

# Review of Pharmacological Aspects of *Nothapodytes nimmoniana* species.

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**Abstract:** Over 100 years of decay, major populace focus on traditional plants for treating massive disease due to the presence of active component. Biologically active compounds present in the medicinal plants have always been of huge curiosity to scientists for focusing on exploring plant products. *Nothapodytes foetida* (also known as *Mappia foetida* or *Nothapodytes nimmoniana*) is an average size tree belonging to family Icacinaceae. It is distributed in Southern India, North India, Srilanka, Myanmar and Thailand. It is an imperative medicinal plant, the foremost source of a potent alkaloid, namely camptothecin, of a wide spectrum of pharmacological activities like anti-cancer, anti-HIV, anti-malarial, antibacterial, anti-oxidant, anti-inflammatory, anti-fungal and also applied in the treatment of anemia. This review article compresses about the phytochemical constituent, pharmacological activity of bioactive component of *N.nimmoniana* species of root, stem, leaves and bark of the plants.

**Key words:** *Nothapodytes foetida*, camptothecin, Icacinaceae, anti-fungal, anemia.

## 1. Introduction

Due to the presence of bioactive compound, always the plants have been acknowledged as a rich source of medicinal value. It is anticipated that over 50% of all drugs and analogs are plant derived products. According to the WHO, about 80% of the people in developing countries still believe on traditional medicine for their primary health care, and about 85% of such medicines involve the use of plant extracts (Suh, S., et al 2007). *Nothapodytes nimmoniana* (J. Graham) belongs to the family Icacinaceae, commonly known as Durvasanemara, kodsa, hedare (Kannada), ghenera (Hindi), amruta, narkya, kalgur, kalagaura (Marathi), arali, choral, perum pulagi, kal kurinj (Tamil) is found in India particularly in Maharashtra, Goa, Kerala, Assam, Jammu and Kashmir as well as Tamilnadu areas. It is an essential medicinal plant, constituent the major effective alkaloid, namely camptothecin in significantly high amount. The component has a wide spectrum of pharmacological activities (Padmanabha.B et al 2006). *N. nimmoniana* is one such plant categorized as a vulnerable and endangered plant, which constitute more bioactive compound. Thus the plant is gaining international recognition due to its diversified medicinal uses.

*N. nimmoniana*, is a small broad-leaved tree commonly referred to as ‘Stinking Tree, a tree crop, has got a 7–8 yr extended conception period. It is a rich source for the effective alkaloid camptothecin (CPT) and 9-methoxy camptothecin. It also contains other compounds such as 3-ketooctadec-cis-15-enoic acid, palmitic acid, stearic acid, oleic acid, linoleic acid and linolenic

acid. Other chemical constituents isolated from this plant are acetylcamptothecin, (+)-1-hydroxypinoresinol,  $\Omega$ -hydroxypropioguaiacone, p-hydroxybenzaldehyde, scopoletin, sitosterol, sitosteryl- $\beta$ -D-glucoside, trigonelline. The species shows a wide array of breeding systems including male, female, hermaphrodite, monoecious, andromonoecious, gynomonocious and trimonoecious individuals (**Hombe Gowda, H et al 2002**). The quantity of potent active component of the plant increases as age of the plant is high. The root of the plant produces the more quantity of CPT than any part of the plant (**Namdeo AG, Sharma A 2012**). The extracts of *N. nimmoniana* showed different activities such as antimicrobial activity, anti-malarial activity, anti-inflammatory activity, antitumor/cytotoxic activity, anti-oxidant, anti-anaemic activities, etc (**Yan et.al 2003**) because of the presence of secondary metabolites.

A unique characteristic of higher plants is their ability to generate various organic molecules with high biological function called as secondary metabolites. The phytochemicals constituent of plants has more potential to battle with free radicals for scavenging the Reactive oxygen species (ROS) such as singlet oxygen, Superoxide ion, Hydroxyl ion and Hydrogen peroxide are highly reactive, toxic molecules which are generated normally in cells during metabolism. Conversely, an over production of ROS leads to severe damage to cellular components and further leads to tissue damage. The plant antioxidants have been much of concern because of their capability to forage these free radicals (**Baba, A. et al 2015**). The presence of antioxidants such as phenolics, flavonoids, tannins etc. in plants may play a major role in providing protection against number of diseases (**Ferguson, L. et al 2010**). Therefore the plants are mortal investigated for their antioxidant property and the demand for these plants is increasing in identification of therapeutic value (**Gulcin, I 2012**). In view of this, the plant is analyzed for identification of the active metabolites, the anticancer compound and natural antioxidants along with their antioxidant potential from *N. nimmoniana* species.

#### **Analysis of Bioactive Compound of Extract:**

Several extraction methods were implemented to determine the percentage of CPT and other secondary metabolites present in various part of plant, reported in (**Fulzele D 2005**). The methods of extraction such as stirring extraction, soxhlet extraction, ultrasonic extraction and microwave-assisted extraction (MAE) were compared to evaluate & analyzed the CPT by GC-MS. The Methanol (90%, v/v) extract has high percentage extraction of CPT as compared to ethanol (90%, v/v), Petroleum benzene, ethyl acetate, Butanol, Aqueous extract. The result suggest that the percentage extraction of CPT from *N. nimmoniana* by MAE was more resourceful followed by soxhlet extraction, ultrasonic and stirring extraction methods (**Sundervelan, R et al 2002**). The upper limit percentage extraction of CPT was obtained by MAE technique.

GC-MS analysis of *N. nimmoniana* suggests that the extract is a rich source of the potent alkaloid CPT and 9-methoxy camptothecin, 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,  $\Omega$ -hydroxypropioguaiacone, p-hydroxybenzaldehyde, scopoletin, uracil, thymine, sitosterol, sitosteryl- $\beta$ -D-glucoside, 3- $\beta$ -hydroxystigmast-5-en-7-one, stigmast-5-en-3- $\beta$ , 7- $\alpha$ -diol, 6- $\beta$ -hydroxystigmast-4-en-3-one, sitost-4-en-3-one, linoleic acid, trigonelline, and pumiloside isolated from the stem of *N. nimmoniana* and characterized [26]. Topotecan is 4-ethyl-4,9-dihydroxy-10-[(dimethylamino)methyl]-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione; irinotecan is S)-4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo-1H-pyrano[3',4':6,7]-indolizino[1,2-b]quinolin-9-yl[1,4'-bipiperidine]-1'-carboxylate, SN-38 is 7-ethyl-10-

hydroxycamptothecin. The quantitative estimation of phytochemical constituent of extract of various sources of *N. nimmoniana* would also suggest that the total flavonoids, total phenol, total antioxidant capacity, alkaloid, reduction potential, are found to be high concentration in methanol extract as compare to all other extracts.

### **Pharmacological studies of Extract:**

#### **Anticancer activity:**

*N. nimmoniana* is highly accepted as a source of anticancer drugs curing sarcomas and carcinomas. Thus the CPT is an antitumor isoquinoline alkaloid, useful in treatment of colon, lungs, breast, uterine, and cervical cancers and is also an active inhibitor of HIV replication in vitro (**Pommier Y 2006**). Even many reports suggest that the CPT is found in several species but *N. nimmoniana* reports for higher concentration of CPT. Hence attracted many scientists for isolation of CPT to explore its mechanism against various diseases in medicinal field (**Fulzele DP 2005**). The CPT mechanism of action in cancer cell is by the inhibition of Topoisomerase I in the course of stabilization of physical barriers to DNA synthesis by bringing Topoisomerase I—DNA cleavable complex stabilization, resulting in cell death due to rear-ender of replication fork at the complex (**Lorence A et al 2004**). The analogues are derived from CPT such as Topotecan and Irinotecan are two important water-soluble anti-cancer drugs used for treatment of lung, cervical, ovarian, and colorectal cancers. Topotecan is permitted in the USA as second-line therapy in patients previously treated with small cell lung and ovarian cancers (**Oberlies and Kroll 2004**). Irinotecan is used in the treatment of joint & further combine with fluoropyrimidines as first-line therapy for treatment of advanced colorectal cancer or single agent after failure of 5-fluorouracil-based chemotherapy and second-line agent for colon cancer (**Edward 2012**).

The antitumor activity of analogues of CPT such as 10-methoxy-9-nitrocamptothecin was reported by Luo *et al.* & found to be having more potential in increase the cellular accumulation of DNA damage & brings apoptosis process. These results suggested that cell cycle regulation might contribute to the anticancer properties of 10-methoxy-9-nitrocamptothecin and strongly supported further anticancer development [**Huang M et al 2008**]. The other studies were also subjected to demonstrate that the plant alkaloid CPT caused DNA damage by specifically targeting DNA topoisomerase, effectively devastating a broad spectrum of tumors. (**Cuong et al 2009**).

A new approach was developed in naturally occurring alkaloid, acetylcamptothecin, along with 17 known compounds. Among these, scopoletin, camptothecin, 9-Omethoxycamptothecin and O-acetylcamptothecin showed significant cytotoxic activity. The research includes 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 (**Rehman S et al 2009**).

#### **Antimicrobial activity:**

To evaluate antibacterial activity of petroleum ether, chloroform and methanol extracts of *N. nimmoniana* were subjected to TLC Bioautography assay. The bioactive containing extracts were coated by agar overlay method to indentified bacterial activity against pathogen such as *S. aureus* and *E. coli* was spread on the TLC plate. The results obtained confirming that camptothecin exhibit the antibacterial potential against *S.aureus* and *E. coli*. Among the extracts, methanol fractions were pioneer to be most efficient combat the entire tested organism (**Kumar et.al 2002**).

### **Anti-malarial activity:**

An in-vitro study were reported by Bodley *et al.* resolute the effects of CPT, a compelling and specific topoisomerase I inhibitor, on erythrocytic malaria parasites. It is demonstrated that camptothecin trapped protein-DNA complexes, inhibited nucleic acid biosynthesis and was cytotoxic in *Plasmodium falciparum*. These results would suggest the topoisomerase I was a susceptible target for novel antimalarial drug development (Nazeerullah khan *et.al* 2013).

### **Anti-inflammatory activity:**

An animal study were proposed for assessing the Anti-inflammatory activities of the *N. nimmoniana* by Sheeja *et al* carrageen an-induced hind paw edema method in rats. The activities of the extracts were compared with control and standard ibuprofen. 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 as superior as with that of the standard, ibuprofen (Sheeja E, *et al* 2005).

### **Immunomodulatory activity**

Even the plant extracts were focused for immunomodulatory activity against novel fungal endophyte *Entrophospora infrequens* isolated from *N. nimmoniana* were reported by Puri *et al.* The study determine the bioactivities of chloroform and methanolic extracts of *Entrophospora infrequens* with respect to their immunomodulatory potential *in vitro* and *in viv* .The endophyte *E. infrequens* was found to synthesize bioactive compound of plant, which was positively tested in chloroform. This result would suggest that the CPT-producing endophyte from *N. nimmoniana* is the neotric potential of immunomodulatory drug. [Qadri M *et al* 2013].

## **2. CONCLUSION**

After reviewing of the plant species it would suggest that the phytochemical aspects and therapeutic potential of *N. nimmoniana* possess a wide spectrum of pharmacological properties such as anti-cancer, anti-AIDS, anti-malarial, antiinflammatory, anti-oxidant, anti-bacterial, anti-fungal, anti-anaemic etc. It is worth mentioning, CPT is the prime source of plant in high amounts. Other phytochemical constituents are acetyl CPT, methoxy CPT, hydroxy CPT, scopoletin,  $\beta$ -sitosterol, sitostery 1- $\beta$ -D- glucoside, trigonelline and pumiloside. Still need to focus on various new modern technologies to explore the potential activity of plant species to discover the new novel approach in combination therapy of medicinal field for treating various dreadful diseases.

## **3. References:**

1. Suhas, S., *et al.* "R., Ganeshaiyah, KN, and Uma Shankar, R., "Chemical profiling of Nothapodytes nimmoniana populations in the western ghats, India for anti-cancer compound, camptothecin". *Current Science* 92 (2007): 1142-1147.
2. Padmanabha, B. V., Chandrasekhar, M., Ramesha, B. T., Hombegowda, H. C., Gunaga, R. P., Suhas, S., Vasudeva, R., Ganeshaiyah, K. N., Uma Shankar, R., "Patterns of accumulation of camptothecin, an anticancer alkaloid in Nothapodytes nimmoniana Graham in the western

- ghats, India. Implications for identifying high yielding sources of alkaloid”, *Current Science*, vol. 90 (1), pp. 95-99, 2006.
3. Hombe Gowda, H. C., Vasudeva, R., Georgi P. Mathachen., Uma Shaanker, R. and Ganeshaiyah, K. N., Breeding types in *Nothapodytes nimmoniana* Graham. *Curr. Sci.*, 2002, 83, 1077–1078.16.
  4. Namdeo AG, Sharma A - HPLC analysis of the camptothecin content in various parts of *N. foetida* collected in different periods. *Asian Pac J Trop Biomed* 2012:389–393
  5. Yan, Xiu-Feng, Yang Wang, Tao Yu, Yu-Hong, Zhang and Shao-Jun Dai, Variation in camptothecin content in *Camptotheca acuminata* leaves. *Bot. Bull. Acad. Sin.*, 2003, 44, 99–105.
  6. Baba, A. S., Malik, S. A., “Determination of total phenolic and flavonoid content, antimicrobial and antioxidant activity of a root extract of *Arisaema jacquemontii*”, *Journal of Taibah University for Science*, pp. 1-6, 2015
  7. Ferguson, L. R., “Chronic inflammation and mutagenesis”, *Mutation Research-Fundamental and Molecular Mechanisms of Mutagenesis*, vol. 690, pp. 3–11, 2010.
  8. Gulcin, I., “Antioxidant activity of food constituents: an overview”, *Archives of Toxicology*, vol. 86, pp. 345–391, 2012.
  9. Fulzele D, Satdive R. Comparison of techniques for the extraction of the anti-cancer drug camptothecin from *Nothapodytes foetida*. *J Chromatogr* 2005; 1063(2):9-13.
  10. Sundervelan, R. B., Desireddy and Veeresham, C., Camptothecine-A novel anti cancer agent from tissue cultures of *Nothapodytes foetida*. *Indian J. Pharm. Sci.*, 2002, 65, 101–105.
  11. Pommier Y - Topoisomerase I inhibitors: camptothecins and beyond. *Nat Rev Cancer* 2006 6:789–802.
  12. Fulzele DP, Satdive RK Distribution of anticancer drug camptothecin in *Nothapodytes foetida*. *Fitoterapia* 76: 2005, 643–648.
  13. Lorence A, Nessler CL Camptothecin, over four decades of surprising findings. *Phytochem* 65: 2004, 2735–2749.
  14. Oberlies NH, Kroll DJ Camptothecin and Taxol: historical achievements in natural products research. *J Nat Prod* 67: 2004, 129–135
  15. Huang M, Ze-Hong M, Hong Z, Yu-Jun C, Wei Lu, Jian Ding. Chk1 and Chk2 are differentially involved in homologous recombination repair and cell cycle arrest in response to DNA double-strand breaks induced by camptothecins. *Mol Cancer Ther.*, 2008; 7(6): 120-27.
  16. Cuong N, Hsieh M, Huang C. Recent development in nano-sized dosage forms of plant alkaloid camptothecin-derived drugs. *Recent Pat Anticancer Drug Discov* 2009; 7(2):333-38.
  17. Rehman S, Shawl A, Sultana S, Kour A, Riyaz-ul-Hassan S, Ghulam Nabi Qazi. In vitro cytotoxicity of an endophytic fungus isolated from *Nothapodytes nimmoniana*. *Annals of microbiology*, 2009; 59(1): 157-61.
  18. Edward M RTI International thinks it can continue to flourish by using minds over matters. *Business North Carolina*. Retrieved, January 6, 2013.
  19. Kumar R, Vishwanathan H, Suresh T, Mohan P. Antibacterial activity of *Mappia foetida* leaves and stems. *Fitoterapia* 2002; 73(2):734-36.

20. Sumitra Poudel Review on *Nothapodytes nimmoniana* and its Nephro Protective, Hepatoprotective and Anti- Oxidant Activities JETIR November 2018, Volume 5, Issue 11.
21. Khan, Nazeerullah, Tamboli, Ennus Sharma, V.K. 2013/03/01 Phytochemical and pharmacological aspects of *Nothapodytes nimmoniana*. An overview - Herba Polonica
22. Sheeja E, Edwin E, Dhanbal S, Suresh B. Antiinflammatory activity of the leaves of *Nothapodytes foetida* Miers. Indian J Pharm Sci 2005; 67(2):251-53.
23. Qadri M, Johri S, Shah BA, et al. Identification and bioactive potential of endophytic fungi isolated from selected plants of the Western Himalayas. Springerplus. 2013 Dec;2(1):8. DOI: 10.1186/2193-1801-2-8.