

Therapeutic Aspects of *Nothapodytes nimmoniana*- A Review

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ABSTRACT

The Southeast Asian forest is blessed with plant sources of anticancer molecules including camptothecin (CPT) but, the irrational harvest is among serious threat to its existence for use by the future generation. Among plant sources of CPT found in the region are *Nothapodytes nimmoniana* and *Chonemorpha fragrance* that are under heavy exploitation pressure for the alkaloid and other medicinal purposes. *Nothapodytes nimmoniana* (Grah.) Mabb. is a high valued medicinal plant endemic to Western Ghats of India, distributed in fragmented populations. The plant is valued for potent anticancer drug camptothecin (CPT). Which is a modified monoterpene indole alkaloid originally isolated from *Camptotheca acuminata* Decne.

Keywords: *Camptothecin, Nothapodytes nimmoniana, Chonemorpha fragrance, Seeds*

1. INTRODUCTION

The medicinal properties of several herbal plants have been documented in ancient Indian literature and the preparations have been found to be effective in the treatment of diseases [1]. The traditional medicinal methods, especially the use of medicinal plants, still play a vital role to cover the basic health needs in the developing countries and moreover the use of herbal remedies has risen in the developed countries in the last decades [2].

The increasing failure of chemotherapeutics and antibiotic resistance exhibited by pathogenic microbial infectious agents has led to the screening of several medicinal plants for their potential antimicrobial activity [3]. In this connection, plants continue to be a rich source of therapeutic agents. The active principles of many drugs are found in plants or are produced secondary metabolites. The remarkable contribution of plants to the drug industry was possible, because of the large number of phytochemical and biological studies all over the world.

2. *N. nimmoniana*: A brief account

Nothapodytes nimmoniana is a medicinal plant belonging to the Icacinaceae family. The species is polygamous in nature with a wide array of breeding types including male, female, hermaphrodite, monoecious, andromonoecious, gynomonoecious, and trimonoecious trees [4].

Nothapodytes nimmoniana is commonly known as *Amruta* and found in Maharashtra, Goa, Kerala, Karnataka, Assam and Tamil Nadu in India [5]. This plant is known by different names: of *N. nimmoniana*, *durvasanemara*, *kodsa*, *hedare* (Kannada), *ghenera* (Hindi), *amruta*, *narkya*, *kalgur*, *kalagaura* (Marathi), *arali*, *choral*, *perum pulagi*, *kal kurinj* (Tamil).

The major source of a potent alkaloid, namely camptothecin, (CPT), which is used in various types of cancer, HIV, malaria, antibacterial, anti-inflammatory and antifungal activity have been reported. *N. nimmoniana* is one such plant which contain camptothecin in significantly high amount [6]. Since there is no convenient synthetic source for CPT, we depend on raw material from natural populations. *Camptotheca acuminata* (tree of Chinese origin) and *N. nimmoniana* are the only convenient sources for large scale extraction and purification of CPT [7].

As CPT accumulates in stem and root of *N. nimmoniana*, whole tree is cut to generate biomass for extraction. In Indian market, the current demand for its biomass is 500–700 metric tons a year. In Maharashtra, overexploitation and habitat destruction for raw material has led to population decline by 50–80% in last decade. Total loss has been recorded from certain areas. Currently, the species population density is as low as 1-2 individuals/hectare in some areas. However, it extends up to 30–40 individuals/hectare at some localities such as forest of Mahabaleshwar, Satara where populations of *N. nimmoniana* survive against the severe threat of destruction [8].

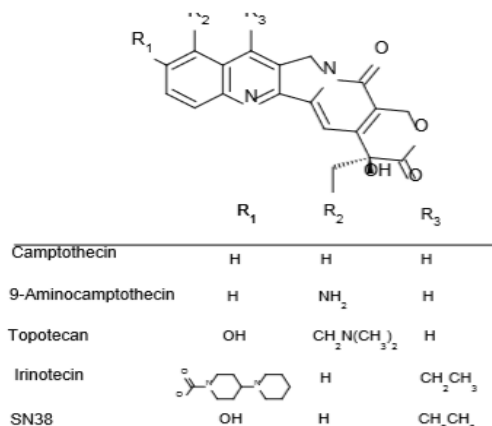


Figure1

Different parts of *N. nimmoniana* tree (A- mature leaves with fruits, B- stems, C- immature leaves, D- mature stem)

3. Brief on Chemical Natures:

N. nimmoniana is a rich source of the potent alkaloid CPT and 9-methoxy camptothecin. It also contains 3-ketooctadec-cis-15-enoic acid (16.0%), palmitic acid (12.3%), stearic acid (4.2%), oleic acid (16.2%), linoleic acid (11.6%) and linolenic acid (39.7%). Other chemical constituents isolated from this plant are acetylcamptothecin, (+)-1-hydroxypinoresinol, Ω -hydroxypropioiguaiacone, p-hydroxybenzaldehyde, scopoletin, uracil, thymine, sitosterol, sitosteryl- β -D-glucoside, 3- β -hydroxystigmast-5-en-7-one, stigmast-5-en-3- β , 7- α -diol, hydroxystigmast-4-en-3-one, sitost-4-en-3-one, linoleic acid, trigonelline, and pumiloside from the stem of *N. nimmoniana* and characterized [9].

Fig-2 Major chemical constituents reported from *N. nimmoniana*

In India, research on clinical trials of CPT is conducted only at laboratory scale. Countries like Japan, USA and Spain are into the commercialization of CPT as a drug. These countries import dried raw material from India which is now one of the leading exporters worldwide. According to State Forest Department records, the annual demand from Japan for dried stem of *N. nimmoniana* was 200–300 tons in 1994 [22]. Since then, there has been an increasing trend. The trade volume increased to 1600 tons in 2002. In 2006–2008, the reported trade in the volumes has exceeded 1000 tons, whereas unreported trade is thought to be at least twice the reported one. The ever-increasing worldwide market of Irinotecan and Topotecan (semi synthetic CPT analogues) has currently reached 1000 million US dollars, which represents approximately 1 ton of CPT raw material [10].

Traditionally, the aqueous extract of *N. nimmoniana* has been used as anti-cancer [11]. It's medicinal use has not been reported in any codified systems of Indian medicine. In fact, CPT is regarded as one of the most promising anticancer drug. In recent years, CPT has also emerged as a promising drug to be used in AIDS chemotherapy. The anti HIV activity of CPT is due to the inhibition of Tat-mediated transcription from the viral promoter. It is also active against parasitic trypanosomes and leishmania. CPT is also active against the malaria, antibacterial activity and anti-inflammatory activity from the leaves of *N. nimmoniana* Miers.

4. Methods of CPT extraction and isolation

Fulzele and Satdive reported the comparison of techniques for the extraction of the CPT from *N. nimmoniana*. Extraction methods using stirring extraction, soxhlet extraction, ultrasonic extraction and

microwave-assisted extraction (MAE) were evaluated for the percentage extraction of CPT and 9-methoxycamptothecin (9-Me-CPT) from *Nothapodytes foetida*. The extracts were analyzed by HPLC. Methanol (90%, v/v) extracted high percentage extraction of CPT and 9-Me-CPT as compared to ethanol (90%, v/v). The result showed that the percentage extraction of CPT and 9-Me-CPT from *N. nimmoniana* by MAE was more efficient followed by soxhlet extraction, ultrasonic and stirring extraction methods. Maximum percentage extraction of CPT was obtained by MAE technique^[12].

5. *N. nimmoniana*: Pharmacological studies:

a) Antimicrobial activity

Kumar et al. successfully determined petroleum ether, chloroform and methanol extracts of *N. nimmoniana*. Leaves and stems were tested for their antibacterial activity. The methanol fractions were found to be most effective against the entire tested organism^[13].

b) Antimalarial activity

Bodley et al. determined the effects of CPT, a potent and specific topoisomerase I inhibitor, on erythrocytic malaria parasites *in vitro*. In *Plasmodium falciparum*, camptothecin trapped protein-DNA complexes, inhibited nucleic acid biosynthesis and was cytotoxic. These results provided the proof for the concept that topoisomerase I was a vulnerable target for new antimalarial drug development^[14].

c) Anti-inflammatory activity

Sheeja et al. reported the anti-inflammatory activity of the *N. nimmoniana* by carrageenan-induced hind paw edema method in rats. The activities of the extracts were compared with control and standard ibuprofen. All the drugs were administered orally. When compared with petroleum ether extract, the anti-inflammatory activity of ethanolic extract was found to be more effective and 200 mg/kg dose of ethanolic extract significantly (p less than 0.01) reduced the inflammation, which was comparable with that of the standard, ibuprofen^[15].

d) Immunomodulatory activity

Puri et al. reported immunomodulatory activity of an extract of the novel fungal endophyte *Entrophospora infrequens* isolated from *N. nimmoniana*. The study evaluated the bioactivities of chloroform and methanolic extracts of *Entrophospora infrequens* with respect to their immunomodulatory potential *in vitro* and *in vivo* (in Balb/c mice). The endophyte *E. infrequens* was found to synthesize CPT, which was positively tested in chloroform. This showed for the first time the immunomodulatory potential of this neoteric CPT-producing endophyte from *N. nimmoniana*^[16].

e) Antitumor activity

Luo et al. reported potent antitumor activity of 10-methoxy-9-nitrocamptothecin. The high cytotoxic potency of 10-methoxy-9-nitrocamptothecin was paralleled with its ability to increase the cellular accumulation of DNA damage. These results suggested that cell cycle regulation might contribute to the anticancer properties of 10-methoxy-9-nitrocamptothecin and strongly supported further anticancer development of 10-methoxy-9-nitrocamptothecin^[17]. Huang et al. reported that CPT activated S or G2-M arrest and the homologous recombination repair pathway in tumor cells^[18]. Cuong et al. demonstrated that the plant alkaloid CPT caused DNA damage by specifically targeting DNA topoisomerase, effectively devastating a broad spectrum of tumors^[19].

Wu et al. reported a new naturally occurring alkaloid, acetylcamptothecin, along with 17 known compounds. Among these, scopoletin, camptothecin, 9-Omethoxycamptothecin and O-acetylcamptothecin showed significant cytotoxic activity^[20]. Rehman et al. reported the *in vitro* cytotoxicity of an endophytic fungus isolated from *N. nimmoniana*. The *in vitro* cytotoxicity of fractions/extracts from endophyte was carried out while ethyl acetate fraction and it showed sufficient growth inhibition against all cell lines.^[21]

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7. CONCLUSION

An exploration of the phytochemical aspects and therapeutic potential of *N. nimmoniana* reveals that it is a natural source of CPT possessing a wide spectrum of pharmacological properties such as anti-cancer, anti-AIDS, anti-malarial, anti-inflammatory, anti-oxidant, anti-bacterial, anti-fungal, anti-anaemic etc. What is noteworthy, CPT is still not available synthetically and plant like *N. nimmoniana* is the prime source of CPT in high amounts. Other phytochemical constituents are acetyl CPT, methoxy CPT, hydroxy CPT, scopoletin, β -sitosterol, sitostery 1- β -D- glucoside, trigonelline and pumiloside. As it is a vulnerable species, biotechnological approaches like plant tissue culture will be a better option for enhancing secondary

metabolite production. Thereby, conserving this significant species using techniques like micro propagation and maintaining genetic uniformity of species.

8. REFERENCES:

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