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The Panoramic View on Pharmacological and Pharmacognostic Profile of *Mappia foetida*

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ABSTRACT

Mappia foetida is from family icacinaceae and is commonly known as Amruta, kalgur or Narkya. Mappia foetida now renamed as Nothapodytes nimmoniana is a moderate sized tree which grows up to 4-10 mts high. There are 11 species occurring in Central America, the West Indies and Asia. The type species for the genus is Mappia racemosa. This plant has anti-cancer properties which has made it an endangered species. It is being exploited clandestinely in the domestic market and is also shipped abroad. The profit potential is enormous as the alkaloid camptothecin is extracted from the plant. This alkaloid is an essential component of chemotherapy. It also contains 3-ketooctadec-cis-15-enoic acid, palmitic acid, stearic acid, oleic acid, linoleic acid and linoleic acid. The active component is camptothecin and its maximum in leaves, and effective in colon, gastric, ovarian, lung cancer. The alkaloid camptothecins has anti-tumour activity based on their binding to and inhibition of topoisomerase i, a nuclear enzyme which reduces torsional stress during DNA replication. This valuable medicinally important tree due its commercial importance is being over exploited. The only alternative is to cultivate the tree and avoid wild collections. Cultivation and large scale plantations depend upon the availability of planting stocks. Natural regeneration is through seeds and is curtailed by several factors leading to low % of germination. Vegetative propagation through rooting the cuttings is also not successful, posing a problem for planting stocks. In the present study various attempts were made to derive a protocol for development of planting stocks.

Keywords: *Mappia foetida*; Camptothecin; Anti-cancer; Pharmacological profile; Pharmacognostic profile

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INTRODUCTION

Mappia foetida is from family *Icacinaceae* and is commonly known as *amruta, kalgur or narkya*. *Mappia foetida* now renamed as *Nothapodytes nimmoniana* is a moderate sized tree which grows up to 4-10 mts high. This plant has anti-cancer properties which has made it an endangered species. It is being exploited clandestinely in the domestic market and is also shipped abroad. The profit potential is enormous as the alkaloid camptothecin is extracted from the plant. This alkaloid is an essential component of chemotherapy, each dose of which costs 1.5-2 lakhs in India. As per a year-old estimate, 1500-2000 tonnes of narakya logs are consumed in India every year and almost the same quantity exported to other countries in powdered form. Reports suggest that at least 1000 tonnes of the plant is consumed in and around the city of Bengaluru every year.

The active component is camptothecin (CPT) alkaloid. It's maximum in leaves, and effective in colon, gastric, ovarian, lung cancer. The alkaloid camptothecins have anti-tumour activity based on their binding to and inhibition of topoisomerase i, a nuclear enzyme which reduces torsional stress during DNA replication. Topotecon and irinotecan (widely used for colon cancer) have been approved for medication use by the us food and drug administration (fda). Foetidine 1 and 2 are alkaloids which also have anti-cancer properties. These alkaloids are

soluble in water and present in all parts of the plant. They are precursors of campothecin and 9-methoxy campothecin which are alkaloids known to have pharmacodynamics properties. But these alkaloids are also insoluble in water.
The particular water solubility of the compounds makes them particularly suitable for the treatment of the patients by the parental route that is avoiding the use of the toxic excipients or of the unsuitable chemical derivatizations. The medicines available in the market for cancer extracted from *nothopodytes* are known as: topotecan, camptothecin, irinotecan, topotican, camptosar (irinotecan hydrochloride) [1].

***Mappia foetida*: A Brief Account**

This plant is known by different names: of *N. nimmoniana*, *durvasanemara, kodsa, hedare* (Kannada), *ghenera* (Hindi), *amruta, narkya, kalgur, kalagaura* (Marathi)[2], *arali, choral, perum pulagi, kal kurinj* (Tamil).The plant is native for Indomalaysia and Indochina. Occurs in Western ghats (Shimoga, Sirsi, Ulvi, Hassan, Joida, and B R Hill), South India, Central and South Maharashtra, Sahyadris, Munnar, Goa in Figure 1.

It is a small tree, 4-10 mt high. Bark smooth, grey, wrinkled, about 5 mm thick. Branchlets slightly angled, corky, with prominent leaf scars. Leaves alternate, slightly leathery, broadly egg-shaped to elliptic-oblong, 1-25 x 4-12 cm, base often unequal, apex acute to acuminate, margin entire, hairless above, thinly hairy beneath, crowded at the ends of branchlets, lateral nerves 8-10 pairs, leaf stalks 3-6 cm long. Flower in cymes, creamy yellowish, foul smelling (strongly foetid), about 5 mm across, in terminal corymbose cymes, petals hairy inside. The fruit resembles jamun or jambul fruit in taste and appearance [3].

Since there is no convenient synthetic source for CPT, we depend on raw material from natural populations. *Camptotheca acuminata* (tree of Chinese origin) and *Mappia foetida* are the only convenient sources for large scale extraction and purification of CPT. As CPT accumulates in stem and root of *Mappia foetida*, 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 in Table 1.

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 *Mappia foetida* survive against the severe threat of destruction [4].

Figure 1: *Mappia foetida* plant

Table 1: Scientific Classification of *Mappia foetida*

Kingdom:	**Plantae**
Clade:	Tracheophytes
Clade:	Angiosperms
Clade:	Eudicots
Clade:	Asterids
Order:	Icacinales
Family	*Icacinaceae*
Genus	*Mapppia*

Mappia foetida Trade and Importance in Traditional Medicine

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 *Mappia foetida* was 200-300 tons in 1994 [5].

Traditionally, the aqueous extract of *Mappia foetida* has been used as anti-cancer [6]. Its 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 *Mappia foetida* [5,6].

LITERATURE REVIEW

Cultivation and Collection of *Mappia foetida*

Nothapodytes foetida (weight) slemuer belonging to family *Icacinaceae* is a medium sized tree distributed throughout Western Ghats of India. This tree was identified as a potent source of Camptothecin and its derivatives. Camptothecin and its analogs are the naturally occurring inhibitors of DNA topoisomerases Cytotoxic activities of CPT and its derivatives was evidenced by Wani et al., (1966). At present two semi synthetic derivatives of Camptothecin, Topotecan (TPT) and Irinotecan (CPT-11) are widely used to treat ovarian and colorectal cancers. CPT-11 has been used in combination chemotherapy along with common chemotherapeutic drugs such as 5-FU and leucovorin for treating colon cancer. Thus the global demand for CPT has increased as it has been recognized as the starting material for the synthesis of these commercially valuable analogues. This valuable medicinally important tree due its commercial importance is being over exploited. The only alternative is to cultivate the tree and avoid wild collections. Cultivation and large scale plantations depend upon the availability of planting stocks. Natural regeneration is through seeds and is curtailed by several factors leading to low percent of germination. Vegetative propagation through rooting the cuttings is also not successful, posing a problem for planting stocks. In the present study various attempts were made to derive a protocol for development of planting stocks [7].

Mature fruits were collected from various geographical locations of Western Ghats such as Amboli, Chandgad, Agumbe, Coorg, Chickmaglore, Karad, Kemmangundi, Mahabaleshwar, Sagar, Kodachadri and Khanapur. Conventional seed propagation randomly selected dried fruits were planted in the soil with and without fruit coat. Seed cultures Mature fruits with and without coat were treated with detergent (Teepol-0.1%v/v) for 10 min and

thoroughly washed under a jet flow of tap water. Later fruits and seeds were subjected to Bavistin (0.1% w/v) treatment for 45 min followed by a sterile water rinse. Final surface sterilization procedure was carried under LAF with freshly prepared Mercuric chloride (0.1% w/v) for 7 min followed by sterile water wash for five times. Fruits and seeds were soaked in sterile water for 24 hours. Disinfected seeds were then placed onto half and full strength MS, B5 medium and WP medium Media was fortified with 3% sucrose (w/v) and gelled with 0.7% agar. The pH of the medium was adjusted to 5.7 prior to autoclaving at 15 psi for 20 min. Cultures were incubated at 16 hours light and 8 hours dark regimes. The % frequency of germination was recorded after 25 days. Three replicates with 100 seeds each were maintained [7].

CHEMICAL COMPOSITION OF *MAPPIA FOETIDA*

Mappia foetida is from family *Icacinaceae* and is commonly known as Amruta, Kalgur or Narkya. *Mappia foetida* now renamed as *Nothapodytes nimmoniana* is a moderate sized tree which grows upto 4-10 mts high. [8]
This plant has anti-cancer properties which has made it an endangered species. It is being exploited clandestinely in the domestic market and is also shipped abroad. The profit potential is enormous as the alkaloid camptothecin is extracted from the plant. This alkaloid is an essential component of chemotherapy, each dose of which costs 1.5-2 lakhs in India. As per a year-old estimate, 1500-2000 tonnes of Narakya logs are consumed in India every year and almost the same quantity exported to other countries in powdered form. Reports suggest that at least 1000 tonnes of the plant is consumed in and around the city of Bengaluru every year [8].

The active component is camptothecin (CPT) alkaloid in Figure 2. It's maximum in leaves, and effective in colon, gastric, ovarian, lung cancer. The alkaloid camptothecins have anti-tumour activity based on their binding to and inhibition of Topoisomerase I, a nuclear enzyme which reduces torsional stress during DNA replication. Topotecon and Irinotecan (widely used for colon cancer) have been approved for medication use by the US Food and Drug administration (FDA). Foetidine 1 and 2 are alkaloids which also have anti-cancer properties. These alkaloids are soluble in water and present in all parts of the plant. They are precursors of campothecin and 9-methoxy campothecin which are alkaloids known to have pharmacodynamics properties. But these alkaloids are also insoluble in water. The particular water solubility of the compounds makes them particularly suitable for the treatment of the patients by the parental route that is avoiding the use of the toxic excipients or of the unsuitable chemical derivatizations. The medicines available in the market for cancer extracted from *Nothopodytes* are known as: Topotecan, Camptothecin, Irinotecan, Topotican, Camptosar (Irinotecan hydrochloride)[8].

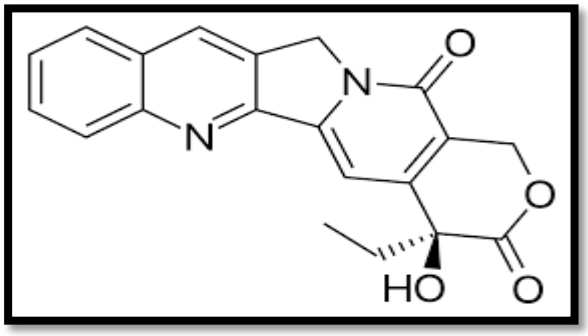

Figure 2: Camptothecin structure

Proven Activity of *Mappia foetida*

Anti-cancer activity: The camptothecins are a maturing class of anticancer agents. In this article, we review the pharmacology and antitumor activity of the camptothecin analogues that are approved for clinical use and those investigational agents undergoing clinical evaluation. Camptothecin is a naturally occurring cytotoxic alkaloid that

has a unique intracellular target, topoisomerase I, a nuclear enzyme that reduces the torsional stress of supercoiled DNA during the replication, recombination, transcription, and repair of DNA.

Topotecan and irinotecan are synthetic analogues designed to facilitate parenteral administration of the active lactone form of the compound by introducing functional groups to enhance solubility. They are now well-established components in the chemotherapeutic management of several neoplasms. Topotecan has modest activity in patients treated previously with ovarian and small cell lung cancer and is currently approved for use in the United States as second-line therapy in these diseases. Preliminary evidence of activity against haematological malignancies is also promising. Irinotecan is a prodrug that undergoes enzymatic conversion to the biologically active metabolite 7-ethyl-10-hydroxy-camptothecin. It is presently the treatment of choice when used in combination with fluoropyrimidines as first-line therapy for patients with advanced colorectal cancer or as a single agent after failure of 5-fluorouracil-based chemotherapy.

Encouraging preliminary results suggest that irinotecan may have an increasing role in the treatment of other solid tumors, including small and non-small cell lung cancer, cervical cancer, ovarian cancer, gastric cancer, and malignant gliomas. Several additional camptothecin analogues are in various stages of clinical development, including 9-aminocamptothecin, 9-nitrocamptothecin, 7-(4-methylpiperazinomethylene)-10,11-ethylenedioxy-20(S)-camptothecin, exatecan mesylate, and karenitecin.

Efforts to further optimize therapeutic effectiveness through drug delivery strategies that prolong tumor exposure to these S phase-specific agents, such as improving oral bioavailability through structure modification and innovative formulation approaches, alternative parenteral dosage forms, and administration schedules, are being actively pursued. Combining camptothecins with other anticancer drugs and treatment modalities, as well as gaining a better understanding of the factors contributing to tumor sensitivity and resistance, continues to be the object of considerable interest [9].

Anti-bacterial activity: Successive petroleum ether, chloroform and methanol extracts of *Mappia foetida* leaves and stem were tested for their antibacterial activity. The methanol fractions were found to be most effective against all the tested organisms [10].

Anti-fungal activity: Camptothecin (CPT) is alkaloid known to have medicinal as well as pesticidal properties. *Mappia foetida* is one of the important sources of camptothecin. Therefore an investigation was undertaken with an objective to extract CPT from *M. foetida* and to evaluate CPT against plant pathogenic fungi and bacteria in pomegranate. High Performance Liquid Chromatography (HPLC) based analysis revealed the CPT content of roots of *M. foetida* was 0.18%. Extracted CPT was tested against the leaf spot, wilt and bacterial blight diseases causing pathogens in pomegranate. *In vitro* bioassays of CPT isolated from *M. foetida* showed effective control of fungal pathogens like *Alternaria alternata, Colletotrichum gloeosporioides* and *Fusarium oxysporum*. Half maximal effective concentration (EC_{50}) of CPT against mycelial growth of *A. alternata* was 250 µg/mL, while against *C. gloeosporioides* it was 500 µg/mL CPT. Mycelial growth of F. oxysporum was effectively controlled upto 50% with 250 µg/mL CPT. Bacterial blight caused by *Xanthomonas axonopodis pv punica*e could not be inhibited by CPT at the concentrations tested during *in vitro* assay [11].

Anti-microbial activity: Kumar, et al. successfully determined petroleum ether, chloroform and methanol extracts of *Mappia foetida*. Leaves and stems were tested for their antibacterial activity. The methanol fractions were found to be most effective against the entire tested organism [12].

Anti-malarial 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 [13].

Anti-inflammatory activity: Sheeja et al. reported the anti-inflammatory activity of the *Mappia foetida* 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[14].

DISCUSSION AND CONCLUSION

An exploration of Mappia foetida's phytochemical features and medicinal ability shows that it is a natural source of Camptothecin with a wide variety of pharmacological properties such as anti-cancer, anti-AIDS, anti-malarial, anti-inflammatory, anti-oxidant, anti-bacterial, anti-fungal, anti-anaemic, etc. Camptothecin is still not synthetically produced, which is noteworthy, and plants such as Mappia foetida are the main source of high concentrations of Camptothecin. There by, using strategies such as micro propagation and ensuring genetic uniformity of plants, retaining this essential species.

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