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# "A REVIEW OF NOTHAPODYTES NIMMONIANA: THE THREATENED SOURCE OF ANTICANCER CAMPTOTHECIN"

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## ABSTRACT:

The Indian native plant Nothapodytes nimmoniana demonstrates nature's remarkable capacity to produce large amounts of camptothecin (CPT), a potent compound that is helpful in the treatment of cancer. Modern cancer treatments rely heavily on CPT and its derivatives, such as topotecan and irinotecan. The FDA and national health agencies throughout the world have approved CPT and its variants for the treatment of various cancers. This plant has antibacterial, antioxidant, anti-inflammatory, anthelmintic, and antimalarial properties in addition to its ability to combat cancer. This demonstrates its wide range of possible medical applications. But there is a chance that this priceless plant will go extinct. The primary cause of overharvesting is the increased demand for CPT, which is difficult to produce in a lab. Because CPT is difficult and costly to generate artificially because of its complicated form, we must obtain it from the plant, which puts further strain on harvesting. Numerous compounds have been discovered in N. nimmoniana via studies:

CPT, or camptothecin: This essential material is present in the roots, bark, wood, and leaves. It has been demonstrated that this substance inhibits the proliferation of cancer cells, such as those seen in cervical cancer (HeLa), Dalton's Asiatic lymphoma, and breast cancer (MDA-MB-231). Other substances: The plant's therapeutic qualities are also influenced by a wide range of other substances, including tannins, flavonoids, carbohydrates, glycosides, proteins, lipids, phenolic compounds, saponins, steroids, terpenoids, and coumarins. It's crucial to keep in mind that although CPT and similar medications are incredibly beneficial, they can also have negative side effects.

Strong conservation measures and sustainable harvesting methods are necessary for N. nimmoniana, a significant medicinal resource that is in danger of going extinct, to remain available for use in medicine in the future.

**KEY WORDS:-** Nothapodytes nimmoniana, camptothecin, anticancer, medicinal plants.

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## INTRODUCTION

The WHO estimates that there will be 9.7 million cancer-related deaths and 20 million new cases in 2022. It was projected that 53.5 million people survived five years after receiving a cancer diagnosis. One in five people will get cancer at some point in their lives; roughly one in nine men and one in twelve women will pass away from the illness. The estimated 20 million new cases of cancer in 2022 are expected to rise by 77% to over 35 million cases in 2050[1].

A vast diversity of chemical compounds with therapeutic potential that can alter biological processes to aid in healing are produced by plants, which operate as a rich store of bioactive molecules. Herbal medicine is a rich source of empirical knowledge about the uses of medicinal plants and is ingrained in cultural traditions all around the world. These treatments reflect the many pharmacological activities of chemicals produced from plants and are widely applicable to a range of health issues, from acute diseases to chronic conditions. Herbal therapy frequently complements or replaces contemporary healthcare, giving patients more options for managing their overall health. With many modern medications derived from or modeled after plant-based chemicals, natural sources continue to drive pharmaceutical innovation, underscoring their continued significance in drug development. Herbal medicines may serve as a primary or crucial healthcare resource in areas with limited access to conventional medical services. The most promising anticancer medications of the twenty-first century, camptothecin (CPT) and 9-methoxy camptothecin, are cytotoxic quinolone alkaloids that are abundant in N. nimmoniana[2].



Native to India, N. nimmoniana is a plant that demonstrates nature's remarkable capacity to produce large amounts of camptothecin (CPT), a potent compound that is helpful in the treatment of cancer. The FDA and national health organizations around the world have licensed CPT and its derivatives, such as topotecan and irinotecan, for the treatment of various cancers. These drugs are crucial to contemporary cancer therapy. This plant has antibacterial, antioxidant, anti-inflammatory, anthelmintic, and antimalarial properties in addition to its ability to combat cancer. This demonstrates its wide range of possible medical applications. But there is a chance that this priceless plant will go extinct. The primary cause of its overharvesting is the huge demand for CPT and the difficulty of producing it in a lab. Because CPT is difficult and costly to generate artificially because of its complicated form, we must obtain it from the plant, which puts further strain on harvesting.

The stinking tree, or Nothapodytes nimmoniana, is a unique plant species in India that is both critically endangered and essential for medicine. An effective source of the anticancer alkaloid camptothecin (CPT) is N. nimmoniana. For the treatment of various malignancies, CPT and its derivatives (such as topotecan and irinotecan) have received approval.

**Table I. The taxonomic hierarchy of Nothapodytes nimmoniana.**

| | |
|---|---|
| Kingdom | Plantae |
| Phylum | Tracheophyta |
| Class | Magnoliopsida |
| Order | Aquifoliales |
| Family | Icacinaceae |
| Genus | Nothapodytes |
| Species | Nothapodytes nimmoniana |

**PLANT DESCRIPTION:** Ten-meter-tall tree with yellowish, wrinkled bark. The branchlets have visible leaf scars and are angled, corky, and strongly appressed-hairy. The lamina is 7-18 x 4-8 cm, broadly ovate, ovate-oblong, or elliptic-oblong, base oblique, rounded or acute, apex acuminate, margin entire, glabrous above, pubescent below, and coriaceous; lateral veins are 6-10 pairs, pinnate, prominent, and accompanied by reticulate venation; domatia are present; and the leaves are simple, alternating, and exstipulate. The petiole is 30-60 mm long, robust, pubescent, and grooved adaxially. Creamy yellow, bisexual, 5-mm-diameter flowers grouped in terminal, pubescent, corymbose cymes or panicles; petals 5, 3 mm long, villous within, and inflexed at the apex; stamens 5, free, disc cup-shaped; ovary ovoid, hairy, 1-locular, with 2 ovules; style angled; stigma robust; calyx cup-shaped, 1 mm long, 5-toothed; calyx cup-shaped, 1 mm long, 5-toothed; stigma robust. The spheroid, black, purple-colored fruits are around 2 cm in length and 1 cm in width, and the seeds are glabrous.

**IMAGES OF DEFFERENT PARTS OF THE N. NIMMONIANA[4]**

[Source- http://www.researchgate.net/figure/Nothopodytes-nimmoniana-J-Graham-Mabb-A-Deomali-Hilles-Koraput-Odisa-the-locality_fig1_343222894[accessed 14 Mar 2025]]

**PHYTOCHEMISTRY:** A significant amount of the alkaloid camptothecin (CPT) is present in the plant. It has been clinically proven to be effective in treating a number of malignancies. Drugs based on derived CPT are available.

- According to Shivani et al. (2024), camptothecin (CPT) [5] This essential compound, which is present in the leaves, bark, wood, and roots, has been demonstrated to inhibit the proliferation of cancer cells, including those that cause cervical cancer (HeLa), Dalton's Asiatic lymphoma, and breast cancer (MDA-MB-231).
- Numerous other substances: The plant's therapeutic qualities are influenced by a wide range of other components, including tannins, flavonoids, carbohydrates, glycosides, proteins, lipids, phenolic compounds, saponins, steroids, terpenoids, and coumarins.
- Although CPT and similar medications are incredibly beneficial, it's crucial to keep in mind that they can have negative side effects.

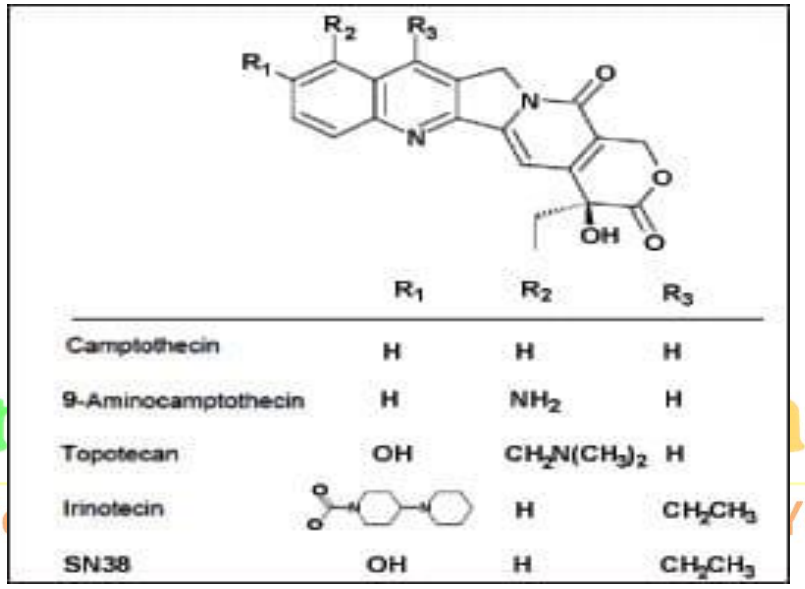
Some semisynthetic, water-soluble derivatives of camptothecin that are commonly used to treat cancer include topotecan, irinotecan, 9-aminocamptothecin, and 9-nitro camptothecin. Among the several kinds of phytoconstituents found in N. nimmoniana are acids, alkaloids, and other substances:

Alkaloids: Mappicine, 9-methoxy camptothecin, and camptothecin (CPT)

Acids include oleic, linoleic, palmitic, stearic, 3-ketooctadec-cis-15-enoic, and linolenic acids. Acetylcamptothecin, (+)-1-hydroxypinoresinol, Ω-hydroxypropioguaiacone, p-hydroxybenzaldehyde, scopoletin, uracil, thymine, sitosterol, trigonelline, and pumiloside are among the other substances that are also present.

**STRUCTURE OF CAMPTOTHECIN:** Camptothecin (CPT) is a heterocyclic compound with a planar pentacyclic ring structure:
Rings A, B, and C: Form pyrrolo [3,4-beta] -quinoline moiety
Ring D: Forms a Conjugated Pyridone Moiety
E-ring: Forms an alpha-hydroxy lactone ring with a chiral center at position 20.

Substituents include hydroxy and ethyl groups at position 4, as well as oxo groups at locations 3 and 14. C20H16N2O4 is the chemical formula for CPT. Originally isolated from the bark and stem of the Chinese tree Camptotheca acuminata, CPT is a monoterpene indole alkaloid. It functions as an antineoplastic agent and is a strong inhibitor of human type-I topoisomerase. Both the lactone and carboxylate forms of CPT contribute to its anticancer properties. A number of derivatives and analogs with enhanced anticancer properties have been developed using CPT as a mother molecule.




| | $R_1$ | $R_2$ | $R_3$ |
|---|---|---|---|
| Camptothecin | H | H | H |
| 9-Aminocamptothecin | H | $NH_2$ | H |
| Topotecan | OH | $CH_2N(CH_3)_2$ | H |
| Irinotecin |  | H | $CH_2CH_3$ |
| SN38 | OH | H | $CH_2CH_3$ |

**STRUCTURE OF CAMPTOTHESIN AND OTHER COMPOUNDS [6]**
**[Nazeerullah et al (2013)]**

**MECHANISM OF ACTION OF CAMPTOTHESIN:** A key enzyme involved in DNA replication, recombination, and transcription, topoisomerase I (TOP1), is targeted and inhibited by camptothecin (CPT) and its derivatives to produce their anticancer effects. CPT traps TOP1 in a stable, dormant compound with cleaved DNA, acting as a "topoisomerase poison." The creation of DSBs during replication is the main mechanism by which CPT causes cell death. Additionally, CPT disrupts transcription by preventing RNA polymerase from progressing. An enzyme called TOP1 temporarily cleaves one strand of the DNA double helix to relieve torsional stress in DNA. The supercoiled DNA can unwind as a result of this cleavage, which makes transcription and replication easier. TOP1 restores the integrity of the DNA strand by resealing it after strand transit.

**CPT Inhibition:** A stable ternary complex is formed when CPT binds to the TOP1-DNA complex.

The split DNA strand is stabilized by this interaction, which stops TOP1 from resealing the break. As a result, "cleavable complexes," in which DNA is irrevocably sliced, accumulate. Cellular Repercussions Collisions of Replication Forks These stable cleavable complexes are encountered by the advancing replication fork during DNA replication. Double-strand breaks (DSBs) in DNA may result from this collision: The most important effect is that DSBs can cause apoptosis, or programmed cell death, and are extremely hazardous to cells. Replication stress and possible genomic instability result from replication fork stalling, which is the inability of the replication machinery to continue. Interference with Transcription During transcription, cleavable complexes may potentially block RNA polymerase's path. Transcription arrest and consequent cell death may result from this.

**PHARMACOLOGY:** Significant anticancer effectiveness against a variety of tumor types has been shown by camptothecin and its derivatives (topotecan, irinotecan). The pharmacokinetics, therapeutic uses, and mechanisms of action of N. nimmoniana's anti-malarial, anti-inflammatory, antibacterial, antifungal, antioxidant, and immunomodulatory characteristics have all been extensively studied.



**CONSERVATION:** Populations of N. nimmoniana have been seriously threatened by overexploitation for camptothecin. Research has shown how urgently conservation measures, including habitat restoration, sustainable harvesting methods, and in-situ and ex-situ conservation tactics, are needed.

**Biotechnology:** To produce camptothecin, research is being done to create biotechnological methods, including tissue culture and micropropagation, which can quickly multiply plants and preserve genetic variety. N. nimmoniana can also be conserved by synthetic biological techniques and metabolic engineering.

**RESULT-**

**TABLE 2. NOTHAPODYTES NIMMONIANA PHYTOCONSTITUENTS**

| PHYTOCONSTITUENT | APPROXIMATE CONTENT/OCCURRENCE |
|---|---|
| Camptothecin (CPT) Primary medicinal alkaloid | Different samples of plant maximum concentrations of camptothecin were found in root (2.62%) collected in the month of February followed by fruits (January, 1.22%), stem (January, 0.81%) and leaves (February, 0.70%). Roots were found to have 3-fold higher concentration of CPT than the leaves and stem, while the fruits showed 2-fold higher concentration.[Namdeo et al(2012)][7] |
| Related Camptothecin Derivatives (e.g., 9-Methoxycamptothecin, 10-Hydroxycamptothecin) | Related alkaloids are present, but concentrations are generally lower than CPT |
| Other Alkaloids (e.g., Mappicine) | Other alkaloid compounds presence confirmed, but quantitative data is limited. |
| Phenolic Compounds, Tannins, Saponins, Steroids, Coumarins | Various phytochemical groups presence confirmed through qualitative tests. Quantitative data varies. |

**TABLE 3. NOTHAPODYTES NIMMONIANA: THERAPEUTIC ACTIVITIES**

| THERAPEUTIC ACTIVITY | DESCRIPTION |
|---|---|
| Anti-cancer | Effective against various cancers, including lung, breast, cervical, colorectal, and ovarian cancers. 9-Methoxycamptothecin. Research focuses on the mechanisms of CPT's action, which involves inhibiting topoisomerase |
| Anti-HIV | Shows promise in AIDS chemotherapy. Studies examine CPT's ability to inhibit Tat-mediated transcription from the viral promoter. |
| Antimalarial | Activity against malaria parasites. Research explores the impact of CPT on parasitic activity. |
| Antibacterial | Shows activity against bacterial infections. Research on the specific compounds responsible for this activity is ongoing. |
| Antioxidant | Scavenges free radicals, potentially useful in preventing oxidative stress-related diseases. Research in finding and isolating responsible phytochemicals. |
| Anti-inflammatory | Reduces inflammation. Research the specific chemicals, and the mode of action on inflammation pathways. |
| Antifungal | Shows activity against fungal infections. phytochemicals. research is done to isolate the active compounds. |
| Treatment of Anaemia | Used in traditional medicine for anaemia. |
| Anti-parasitic | Active against parasites like trypanosomes and leishmania. |
| Immunomodulatory activity | Immunomodulatory activity of an extract from the novel fungal endophyte Entrophospora infrequens.[8] |

## DISCUSSION

One important source of camptothecin, a promising anticancer drug, is N. nimmoniana. For this medicinal plant to be used sustainably and for camptothecin-based cancer treatments to be developed, more research in phytochemistry, pharmacology, biotechnology, and conservation is essential.

## CONCLUSION

The review identifies a number of crucial requirements. Using best practices for natural harvesting, investigating alternate cultivation techniques, and setting up banks are all examples of sustainable harvesting and cultivation strategies. protecting N. nimmoniana in its natural habitat by utilizing additional conservation technologies. Increasing the production of CPT by biotechnology: Making use of metabolic engineering, bioreactor systems, and in vitro culture. Current studies: To look into the biosynthesis of CPT and create new medication options. We can guarantee the sustainable use of N. nimmoniana while preserving its biodiversity for upcoming generations by combining these tactics.

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## CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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## DATA SOURCES

The data source is a combination of Peer-reviewed scientific literature.

## ETHICAL CONSIDERATIONS

This study involved the analysis of publicly available data. Therefore, ethical approval and informed consent were not required.