ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 6, Issue, 05, pp.6497-6507, May, 2014

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

REVIEW ARTICLE

DISTRIBUTION OF CAMPTOTHECIN THROUGH THE PLANT KINGDOM

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ARTICLE INFO

Article History:
Received 15th February, 2014
Received in revised form
04th March, 2014
Accepted 19th April, 2014
Published online 20th May, 2014

Key words:

Camptothecin, Plant kingdom,
Endophytic fungi.

ABSTRACT

Many plant derived compounds have been used as drugs both in their original form and in semi-synthetic form. Camptothecin (CPT), a pyrole quinoline alkaloid, is one of the most promising anticancer drug of 21st century. It was first extracted from *Camptotheca acuminata*, since then it has been reported to exist in several plant species and also in plant endophytic fungi. Indiscriminate harvesting of these species for drug has led to a serious threat to these species. The distribution of CPT in the plant kingdom is being described here, so that the stress on the existing sources of CPT can be relieved by finding alternative sources.

INTRODUCTION

Nature has been recognized as a rich source of medicinal compounds for hundred of years. About 20% of the plant species contain alkaloids, which are a diverse group of low molecular weight, nitrogen-containing molecules. Many of these alkaloids are produced as a defense mechanism of plants against herbivores, microbes, viruses and competing plants (Wink, 2003). The potent biological activity of some alkaloids has traditionally been exploited by humans for the treatment of many diseases. The most serious proximate threats when extracting medicinal plants generally are habitat loss, habitat degradation, and over harvesting (Hamilton, 2003). An incredibly large number of people in the world rely on plants as a source of drugs (Raskin *et al.*, 2002; Fransworth *et al.*, 1988). It is estimated that over 50% of all drugs in clinical use are plant derived natural product (Fransworth *et al.*, 1976).

Plants are a common host to a number of microbes including endophytes, which may also influence the production of plant metabolites and may itself capable of producing metabolites as produced by the host plants. Plant endophytic fungi are also an important and novel resource of natural bioactive compounds with their potential applications in pharmaceutical industry. In past two decades, it has been discovered that endophytic fungi contain many valuable compounds with antimicrobial, insecticidal, cytotoxic and anticancer properties (Zhao *et al.*, 2010). There are several plant derived alkaloids, which are currently in clinical use. These include anticancer agent camptothecin (CPT), vincristine, taxol and vinblastine, the muscle relaxant tubocurarine, the analgesics codeine and morphine, the anti malarial quinine, the antiarrythmic ajmalicine, the antibiotic sanguinarine, the sedative scopolamine and the topical analgesic capsaicin (Raskin *et al.*, 2002). National Cancer Institute USA has screened over 435,000 plants for antineoplastic effects (Daniel *et al.* 2001). Considering the enormous significance of these compounds, an extensive research work is going on for the standard methodologies for their large scale production. It is estimatsd that plant derived compounds constitute more than 50% of anticancer agent (Newman *et al.*, 2003; Nikun *et al.*, 2011). More than 3000 plant species have been reported to be used in cancer treatment. Over 60% of currently used anticancer agents are derived from natural sources including plants, marine organisms and microorganisms (Cragg *et al.*, 2003).

Among the plant derived compounds, Camptothecin, a quinoline alkaloid, has emerged as successful antineoplastic agent. It was discovered in 1966 by M.E Wall and M.C Wani in systemic screening of natural products for anticancer drugs. It was isolated from the bark and stem of *Camptotheca acuminata* a tree native to China used as a cancer treatment. During the last half century, scientists have discovered its potential as a selective anticancer drug (Wu *et al.*, 1995). Camptothecin is an expensive chemical, costing about US$ 170/250 mg. The development and marketing of this drug have been approved for treatment of ovarian, breast, lung, and colon cancer (Giovanella *et al.*, 1989). It has been used for leukemia and diseases of liver, gall bladder, spleen, and stomach and to improve chemotherapy of patients with locally advanced or metastatic colon carcinoma (Suchita Kamble *et al.*, 2011).

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Camptothecin compounds are effective inhibitors of hemoflagellate growth and are useful in treating leishmaniasis and trypanosomiasis in livestock, other domestic animals and humans. It inhibits Tat-mediated transactivation of HIV-1(Li *et al*., 1994). When put on clinical trials, camptothecin was more effective than any previous cancer therapies. However, there was a downside. Camptothecin was proven to be too toxic. The result was discouraging, but the research did not halt, in 1995, after forty years since camptothecin was discovered, its two water soluble derivatives came into light. These two derivatives, Irinotecan (CPT-11) (Masuda *et al.,* 1992; Abigeres *et al*., 1995) and topotecan (TPT) (Lilenbaum *et al*., 1995; Romanelli *et al.,* 1998; Clements *et al.,* 1999), have gained approval by the Food and Drug Administration of the United States of America (FDA) for treating colorectal and ovarian cancer. Other camptothecins, such as 9-aminocamptothecin (9AC), 9-nitrocamptothecin (9NC), and 7-(4-methylpiperazino-methylene)-10,11-ethylenedioxycampto thecin (GG211)—have also showed remarkable potential in the treatment of carcinoma (Wall and Wani, 1996; Giovanella, 1997; Stevenson *et al.,* 1999). Camptothecins are lauded as one of the most promising anticancer drugs of the twenty-first century (Li and Adair, 1994).

The unique mode of action for this potent cytotoxic compound was found to act via inhibition of the enzyme DNA topoisomerase (M.R. Mattern *et al*. 1991). It was discovered that camptothecin interacts with DNA topoisomerase I, essential for DNA replication. This leads to the formation of putative covalent reaction intermediate, a reversible Topo I-CPT-DNA ternary complex. The interaction between the DNA replication machinery and the ternary complex causes cell death (Kjeldesen *et al*., 1992). Camptothecin is not selective in its action. It cannot differentiate tumor and normal cells. Both cells will be killed. However, normal cells grow back (Wu Du, 2003). It is well known from chemotaxonomy that members of a family and related family have similar metabolites. Quite often, even allelochemicals of high structural specificity and complexity occur simultaneously in unrelated families of the plant kingdom. Camptothecin is an example of this kind of metabolites. Chemotaxonomists have compared the known distribution patterns of camptothecin with the phylogenetic system of classification of the angiosperms, finding surprising results (Wink, 2003). Hence, the search for camptothecin in other plants is on. Some endophytes have also the ability to produce camptothecin as originated from the host plants (Table 2).

At present, the major supply of this bioactive compound CPT is still from the wild trees *Camptotheca accuminata* and *Nothapodytes foetida.* As the growing demand of this compound, it has resulted in extensive cropping of trees in India and China. It is necessary to further find high yielding candidates and alternative sources to produce this bioactive compound and its analogues (Amna *et al.* 2006; Shweta *et al.,* 2010). With the ever increasing demand for camptothecin supply, it is essential to establish a feasible system for its sustainable and economically viable large scale production. Although camptothecin was originally isolated from *C.accuminata,* this compound has been known to be distributed in a relatively wide range of species of 5 families from China, Tibet, Australia and India namely Apocynaceae, Icacinaceae, Gelsemiaceae, Rubiaceae and Nyssaceae. It is also found to be produced by some endophytic fungi namely *Entrophospora infrequens, Fusarium solani and Neurospora sp.* Table 1 gives the brief account of camptothecin distribution in different parts of various plant species.

Family Apocynaceae:

Apocynaceae is a family of angiosperms that includes trees, shrubs, herbs, stem succulents, and vines. Members of the family are native to European, Asian, African, Australian and American tropics or subtropics, with some temperate members (Endress *et al.,* 2000). There are also perennial herbs from temperate zones. A characteristic feature of the family is that almost all species produce milky sap (Wong *et al.,* 2001). Many genera of this family are known to yield camptothecin.

Chonemorpha fragrans: It is a liana belonging to Western Ghats which shows the presence of camptothecin (Kulkarni *et al*., 2006). Kedari *et al.* (2013) established the *in vitro* culture of *Chonemorpha fragrans* and detected the presence of camptothecin. The highest amount of camptothecin was found to present in root (0.026% ±0.0005 of dry weight) followed by stem bark (0.014%±0.00043). In case of *in vitro* cultures, shoots showed 0.002%±0.00004 of the dry weight and callus showed 0.001%±0.00062 of the dry weight (Kedari *et al.,* 2013).

Chonemorpha grandiflora*:* It is a shrub widely distributed in moist forests of India (Nishitha 2006). It is a medicinal plant, which has been assigned endangered status in Karnatka and vulnerable in Kerala (Kha *et al.,* 2006). Phytochemicals investigations have revealed the presence of steroidal alkaloids in this plant (Banerji *et al.,* 1973). Camptothecin was detected and identified in ehanolic extracts of stem with bark and callus derived from *Chonemorpha grandiflora*. Camptothecin content was 0.013 mg/g in stem bark and 0.003 mg/g in callus (Kulkarni *et al.,* 2010).

Ervatamia heyneana*:* Many indole alkaloids, sterols, triterpenoids have been reported from latex, root bark, roots, seeds, and stem bark of the plant *E. heyneana*. (Sati *et al*., 2009). Joshi Dighe *et al.* developed HPTLC method for quantification of camptothecin from stem bark powder of *Eravitamia heyneana* (Wall.) collected from Dapoli, Maharastra, India. The mean percent content of camptothecin found from ethanolic extract of dry stem powder by the proposed method, was found to be 0.0413 mg/g (Dighe *et al.,* 2007).

Family Icacinaceae

Icacinaceae is a family of flowering plants, consisting of trees, shrubs, and lianas, primarily of the tropics. Many genera of this family produces many useful drugs. Maximum yield of camptothecin has been recorded in the member of this family (Namdeo *et al.,* 2012; Kestur *et al.,* 2012). In a recent study, thirteen species of this family namely, *Apodytes dimidiata, Codicarpus andamanicus, Gomphandra comosa, Gomphandra coriacea, Gomphondra polymorpha,*

Table 1. Sites of accumulation of CPT in several natural sources

Species	Tissue Analysed	CPT Content (%)	Reference
	Young leaves	0.4-0.5	
	Bark	0.18-0.2	Lopez-Meyer *et al.* (1994)
	Roots	0.04	
	Seeds	0.3	
		0.03-0.084	Jingle *et al.*, 2011
	Fruit	0.102	Zeng *et al*., 2013
	Leaves	0.0238	
Camptotheca acuminata	Hairy roots	0.1	Lorence *et al.* (2004)
		0.112	Xiaoning *et al*., 2011
	Callus	0.2040-0.2360	Wiedenfeld *et al.* (1997)
	Cell cultures	0.00025-0.0004	Sakato *et al*. (1974); van Hengel *et al.* (2002)
Camptotheca lowreyana	Young leaves	0.3913-0.5537	Li *et al.* (2002)
	Old leaves	0.0909-0.1184	
Camptotheca yunnanenis	Young leaves	0.2592-0.4494	Li *et al*. (2002)
	Old leaves	0.059	
Chonemorpha fragrans	Root	0.026	
	Stem bark	0.014	Kedari *et al*., (2013)
	In vitro shoots	0.002	
	Callus	0.001	
Chonemorpha grandiflora	Stem bark	0.0013	Kulkarni *et al.* (2010)
	Callus	0.0003	
Ervatamia heyneana	Wood and stem bark	0.13	Gunasekera *et al.* (1979)
	Stem	0.00413	Dighe *et al*, (2007)
Ixora coccinea	Young leaves	0.041	Saravanan *et al*. (2011)
	Mature leaves	0.51	
Nothapodytes foetida	Callus	1.3	Thengane *et al.*,(2003)
	Bark	0.23	Namdeo *et al*., (2010)
	Seeds	0.74	Lokesh *et al*., (2011)
	Leaves	0.08	Dandin *et al*., (2012)
	Roots	2.62	Namdeo *et al.*, (2012)
	Fruits	1.22	
	Stem	0.81	
	Leaves	0.7	
Nothapodytes pittosporoides	Roots	0.172	Zeng *et al*., (2013)
Merriliodendron megacarpum	Leaves and stem	0.0530	Arisawa *et al.*, (1981)
Miquelia dentata	Seeds	1-1.4	Ramesh *et al.*, (2013)
Mostuea brunonis	Entire plant	0.0300	Dai *et al*., (1999)
Ophiorrhiza alata	Wild plant	0.0083-0.0388	Pornwilai *et al.*, (2011)
	In vitro plants	0.0094-0.0556	
	Hairy roots	0.0785	
Ophiorrhiza japonica	Entire plant	0.0073	Wang *et al.*, (2009)
Ophiorrhiza kuroiwai	Hairy roots	0.0219	Asano *et al*., (2004)
Ophiorrhiza liukiuensis	Hairy roots	0.0083	Asano *et al*., (2004)
Ophiorrhiza mungos	Multiple shoots	0.063	Dintu *et al.*, (2012)
	Wild plant	0.052	
Ophiorrhiza prostrata	Adventitious roots	0.16	Martin *et al*., (2008)
Ophiorrhiza pumila	Leaves	0.0300-0.0400	Saito *et al.*, (2001)
	Young roots	0.1	
	Hairy roots	0.1	
Pyrenacantha klaineana	Stems	0.00048	Zhou *et al.*, (2000)

CPT- Camptothecin

Table 2. Camptothecin producing endophytic fungi and their host plants

Endophytic fungus	Fungal strain	Host plant	CPT yield	Reference
	RJMEF 001		-	Puri *et al*., (2005)
Entrophospora infrequens		*Nothapodytes foetida*	49.6 µg/g	Amna *et al.*, (2006)
	5124			
Neurospora sp.	ZP5SE	*Nothapodytes foetida*	-	Rehman *et al.*, (2008)
Fusarium solani	INFU.Ca/KF/3	*Camptotheca acuminata*	-	Kusari *et al*., (2009)
	MTCC 9667	*Apodytes dimidiata*	0.37 µg/g	Shweta *et al*., (2010)
	MTCC 9668		0.53 µg/g	
Unidentified	XK001	*Camptotheca acuminata*		Min *et al*., (2009)
Phomopsis sp.	UAS014	*Nothapodytes nimmoniana*	21.7µg/g	Gurudatt *et* al., (2010)
Fomitopsis sp.	MTCC 10177		-	Shweta *et al*., (2013)
Alternaria alternata	MTCC 5477	*Miquelia dentata*	-	
Phomposis sp.			-	
Aspergillus sp.	LY341		7.93µg/L	
Aspergillus sp.	LY355	*Camptotheca acuminata*	42.94µ/L	Pu *et al.*, (2013)
Trichoderma atroviride	LY357		197µ/L	

CPT- Camptothecin

Gomphandra tetrandra, Iodes cirrhosa, Iodes hookeriana, Miquelia dentate, Miquelia kleinii, Natsiatum herpeticum, Pyrenacantha volubilis and *Sarcostigma kleinii*, are reported to produce camptothecin (Ramesh *et al.*, 2013).

***Nothapodytes foetida*:** It is a small tree occurs in the wild in the forests of the Western Ghats, more frequent in the Maharashtra region. Calluses and cell suspension culture of *Nothapodytes foetida* were found to produce small amount of CPT and MCPT (Roja and Heble 1994; Ciddi and Shuler 2000; Fulzele *et al*., 2001). Latter on attempts were made to enhance the CPT content in the *in vitro* cultures of *N. foetida* by changing the growth conditions, media composition etc. In relation to media composition maximum concentration of CPT was recorded 0.01% DW (Fulzele *et al*., 2002), 1.306% DW (Thengane *et al*, 2003) in the callus culture and untransformed root of *N. Foetida* respectively. Recent studies indicated the increase in CPT content which ranged from 0.021% DW(Kestur *et al.*, 2012), 0.08% Dw (Dandin *et al.*, 2012) in regenerated leaves to 2.62% in roots, 1.22% in fruits, 0.81% in stem and 0.7% in leaves (Namdeo *et al.*, 2012).

***Nothapodytes pittosporoides*:** It is a traditional Chinese herbal medicine. Pan *et al.*, recently reported that *N. pittosporoides* also contain camptothecin (Pan *et al*., 2010). Roots of *N. pittosporoides* were found to contain 0.172% camptothecin (Zeng *et al.*, 2013).

***Miquelia dentate*:** It is found in southern Western Ghats mainly in Kerela, Karnatka and Tamil Nadu. It is a climbing shrub and found to produce camptothecin. Seeds of *M. dentate* were found to produce 1.0-1.4 % by dry weight CPT. Further analysis revealed the presence of other derivatives of camptothecin like, 10-hydroxycamptothecin, 9-methoxycamptothecin and 20-deoxycamptothecin (Ramesh *et al.*, 2013).

Family Gelsemiaceae

Gelsemiaceae is a family of flowering plants, belonging to order Gentianales. The family contains only two genera: *Gelsemium* and *Mostuea*. *Gelsemium* has three species, one native to Southeast Asia and southern China and two native to Southeastern United States, Mexico and Central America. The eight species of *Mostuea* are native to tropical South America, Africa, and Madagascar.

Mostuea brunonis: It occurs from Ghana east to Kenya and south to Angola and Mozabique. It is also found in Madagascar. It is much branched shrub, undershrub or occasionally a liana upto 7 m tall. It is widely distributed and hence not threatened by genetic erosion. It contains several indole alkaloids. The active ingradient of *Mostuea brunonis* found so far (camptothecin and its derivatives) have interesting anticancer activities. The cytotoxic crude organic extract of *M. brunonsis* was initially fractioned through a solvent-solvent partition protocol (Wagenen *et al*., 1993). After few years bioassay-directed fractionation led to the identification of new quinoline and indole alkaloids glycosides, 20-β-glocopyranosyl camptothecin and the yield estimated by HPLC was 0.01% DW (Dai *et al*., 1999).

Family Rubiaceae

A wide variety of growth forms are present in the Rubiaceae. While shrubs are most common, members of the family can also be trees, lianas or herbs. Although Rubiaceae are found in nearly every major regions of the world, diversity is high in humid tropics. Several species had been reported in this family as new sources of camptothecin.

Ixora coccinea: It is a common flowering shrub native to Asia including Bangladesh, Southern India, and Sri Lanka (Ghani, 2003). *Ixora coccinea*, is a dense, multi branched ever green shrub commonly 1- 2 m in height, but capable of reaching up to 3.6 m height. Various parts of this plant are used for treating diarrhea (Ghani, 2003), dysentery, leucorrhoea, dysmenorrhoea, hemoptysis and catarrhal bronchitis (Ghani, 2003). Latha *et al.*,1998 reported the Cytotoxic and antitumour principles from *Ixora coccinea* flowers using intraperitoneally transplanted Dalton's lymphoma (ascitic and solid tumours) and Ehrlich ascites carcinoma (EAC) tumours in mice. Further the presence of this compound was confirmed through authentic samples and the CPT content for mature and young leaves was found to be 0.51% and 0.041% respectively (Saravanan *et al.*, 2011).

Ophiorrhiza pumila: Hairy roots of *Ophiorrhiza pumila* contained 0.79 mg/g DW CPT on average. CPT was also examined in the regenerated plants derived from hairy roots and it was found to be 66-111% of CPT compared with that in wild type *O. pumila* plant (Watase *et al.*, 2004).

Ophiorrhiza rugosa: It is a rare herb found in northern Western Ghats of India. It is usually found in semi-green and evergreen forests along the banks of perennial streams or moist soils along water sources. It is an understorey herb and grows up to a height of 20-30 cm. In a study conducted for the estimation of camptothecin in the natural populations of *Ophiorrhiza rugosa*, significant higher levels of CPT were found in the roots (0.16%), than stem (0.8%), fruits (0.01%) and old leaves (0.002%). Vineesh *et al*., established multiple shoot and root culture of *O. rugosa* and studied the effect of growth hormones on CPT production. Maximum amount of CPT in multiple shoots was 0.039% and in roots it was 0.065% (Vineesh *et al.*, 2007).

Ophiorrhiza prostrate: It is a herbaceous species, distributed in tropical Indo-Malaysian region (Valdu *et al*., 2000). It is exploited for the production of camptothecin, which is mainly accumulated in the roots (Beegum *et al*., 2007). Adventitious roots showed a stable production of camptothecin i.e. 0.16% (Martin *et al.*, 2008). A study was conduted for the detection of CPT in *O. prostrata* by DART-MS and it was estimated by HPTLC which was found to be 1.465 µg/g dry weight (0.0001465%) (Krishankumar *et al.*, 2012).

Ophiorrhiza mungos: It is a small under shrub grow upto 60 cm height, mainly distributed in the primary and secondary forests of India, Srilanka, China, Thailand, Peninsular Malaysia, Sumatra, Java and the evergreen forests of Philippines (Deb *et al*., 1997). It is important due to the presence of camptothecin (Tafur *et al*., 1976). The stem of

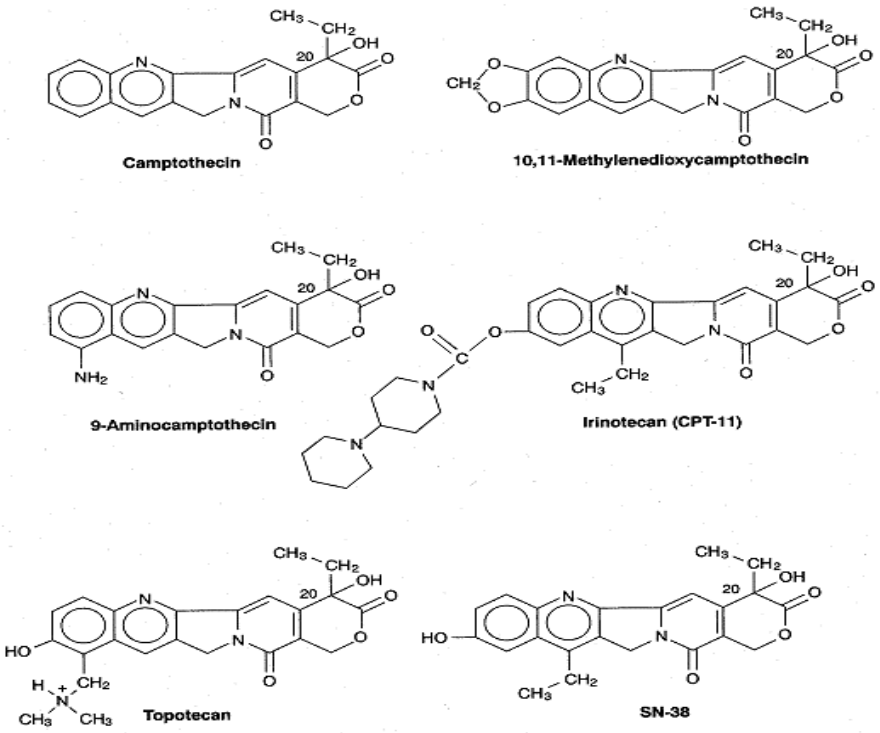

Fig. 1.Camptothecin and other candidates from camptothecin family

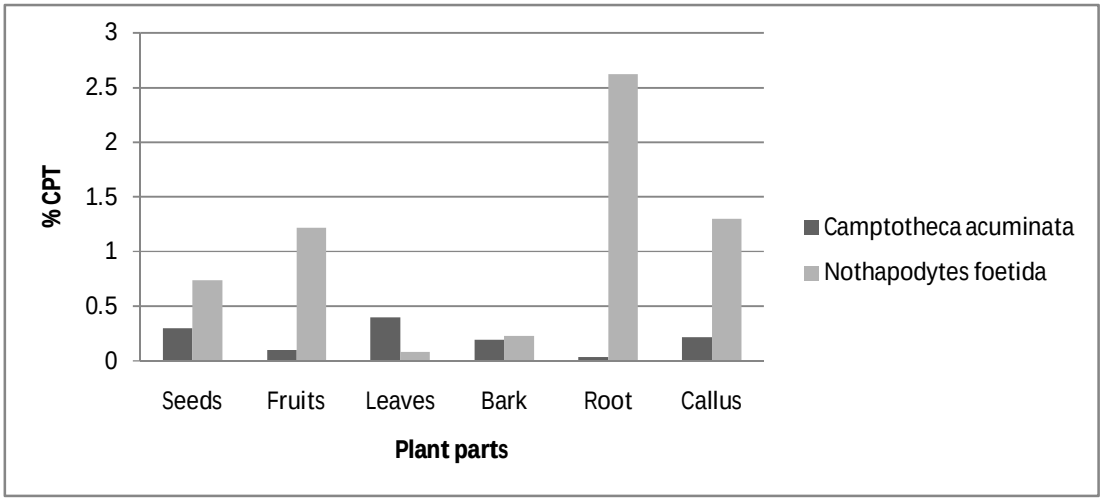

Fig.2. Comparison of CPT content in different parts of *C. acuminata* and *N. foetida*

O.mungos had the highest CPT content (0.009 ± 0.002% DW) compared to roots (0.0027 ± 0.0002% DW) and leaves (0.0005 ± 0.0001% DW) (Jisha 2006). CPT content in both wild and *in vitro* derived multiple shoots showed a significant difference. Multiple shoots contain 0.063% of CPT where as plants collected from the wild contain 0.052% of CPT (Dintu *et al.*, 2012). A study showed the CPT content of 188.60 µg/gm DW in *O.mungos* (Krishankumar *et al.*, 2012).

Ophiorrhiza japonica: *It is* a indigenous Chinese medicinal plant commonly used for ulcers, poisonous wounds and leprosy in China. It was speculated that CPT analogues might also exist in *O. japonica*. One study's results revealed that 0.0073% dry weight of camptothecin was detected in the whole *O.japonica* plant and hydroxycamptothecin was detected only in trace amounts of 0.0001% dry weight (Wang Wei *et al*, 2009). An efficient plant regeneration system from leaf-derived callus of *O. japonica* has been successfully established (Wang *et al*,

2008). As a kind of herb, *O. japonica* grew rapidly, which may be an alternative drug source of raw material for the production of camptothecin.

Ophiorrhiza liukiuensis: It is distributed in Okinawa, Japan, Taiwan and Philippines. One study revealed the *O. liukiuensis* produced camptothecins and other alkaloids (Kitajma *et al.*, 2005). For the feasible production of camptothecin tissue cultures of *Ophiorrhiza liukiuensis* have been investigated. Camptothecin content was found to be 83 ±27.4 µg/g DW in the hairy roots (Asano *et al.*, 2004).

Ophiorrhiza kuroiwai: Camptothecin is also produced in *Ophiorrhiza kuroiwai*. Tissue cultures and hairy roots of this species were established and it was found to be 219.3 ±31.4 µg/g DW in the hairy roots (Asano *et al.*, 2004).

Ophiorrhiza alata*: Ophiorrhiza alata* is an indigenous herbaceous plant found in southeastern Thailand. Comparison of the camptothecin contents in various parts of this plant was done. The soil grown plant contained camptothecin which ranged from 83±21.4µg/g DW to 388±31.5 µg/g DW. In vitro grown plant contain CPT ranged from 94±15 µg/g DW to 556±43.2 µg/g DW where as hairy roots contain 785± 52.4 µg/g DW of CPT (Pornwilai *et al.*, 2011).

Chonemorpha fragrans

Ervatamia heyneana

Nothapodytes foetida

Camptotheca acuminate

Ixora coccinea

Miquelia dentate

Mostuea brunonis

Ophiorrhiza mungos

Pyrenacantha klaineana

Fig.3. Plant species containing Camptothecin

Family Nyssaceae

Small family of flowering trees and shrubs. It is found in Temperates to Tropicals, mainly in Southeast and Eastern Asia and Eastern USA.

Camptotheca acuminate: It is found in south China from the tropical to sub tropical regions, with naturalization to some temperate regions of China (Liu *et al*., 1998). The various organs of the species contain an alkaloid camptothecin and its derivatives. Chinese doctors have used *Camptotheca acuminata* for hundreds to thousands of years in treating colds, psoriasis, cancers and leukaemia of liver, gallbladder, spleen and stomach. The content in the raw material was: bark 0.012%, roots 0.02%, wood 0.05% and fruits 0.02%. The study of *C. acuminata* tissue culture was initiated in Japan by Sakato and Misawa (1974) and camptothecin content in cell suspension culture was found to be 2.54×10^{-4}% DW (Sakato *et al*., 1974). Latter reports of *in vitro* CPT production in this plant ranged from 0.004 mg/g DW in all suspension cultures (Hengel *et al*, 1992) to ≈2 mg/g DW in callus cultures (Wiedenfeld *et al*., 1997). CPT content in young leaves was much higher than in old leaves and was logarithmically related to leaf area and leaf biomass while suggesting a juvenile chemical defense strategy (Yan *et al.*, 2003). The production of camptothecin was 1.5 fold higher than the control in the hairy roots of C. acuminate (Xiaoning *et al*., 2011).

Camptothecin from endophytic fungi

In recent years, endophytic fungi have generated a great deal of attention for the potential role they could play in as important alternative sources of novel plant metabolites (Strobel, 2002). The production of camptothecin by endophytic fungus supports the theory of Young and coworkers that during the course of evolution the symbiotic endophytes developed machinery and survive in association with the medicinal plants. Previously, the production of antileukemic and antitumor drug taxol from endophytes of *Taxus spp.* like *Taxomyces andreanae* and *Pestalotiopsis microspore* has been reported (Strobel *et al*., 2003). Endophytic fungus *Entrophora infrequens* obtained from *Nothapodytes foetida* was reported to have the ability to produce camptothecin (Puri *et al*., 2005). Later, kinetic studies of the growth and camptothecin accumulation of the endophyte *E. infrequens* in suspension culture was performed, and it was demonstrated that this endophyte would be a potential alternative source to produce camptothecin (Amna *et al*., 2006). Another camptothecin producing endophyte *Neurospora sp.* from the seeds of *Nothapodytes foetida* was discovered (Rehman *et al.*, 2008). Kusari *et al.* reported an endophytic fungus *Fusarium solani* from *Camptotheca acuminata* which was able to produce camptothecin, 9-methoxycamptothecin and 10-hydroxycamptothecin (Kusari *et al*., 2009). An unidentified fungal strain was reported to produce 10-hydroxycamptothecin with the yield of 677µg/L (Min *et al*., 2009). Two more strains of the endophyte *Fusarium solani* were found to produce camptothecin and 9-methoxycamptothecin (Shweta *et al.*, 2010). These results give a promising way of exploring the endophytic fungi as a source to produce camptothecin and its analogues. Table 2 gives the available work on endophytic fungi producing camptothecin from various host plants.

Conclusion

Plants have been a major source of pharmaceutically important compounds worldwide. In most cases, the plants are entirely sourced from the wild. The continued commercial exploitation of these plants has resulted in receding the population of many species in their natural habitat. Thus, unless alternative sources

are developed, the extraction from most of the medicinal plants to meet the global demands will be unsustainable. If timely steps are not taken for their conservation, they may be lost from the natural vegetation forever. As we all know there is no synthetic source of camptothecin and with an increasing global demand, it has become imperative that the demand for camptothecin is met from a sustainable supply rather than the current destructive harvesting. Therefore the alternative sources of camptothecin should be searched, thereby relieving the pressure on the endangered species. The previously given methods for increased production of camptothecin are either through the clonal propagation of the elite species, or through the repeated harvest of young leaves , without the destruction of tree (Lorence *et al*., 2004). In the present paper, the various plants species have been described which are the potential source of camptothecin. It has been revealed that some of these new sources yield camptothecin comparable to the plant species which have been exploited in the past for the extraction. Plant endophytic fungi is emerging out to be an important source of camptothecin and further optimization of fermentation conditions and molecular studies of these fungus to get an efficient amount of camptothecin is under way (Rehman *et al*., 2008). It is suggested that rather than putting stress on the endangered plants species, alternative sources should be exploited. It is clear from the above discussion that members of related families as well as unrelated families could be a potential source of camptothecin. Therefore, prospecting for camptothecin from the new sources could create a platform for its production.

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