month	[21]
Nodal segments having axillary buds	Woody Plant Medium	1 mg/L IBA and cytokinins (TDZ, IBA, Kn)	45day	[22]
Young seedlings (Leaves, Nodal Segment, Hypocotyl and Radical	Murashige and Skoog	-	3-4 weeks	[23]
Dried seeds	Murashige and Skoog	NAA + BAP (2.0 + 1.0 mg L-1)	45 days	[24]
Leaf and nodal explants	MS media	Amended with IBA (2 mg/L) + KN (1 mg/L)	50±5 days	[25]
Leaf and nodal explants	Murashige and Skoog	N^6-benzyladenine (BA)	-	[26]
Dry leaf, fresh barks of plant	Murashige and Skoog	2,4-D (2, 4-Dichlorophenoxyacetic acid) 0.5 mg/L and BAP (6-Benzylaminopurine) 3.0 mg/L.	35-40 day	[27]
Seeds (embryo axis)	Murashige and Skoog with GA3	GA3	3-4 weeks 7-8 weeks	[28]
Mature embryos	Murashige and Skoog	Kn (1.0mg/L) and NAA (0.2mg/L).	-	[29]
Leaves and stems	Murashige and Skoog	Supplemented with 1.0, 2.0, 5.0 and 10.0 µM 6-benzylaminopurine or kinetin or 2-isopentenyl adenine (2-iP)	-	[30]
Hypocotyl explants	Murashige and Skoog	2-mg/L 2, 4-D and 0.3 mg/IBAP	4 to 5 weeks	[31]
Hypocotyl explants	Murashige and Skoog	(NAA & 2, 4-D) along with cytokinin (BAP).	-	[31]
Seeds and Leaf	Murashige and Skoog	2,4 D	4 months	[32]
Leaves, tender leaf, cotyledons and whole seeds	Murashige and Skoog	Picloram (2.0 mg L^{-1}). BAP (0.5 mg L^{-1}) and GA_3 (0.5 mg L^{-1}).	4 weeks	[33]
Nodal explants	Murashige and Skoog	NAA	3 weeks of incubation	[34]

Part used for callus Production	Medium	Hormone	Duration for Callus induction	References
Isolated seed embryos	M Murashige and Skoog S with Thidiazuron (TDZ), 3% sucrose, 0.8% agar and pH 5.8	One mg/L IBA	3 weeks	[34]
Leaf segments	AR281, AR1600, and ATCC15834	-	5-8 weeks	[35]
Young seedlings	*Agrobacterium rhizogenes* (A4, LBA 9204, MTCC 532, MTCC 2364 and NCIM 5140)	-	5-8 weeks	[36]
Leaf, radical, nodal segment and petiole	*Agrobacterium rhizogenes* strains: MTCC 532 & MTCC 2364	-	5-8 weeks	[37]
Callus as an explant	*Agrobacterium* strains viz. ATCC15834, LB9402 and A4	-	5-8 weeks	[38]

overexpression of strictosidine synthase in *N. nimmoniana* cell lines resulted in a fivefold increase in CPT production, achieving yields up to 5 µg/g.

Table 2 summarised the *in vitro* propagation of *N. nimmoniana* by different techniques with details of medium, hormones and explant.

CONCLUSION

The increasing global demand for camptothecin has led to overexploitation of *N. nimmoniana*, raising conservation concerns. Consequently, research efforts are focusing on sustainable production methods, including plant tissue culture techniques, to meet pharmaceutical needs without depleting natural populations. Biotechnological research will be pivotal in enhancing camptothecin production and ensuring sustainable sourcing of *N. nimmoniana*.

ACKNOWLEDGEMENT

The authors are thankful to AICTE, Delhi for financial assistance under RPS scheme.

ABBREVIATIONS

IUCN: International union for conservation of nature; **CPT:** Camptothecin; **AR:** *Agrobacterium rhizogenes*; **IBA:** Indole-3-Butyric acid BAP-6-Benzylaminopurine; **NAA:** Naphthalene acetic acid; **2,4-D:** 2,4-Dichlorophenoxyacetic acid; **GA:** Gibberellic acid; **TDZ:** Thidiazuron.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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Cite this article: Deore SL, Vighne RC, Baviskar BA. *Nothapodytes nimmoniana*: Untapped Potential. Pharmacog Rev. 2025;19(38):148-53.