Match Maker/ Renewable Chemicals & Materials/ 16 Apr 2021

Microbial process for the synthesis of camptothecin, an anti-cancer compound and starting material

Lead Inventor: Dr Smita Srivastava

Organization: IIT Madras

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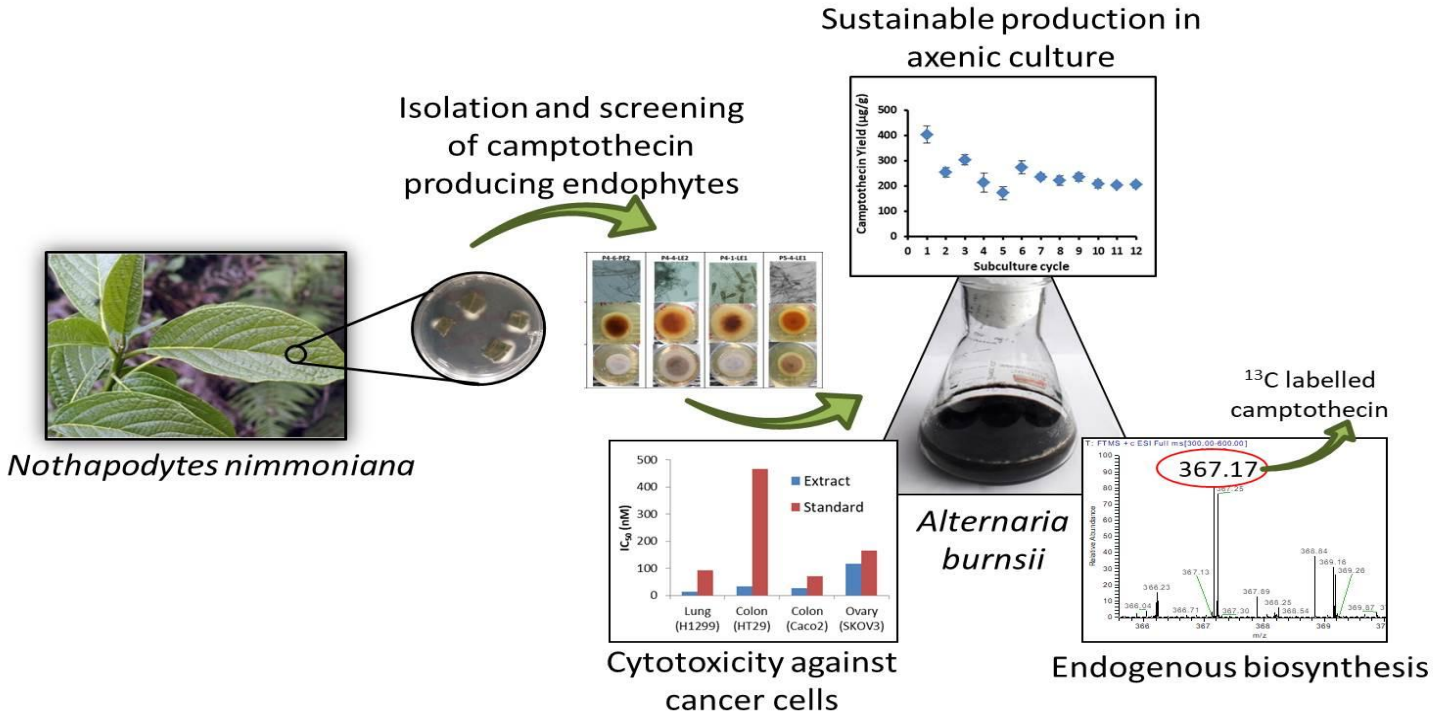
The Opportunity

- The global Camptothecin market value is estimated to reach ~US$ ….. Mn by the end of 2020. According to the report, the camptothecin market is anticipated to reach ~US$ … Mn by 2030, at a CAGR of ~…%.
- Finds applications in: Pharmaceutical applications
- Price realization : 1kg of CPT costs ~Rs. 3 Lakhs in India
- Leading key players in Camptothecin market: **SM herbals, Aphios Corporation, Cayman Chemical, HAOXUAN, Yuannan Hande, Sai Phytoceuticals, Sarv Biolabs Pvt, Hainan Yew Pharmaceutical, Indena, South Pharmaceutical,**

Who should be interested and why?

Who?	Why?
Companies using camptothecin as starting material	• Competitive edge • New value proposition
Companies manufacturing camptothecin as cancer drug	• Competitive edge • New value proposition

About the technology



Process technology features:

- Cost effective process
  - Uniform and consistent product quality and quantity with less impurities than in natural plant extracts.
- Improved productivity
  - Faster growth rate of the microbe in comparison to the natural plants.
- Product yield comparable to that in nature.

Comparison with other alternatives

Aspect	IITM Process	Current standard process
Extraction of camptothecin	• Uniform • Sustainable supply	• Non-uniform • Non-sustainable supply (lead plant resources under endangered list)
Yield	Good yield ?	Low yield ?
Scale-up	Highly scalable	Limitations
Environmental impact	None	Deforestation/ depletion of flora in specific regions.

Current status

Technology status:

- Demonstrated at lab scale; 3 L fermenter
- Patent protected

Patents:

- Priority document:
- Coverage:
- Approved: Pending

Publications:

- Sustainable production of camptothecin from an Alternaria sp. isolated from *Nothapodytes nimmoniana.* I.A. H. Khwajah Mohinudeen, Rahul Kanumuri, K. N. Soujanya, R. Uma Shaanker,Suresh Kumar Rayala & Smita Srivastava. Nature Research, (2021) 11:1478.

Team and Organization

Lead Scientist: Prof. Smita Srivastava
Associate Professor, IIT Madras

Expertise: Biochemical Engineering, Plant cell, Microbial technology

Guided: 7 PhDs, **1** post-doc and **8** graduate and under graduate students

Researchers identify alternative source for anti-cancer drug

CHENNAI: Researchers at the Indian Institute of Technology-Madras have identified a sustainable and high-yielding alternative source for the anti-cancer drug camptothecin. This novel microbial fermentation process can be an economically-efficient method of production to fulfill the market demand at scale, claimed a statement from the university on Thursday.

Topotecan and Irinotecan are two widely used anticancer drugs that are produced by using camptothecin as the lead molecule. More than a dozen derivatives and conjugates of camptothecin are under various stages of clinical trials for anti-cancer applications. Camptothecin is the third most in-demand alkaloid that is isolated from the Chinese tree Camptotheca acuminata and the Indian tree Nothapodytes nimmoniana.

Nearly 1,000 tonnes of plant material is required to extract just one tonne of camptothecin. Due to extensive overharvesting to meet the demand, both these plants are now critically endangered. The N. nimmoniana population has declined more than 20 per cent in the last decade alone.

To meet the demand and conserve natural sources, the researchers at IIT-Madras have now developed an alternative method of camptothecin production through a microbial fermentation process.

Highlighting the applications of the research, Smita Srivastava, Associate Professor, Department of Biotechnology, IIT Madras, and the principal investigator of the study, said, "The novelty of the work lies in the fact that unlike other potential microbial strains reported, this strain has been found to show sustainable production even beyond 100 generations. The plan now is to use the isolated novel strain for the development of a microbial fermentation-based sustainable bioprocess for large-scale in vitro production of camptothecin, preferably in collaboration with industries."

Apart from Dr Srivastava, the research team included Prof Suresh Kumar Rayala, Khwajah Mohinudeen, PhD research scholar and Rahul Kanumuri, SRF, Department of Biotechnology, IIT Madras; Prof R Uma Shaanker and KN Soujanya, researcher, School of Ecology and Conservation, University of Agricultural Sciences, GKVK, Bengaluru.

The work was recently published in the reputed peer-reviewed, International Journal of Scientific Reports, a Nature Research Publication.

THE TEAM: Professor Smita Srivastava (fourth from right) of the biotechnology department of IIT Madras with researchers

IIT devises eco-friendly way to produce crucial cancer drug compound

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IIT-Madras researchers have found a new source and an alternative method to produce camptothecin, a compound crucial in making widely used anticancer drugs. The findings can possibly put an end to the commercial exploitation of a now-endangered plant in the Western Ghats from which the compound is extracted.

The team has isolated a microorganism from the leaf of nothapodytes nimmoniana, the plant, and has developed a process to produce the compound in a controlled environment.

Professor Smita Srivastava from the department of biotechnology and principal investigator of the study said the novel strain they have isolated and the method to produce camptothecin is high-yielding, sustainable, economical and can meet market demands. Camptothecin is the lead molecule used to make topotecan and irinotecan, two widely used anticancer drugs.

"The strain, Alternaria Burnii, which we have isolated from the leaf, during its life in the plant adapts certain metabolism which includes camptothecin, a defence-related compound, possibly from the host plant that produces it," she said. "If we can isolate and cryo-preserve this microorganism, we can repeatedly and indefinitely subculture it and use it. We don't have to go back to the tree and isolate the strain every time," she said.

At present, camptothecin is extracted from the bark of nothapodytes nimmoniana, which takes five to seven years to grow. As the compound is present in various parts of the tree, researchers said the entire tree is uprooted for financial gains. It is also extracted from a Chinese tree, camptotheca acuminata. Nearly 1,000 tonnes of plant material is required to extract one tonne of camptothecin. Due to overharvesting, the plants are now endangered. Researchers said the Indian species has declined more than 20% in the past decade.

HOW IT'S DONE

- IIT-M researchers have developed an alternate method to produce camptothecin, a lead molecule to make topotecan and irinotecan, anticancer drugs
- Researchers isolated a microorganism, Alternaria burnsii, from the **leaf of nothapodytes nimoniana**, an endangered plant native to Western Ghats
- Researchers said the organism extracted from the leaf adapt certain metabolism, including camptothecin, which is believed to have been adapted from the host plant
- The strain, which gives a better yield than other strains, once isolated can be cryo-preserved and can be repeatedly sub-cultured (microbial fermentation process) in a controlled environment to produce camptothecin
- At present camptothecin is extracted from the bark of the tree
- Demand for the molecule is likely to go up as more than a dozen derivatives and conjugates of camptothecin are under various stages of clinical trials for anti-cancer applications

Institute of Technology Madras

- India's premier institute
- Key assets and strengths of Dr Srivastava's lab:
  - 3 Indian patents filed , 1 PCT application. **18** research publications, 4 book chapters on bioprocessing, fermentation and genetic engineering.
  - Team strength: **8**
  - Well equipped labs and analytical facilities
    - Fermenter
    - HPLC
    - LC-Mass Spectrometer
    - Thermocycler, RT-PCR
- Industry Project /Tech transfer: Institute has track record of tech transfers in the the past
- Companies that have approached so far for the same technology: Novartis, GSK, Pfizer, Merrimack Pharmaceuticals, Biocon, Dr. Reddy's Laboratories

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Next Steps

- Upstream process optimization to improve yield and productivity of camptothecin
- Bioreactor cultivation to improve productivity of camptothecin and scale-up (up to 50 L)
- Downstream process development to achieve max product yield and purity (>90%)
- Strain improvement using epigenetic modulators and/or host-plant associated camptothecin biosynthesis enzyme(s) over-expression

Seeking:

- Industrial partners interested in technology licensing
- Industrial partners interested in sponsoring further technology advancement and scale-up
- Industrial partners interested in raising 3rd party funds for a collaborative project.

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