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Xi Shu, A Promising Anti-tumor and Anti-viral Tree for the 21st Century

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Camptotheca acuminata Decaisne

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喜樹

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(Chinese Happytree)

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Shiyou Li and Kent T. Adair

Foreword by MONROE E. WALL

Preface by BEPPINO C. GIOVANELLA

A Henry M. Rockwell Monograph
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Warning: This book is not intended for prescribing medication or for curing afflictions. The use of any of this information for purposes of self-treatment without consulting a physician can be dangerous.

This work is dedicated to

Dr. Monroe E. Wall

for his contribution to camptothecins

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FOREWORD

Camptothecin (CPT) is a secondary metabolite formed by a tree, *Camptotheca acuminata* Decaisne, which is a native of China. During the period 1950-1960, I was the director of a group of chemists at the Eastern Regional Research Laboratory, USDA, searching the Plant Kingdom for plants which might contain suitable precursors for the synthesis of cortisone, a recently discovered anti-inflammatory agent then in short supply. USDA botanists collected more than 7,000 plant samples. A number of these had never received chemical examination, hence we saved extracts of these plants. One of these extracts was prepared from the fruit of *C. acuminata.* In 1957, Dr. Jonathan Hartwell, NCI, visited my laboratory and requested available plant extracts for antitumor testing in mice. I readily complied, and by 1958 learned of the extraordinary activity of *C. acuminata* extracts. In 1960, I joined the Research Triangle Institute and organized a natural products group, which was joined in 1962 by my long time collaborator, Dr. M.C. Wani. This led to the isolation and structure elucidation of camptothecin from bark and wood of *C. acuminata* trees in 1966. A few years later in 1971, our same group isolated taxol.

Drs. Shiyou Li and Kent T. Adair have prepared a monograph which reviews in a thorough manner the subsequent history of CPT and analogs from discovery to

promising clinical drugs. In addition, the monograph provides a wealth of novel data concerning botanical, ecological, agronomical, and cultural information, much of it presented for the first time in this interesting monograph.

Monroe E. Wall, Ph.D.

Chief Scientist
Chemistry and Life Sciences
Research Triangle Institute
Research Triangle Park, NC
September 1994

PREFACE

This book appears at a time when interest in camptothecin and its derivatives is beginning to grow exponentially. Interestingly, the product(s) of *Camptotheca* tree have been known for quite a few years since the finding that *Camptotheca* extracts possess anticancer activity and the isolation and characterization of the active component, camptothecin, respectively, in 1958 and 1966. Unfortunately, there was a false start due to the use of the sodium salt for clinical trials instead of the natural product because of the good water solubility of the salt. When the salt was found to be inactive and toxic, as it is, camptothecin was assumed to be also inactive and discarded, a classical case of throwing the baby away with the water. A period of eclipse followed but not of inactivity. It was found that camptothecin is the main inhibitor of DNA topoisomerase I, explaining its mechanism of action as cell growth inhibitor and a big clue to its anticancer activity. Water soluble derivatives were synthesized, some of which maintained part of the anticancer activity of the mother compound. Finally, a series of water insoluble derivatives was synthesized by Wall and Wani which, in 1989, were found to have anticancer activity superior to camptothecin. The difference in activity between camptothecin and its sodium salt was established. Camptothecin itself was re-evaluated and successfully run

through Phase I Clinical Trials at the Stehlin Foundation, demonstrating tolerable toxicity almost exclusively of intestinal origin. Phase II Clinical Trials are now due to begin treating breast cancer by oral administration at the Stehlin Foundation and at Dana Farber Cancer Institute in Boston. Another non-water-soluble derivative, 9-amino-camptothecin, has undergone Phase I Clinical Trials at Dana Farber and at the Naval Hospital in Bethesda administered intravenously in a special solvent. Other derivatives are under study and in various phases of development for utilization as anticancer, antiviral, and antiparastic drugs. It appears that we are now poised for the big leap forward of this group of compounds into practical utilization of the potent biological activity of camptothecin and its derivatives. This book is arriving at the right moment, bringing a large amount of very welcome basic information on the subject.

Beppino C. Giovanella, Ph.D.

Laboratory Director
The Stehlin Foundation for Cancer Research
Houston, Texas
October 1994

AUTHORS' PREFACE

Many important scientific discoveries are made retrospectively. One well-known example is the rediscovery of Mendel's findings in genetics. However, camptothecins, promising anti-tumor drugs extracted from Xi Shu (Chinese happytree, *Camptotheca acuminata* Decaisne), are a recent example. Dr. M. E. Wall at Research Triangle Institute found the anti-tumor activity potential of camptothecin about thirty years ago. However, studies were almost abandoned in the United States for nearly two decades after a finding of high toxicity. Recently, the drugs were "rediscovered" in the United States as promising drugs. Consequently, Xi Shu extracts are now in a position to play a major role in the fight against cancers.

Taxol, a potent anti-tumor drug that was first isolated from the bark of the Pacific yew (*Taxus brevifolia*) by Dr. Wall and associates in 1971 recently caused a stir throughout the scientific community. It brought new hope to millions of cancer patients. The clinical trials show that taxol is particularly outstanding for ovarian cancer. Camptothecins, are also very valuable drugs with different uses. Chinese and Japanese long-term clinical trials since 1970 show that camptothecins have a broad spectrum of medical uses. The recent discovery of its unique mechanism of action has shown the clinical value of the drug. Dr. B. C. Giovanella, world-renowned scientist from the Stehlin Foundation for Cancer Research in Houston, clearly stated that camptothecin is the most promising

anti-cancer drug that has ever been found. In addition, recent experiments show camptothecins have activity against many DNA viruses and even some RNA viruses, including retroviruses that cause some severe diseases in humans and animals. Xi Shu, as the main botanical source of camptothecins, grows very fast, up to about 1.6 meters a year in favorable conditions, and all parts can be used for drug extractions. All these features give Xi Shu status as an anti-tumor plant in drug development. Thus, Xi Shu provides renewed hope for cancer treatment.

It is expected that at least 100 million young Xi Shu will be needed annually for the drugs camptothecins in the United States in very near future. However, the seed source is scarce and the gene pool is very small in the United States. Thus, the drug supply will be limited by the Xi Shu supply. This monograph is an update summary of botanical, ecological, chemical, and medical research on Xi Shu. And the bibliography includes about 1,300 publications in English, Chinese, Japanese, and other languages. Hopefully, it provides a stimulus and guide to further studies, especially in resource development, of drug derivatives from this very interesting tree.

Shiyou Li, D.F.

Kent T. Adair, Ph.D.

Nacogdoches, Texas
August, 1994

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1. INTRODUCTION

Cancers and Taxol

Today, about 75% of the world's population still relies on plants or plant extracts as traditional medicine for primary health care. There are 119 pure chemical substances extracted from higher plants that are clinically used throughout the world (Farnsworth 1988). These plant-derived drugs are obtained from less than 90 species, or only 0.036% of the total 250,000 described plant species. Extensive studies of plants for possible medical applications are very limited. Regardless, the finding of each new drug brings new hope for humans and may even cause a revolution in human life itself. Taxol, for example, an alkaloid that was first extracted from the bark of the native Pacific yew (*Taxus brevifolia* Nutt.) by Dr. Monroe E. Wall in 1971 has recently caused a stir throughout the scientific community as a very promising drug in the treatment of certain cancers. Several thousand terminal cancer patients have taken taxol since trials began in 1983 (Joyce 1993). These clinical trials have confirmed that taxol can shrink tumors by at least one half in 20 to 30% of patients with refractory ovarian cancer. The Food and Drug Administration (FDA) approved taxol for general use in advanced ovarian cancer in 1992. The result is a multi-billion-dollar industry with an international network to produce taxol. Consequently, for a time, the Pacific yew became one of the most valuable plant species in the world. However, three major obstacles limited early development of the drug: source scarcity, toxicity, and poor water solubility.

The short supply of the Pacific yew was a critical problem. Currently, 20,000 women are diagnosed with ovarian cancer and 12,000 die each year in the United States (Murray 1991).

The National Cancer Institute (NCI) of the National Institutes of Health (NIH) contracted with Bristol-Myers Squibb to obtain 337,500 kg (750,000 pounds) of yew bark a year to meet this requirement (Johnson 1992). This requires up to 144,000 new mature trees each year because stripping the bark (at that time the sole source of the drug) kills the tree. In 1993, about 1,170,000 people in the United States were diagnosed as having cancer and 526,000 died of this disease (Boring et al. 1993). Each year one in ten women is confronted with breast cancer and must make decisions regarding treatment (Scanlon 1991). If taxol is approved for treatment of some of these cancers (e.g., breast cancer), the annual demand for yew could jump to many millions of trees. However, it is estimated that the total number of yew trees with trunks of 25.4 cm (10 inches) or more in diameter is only 1.2-4.0 million (Murray 1991, Joyce 1993). This is not enough to meet a single year's total demand in the United States alone! Moreover, the yew is one of the world's slowest-growing species, it takes 100 years or more to mature. To meet the demand for taxol, an international effort, led by Bristol-Myers Squibb, taxol's only manufacturer, has been undertaken to look for new ways to provide taxol, especially semisynthetic procedures using the needles and top portions of *Taxus baccata,* a shrub, and production of totally synthetic taxol. In early 1994, two groups of scientists (K. C. Nicolaou of the Scripps Research Institute and R. Holton of Florida State University) announced a total synthesis of taxol. Unfortunately, according to Matthew Suffness, a chemist in the NCI, neither of these two groups' methods are likely to be commercially viable at this early stage; even after the synthesis technique has been refined, it may be less expensive to make commercial taxol out of trees (Flam 1994). Also, the synthesis of taxol cannot, in any way now known, increase the drug supply in the near future. Moreover, toxicity and poor solubility of taxol make it hard to administer, and tumor cells tend to develop resistance to the drug thus making Xi Shu an attractive source of camptothecin for treatment of some forms of cancer.

Camptothecins and Hope

Camptothecin (CPT, also known as camptothecine) and its analogs are promising anti-tumor drugs with many different uses (**Table 1**). The drugs are extracted from Xi Shu (*Camptotheca acuminata* Decaisne), a Chinese deciduous tree of the family Nyssaceae, and have unique mechanisms of action. Unlike taxol and its analogs that can be extracted principally from bark of mature yew trees, camptothecins can be collected from all parts and all ages of Xi Shu. Also, recent experiments showed that camptothecins have activity against viruses including retroviruses, the causative agents of acquired immune deficiency syndrome (AIDS) and many other severe diseases in humans and animals (Priel et 1991, 1993, Li et al. 1994a, b; **Table 2**).

The anti-tumor activity of Xi Shu was discovered in 1957 (Perdue et al. 1970) and its anti-viral activity was reported in 1971 (Horwitz and Horwitz 1971). These activities have been emphasized recently. The isolation of CPT, a potential drug extracted from Xi Shu, was accomplished in 1965, several years earlier than that of taxol. The first report of clinical trials of CPT appeared in 1970 (Gottlieb et al. 1970); thirteen years earlier than those of taxol. Unfortunately, further investigation of CPT ceased several years later in the United States because of the severe, unacceptable bladder toxicity of the sodium salt, which was thought a necessity for effective use of CPT. However, the use of CPT in clinical trials has continued in China since 1970.

In China CPT is directly used in treatments, not with the toxic sodium salt. Also, 10-hydroxycamptothecin, a less toxic and more effective analog of CPT, has been successfully used to treat liver, neck, and head cancers in China. The discovery in 1985 that camptothecins uniquely inhibited the activity of the DNA topoisomerase I (topo I) along with the factors mentioned above resulted in a rapid resurgence of international research and commercial interest in these drugs. Xi Shu promises to be one of the most important anti-tumor and probably also anti-viral trees worldwide.

TABLE 1. **General profiles of camptothecins and taxols.**

Property	Camptothecins	Taxols
Main Source	Xi Shu (*Camptotheca acuminata*)	Pacific yew (*Taxus brevifolia*)
Anti-tumor Activity	Discovered in 1957 and documented in 1966 by M.E. Wall and co-workers (Perdue et al. 1970)	Discovered in 1963 and documented in 1966 by M.E. Wall and co-workers (Hawkins 1992)
Anti-viral Activity	Reported in 1971 by Horwitz and Horwitz (1971) and emphasized in the early 1990s by others	No
Drug Isolation	In 1965	In 1971
Chemical Classification	Quinoline	Complex diterpene
Water Solubility	CPT is insoluble, and some analogs are water-soluble	Insoluble, and some analogs are water-soluble
Toxicity	Sodium salt: toxic; suspension: less toxic	Toxic
Physiological Action	Inhibit DNA synthesis through stabilizing the cleavable complex of DNA and the enzyme topoisomerase I	Binds to mitotic spindles so that cells cannot replicate
Parts for Drug Extraction	All parts (stem, stem bark, leaf, root, root bark, and fruit)	Stem bark
Plant Supply	Short, not native and rare cultivation in the United States	Short, native but rare in the United States
Tree Growth	Fast, 20 years to maturity, up to 30 m tall	Slow, 100 years to maturity, up to 15 m tall

TABLE 2. **Citations on the uses of camptothecins cross-referenced to taxols.**

Use	Camptothecins	Taxols
Clinical Trials and Responses in Cancers:	First reported in 1970, mostly from the United States, China, and Japan	First reported in 1983, mostly from the United States
Breast	1a	37, 38
Central Nervous	81a	---
Colon & Rectum	1a, 3, 5, 7c, 8c, 9, 11b, 29c, 30a, 36c, 64, 72ac, 73a, 76a, 77a	---
Esophageal	10a, 70ac	---
Head	6, 11b, 36c	39
Kidney	1a, 35a	40
Leukemia	3, 12c, 13, 14a, 68a	---
Liver	11b	---
Lymphoma	11b, 12c, 28c	---
Melanoma	1, 15, 36c	41, 42
Neck	6, 10a, 36c	39
Non-small-cell Lung	1a, 3, 4, 16a, 18a, 19c, 21c, 22a, 23c, 24c, 25c, 26c, 27c, 48c, 71bc, 75c, 78c, 79c, 82	43-45
Ovarian	1a, 2c, 16a, 17c, 36c, 69ac	46-48, 65
Prostate	80	49, 66
Psoriasis	32-34	---
Small-cell Lung	18a, 20c, 25c, 35a, 78c, 79c, 82	---
Stomach	4, 6, 15, 35a	---
Testis	36c	---
Trophoblastic	11b	---
Urinary Bladder	6, 30a	67
Uterine Cervix	2c, 7c, 17c, 36c, 74c	---
Anti-viral Activity	51-56	---
Insect Chemo-sterilant	57, 58	---
Plant Growth Regulator	59-63	---

NOTES TO TABLE 2.

Subscripts: a—topotecan (TPT); b—10-hydroxycamptothecin (HCPT); c—irinotecan (CPT-11); others—camptothecin (CPT); ----no data available.

References (see Literature Cited):

1—Burris et al. 1992;
2—Takeuchi et al. 1991a, b;
3—Gottlieb et al. 1970;
4—Muggia et al. 1972;
5—Moertel et al. 1972;
6—Xu et al. 1979;
7—Rowinsky et al. 1992;
8—Gandia et al. 1992;
9—Bertrand et al. 1992;
10—Sirott et al. 1991;
11—Shanghai Institute 1975;
12—Ohno et al. 1990;
13—Furuta and Yokokura 1991;
14—Beran et al. 1992;
15—Gottlieb and Luce 1972;
16—Rowinsky et al. 1992;
17—Takeuchi et al. 1992;
18—Verweij et al. 1992;
19—Masuda et al. 1992;
20—Masuda et al. 1992;
21—Musuda et al. 1993;
22—Lynch et al. 1994;
23—Shinkai et al. 1994;
24—Noriyuki et al. 1994;
25—Negoro et al. 1991;
26—Fukuoka et al. 1992;
27—Kanzawa et al. 1992;
28—Tsuda et al. 1992;
29—Shimada et al. 1993;
30—Hass et al. 1992;
31—Gu et al. 1987;
32—Chiao and Li 1974;
33—Lin 1987;
34—Lin et al. 1988a, b;
35—Saltz et al. 1993;
36—Abigerges et al. 1994;
37—Holmes et al. 1991;
38—Seidman et al. 1992;
39—Forastiere 1993;
40—Einzig et al. 1988a;
41—Einzig et al. 1988b;
42—Legha et al. 1990;
43—Chang et al. 1992, 1993;
44—Murphy et al. 1992, 1993;
45—Eisenhauer 1993;
46—McGuire et al. 1989;
47—Thigren et al. 1990;
48—Einzig et al. 1990, 1992;
49—Roth et al. 1992;
50—Shinkai et al. 1994;
51—Prielet al. 1991;
52—Priel et al. 1991;
53—Cheng et al. 1992;
54—Kerr et al. 1993;
55—Priel et al. 1993;
56—Li et al. 1994a, b;
57—DeMilo and Borkovec 1974;
58—Hunan Institute 1978;
59—Buta and Worley 1976;
60—Worley et al. 1979;
61—Buta and Spauding 1986;
62—Tao and Buta 1986;
63—Buta and Kalinski 1988;
64—Giovanella et al. 1989;
65—Caldas and McGuire 1993;
66—Yeap and Wilding 1993;
67—Rangel et al. 1994;
68—Kantarjian et al. 1993;
69—Johnson 1992a;
70—Johnson 1992b;
71—Johnson 1992c;
72—Johnson 1993;
73—Burris et al. 1992;
74—Takeuchi 1992;
75—Negoro 1991;
76—Haas et al. 1992;
77—Haas et al. 1994;
78—Niitani 1991;
79—Fukuoka 1991;
80—Stehlin Foundation 1993;
81—Friedman et al. 1994;
82—Burris 1993.

CAMPTOTHECINS,

PROMISING DRUGS

Life is limited, but knowledge is limitless.

——Zuang Zi (c. 4th-3rd century B.C.)

2. HISTORICAL REVIEW

Discovery of Camptothecins

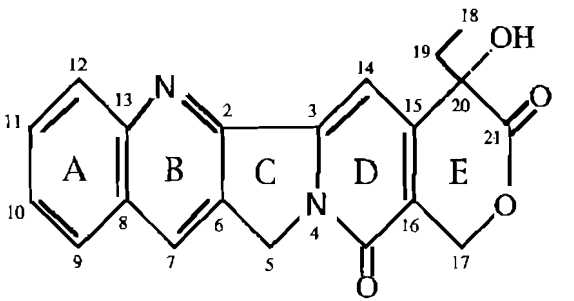
It is widely recognized that Xi Shu had little human use in its native region of China before the 1960s (Perdue et al. 1970). The discovery of its anti-tumor activity has now made it the "Cinderella of the forest."

Recognition of the anti-tumor activity of CPT was established in the United States at about the same time as taxol. In 1950, the United States Department of Agriculture (USDA) began a search of the world's plant resources for species that produce chemical substances which could be converted to cortisone. The chemical branch of the USDA involved in this program was located at the Eastern Regional Research Laboratory, Philadelphia, Pennsylvania, and was under the direction of Dr. M. E. Wall. Xi Shu was one of the plant materials supplied by the Chico Plant Introduction Station in California for the cortisone program. However, an extract of leaves was negative in a test for cortisone precursors. The unused extract was placed on the laboratory shelf where it remained for almost six years. In 1957, Johnathan Hartwell of the Cancer Chemotherapy National Service Center (CCNSC), National Cancer Institute started a plant anti-tumor screening program. Of 1,000 ethanolic plant extracts for testing for antitumor activity sent by Wall, the crude extract of the leaves of Xi Shu were the only ones to have high activity in two tumor systems. But only two trees were known in Chico as the remaining living specimens in the United States. This supply was inadequate to complete any required series of tests (Perdue et al. 1970).

In 1960, Dr. Wall joined the Research Triangle Institute in Durham, North Carolina. He and associates reviewed the

anti-tumor screening data on the old extracts and requested new supplies of Xi Shu. The Chico Station provided new samples of leaves, twigs, and fruits in September 1961. Soon, it was found that leaves were inactive but fruits and twigs were active against lymphoid leukemia L1210 without toxicity *in vitro* (Perdue et al. 1970). By late 1963, Wall and associates started intensive chemical research on isolation and identification of the active compound from Xi Shu. In order to provide adequate raw material for this program, a systematic search for individual specimens of Xi Shu was undertaken along the western coast of the United States. Finally, thirteen trees were found in central and southern California and most of these trees were removed for chemical tests. In March 1965, from the stem wood of Xi Shu, Wall and his colleagues successfully isolated a minute quantity of a pure crystalline substance, CPT, which is responsible for Xi Shu's anti-tumor activity (Wall et al. 1966). The latter techniques established that camptothecin ($C_{20}H_{16}O_4N_2$) is a pyrrolo (3,4,-*b*)quinoline alkaloid, that is, 4(*S*)-4-ethyl-4-hydroxy-1*H*-pyrano-(3',4':6,7)indolizino(1,2,-*b*)quinoline-3,14(4H,12H)-dione **(Figure 1).** The announcement of CPT's structure in 1966 caused considerable excitement in the scientific community. The novel structure and significant anti-tumor activity of CPT greatly stimulated scientists' research.

By 1969 isolation of the alkaloid was also completed in China. Since then, a number of hydroxyl and methoxyl derivatives have been reported by scientists in the United States, China, and Japan. Wani and Wall (1969) first isolated two minor compounds, 10-hydroxycamptothecin (HCPT) **(Figure 1)** and 10-methoxycamptothecin from the stem wood of Xi Shu. Later, Hsu and co-workers (1977) and Lin and others (1979) isolated 11-hydroxycamptothecin, 11-methoxycamptothecin, and 20-deoxycamptothecin from the fruit. Recently, Lin and Cordell (1989, 1990a, b) isolated 22-hydroxyacuminatine and 19-hydroxy-mappicine and pyridoindole alkaloid 19-*O*-methy-langustoline from the fruit. In addition, quercetin, kaempferol, trifolin, and gallic acid have been isolated from Xi Shu (Tien et al. 1977).



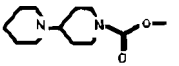
	7	9	10
CPT	H	H	H
TPT	H	$-(CH_3)_2NHCH_2-$	OH
CPT-11	$-CH_2-CH_3$	H	
HCPT	H	H	OH
9AC	H	NH_2	H

FIGURE 1. **Chemical structure of camptothecin and its main analogs.**

CPT and its derivatives are quinoline alkaloids with a novel ring system. But its lack of significant basicity causes it to behave as a neutral molecule so that CPT is not an alkaloid in the usual sense of the definition. Water insolubility and high toxicity of CPT were major problems in clinical trials. In order to overcome the side effects obtained with the sodium salt of CPT in the early 1970s, a number of water-soluble derivatives have been synthesized recently. Two of these derivatives, topotecan (TPT) and irinotecan (CPT-11) are water-soluble, they are in clinical trials and their chemotherapeutic efficacy is promising. HCPT is the basis for making both TPT and CPT-11, and that HCPT can be made readily by synthesis from CPT. Another derivative, 9-aminocamptothecin (9-AC) is not soluble in water, and it is also being introduced into clinical trials. 9-Ac can be prepared either by total synthesis or from CPT.

The procedure for synthesis of CPT is rather complicated, and the first total synthesis was reported in 1971 in the United States by Stork and Schultzin (1971). The total synthesis of more complex HCPT and 10-methoxycamptothecin was first announced in 1977 in China (Cai et al. 1977). In 1980, Wall and associates greatly improved the synthesis of CPT and prepared a number of analogs (Wani and Wall 1980). Wall and co-workers reviewed the synthesis and structure activity of CPT analogs (Wall and Wani 1993, Wall et al. 1993). Many syntheses rely on the Friedlander quinoline synthesis to construct ring B. Although much synthetic work has been reported, most of the syntheses are not commercially attractive.

Several major international drug agents are actively working with camptothecins. NCI is conducting studies with 9-AC. Daiichi Pharmaceutical Company and Yakult Honsha Company in Japan are developing CPT-11. SmithKline Beecham Pharmaceutical Company in the United States is producing TPT. In addition, Glaxo Pharmaceutical Company in the United States, at one time, had the worldwide rights to develop and market CPT analogs for the Research Triangle Institute.

Literature Records

Historical research interest in camptothecins and Xi Shu is clearly recorded in the scientific literature. Totally, 1,113 publications on camptothecins and Xi Shu including books, articles, dissertations, symposium reports, and government documents between 1846 and 1993 have been located and are cited in the Bibliography. 928 publications or 83.4% of the total publications are in English, 89 in Japanese (8.0%), 88 in Chinese (7.9%), and 8 in other languages (0.7%) including Russian, Korean, Italian, French, German, and Turkmen. However, about 40% of the total studies were conducted outside the United States and many of these are published in English.

FIGURE 2. **Description and illustration of Xi Shu in *Zhiwu Mingshi Tukao* by Wu in 1848.**

The first appearance of Xi Shu was in a Chinese book *Zhiwu Mingshi Tukao* (植物名實圖考) (Illustrated investigation of the names and natures of plants) in 1848 (Wu 1848). This Chinese herbal book briefly described morphology and habitat, but not uses (**Figure 2**). It recorded that *Han Lian* (Xi Shu) grows in the western mountains in Nanchang (in Jiangxi), has reddish brown bark, green stems, leaves like those on no-floral shoots of paper mulberry, fruiting in the fall, with tens of fruits together in a ball about

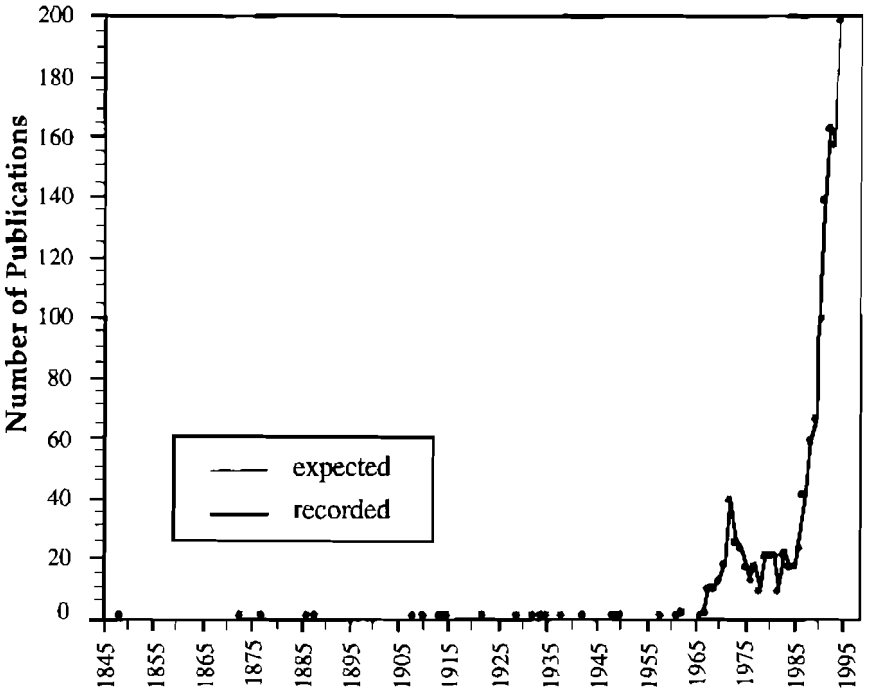


FIGURE 3. **Number of publications on camptothecins and Xi Shu, 1848-1994** (1,113 publications were recorded from 1848 to 1993 with an additional 200 publications expected in 1994. The literature search covers Chemical Abstracts, Biological Abstracts, AGRICOLA, CAB, Life Sciences Collection, Pascal, and MEDLINE through STN International, DIALOG, and others).

the same as the water bean in size, and which resembles *qiu* (a fur ball for a traditional Chinese game).

Only 25 publications from 1848 to 1965 can be found about Xi Shu and all are concerned with botany. Since the isolation of CPT in 1965, publications have shown two active periods (**Figure 3**). The first period was from 1971 to 1974, which averages about 28 publications each year (total 110 items or about 9.9% of a total of 1,113 publications) and the research had expanded to include a wide variety of topical

areas connected to botany, ecology, chemistry, pharmacology, and clinical trials. However, publications then decreased until the late 1980s after the finding of toxicity constraints of CPT. During the period from 1975 to 1986, the research was limited, especially in the United States, because the CPT was found very water-insoluble and toxic. During these 12 years, only 209 items were published and the studies had been largely conducted in the field of chemistry, with 36% in Chinese and Japanese. The novel mechanism of action of CPT and analogs found in 1985 and extensive clinical trials in China and Japan has led to renewed research interest and produced the second peak publication period in the late 1980s and early 1990s. During the 1987-1993 period, 730 publications were published (65.6% of the total publications) with an average of about 104 items each year.

3. MECHANISMS OF ACTION OF CAMPTOTHECINS

Camptothecins have exhibited a broad spectrum of anti-tumor activity both *in vitro* and *in vivo*. As stated by Dr. B. C. Giovanella of the Stehlin Foundation for Cancer Research in Houston, camptothecins are the most promising drugs that have ever been found. In sufficient quantity, they are toxic to many plants, insects, and animals. Moreover, camptothecins show potent activity against many DNA viruses and some RNA viruses such as retroviruses. The physiological action of camptothecins is unique. Unlike taxol and other anti-tumor agents, camptothecins stabilize the cleavable complex between eukaryotic DNA and enzyme topoisomerase I (topo I, Hsiang et al. 1985). The mechanisms of action of camptothecins have stimulated great research interest.

Initial experiments suggested that the principal effect of CPT on cultured mammalian cells is its immediate and potent inhibition of DNA and RNA biosynthesis (Horwitz et al. 1971, Kessel 1971, Kessel et al. 1972, Abelson and Penman 1972, 1974). It was observed that CPT causes shortened RNA chains but the effect is rapidly reversible when the drug is removed (Abelson and Penman 1972). The drug affects the biosynthesis of ribosomal RNA more than other types of cellular RNA (Cai and Hutchinson 1983). The inhibition of DNA synthesis, on the other hand, is only partially reversible upon drug removal (Horwitz et al. 1971, Kessel et al. 1972). CPT is a much stronger inhibitor of DNA synthesis than RNA synthesis in human lymphocytes stimulated by phytohemagglutinin (Gallo et al. 1971). Also, it was reported that CPT inhibits the replication of DNA viruses but not RNA viruses (Becker and Olshevsky 1973, Horwitz 1975). Thus, both

cellular and viral observations lead to the conclusion that the cytotoxic effect of CPT results from a disruption of the normal function of DNA. However, CPT itself does not cleave either purified DNA polymerase or purified RNA polymerase (Horwitz et al. 1971). Since CPT does not affect the enzymes involved in DNA biosynthesis, the inhibitory effect of CPT is believed to be the result of some action on the template function of DNA rather than on the enzyme activity of DNA polymerases (Hutchinson 1981, Cai and Hutchinson 1983). It was believed that the molecular mechanism of action of CPT included a DNA-binding component and a mechanism for covalent bond breakage in polydeoxyibonucleotides. In 1985, however, Hsiang and his colleagues found that CPT has no effect on DNA alone, but the addition of CPT to a solution containing nuclear enzyme topo I and DNA results in nicking of the DNA (Hsiang et al. 1985). This important finding stimulated further investigations on mechanism of action of camptothecins. Now it is commonly recognized that the DNA enzyme topo I is the main target of camptothecins inhibiting cells and DNA viruses. CPT and its analogs are one of few inhibitors of topo I possessing known anti-tumor activity. Thus, recognition of this novel mechanism of action has led to great interest in additional clinical tests of CPT and its analogs.

DNA topoisomerases (I and II) are found in the nuclei of all eukaryotic cells and play a major role in DNA replication and transcription (Horwitz and Horwitz 1973), and each is probably encoded by a single gene (Wang 1985). They are highly active in cells that are metabolically active, especially in those from rapidly dividing tissues. Also, topo I is active in replication of retroviruses such as HIV, EIAV, and Mo-MuLV that cause many severe diseases in humans and animals including AIDS, but it differs in character from that in cells (Priel et al. 1991b). The function of these enzymes appears to be to facilitate the relaxation, unwinding, controlled cleavage, and rejoining of the DNA helix during replication and transcription (**Figure 4**). Without topoisomerases, DNA

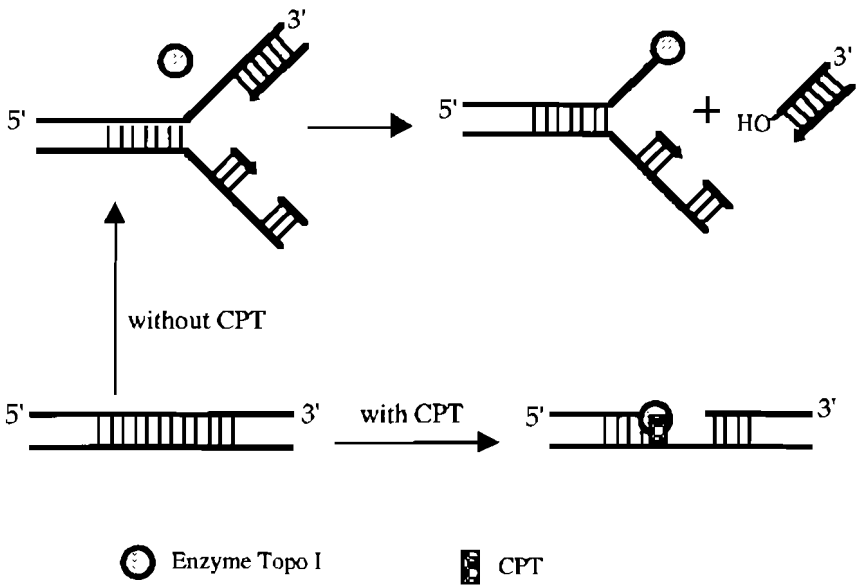


FIGURE 4. **Mechanism of the inhibition of topo I by camptothecins** (redrawn from Slichenmyer et al. 1993). Interaction of topo I with advancing replication forks results in DNA double-strand breaks. CPT, which is unable to bind to free topo I, binds to the topo I-DNA adduct and thus inhibit DNA synthesis.

would be unable to participate in many biochemical reactions and would degenerate into an irretrievable tangle. Topoisomerase I can cleave only a single DNA strand whereas type II cleaves both strands of the helix. The enzyme forms a protein bridge across the ends of the divided DNA molecule until continuity is restored, but camptothecins stabilize the DNA/protein complex so that the normally rapid process of strand division, disentangling, and rejoining is arrested at mid-stage (Editorial 1990). The mid-stage arrest appears to activate endogenous nucleases so that the cell does not merely stop growing—its DNA is degraded and it dies.

Topoisomerase II (topo II) relieves torsional strain in replicating DNA by causing and then repairing double-stranded breaks (Saltz et al. 1993). It requires ATP, which

may offer more targets for inhibitors' action. Therefore, a number of anti-tumor agents stabilize the formation of a cleavable complex between DNA and topo II. Topo I is a monomeric 100-kDa polypeptide encoded by a single-copy gene (Liu and Miller 1981, Juan et al. 1988). It causes a single-stranded DNA break, permits the passage of the intact strand through the break, and then reseals the broken strand. It does not require a cofactor. There are few topo I inhibitors. Two other recently found topo I inhibitors that have anti-tumor activity are ß-Lapachone (Li et al. 1993) and intoplicine (Eckardt et al. 1994). But unlike camptothecins, these two do not stabilize the cleavable complex between DNA and topo I. Camptothecins are the only topo I inhibitors whose ability to stabilize the cleavable complex has been well characterized.

CPT and its analogs inhibit topo I catalytic activity and bind the topo I-DNA adduct. The observed DNA single-strand breaks observed with addition of CPT represent the nicks that form when CPT stabilizes covalent adducts between genomic DNA and enzyme topo I (Slichenmyer et al. 1993). At present, the interaction between CPT and the topo I-DNA complex seems central to the cytotoxicity of CPT and its analogs. But the nature of the binding between CPT and the topo I-DNA adducts remains unclear.

Structure-activity studies indicate that substitutions at the 9- and 10-positions of CPT generally increased topo I inhibition (Hsiang et al. 1989, Kingsbury et al. 1991, Pommier et al. 1991). It was observed that 10-hydroxycamptothecin (HCPT) is more potent than CPT (Shanghai Institute of Materia Medica 1978, Zeng 1982, Han 1988) and SN-38 (7-ethyl-10-hydroxycamptothecin) is remarkably more potent than CPT and HCPT (Tanizawa et al. 1994). Therefore, the 7-ethyl group appears to increase the drug potency. However, this increased potency does not appear to result from the induction of more cleavage sites but from the great stability of individual sites (Tanizawa et al. 1994). It is well established that in solution at physiologic pH, CPT and its analogs exist in an equilibrium between the closed-ring lactone form and the open-ring carboxylic acid form. The cleavable complexes

between DNA and topo I result from a constant equilibrium between such drug stacking (Jaxel et al. 1991, Pommier et al. 1993) and drug dissociation (Covey et al. 1989). Once administered, the drugs are rapidly hydrolyzed in plasma to the open-ring form, producing a complete loss of biological activity (Wani et al. 1987, Kuhn et al. 1990, Rowinsky et al. 1992). The full therapeutic utility of camptothecins is limited by the aqueous instability of the lactone ring moiety, and reduction of drug dissociation would be expected to increase the persistence time of cleavable complexes and their overall frequency. The 7-ethyl and 10-hydroxyl groups seem to slow the drug dissociation from the cleavable complexes (Tanizawa et al. 1994). Also, Burke and co-workers (1992) recently found that liposome-bound CPT is stable. This suggests that liposomes may serve as an effective drug delivery system for soluble camptothecins, conserving its lactone ring and the anti-tumor activity. The stabilization results from penetration of CPT's lactone ring into the bilayer, isolating it from solution (Burke et al. 1992).

CPT and analogs inhibit not only cellular but also viral topo I. 10-Methoxycamptothecin is more effective than CPT as an inhibitor of DNA viruses (Tafur et al. 1976). Camptothecins therefore represent a new direction in virus diseases chemotherapy. The mechanism of anti-viral action of camptothecins is discussed in detail in chapter 5.

4. PRECLINICAL AND CLINICAL TRIALS OF CAMPTOTHECINS IN CANCER TREATMENT

The development of new anti-tumor agents is a complex, stepwise process proceeding from discovery to demonstration of anti-tumor activity in preclinical tests and evaluation of normal tissue toxicity prior to initiation of clinical trials. The major purpose of phase I clinical trials is to determine the toxic effects of the agent and the recommended phase II dosage. Thus, phase I trials address an estimation problem rather than the testing of a hypothesis (Ratain et al. 1993). Phase II trials are generally studies with no control group that are aimed at estimating the anti-tumor efficacy of a new agent in a particular disease.

CPT and its analogs belong to a group of anti-tumor agents with unique mechanisms of action: stabilizing the cleavable complex between eukaryotic DNA and enzyme topoisomerase I. CPT and some analogs (HCPT, TPT, CPT-11, and 9-AC) are in clinical trials in China, Japan, United States, and Europe and their chemotherapeutic efficacy appears promising. The drugs are usually intravenously injected. Oral CPT is being used both in its traditional formulation in China and Japan and in a recently opened phase I trial in the United States. In the United States, however, phase II evaluations have been limited relative to China and Japan. At present, at least 10 cancer hospitals are running clinical trials of camptothecins in the United States. Since camptothecins are experimental drugs, FDA requires that camptothecins be given at extremely low doses in clinical trials. In general, camptothecins show promising antitumor activity in clinical trials. As Wall points out, however, there are many

problems, particularly for the water-insoluble analogs, but these problems are being solved (Wall 1993).

Camptothecin (CPT)

In solution at physiologic pH, CPT (NSC-100880) exists in an equilibrium between the closed-ring lactone and the open-ring hydroxy acid form. The closed-ring form is favored at lower pH. Because CPT lactone is extremely insoluble in aqueous solutions, the readily water-soluble sodium salt of the open-ring hydroxy acid was utilized in the initial clinical trials. Animal tests had revealed that the sodium salt was 10-fold less potent than CPT lactone, although it had a similar spectrum of activity against murine tumors (Wani et al. 1980). Dr. Beppino C. Giovanella and his colleagues at the Stehlin Foundation for Cancer Research, Texas, found that a total 23 out of 23 human cancers (lymphoma, colon, lung, breast, melanoma, ovary, pancreas, and stomach) growing in nude mice responded to CPT.

Three intravenous administration schedules were evaluated during the phase I trials in the United States in the early 1970s. At the 1970 annual meeting of the American Association for Cancer Research, Dr. J. A. Gottlieb and co-workers of the NCI reported on results of administering the water soluble sodium salt of CPT to 17 adults with various types of cancer with single doses of sodium CPT (0.5-10 mg/kg) every 2-4 weeks (Gottlieb et al. 1970). Of nine patients with advanced cancer of the intestine and rectum, four achieved tumor reductions greater than 50%; in four others tumor masses decreased 25 to 50%. One patient with melanoma experienced greater than 50% reduction in tumor nodules; one adult with lung cancer and another with acute myelocytic leukemia had from 25 to 50% decreases in tumor mass. Later, F. M. Muggia and co-workers (1972) reported that there were two partial responses in 10 patients with gastric adenocarcinoma and non-small-cell lung tumors after treatment once daily for 5 consecutive days every 3 weeks. In

a phase II trial, only two patients showed partial responses in 61 patients with adenocarcinomas of the gastrointestinal tract (Moertel et al. 1972). Also, unfortunately, the toxic effects of CPT sodium salt were observed in both phase I and II trials. These include myelosuppression, gastrointestinal toxicity, hemorrhagic cystitis, and alopecia at the higher dose levels (Gottlieb et al. 1970, Muggia et al. 1972, Schaeppi et al. 1974). These initial clinical results using the sodium salt of CPT were disappointing, and clinical interest in CPT languished from 1972 to 1988 in the United States (Schultz 1973, Cai and Hutchinson 1983, Wall 1977, 1993). During the late 1970s and early 1980s, CPT was used in clinical treatment of cancer only in China.

In China, clinical trials started in 1968 in the Chinese Academy of Medical Sciences, and responses were observed in those patients with leukemia (Lin et al. 1977). In China, the sodium salt of CPT was originally used. However, studies on the improvement of CPT formulations were performed at the Shanghai Institute of Materia Medica soon after the sodium salt was found to be toxic. The trials showed that CPT prepared in particle sizes less than 1 μm were quite effective in animal experiments. Clinical trials with 450 patients in Guangxi Medical College (Zeng 1982) confirmed this result.

Although the original CPT sodium salt solution was reported to possess very low activity against primary liver cancer, the non-sodium CPT suspension was considered to be effective. After treatment, 18.2-49.0% of the patients who originally could not be treated by surgical operation became suitable for surgery (Zeng 1982). Similarly, nausea, vomiting, and hematuria occurred in 64% of the sodium salt treated group, but only 10% of the suspension treated group. Later, Wall and others further confirmed that the CPT sodium salt has only one-tenth the potency of CPT in one anti-tumor assay (Hutchinson 1981).

In May 1992, the Stehlin Foundation for Cancer Research in Houston began its clinical study of CPT in a pill form. Major responses have been seen in breast and prostate cancers, lymphoma, and malignant melanoma (Stehlin

Foundation for Cancer Research, 1993).

In the United States, phase II evaluations were limited to trials in patients with advanced gastrointestinal adenocarcinomas (Moertel et al. 1972) and malignant melanoma (Gottlieb and Luce 1972). However, response rates were lower than in phase I trials.

Recently, CPT has been studied using the closed lactone ring and found very active against human cancer xenografts (Giovanella et al. 1991). Phase I trials of CPT have been completely successful demonstrating tolerate toxicity at effective doses administered orally (Stehlin et al. 1994). Presently, CPT is undergoing extensive phase I trials and phase II trials in breast cancer.

10-Hydroxycamptothecin (HCPT)

10-Hydroxycamptothecin (HCPT) was isolated by Wani and Wall (1969). Later they found that HCPT was the most active compound in the series and was more active than CPT in both L1210 and P388 leukemia life prolongation assays (Wani et al. 1980, Wall 1993). HCPT is a water-insoluble agent, but its potent anti-tumor activity stimulated synthetic efforts of TPT and CPT-11 water-soluble analogs of HCPT by SmithKline Beecham and a Japanese pharmaceutical company.

The water-soluble salt of HCPT was first clinically used in China (Cai and Hutchinson 1983). The studies showed that the salt HCPT is more active and less toxic than the sodium CPT, especially for head and neck cancer, liver carcinoma, leukemia, gastric cancer, and urinary bladder carcinoma (Shanghai Institute of Materia Medica 1978, Zeng 1982, Han 1988). At the Shanghai Institute of Materia Medica, it was found that the disodium salt of HCPT exhibited an obvious inhibitory action on both ascites and solid tumors, such as Ehrlich ascites carcinoma, ascetic reticule cell sarcoma, Yoshida sarcoma, sarcoma S37, and Walker carcinoma. In the phase II clinical trials 63 cases were evaluated. The effective

rate of reduction in tumor activity was 42.1% (8 of 19 patients) in the treatment of liver cancer and 39.8% (11 out of 28 patients) in head and neck cancers (Zeng 1982). It was reported that the sodium HCPT inhibited the clonogenicity of KB cells and exhibited DNA damage in L1210 cells (Wang et al. 1986). Cai and Hutchinson (1983) stated that HCPT had the best activity against lung tumor among camptothecins. The toxicity of the sodium salt of HCPT was much less than that caused by the sodium salt of CPT, especially with respect to irritation of the urinary tract.

Topotecan (TPT)

Topotecan (TPT), 9-dimethylaminomethyl-10-hydroxy-camptothecin (SK&F104864, SK&F104864A, or NSC609699), previously called hycamptamine, is a semisynthetic analog of HCPT. It was identified by R. K. Johnson and co-workers at SmithKline Beecham in 1989 as a water-soluble agent with a broad spectrum of anti-tumor activity (Johnson et al. 1989). The structure of TPT incorporates a stable basic side chain at the 9 position of the A-ring of HCPT. This permits the formation of a hydrochloride salt with greatly increased aqueous solubility over that of the parent compound and thus reduces some toxic effects while still maintaining preclinical activity.

TPT has been shown to posses considerable anti-tumor activity *in vitro* against a large number of murine leukemias and transplantable solid tumors, including P388 leukemia, L1210 leukemia, B16 melanoma, M-5076 reticulum cell sarcoma, Lewis lung carcinoma, central nervous system tumor, and HT-29 human colonic adenocarcinoma (Saltz et al. 1993, Friedman et al. 1994).

A number of TPT single-agent studies were made in phase I trials. Major responses to TPT have been observed in patients with ovarian cancer (Rowinsky et al. 1992a, b), non-small-cell lung cancer (Rowinsky et al. 1992a, b, Verweij et al. 1992), small-cell lung cancer (Verweij et al. 1992), esophageal

cancer (Sirott et al. 1991), and colorectal cancer (Haas et al. 1992) as well as acute leukemia (Beran et al. 1992). The principal dose-limiting toxic effect on most schedules is brief, noncumulative neutropenia, occurring either alone or with thrombocytopenia. Other side effects such as nausea, vomiting, rashes, diarrhea, and alopecia were usually mild and rare at TPT doses associated with severe myelosuppression (Slichenmyer et al. 1993). Bladder toxicity has not been reported following administration of topotecan (Hawkins 1992). The maximum tolerated dose was highly schedule dependent, and less drug was tolerated when given by continuous infusion. However, prior cytotoxic therapy decreased the ability of patients to tolerate TPT. Thus, L. Saltz and co-workers (1993) suggest that the doses of TPT recommended for use in phase II clinical trials in solid tumors are 1.5 and 1.25 mg/m^2 of surface skin area daily in previously untreated and previously treated patients, respectively. Based on observed rates of recovery from myelosuppression, treatment should be possible on a 21-day cycle.

Phase II trials have begun in patients with a wide range of solid tumors (Slichenmyer et al. 1993). Testing using daily administration of 1.5 mg/m^2 for 5 days is currently underway (Hawkins 1992).

Irinotecan (CPT-11)

Irinotecan, 7-ethyl-10-[4-(1-piperidino)-1-piperidino] carbonyloxycamptothecin (NSC616348) is another water soluble analog of HCPT. It was initially developed in Japan by Kunimoto and his colleagues (1987). Unlike CPT and TPT, CPT-11 has little inherent anti-tumor activity *in vitro* (Slichenmyer et al. 1993). Instead, CPT-11 is a pro-drug that undergoes de-esterification *in vivo* to yield SN-38 (7-ethyl-10-hydroxycamptothecin), which is approximately 100-fold more potent than the parent compound against tumor cells *in vitro* (Kaneda et al. 1990, Kawato et al. 1991a). Therefore, the clinical activity of CPT-11 may strongly depend on its

hydrolysis to SN-38 (Tanizawa et al. 1994).

CPT-11 has shown substantial activity *in vivo* against a variety of tumor xenografts when administrated by intraperitoneal, intravenous, or oral routes (Kunimoto et al. 1987). The agent was more active than other analogs over a broad dose range. It demonstrated activity against some human tumor xenografts, including colon adenocarcinoma Co-4, mammary carcinoma MX-1, gastric adenocarcinomas St-15 and SC-6, as well as squamous cell lung carcinoma QG-56 implanted subcutaneously in nude mice (Kawato et al. 1991b). It also has anti-tumor activity against rat Walker 256 carcinoma (Furuta et al. 1988).

Phase I clinical trials have been performed in Japan and more recently in the United States and Europe. Major responses have been observed in patients with non-small-cell lung cancer (Negoro et al. 1991), colorectal cancer (Rowinsky et al. 1992a, b, Gandia et al. 1992, Sasaki et al. 1994), cervical cancer (Rowinsky et al. 1992a, b), and breast cancer (Clavel et al. 1992). In contrast to TPT, CPT-11 produces prominent nonhematologic toxic effects at myelosupressive doses. Diarrhea is a serious side effect occurring on virtually all schedules of administration studied to date. On schedules where larger individual doses are administrated, diarrhea begins during or immediately after a 60-90 minute infusion of CPT-11 (Slichenmyer et al. 1993). When CPT-11 is given by bolus or short-duration IV infusions, leukopenia occurs more frequently than diarrhea (Ohe et al. 1992, Takeuchi et al. 1991a, b). Thus, diarrhea is the dose-limiting toxic effect, depending on the schedule of administration (Ohno et al. 1990, Burris et al. 1992b, Ohe et al. 1992). Using a single administration every 3 weeks, the maximum tolerated dose reported was 250 mg/m^2 (Ohno et al. 1990) and 290 mg/m^2 (Burris et al. 1992b, Rowinsky et al. 1992a, b), with diarrhea as a dose-limiting toxicity in addition to neutropenia. The schedule was not chosen for phase II studies, because a weekly schedule allowed a higher dose intensity (Abigerges et al. 1994). Recently, D. Abigerges and others (1994) used a loperamide protocol to control diarrhea that clearly allowed

the administration of higher dose levels of CPT-11 (given every 3 weeks, the maximum tolerated dose was 750 mg/m^2).

Phase II trials of CPT-11 have been performed in Japan. Most trials in adults with solid tumors have evaluated CPT-11 administered on a weekly schedule, whereas most studies for leukemia and lymphoma evaluated CPT-11 administered over 60-90 minutes for either 3 consecutive days every week or 5 consecutive days every 3-4 weeks (Slichenmyer et al. 1993). CPT-11 has demonstrated activity against a variety of tumors, including colorectal cancer (46% response rate in patients with prior chemotherapy, Shimada et al. 1993), ovarian cancer (21% response rate in patients with prior chemotherapy, Takeuchi et al. 1991b), cervical cancer (43% response rate with some complete responses, Takeuchi et al. 1992), non-small-cell lung carcinoma (31.9% response rate in patients with no prior chemotherapy, Fukuoka et al. 1992), and small-cell lung cancer (33-50% response rate, Negoro et al. 1991, Masuda et al. 1992) as well as lymphomas and leukemias (Ohno et al. 1990, Tsuda et al. 1992). Side effects of CPT-11 during phase II are similar to those observed during phase I studies. Also, pulmonary toxicity has been observed for patients with lung cancers (Fukuoka et al. 1992).

9-Aminocamptothecin (9-AC)

9-Aminocamptothecin (NSC603071) is a synthetic analog of CPT and not soluble in water. 9-AC was first investigated by Wall and Wani at the Research Triangle Institute. Wani et al. (1987) showed that 9-AC has potent activity in the L1210 mouse leukemia. The animal tests show that 9-AC is a potent anti-cancer agent, highly effective against three lines of human colon cancer (Giovanella et al. 1989). It is much more effective in colon cancer than fluorouracil (5-FU), doxorubicin, or several other cytotoxic drugs. The overall drug toxicity was low and allowed for repeated courses of treatment. Its high efficacy, however, is not completely understood. This drug has been introduced into clinical trials because it exhibits

strong antitumor activity against solid tumor xenografts (Giovanella et al. 1989, Potmesil et al. 1993). It is in clinical trials in patients with a variety of cancers at the National Cancer Institute and other facilities.

In addition, other analogs of CPT show anti-tumor activity. According to Cai and Hutchinson (1983), 9-methoxycamptothecin showed marked activity against leukemia P388, but only fair activity in L1210. 10-Methoxycamptothecin is somewhat less active than CPT (Wall 1993). 11-Methoxycamptothecin was found also to have anti-tumor activity (Zeng 1982). More recently, Giovanella and associates found that 9-nitrocamptothecin, which is much easier to prepare and non stable derivative of 9-AC also possess very high anti-cancer activity against human cancer xenografts in nude mice (Pantazis et al. 1993). It has also been demonstrated that 9-nitrocamptothecin is transformed into 9-AC when administered to mice, dogs, and humans (Hinz et al. 1994).

In summary, camptothecins are anti-cancer agents with unique mechanisms of action and great chemotherapeutic efficacy. Recently, A. Tanizawa and co-workers (1994) evaluated CPT and some derivatives presently in clinical trials in HT-29 cells and in isolated nuclei. It was found that both the cytotoxic potency and the potency of the compounds to induce protein-linked DNA breaks are in the following order: SN-38 > CPT > 9-AC > TPT > CPT-11. SN-38 is the most potent compound and 9-AC and TPT less active than CPT *in vitro*. The effect of CPT-11 is minimum.

However, Wall and associates found that 9-AC is always more potent than CPT, both in cytotoxicity and, even more importantly, in the inhibition of topoisomerase I (M. E. Wall, pers. comm., September 1994). According to T. D. Moore of NCI, CPT-11 has the greatest activity in colon cancer, TPT has the greatest activity in small-cell lung cancers, some activity in ovarian cancer, and very exciting activity in several pediatric cancers, and 9-AC should work in all these disease sites (Jenks 1994).

Because camptothecins work at specific phases of the cell cycle, they are more effective when administered continuously than intermittently (Slichenmyer et al. 1993, Tanizawa et al. 1994, Jenks 1994). The longer you retain drugs, the longer breaks occur in the DNA, according to J. Eckardt at the University of Texas Cancer Therapy and Research Center in San Antonio (Jenks 1994). In certain instances, according to T. Pantazis, cancer cells have been able to evade CPT's toxicity by developing different metabolic routes, but the cells then become ultrasensitive to other drugs to which they were not sensitive before they were exposed to camptothecin (Stehlin Foundation for Cancer Research, 1993). Also, because of its unique mechanism of action and lack of bone marrow depression, CPT can be used in combination with other drugs that have different mechanisms of action (Stehlin Foundation for Cancer Research, 1993). For instance, John Eckardt and his colleagues at the University of Texas Cancer Therapy and Research Center in San Antonio recently used TPT and cisplatin in patients with untreated non-small-cell lung cancer. The working hypothesis is that the best way to effect a response is first to damage the DNA with non-cell-cycle-specific drug cisplatin and then bring in the TPT, a cell-cycle-specific drug, whose inhibitory effect on cell repair causes cells to die (Jenks 1994). They found that TPT enhanced the ability of the cisplatin to kill tumor cells, but the reverse is not true. R. C. Lilenbaum of the Cancer and Leukemia Group B in Lebanon, New Hampshire used taxol and TPT together in patients with a variety of advanced solid tumors. Because taxol in essence freezes the cell, and TPT inhibits DNA repair, the two will act at different phases of the development to destroy tumor cells (Jenks 1994).

5. POTENTIAL ANTI-VIRAL ACTIVITY OF CAMPTOTHECINS

Camptothecins, Potential Anti-viral Drugs

Viruses are minute packages of a single type of nucleic acid, either DNA or RNA surrounded by a protein coat and sometimes a lipid membrane. There are thus two different categories of viruses: DNA viruses and RNA viruses, and hundreds of kinds of viruses, many of which cause plant and animal diseases (Postlethwait et al. 1991).

DNA viruses include 6 families: Hepadnaviridae, Papovaviridae, Adenoviridae, Herpesviridae, Poxviridae, and Parvoviridae. The hepadnaviruses cause hepatitis, which may progress to cirrhosis and primary hepatocellular carcinoma. Papillomaviruses of the family Papovaviridae cause human warts and some species are oncogenic while polyomaviruses commonly produce inapparent infection. Human adenoviruses are associated with infections primarily of the respiratory tract.

RNA viruses have 13 families (White and Fenner 1986). Retroviridae (re = reverse, tr = transcriptase) is a large family. The subfamily Oncovirinae includes the human T-cell leukemia virus (ATLLV), which causes leukemia carcinoma. The subfamily Lentivirinae of retroviruses includes causative agents of severe diseases in humans and animals, such as human immunodeficiency virus (HIV), equine infectious anemia virus (EIAV), Friend spleen focus forming virus (SFFV), and Moloney murine leukemia virus (Mo-MuLV). HIV causes the acquired immune deficiency syndrome (AIDS) in humans. Other retroviruses cause animal diseases such as

erythroleukemia, lymphoma, viremia, anemia, tissue injury, and erythrocyte destruction.

As early as in 1970s, CPT was found to inhibit the replication of DNA viruses such as adenovirus, vaccinia virus (Poxviridae), and herpesvirus, and to have no effect on the replication of poliovirus, an RNA virus (Becker and Olshevsky 1973, Horwitz 1975). 10-Methoxycamptothecin was found to be about eight times more potent than CPT as an inhibitor of herpesvirus (Tafur et al. 1976). In the 1970s, it was believed that CPT was active only on DNA viruses (Cai and Hutchinson 1983), with DNA topoisomerase I being the primary target for the inhibitory role of CPT in DNA replication (Liu 1989, Bjornsti 1991, Champoux 1992). Deng and co-workers recently evaluated the effects of selected DNA repair inhibitors on the an increased frequency human cytomegalovirus (HCMV)-induced chromosome aberrations in human peripheral blood lymphocytes (Deng et al. 1992). They found that CPT is a significant agent causing frequency of HCMV-induced chromosome damage. In addition, recent studies have demonstrated that at very low concentrations, CPT is able to block replication of RNA viruses (retroviruses) in infected cells (Priel et al. 1991a, 1991b, 1993, Kerr et al. 1993, Li et al. 1993, 1994a, b).

CPT inhibited HIV replication in acute infection of H9 cells at a high efficacy (>90%) at noncytotoxic doses (Priel et al. 1991a). The study of C. J. Li and co-workers (1993) shows that TPT potentially inhibits both acute and chronic infection of HIV-1. It is also found that CPT inhibits the replication of EIAV in chronically infected CF2Th cells (Priel et al. 1991b). According to E. Priel and co-workers (1991b), continuous exposure of these cells to the drug for 52 days revealed 85 to 92% inhibition of virus production. Recently, it was observed that CPT, administrated together with the virus (NFFV or Mo-MuLV) or 1 or 2 days after virus injection, prevented the onset of the disease in mice (Priel et al. 1993). No effect on the viability or growth rate of the cells was detected in drug administration according to these studies. Presently, some anti-viral agents block retroviral replication only at early

stages of the viral infection process; whereas, other agents suppress HIV expression only in chronically infected cells (Ho et al. 1985, Priel et al. 1991b). However, CPT acts as an anti-viral drug at both levels, inhibiting retroviral replication in both acutely and chronically infected cells. It thus has potential advantages as a legitimate remedy for the treatment of retroviral diseases over other drugs.

CPT and its analogs have an inhibitory effect not only on HIV-1, but also on other viruses associated with AIDS. Human polyomavirus (JCV, Papovaviridae), is the causative agent of progressive multi-focal leukoencephalopathy, a subacute demyelinating disease of the central nervous system. This disease occurs in association with a defect in cell-mediated immunity. According to the study of D. A. Kerr and co-workers (1993), pulse-treatment of glial cells with non-toxic levels of CPT specifically blocked JCV viral DNA replication with no inhibitory effect on host transcription and translation processes as examined by viral gene expression in the transfected cells.

Mechanism of Action

It is essential to know the life cycle of a virus in order to understand the mechanism of the anti-viral action of a drug. Viruses are not cells, and they are completely dependent upon their cellular hosts for the machinery of protein synthesis and energy production. They infect both prokaryotic and eukaryotic cells by attaching to the plasma membrane and then allowing their DNA or RNA to enter the cell. Once inside, the viral genes take over the cell's protein-synthesizing machinery for viral replication. The speed of viral reproduction is astounding. In 24 hours, one virus particle could generate enough particles to fill the universe (Postlethwait et al. 1991). In nature, however, reproduction is always limited by the availability of cells, since viruses lack the machinery for replication.

Some anti-viral drugs prevent certain viruses from shedding their coats so that the viruses cannot infect cells. Some drugs (e.g., interferon) prevent cells from replicating viruses whereas others block the activity of the viral enzymes. Because DNA enzyme topo I is the main target of camptothecins, it is understandable that camptothecins show potent inhibitory effects on the replication of DNA viruses. Surprisingly, however, camptothecins also inhibit the RNA viruses such as retroviruses that do not contain DNA. Although the DNA enzyme topo I is active in the viral core of EIAV and is at least actively associated with HIV and Mo-MuLV, it seems reasonable that topo I may be the main, if not the exclusive, target of CPT (Priel et al. 1991b, 1993). But the mechanism of action of camptothecins on RNA viruses is possibly more complicated.

It is well established that the hallmark of infection by HIV-1 and other retroviruses is formation of provirus through reverse transcription, integration, and then transcription from proviral DNA. Transcription of this proviral DNA is an essential step for viral replication, and controlled by the long terminal repeat (LTR). HIV-1 LTR has recently become a promising site for ant-viral action (Li et al. 1994b). C. J. Li and co-workers (1993, 1994a) found that CPT and TPT inhibit HIV-LTR activity induced by viral transactivator (Tat) and cytokinesis. The exact mode of action of the inhibition is still unclear. One possibility is that DNA topo I influences Tat/TAR-mediated transcription by selectively interacting with Tat/TAR or their associated protein, and that DNA topo I is the CPT-inhibited step here. However, C. J. Li and co-workers (1994a) believe that the inhibition by CPT of HIV-1 long terminal repeat (LTR) is probably independent of its inhibition of DNA topo I, and that the target may be a novel cellular factor, probably a Tat- or TAR-associated protein.

While it is still too early in the investigative process to proclaim with certainty the anti-viral properties of camptothecins, the evidence clearly shows the potential of drugs for that purpose.

6. OTHER USES OF CAMPTOTHECINS

Plant Regulator

CPT is a selective plant growth regulator (Buta and Worley 1976, Worley et al. 1979, Buta and Spaulding 1986, Tao and Buta 1986, Buta and Kalinski 1988, Kieber et al. 1992). DNA topo I is the main target of CPT inhibiting plant cells. CPT inhibited the seedling growth and seed germination of some grasses and crops in which topo I is essential and active. However, it was reported that CPT stimulated some other species such as watermelon (*Citrullus vulgaris* Schrad.) (Buta and Spaulding 1986). Therefore, managers can effectively control the growth of some competing crops and grasses with CPT in order to meet management goals.

Generally, CPT inhibits the growth of the taproot and primary leaf of monocot seedlings more than those of dicots. In some grasses and crops such as Italian ryegrasses (*Lolium multiflorum* Lam.), barley (*Hordeum vulgare* L.), maize (*Zea mays* L.), sorghum (*Sorghum bicolor* Moench.), wheat (*Triticum aestivum* L.), and tall fescue (*Festuca arundinacea* Schreb.), growth of seedlings is inhibited by CPT even at low concentrations (50 μM). But in other grasses such as Kentucky bluegrass (*Poa pratensis* L.) and ryegrass (*Lolium perenne* L.), seedling growth is less affected. Growth and germination of legumes (Fabaceae) is affected by CPT, however, soybeans (*Glycine max* Merr.) and cowpea (*Vigna radiata* L.) are less affected than other legumes such as red clover (*Trifolium pratense* L.) and bird's foot trefoil (*Lotus corniculatus* L.). In tobacco (*Nicotiana tabacum* L.), seedling growth is only affected at the high CPT concentration (500

μM). However, lettuces (*Lactuca* spp.) are inhibited by both low and high CPT concentrations (50 and 500 μM). Tomato (*Lycopersicon esculentum* Mill.), broccoli (*Brassica oleracea* var. *italica*), and mustard (*Brassica campestris* L.) are affected by CPT. Interestingly, both seed germination and seedling growth of watermelon is stimulated by CPT at both low and high concentrations (Buta and Spaulding 1986).

Insect Chemosterilant

CPT alkaloid is also a potent chemosterilant against the house fly (*Musca domestica* L., Muscidae, Diptera) (DeMilo and Borkovec 1974). Fecundity and hatchability of the fly are remarkably reduced after exposure. In China, the alkaloid is also used for control of Masson pine caterpillar (*Dendrolimus punctatus* Walker, Lasiocampidae, Lepidoptera), the most serious forest pest in China (Hunan Institute of Forestry 1978). The mortality of larvae, pupae, and adults of insect increased after treatment with CPT, and the hatchability of eggs decreased after treatment with 0.05% CPT.

In addition, according to the Lanzhou General Hospital of the Chinese People's Liberation Army (Chiao and Li 1974), Psoriasis vulgaris was treated in 33 patients with the CPT with improvement in all cases. CPT-dimethyl sulfoxide solution was applied to psoriatic lesions 2-3 times daily. Twenty-one patients were cured and the rest were greatly improved. No constitutional reactions to the treatment were noted.

Ethnic Uses

The tree has been planted as a "four-sites" (waterside, hillside, roadside, and homeside) tree throughout the provinces south of Changjiang (Yangtze) River in China. Xi Shu is also a nectariferous plant. However, to date there is no report available about honey production from Xi Shu.

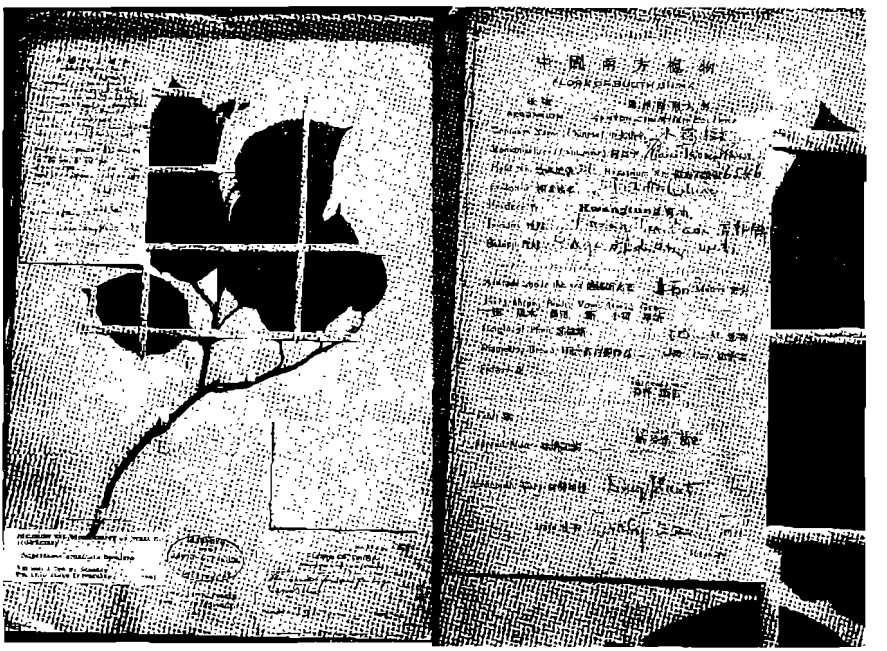


FIGURE 5. **Specimen McClure 6546** (deposited at the Harvard University Herbaria) **collected on July 22, 1921 from Koung Tse Paai** (in Guangdong Province) **indicates Xi Shu as "drug plant" in the label** (photos by D. E. Boufford, Harvard University).

It is commonly recognized that there were no medicinal uses of the tree until its anti-neoplastic activity was discovered in the 1960s. Also, it was not mentioned in Chinese herbal books. But the label of the specimen F. A. McClure 6546 (deposited at the Harvard University Herbaria) collected from Guangdong on July 22, 1921 indicates "drug plant", but provides no further information on this use (**Figure 5**). In fact, 35 ethnic groups are in the natural range of Xi Shu and at least 16 local names of Xi Shu occur in China (see chapter 8). This variety of names may indicate the tree has important human uses. Most probably, therefore, Xi Shu may be used for medicine by native ethnics, but the uses are unknown to others because of cultural and geographic barriers. An ethnobotanical investigation is needed in future studies.

POTENTIAL DEVELOPMENT

OF XI SHU IN THE UNITED STATES

If you plan for one year, grow rice;
If you plan for ten years, plant trees;
If you plan for a hundred years, educate people.

——Zuang Zi (c. 4th-3rd century B.C.)

7. SOURCES OF CAMPTOTHECINS

Drugs Extracted from All Parts of Xi Shu

Unlike taxol found only in the bark of the Pacific yew, camptothecins are present in all parts of the Xi Shu at all stages of growth during all seasons of the year. J. S. Hsu and co-workers (1977) found that the content of CPT occurs in different parts of Xi Shu at the rate of 5:10:5:2:15 of roots: root bark: stem bark: twigs: fruits (**Table 3**). According to Hsu and associates, fruits have the highest content of all plant parts. However, surprisingly, H. J. Tien and co-workers (1977) reported that the leaves have higher content of CPT than either fruits or roots (**Table 3**). G. R. Cao and others (1992) reported that leaves contain 0.016% of CPT by dry weight. Although the CPT content in leaves varied from report to report, it has been observed that leaves contain sufficient levels of CPT to cause death in goats feeding on the leaves (Cao et al. 1992). The common parts used for drug production are bark or wood, but both fruits and leaves are still used in China to treat leukemia and skin diseases, respectively.

In addition, K. Sakato and co-workers obtained CPT from leaf callus tissues by using plant cell culture techniques (Sakato and Misawa 1974, Sakato et al. 1974).

The yield of HCPT, another active compound, is low, and amounts to only 0.002% of bark weight. K. P. Chu and co-workers (1979) obtained HCPT from CPT with 10% yield by biotransformation with fungi. This bio-connection provides another opportunity for significant study in recovery of CPT from Xi Shu.

TABLE 3. **Contents of camptothecin in various parts of Xi Shu.**

Fruits	Twigs	Stem Bark	Leaves	Roots	Root Bark
0.030%	0.004%	0.010%	0.016%**	0.010%	0.020%
0.030%	0.016%*		0.040%*	0.036%*	

Notes: Dry weight basis. * From Tien et al. (1977); ** from Cao et al. (1992); others from Hsu et al. (1977).

Other Botanical Sources of Camptothecins

The potent anti-tumor activity of CPT and its analogs and the supply shortage of suitable trees stimulated scientists to look other plants as sources of these compounds. T. R. Govindachari and N. Viswanath (1972) isolated CPT, 9-methoxycamptothecin (9-MCPT), and another related alkaloid mappicine from *Nothapodytes foetida* (Wight) Sleumer (formerly *Mappia foetida* Miers). *N. foetida* is a small tree of Icacinaceae, it is distributed in southern India, Sri Lanka, Burma, Thailand, Cambodia, Sumatra (Indonesia), Luzon (Philippines), and Taiwan (China) (Chuang 1981). The genus *Nothapodytes* Bl. contains 9 species and is restricted to southeastern Asia. Six species are distributed in southern China (Ku and Tang 1980). According to Govindachari and Viswanath (1972) and Govindachari and others (1974), contents of CPT and 9-MCPT in *N. foetida* is much higher than those in Xi Shu (**Table 4**). J. S. Agarwal and R. P. Rastogi (1973) and G. Roja and M. R. Heble (1994) support this result; they also isolated 21-methylenecycloartanol from *N. foetida*.

S. Tafur and co-workers (1976) isolated CPT and 9-MCPT from *Ophiorrhiza mungos* L., a herbaceous plant of the Rubiaceae from Sri Lanka, India, Malaysia, Sumatra, Java, and Guangxi and Yunnan of China. *Ophiorrhiza* L. contains about 50 species and is restricted to tropical Asia. About 20 species have been identified in China (Ku and Tang 1980).

TABLE 4. **Contents of camptothecins in various parts of *Nothapodytes foetida*.**

Sources	Stem	Stem Bark	Leaves	Roots
Camptothecin	0.06%	0.08%	0.01%	0.10%
9-Methoxycamptothecin	0.001%	0.001%		0.002%

Notes: Dry weight basis. Data from Govindachari and Viswanath (1972) and Govindachari et al. (1974).

S. P. Gunsekera and others (1979) found that *Ervatamia heyneana* (Wall) Cooke (also known as *Tabernaemontana heyneana* Wall) contain low concentrations of CPT (0.00013%) and 9-MCPT (0.00004%). *E. heyneana* is a shrub or small tree species of Apocynaceae from southwestern India. The genus *Ervatamia* Stapf contains 120 species in tropical Asia (Ku and Tang 1980). Fifteen species are found in southern China(Tsiang and Li 1977).

In summary, plants containing camptothecins are distributed throughout Southeast Asia. All other species except Xi Shu are tropical species. *Ophiorrhiza mungos* and *Ervatamia heyneana* have very low contents of camptothecins. *N. foetida* has a higher content of CPT than all other species. But it is a small tree and restricted to a tropical climate. However, Xi Shu is a fast-growing large tree and is easy to grow in most warm and humid regions of the world. Therefore, Xi Shu is the most promising species for development of the camptothecin family of drugs.

8. BOTANY OF XI SHU

Phylogenetic Relationships

Xi Shu (*Camptotheca acuminata* Decaisne) is a Tertiary relict and the only living species of the genus *Camptotheca* Decaisne. The genus had more members and wider distribution in the Tertiary (Suzuki 1976, Tanai 1977). Like many other monotypic taxa, the genus displays distinctive morphology due to a long time independent evolution and is relatively isolated in phylogeny. The genus *Camptotheca* is now recognized in the family Nyssaceae by most taxonomists.

Nyssaceae is distributed disjunctly between Asia and North America (Ying et al. 1993). It contains three genera *Davidia* Baillon and *Nyssa* Gronov ex L. and 11 species besides *Camptotheca* Decaisne. *Davidia* is a monotypic genus endemic to the southern China; its species *Davidia involucrata* Baillon (dovetree) is only remotely related to *Camptotheca* so that the genus is often treated as a separate family.

Nyssa has 10 species and is distributed disjunctly between eastern and southeastern Asia and eastern North America. *Nyssa aquatica* L. (water tupelo), *N. ogeche* Bertr. ex Marsh. (Ogeechee tupelo), and *N. sylvatica* Marsh. (black tupelo) are distributed in eastern North America; *N. javanica* (Bl.) Wanger. (Javan tupelo), *N. leptophylla* Fang et Chen (small-leaf tupelo), *N. shangszeensis* Fang et Soong (Shangsze tupelo), *N. shweliensis* Airy-Shaw (Shweli tupelo), *N. sinensis* Oliv. (Chinese tupelo), and *N. wenshanensis* Fang et Soong (Wenshan tupelo) are Asian species. *Nyssa* is relatively related to *Camptotheca*, in particular, *N. javanica* and *N. sinensis* might share a common ancestor with *Camptotheca acuminata*. American *N. aquatica* is closely related to Asian

N. javanica in fruit morphology (Titman 1949). Some of these species were screened for anti-tumor activity in the Cancer Chemotherapy National Service Center Screening Laboratories during the middle 1960s. According to Perdue and co-workers (1970), no antitumor activity of consequence was demonstrated by any extract of *Davidia involucrata, Nyssa aquatica, N. biflora, N. javanica,* or *N. ogeche*, and only *Nyssa sylvatica* showed minimal activity.

Morphology and Taxonomy

Xi Shu (*Camptotheca acuminata* Decaisne) is the only species of the genus *Camptotheca* Decaisne. It is native to southern China. The tree was first recorded in the *Zhiwu Mingshi Tukao* in 1848 (Wu 1848, see **Figure 2**). Based on specimens collected by Father Armand David in Lushan, Jiangxi Province during his 1868-1870 exploration in China, Joseph Decaisne, Director of the Jardin Des Plantes, Paris, scientifically described and named it in 1873. The genus name *Camptotheca* is from the Greek—*campto* (bend or curved) and *theca* (a case), refering to the anthers which are bent inward in a distinctive manner. The species name *acuminata* refers to acuminate tips of leaves. In China, this tree is widely called *Xi Shu* (喜樹), which means happytree (or tree of joy). It is also known as *Han Lian* (旱蓮) *or Han Lian Mu* (旱蓮木) (dry lotus tree, in Jiangsu, Jiangxi, and Sichuan), *Huagan Zi Shu* (滑杆子樹, in Yunnan), *Qian Zhang Shu* (千張樹, thousand-sheet tree, in Sichuan), *Qian Zhang Shu* (千丈樹, thousand *zhang* tree, in Sichuan), *Shui Donggua* (水冬瓜, water white gourd, in Sichuan), *Shui Li Zi* (水栗子, water chestnut, in Sichuan), *Shuime Zi* (水沫子樹, in Yunnan), *Shui Tong Shu* (水桐樹, water tung tree, in Guangdong and Guangxi), *Shui Zong Shu* (水棕樹, water palm, in Guangdong), *Tian Zi Shu,* (天梓樹, heavenwood tree, in Hunan), *Tu Bajiao* (土八角, wild anise, in Guizhou), *Yangqing Shu* (秧青樹, in Sichuan), *Ye Bajiao* (野巴蕉, wild banana, in Guizhou), and *Yuan Mu* (圓木, round wood, in Guizhou).

Camptotheca acuminata Decaisne in *Bull. Soc. Bot. France* XX:157 (1873); Baillon in *Hist. Pl.* VI. 282 (1877); Franchet in *Nouv. Arch. Mus. Paris* II. 8:241, t. 9 (*Pl. David.* 2:59, t. 9) (1886); Hemsley in *Jour. Linn. Soc.* XXIII. 346 (1888); Diels in *Bot. Johrb.* XXIX. 504 (1900); Dode in *Bull. Soc. Bot. France* LV. 650 f. b (1908); Wanger in *Engl. Pflanzenr.* 41 (IV. 220a): 17, f. 3 (1910); Wilson in *Pl. Wilsonianae* IV. 254-255 (1914); Hu and Chun in *Ic. Pl. Sinicarum* t. 41 (1927); Lee in *For. Bot. China* 856-858, pl. 242, 243 (1935); Fang in *Icon. Pl. Omeiens.* 1: Pl. 1(1942); Steward in *Man. Vas. Pl. Low. Yangtze Val. China* 271, f. 258 (1958); Eyde in J. *Arnold Arbor.* XLIV. 1:18, 20 (1963); Ann. in *Fl. Sichuanica* Tom. 1:314-315, pl. 120 (1981); Fang and Zhang in *Fl. Reip. Pop. Sin.* 52(2):144-146 (1983); Xu in *Icon. Arbor. Yunnanicorum* 816, 818, f. 431 (1990) —*C. yunnanensis* Dode in *Bull. Soc. Bot. France* LV. 651, f. c (1908).

Camptotheca acuminata is a polygamo-monoecious deciduous tree. It can reach 30 m in height and 100 cm in stem diameter under favorable conditions. The trunk is usually without branches for 10 m above the ground **(Figure 6)**. Its lightly gray rough bark is cracked and fissured **(Figure 7)**. Twigs are gray-green, and young ones are red or green and usually pubescent **(Figure 8)**. Leaves are simple, alternative, papery, pinnately veined, ovaloblong to oblong-elliptic, slightly pubescent, acuminate, entire, occasionally toothed, 10-30 cm long and 6-15 cm wide, lateral veins 11-15 on each side, with 1.5-3.0 cm long stalk. Usually, two sessile flowers form a cyme, and 15-30 cymes form a dense global head (1.5-2.0 cm in diameter). Two to ten heads are arranged into a terminal or axillary raceme-like or panicle-like compound inflorescences (**Figure 9**). Flowers in heads on the upper part of the compound inflorescence are bisexual and bloom first, and those on the lower part are male or sometimes bisexual. Bracts are three, triangular ovate, pubescent. Calyx are cup-form, 5 toothed, margins ciliate. Petals are 5 valvate, 2 mm long, light green, and pubescent. Ten white stamens grow in two whorls, and the outer matures first **(Figure 10)**. Filaments are slender, glabrous; anthers are apicifixed and 4-locular. Pollen is 3-colporate, suboblate, obtuse-triangular in polar view, 29-38 μm (polar axis) × 38-54 μm (equatorial axis), sexine punctitegillate. Colpi is not very

FIGURE 6. **A 12-year old Xi Shu in Kingwood, Texas is 13 m in height and 18 cm in diameter measured at 1.4 m in height in June 1993** (photo by L. R. Lowrey, Anderson Landscape and Nursery).

FIGURE 7. **The bark of Xi Shu is slightly gray and fissured** (photo by P. R. Blackwell, Tucker Center).

FIGURE 8. **Young twigs of Xi Shu are dark red or green; the older ones are gray-green** (photos by T. R. Moore, XyloMed Research Foundation).

FIGURE 9. **Xi Shu has showy white flowers in May-August. 30-60 flowers form the head and 2-10 heads are arranged into a terminal or axillary raceme-like or panicle-like compound inflorescence** (photo by Z. L. Nong, Jiangxi Agricultural University).

distinct, and colpi margins are provided with nexinous thickenings (Erdtman 1966). At pollen shedding, each sporangium dehisces inwards without forming two cavities. The suture of the anthers is spiral. A ring-like nectar exists between the stamens and pistil. The pistil consists of three (two) carpels, with one glabrous two- or three-lobed style. Ovary is interior, unilocular, and has one ovule per locule. Flowers bloom in May-August. Fruits are samara-like, sessile, disc persistent, grouped in globose heads (apitula), 2.5-3.0 cm long and 6-9 mm wide, glossy brown, with 3-8 cm long stalk (**Figure 11**). The fruits ripen in September-November. Usually, trees start to bear fruits at ages of 7-10. Cotyledons (**Figure 12**) are simple, glabrous, lanceolate,

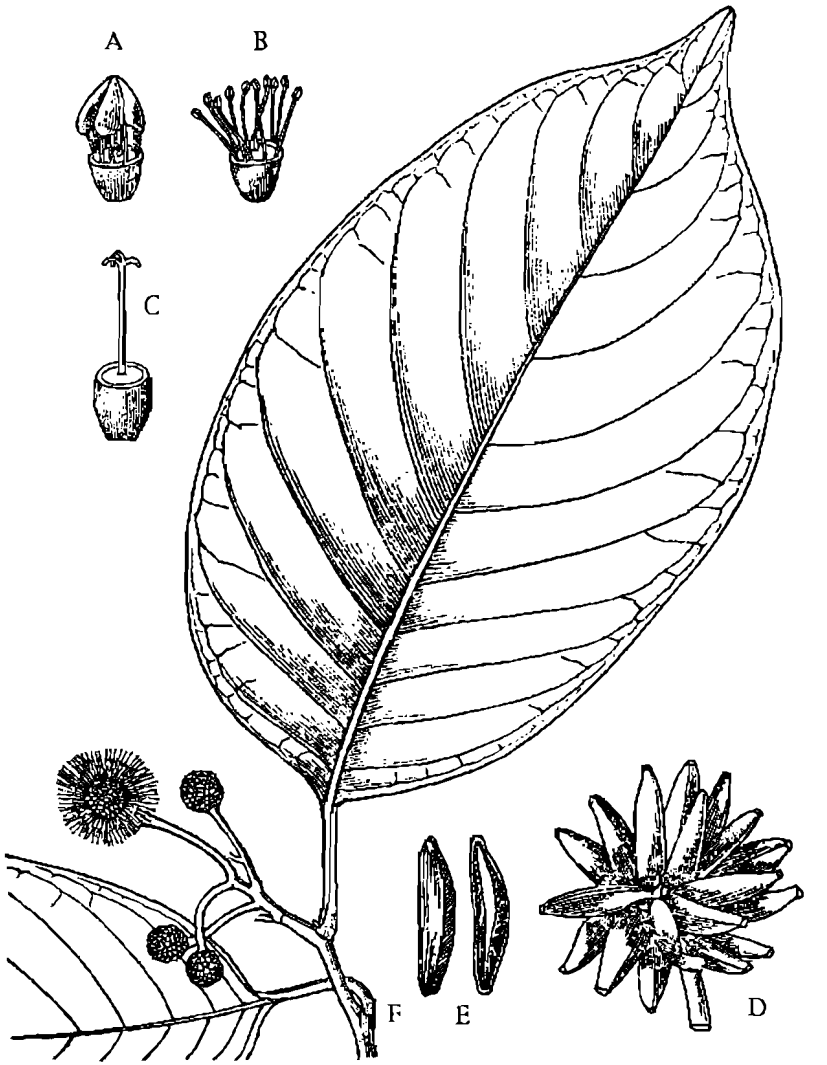


FIGURE 10. ***Camptotheca acuminata*** **Decaisne** (modified from Flora Sichuanica, 1981. A—male flower; B—male flower without petals; C—female flower without petals; D—fruit inflorescence; E—fruit; F—floral shoot).

FIGURE 11. **Fruits of Xi Shu are samara-like, sessile, 2.5-3.0 cm long** (photo by P. R. Blackwell, Tucker Center).

FIGURE 12. **Cotyledons are simple, glabrous, opposite, lanceolate, sessile** (photo by L. R. Lowrey, Anderson Landscape and Nursery).

2-4 cm long, about 1 cm wide and the two are opposite. Chromosome number (2n) is 44.

The wood is light yellowish brown, occasionally with dark-tinged sapwood, without special odor. The wood is moderately soft and light with a rather curly grain, which has a fine to very fine texture. Annual rings are moderately distinct and inner ones are wider. The wood has fine rays and small, numerous, evenly distributed pores. It will not take a smooth cut, but can be split off along the rings. It is easy to dry under natural conditions, but tangential fissures and radial cracks develop when the wood is air dried. The wood is not rot-resistant. Root rot is a major disease. The wood may be used for packaging materials and paper-making. Industrial oil can be extracted from the fruit.

There are two varieties of *Camptotheca acuminata* except for the original variety var. *acuminata*.

1. *Camptotheca acuminata* var. *tenuifolia* Fang et Soong in *Act. Phytotax. Sin.* 13(2):86. pl. 14, f. 3, 1975; Fang and Zhang in *Fl. Reip. Pop. Sin.* 52(2):144-146, 1983.

The Chinese name of var. *tenuifolia* is *Baoye Xi Shu* (薄葉喜樹, tenuous leaf happytree). The variety is identified based on the specimen collected from Huaiji County, Guangdong Province. It is distinguished by its longer fruit (3.0-3.2 cm long) and smaller leaves (8-10 cm long, 4-6 cm wide with 11-12 lateral veins on each side) **(Figure 13)**. The type (Bingming Zhang 20309, November 4, 1952) is deposited at the Herbarium of Sichuan University at Chengdu, Sichuan Province. The tree grows to 5 m in height and is found growing along streams at Luegang Xiang, Huaiji County.

2. *Camptotheca acuminata* Decaisne var. *rotundifolia* Yang et Duan in *Nat. Sci. J. Hunan Norm. Univ.* 11(1):63-64 (1988).

The Chinese name of var. *rotundifolia* is *Yuanye Xi Shu* (圓葉喜樹, round leaf happytree). It was recently found growing in Nanxian County, Hunan Province, China. It differs from var. *acuminata* and var. *tenuifolia* by brown bark, a round or sub-round and small leaf (4.5-6.5 cm long, 5.5-6.5

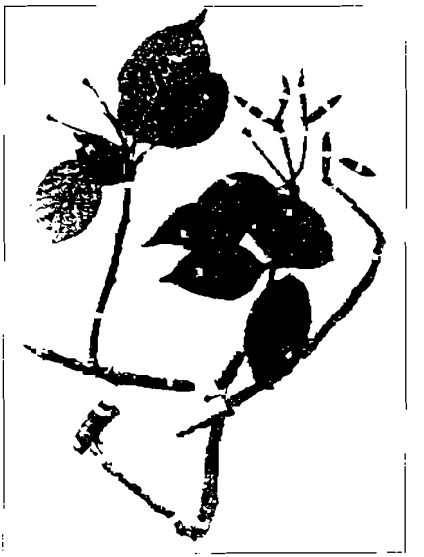


FIGURE 13. ***Camptotheca acuminata*** **Decaisne var.** ***tenuifolia*** **Fang et Soong** (after Fang and Soong 1975, type specimen: Bingming Zhang 20309).

cm wide, with 4-7 lateral veins on each side) **(Figure 14)**. The type (Lindong Duan 1001, August 1981, at 45 m above sea level) is deposited at the Herbarium of Hunan Normal University at Changsha, Hunan Province. The tree grows to 10 m tall and is found at low elevations.

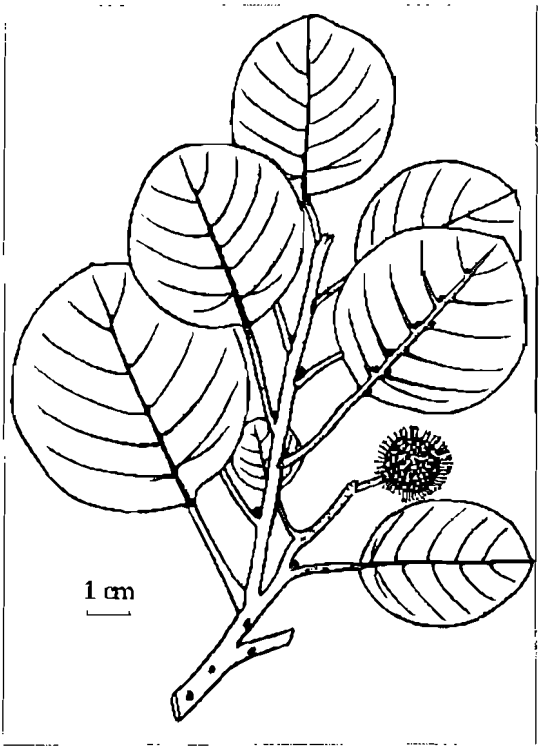


FIGURE 14. ***Camptotheca acuminata*** **Decaisne var.** ***rotundifolia*** **Yang et Duan** (after Yang and Duan 1988).

9. GEOGRAPHY OF XI SHU

Natural Range

Xi Shu is a Tertiary relict. It was widely distributed in Japan in the Tertiary Period (Suzuki 1976, Tanai 1977). It is now native only to central, southern, and southeastern China, including Anhui, Zhejiang, southern Jiangsu, Jiangxi, Fujian, Hubei, Hunan, Guangdong, Guangxi, Guizhou, Sichuan, and Yunnan provinces (**Figure 15**). Xi Shu usually grows in moist and fertile sites below 1,500 m in elevation, especially in thickets, but is occasionally found up to 2,400 m in elevation in the southern portion of its range. It occurs on deep, well-drained, friable clay soils at the edges of forests, on slopes, and along streams.

Cultural Range

In China, Xi Shu is widely cultivated as an ornamental "four-sites" tree within its natural range and Henan and Taiwan provinces. It is also largely planted beside irrigation ditches as a firewood species because of its rapid growth and regeneration. The species was introduced into Japan, South Korea, Europe, and the United States in this century.

United States

The first introduction of Xi Shu to the United States was in 1911 (Perdue et al. 1970) (**Figure 16**). The seeds collected from the Omei Mountain, Sichuan Province by E. H. Wilson (No. 4405) were sown at the Arnold Arboretum (USDA 1915). No records are now available indicating further distribution by either the Arnold Arboretum or the USDA (Perdue et al.

FIGURE 15. **Natural distribution of Xi Shu in China** (the dots—*Camptotheca acuminata* var. *acuminata*; the star—*C. acuminata* var. *tenuifolia* Fang et Soong; and the square—*C. acuminata* var. *rotundifolia* Yang et Duan).

1970). According to computer searches and personal interviews with P. White and S. Kelley at the Arnold Arboretum (1994), there is no living collection and even no record of it ever having been at the Arnold Arboretum.

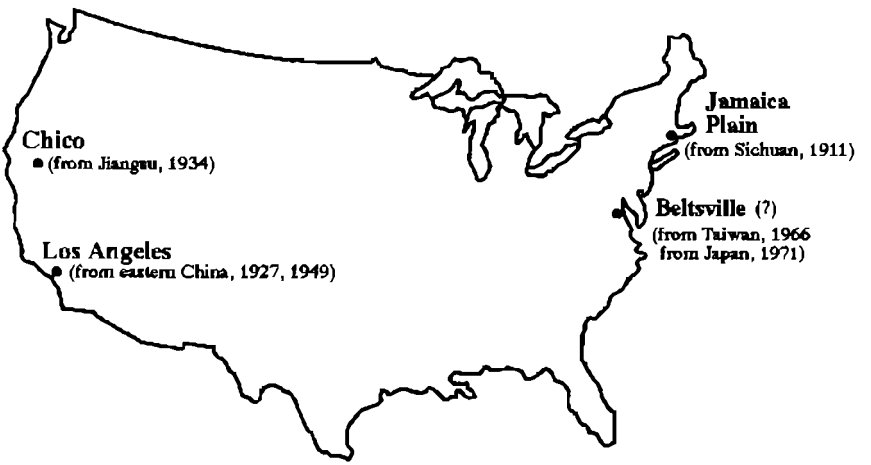


FIGURE 16. **Early introduction of Xi Shu in the United States.**

In 1927, seeds collected from Jiangsu Province, China by W. T. Swingle (No. 803) were sown in Los Angeles, California (Perdue et al. 1970). However, no records are available on survival and redistribution of the seedlings (USDA 1929).

In 1934, seeds Steward No.75 were received by the USDA in April 1934 and accessioned in April 1939 as P.I. 132293. The seeds were sown at the Plant Introduction Station at Glenn Dale, Maryland in June 1934 (USDA 1950). About 150 plants were available in 1935. Some of these plants were distributed in Honolulu, Hawaii; San Diego, California; Mayaguez, Puerto Rico; and Atkins Garden near Cienfuegos, Cuba in 1937; and Chico, California in 1938 (Perdue et al. 1970). Only two trees at Chico have survived (Perdue 1968, see **Figure 17**). The Steward No. 75 was collected by A. N. Steward, a professor at the College of Agriculture and Forestry at Nanjing University (now the Nanjing Forestry University) from Changan, Yung Hsien, but the record did not indicate which province. There are at least two counties named after Yung Hisen (or Jung Hsien, Yung Xian) in China. One is in northern Guangxi

FIGURE 17. **A 60 year-old mature tree of Xi Shu in Chico, California, August 1994** (photo by L. E. Hartman, USDA Forest Service).

Province, 50 miles north of Liuzhou. Another one is in southwestern Sichuan Province, 38 miles east of Loshan. The seeds may have been collected from one of these two counties.

In 1935, the Arnold Arboretum received seeds from Lushan Arboretum and Botanical Garden, Jiangxi Province. The seeds were sown in pots in February 1935 and died in 1942. This introduction was not distributed (Perdue et al. 1970).

In 1949, Willard Hagen in Arcadia, California obtained seeds from Lushan Arboretum and Botanical Garden. The plants raised from these seeds were distributed to private purchasers, city parks, and botanical gardens on the west coast from California to Washington; but less than 30 trees were found in the United States before 1965. During the late summer of 1965, most of the trees were harvested for drug collection with probably only **TWO** trees left at the Chico Plant Introduction Station (seed source: Steward No. 75, from Jiangsu) and **ONE** in Los Angeles State and County Arboretum (1952 from Hagen Nursery, which had received its seed from Lushan, Jiangxi). After discovery of the tree's anti-tumor activity, Xi Shu reproduction increased rapidly. Chico Plant Introduction Station (now Genetic Resource Center) in California started to produce seedlings from its two trees in 1964, reaching 1,300 seedlings in 1966, 5,000 by 1967, and 8,500 in 1992. Current collections in many gardens and nurseries in the United States are from this seed source (or originally Steward No. 75 from Jiangsu).

In 1966, the New Crops Research Branch (NCRB), Crops Research Division, Agricultural Research Service, USDA received seeds from Taiwan (as I.P. 317685-317688, see USDA 1969). The seeds were collected from four trees by Ta-Wei He at the Forestry Division of the Joint Commission on Rural Reconstruction, Taipei. No record indicates the distribution of the seeds.

In 1971, the NCRB of USDA obtained seeds from Japan (USDA 1974). The seeds were collected by R. E. Perdue from a single tree at the Kyoto Botanical Garden, Kyoto (Perdue No. 10265) and two trees at the Kamigamo Experimental Forest of Kyoto University (Perdue No. 10267). The tree at Kyoto Botanical Garden was about 25 years old then and the two trees from Kamigamo were originally from it. The seeds

probably were sown at the Plant Industry Station, Beltsville, Maryland. No record indicates further distributions from this collection.

The Genetic Resource Center, USDA at Chico has received seeds from many sources since 1991. The main seed sources include (L. E. Hartman, pers. comm., September 1994):

- China: Tongshan, northern Anhui; Zhoushan, Zhejiang; Nanjing, Jiangsu; Changsha, Hunan; Wuhan, Hubei; Luzhou, Sichuan; Shanghai; and Guangxi
- Japan: Kyoto University Experimental Forest Station
- United States: Smith College, Massachusetts (from Korea, unknown origin), Texas A & M University, Texas (from China, unknown origin), Yucca Do Nursery, Texas (from Chico?), and Anderson Landscape and Nursery, Houston, Texas (from San Antonio, originally from Chico?).

Seedlings grown from all of the above listed seed have been planted in a 2.5 acre breeding arboretum at Chico for long term seed and cutting production (**Figure 18**).

Nurseries in Montana, Hawaii and California, recently purchased seeds from China. The seeds are distributed to several nurseries in the United States.

At present, Xi Shu has been introduced into California and most states of the southeastern United States. The Chico Genetic Resource Center has established a 1.5 acre plantation planned for harvest in 1995 under an agreement with the NCI (L. E. Hartman, pers. comm., September 1994). However, the seedlings or young trees are largely grown in gardens and experimental field plots, and Xi Shu plantations are still in an early trial stage especially in the southeastern United States. The genetic quality of the tree is a critical problem in the development of plantations because the seed source is limited.

In South Carolina, E. Cuthbert received seeds from Hurov Tropical Seeds, Honolulu, Hawaii in 1970. One tree in Summerville, South Carolina is now about 11.5 m tall and 16 cm in diameter. The tree has never shown any obvious

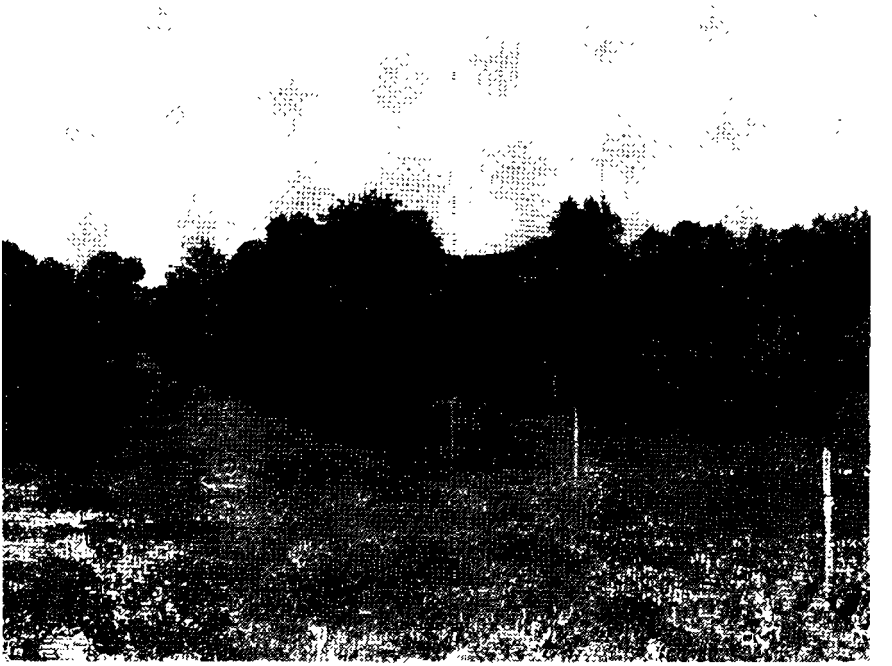


FIGURE 18. **Xi Shu seed orchard of the USDA Forest Service at Chico, California, August 1994** (photo by L. E. Hartman, USDA Forest Service).

damage from drought and hurricane Hugo (the eye of the storm passed directly over the tree, Cuthbert, pers. comm., August 1994). The growth of the tree is slow largely because it is shaded by several larger trees around it.

In Texas and Louisiana, plantation trials of Xi Shu started in the early 1990s. The seeds or seedlings are basically from L. R. Lowrey at Anderson Landscape and Nursery, Houston, Texas. In 1979, Lowrey received about 20 seedlings from the San Antonio Botanical Center, Texas. The San Antonio parent tree was about 10 years old then, it is probably from one of the two mother trees at Chico, California. Lowrey and K. K. Ferguson distributed these seedlings in Texas in the

early 1980s, and two trees are left today: one in Kingwood (in D. Morgridge's back yard) and the other in Houston (at the Stehlin Foundation for Cancer Research). These trees started to bear fruit in the late 1980s. The seeds or seedlings from the Kingwood tree were distributed to many of above people or organizations in Texas and Louisiana by Lowrey and T. R. Moore of the XyloMed Research Foundation at Monroe, Louisiana (see Louisiana Public Broadcasting Report on Tracy and Camptothecins, video type produced by Arcie Chapa Broadcast June 3, 1993 and Tracy and the Tree of Joy, video tape produced by JRWL Videomaker LLC 1994).

The San Antonio parent tree was destroyed several years ago. Fortunately, one tree from this parent tree is growing at the San Antonio Zoo, Texas. The seedlings reproduced from seeds of this tree were sent to the National Arboretum in Washington D.C. in 1991.

In 1991, Lowrey obtained two pounds of seeds from a seed company in Montana. The seeds were collected from Zhejiang Province, China. In 1993, Lowrey received seeds from Cuthbert who collected seeds from his Summerville tree. Seedlings were raised from these seeds, and some plants were propagated by cuttings from these seedlings and the Kingwood tree, by Lowrey and his son-in-law and daughter, M. and P. Anderson in Houston, Texas. Lowrey and his family have donated seeds and seedlings directly to many people and organizations throughout the United States since 1991. These people and organizations include:

- D. L. Creech and S. Y. Li of Stephen F. Austin State University, Nacogdoches, Texas (30 seedlings)
- M. Ellis of Gibbs Brothers in Huntsville, Texas (now with Black Stone in Houston)
- L. Atlas in Houston, Texas (later, Atlas gave his seedlings to TreeCo in Oregon specializing in tissue culture and fruit tree understocks)
- San Antonio Botanical Center in Texas (50 seedlings)
- USDA Genetic Resource Center (formerly Plant Introduction Station), Chico, California (50 seedlings)

- Sam Houston State University, Huntsville, Texas (hundreds of seedlings)
- J. Harrington of Orange, Texas
- Lowrey's sister and cousin at Sulphur, Louisiana
- M. Brennan of the Louisiana-Pacific Corporation, New Waverly, Texas
- T. R. Moore in Monroe, Louisiana (about 600 seedlings).

Moore received the plants from Lowrey and his family in the late fall 1992. He also received 5 pounds of seeds from a seed company in Montana by the end of 1992. He gave the seedlings and seeds from these sources to universities and companies for field trials and laboratory tests:

- G. H. Weaver and J. Adams of the School of Forestry at Louisiana Tech University, Ruston, Louisiana. The seeds were sown in February 1993 and about 2,000 seedlings are growing well at the Columbia Nursery, Columbia, Louisiana.
- S. Carpenter and Z. J. Liu of the Louisiana State University School of Forestry, Wildlife, and Fisheries. These seedlings were planted at LSU experimental stations in New Iberia and Port Sulphur, Louisiana. About 500 seedlings are growing very well in Port Sulphur (**Figure 19**). In addition, they received about 200 seedlings from Weyerhaeuser Company in the spring 1994; these seedlings came from seeds of the Chico trees.
- Boise Cascade in DeRidder, Louisiana has a seed tree farm with about 100 plants established. In the fall of 1993, Moore founded the non-profit XyloMed Research Foundation in Monroe, Louisiana to support studies of Xi Shu.

Studies on propagation by cuttings and field trials are now being conducted by almost all of these institutions and individuals.

In addition, field trials are being conducted in southern Arkansas. In the fall of 1992, about 100 seedlings were planted in Crossett, Arkansas by Georgia-Pacific Corporation. The seedlings were from Louisiana Tech University. Field

FIGURE 19. **A Xi Shu plantation including 500 seedlings was established by the Citrus Research Station in Port Sulphur, Louisiana in early 1993** (photo by T. R. Moore, XyloMed Research Foundation).

trials are also being conducted in Louisiana by International Paper Company.

Other Countries

Xi Shu trees are available in many gardens and experimental forests in Japan and South Korea. In the United Kingdom, Xi Shu has been introduced several times. According to R. J. Pankhurst (pers. comm., August 1994), for example, the Royal Botanic Garden in Edinburg introduced Xi Shu from China in 1980. The source is unknown and no provenance information is available. In 1993, there were two

direct seed introductions from China by the Royal Botanical Garden. On April 14, seeds were received from Kunming Botanical Garden, Yunnan, China, but the origin is wild and is not known. Two months later, the garden received seeds from the Shanghai Botanical Garden, Shanghai, and the wild origin was from western Zhejiang (400 m at elevation, 30°30'N 119°17'E).

10. ECOLOGY OF XI SHU

Synecological Feature

Xi Shu is a shade-intolerant species (**Figure 20**). It is a canopy species but less dominant in mixed evergreen and deciduous hardwood forests, especially at elevations from 1,000 to 2,000 m in the central subtropical region of China (Chou and Li 1990). The forest canopy is usually 15-20 m high. According to Y. L. Chou and S. Y. Li (1990), the upper canopy consists of Xi Shu and other deciduous species, including *Fagus longipetiolata* Seem., *F. lucida* Rehd. et Wils., *F. engleriana* Seem., *Sapium japonicum* Pax et Hoffm., *Cyclocarya paliurus* (Batal.) Iljinskaja, *Alniphyllum fortunei* (Hemsl.) Perk., *Meliosma* spp., *Liquidambar acalycina* Chang, *Acer sinense* Pax., *Carpinus fargesiana* Winkl., *Toxicodendron succedaneum* (L.) Kuntze, and *Nyssa sinensis* Oliv. The lower canopy largely includes evergreen trees such as *Cyclobalanopsis glauca* (Thunb.) Oerst., *C. oxyodon* (Miq.) Oerst., *Castanopsis eyrei* (Champ. ex Benth) Tytch., *Schima supera* Gardn. et Champ., and *Lithocarpus* spp. In addition to Xi Shu, the forest contains some other Tertiary relics such as *Davidia involucrata* Baill., *Liriodendron chinense* (Hemsl.) Sarg., *Cercidiphyllum japonicum* var. *sinense* Rehd. et Wils., *Tetracentron sinense* Oliv., *Aesculus chinensis* Bunge, *A. wilsonii* Rehd., *Bretschneidera yunshanensis* Hemsl., *Euptela pleiospermum* Hook. et Thomas., *Dipteronia sinensis* Oliv., and *Eucommia ulmoides* Oliv. (Chou and Li 1990). The undergrowth species are numerous. *Sinarundinaria* spp. and ferns are relatively common. Xi Shu does not regenerate well naturally in a closed forest, but the seedlings grow well in open places (**Figure 21**).

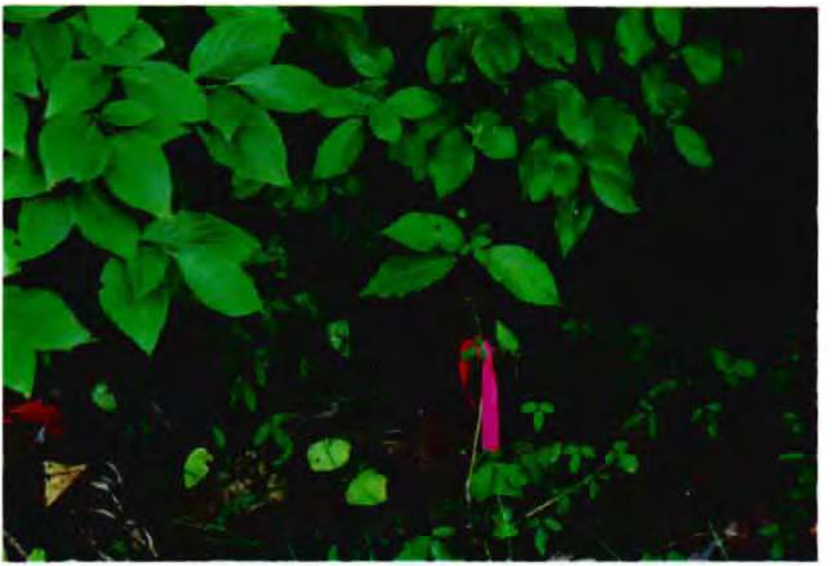


FIGURE 20. **Xi Shu is a shade-intolerant species. A 2 year old seedling under dogwood (*Cornus florida*) canopy is only 25 cm tall, while the seedlings of the same age under full sunlight can grow up to 2 m tall** (photo by S. Y. Li, Tucker Center, July 15, 1994).

FIGURE 21. **Xi Shu regenerates well naturally under the parent tree, especially in shade gaps** (photo by L. R. Lowrey, Anderson Landscape and Nursery).

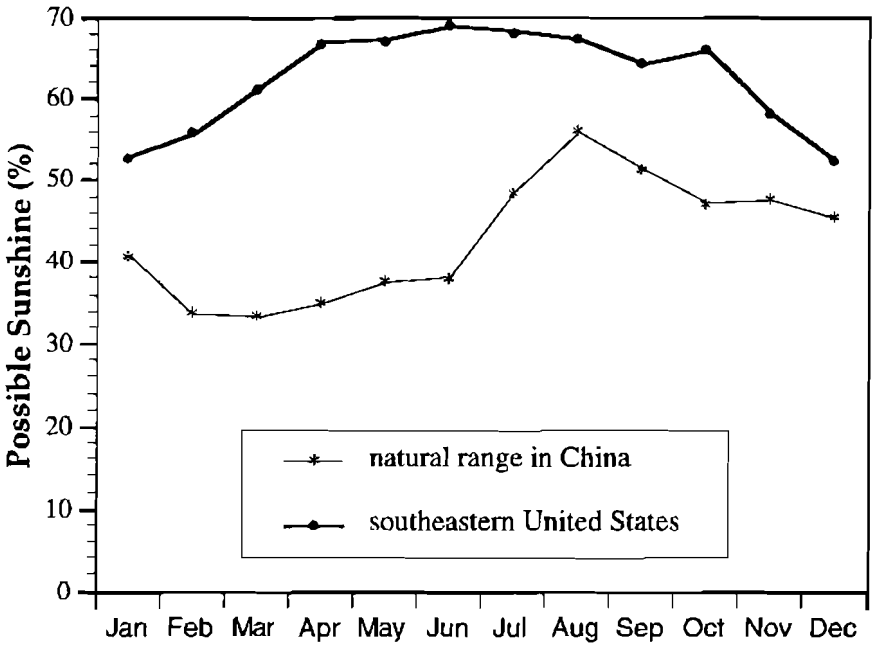


FIGURE 22. **Monthly changes in mean percentage of possible sunshine in the natural range of Xi Shu in China and its potential range in the southeastern United States** (1961-1990).

Autecological Feature

The ecological requirements of Xi Shu are largely a warm and humid subtropical climate and fertile well-drained subtropical soils. The environment of its native range in China is favorable for the growth of Xi Shu. The annual mean percentage of possible sunshine ranges from 28 to 57 within the natural range of the tree (see Appendix Table 1). Normally, sunshine is least in the spring (**Figure 22**). The growing season is usually 250-300 days. The monthly mean temperatures display a bell shaped curve over the year (**Figure 23**). The annual average temperature varies from 15°C to 23.0°C at low elevations within the natural range (see Appendix Table 2). At higher elevations (above 2,000 m), the

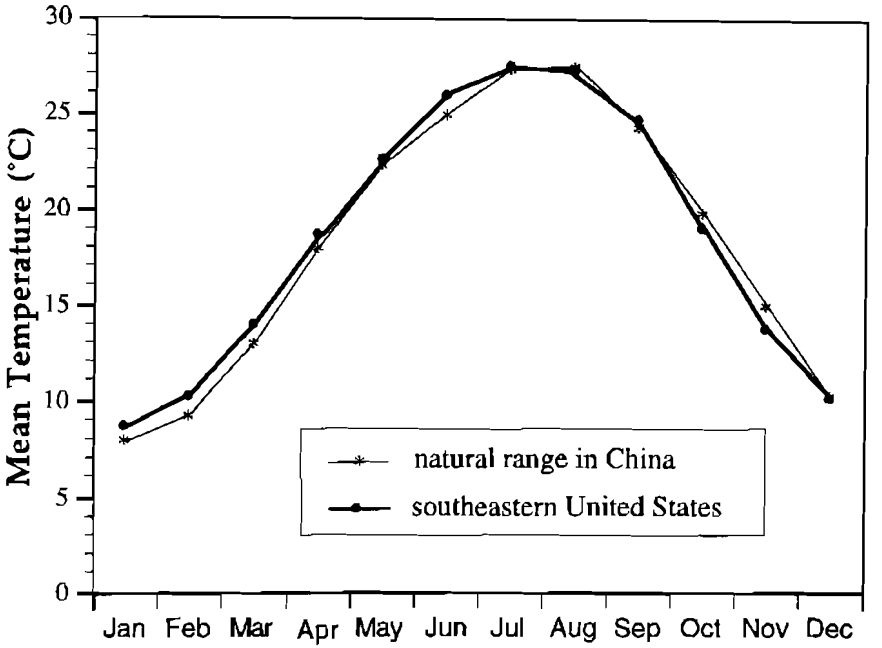


FIGURE 23. **Monthly changes of mean temperature in the natural range of Xi Shu in China and potential range in the southeastern United States** (1961-1990).

annual average temperature may decrease to about 10°C. The mean temperature of the coldest month (January) ranges from 2°C to 14°C, and the recorded low temperature is -20°C (Chou and Li 1990). Annual precipitation is usually 1,000-2,000 mm and about 75% falls in the April-September (**Figure 24**, see Appendix Table 3). However, winter drought is evident throughout the range. Relative humidity is usually about 80% especially during the growing season (**Figure 25**, see Appendix Table 4). Xi Shu is more likely to be found along moist valley bottoms than on the upper slopes. The soils in the natural range are red and yellow podzolic soils with a pH ranging from 4.5 to 6.0, but slightly acid soils favor the growth of the plant (J. C. Ran, pers. comm., May 1994).

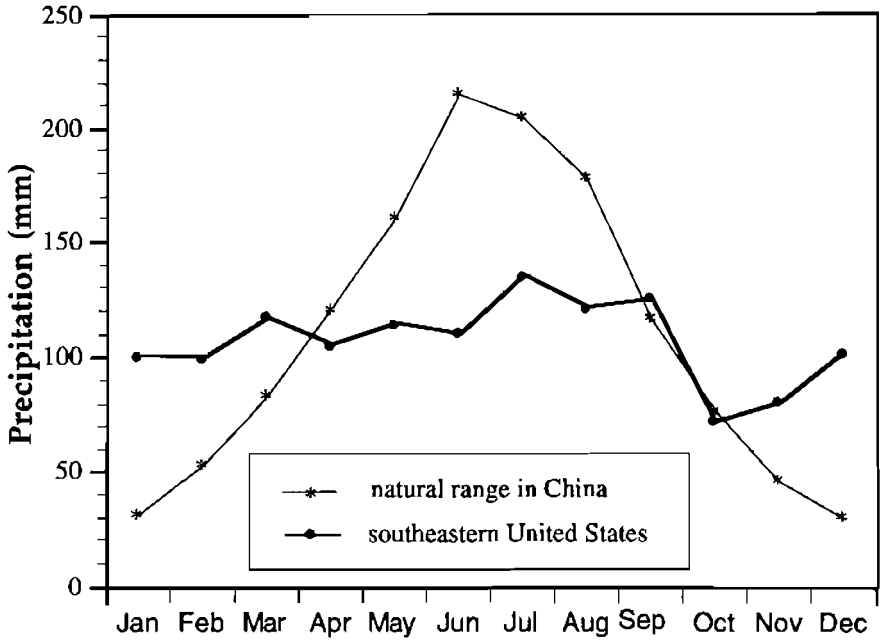


FIGURE 24. **Monthly changes of mean precipitation in the natural range of Xi Shu in China and potential range in the southeastern United States** (1961-1990).

Ecological Conditions of the Potential Cultural Range

The physical environment of the southeastern United States, especially temperature and soil conditions, are similar to those of the natural range of Xi Shu in China. Therefore, Xi Shu may be fully adaptive to the southeastern United States (roughly at the 1990 USDA Plant Hardiness Zone 8a, 8b, 9a, and 9b). In East Texas, for example, young plants have grown rapidly and are root hardy after growing outdoors for only a few weeks. But, there are several reports of frost damage to Xi Shu in East Texas and San Antonio, Texas (David L. Creech and Paul Cox, pers. comm., August 1994).

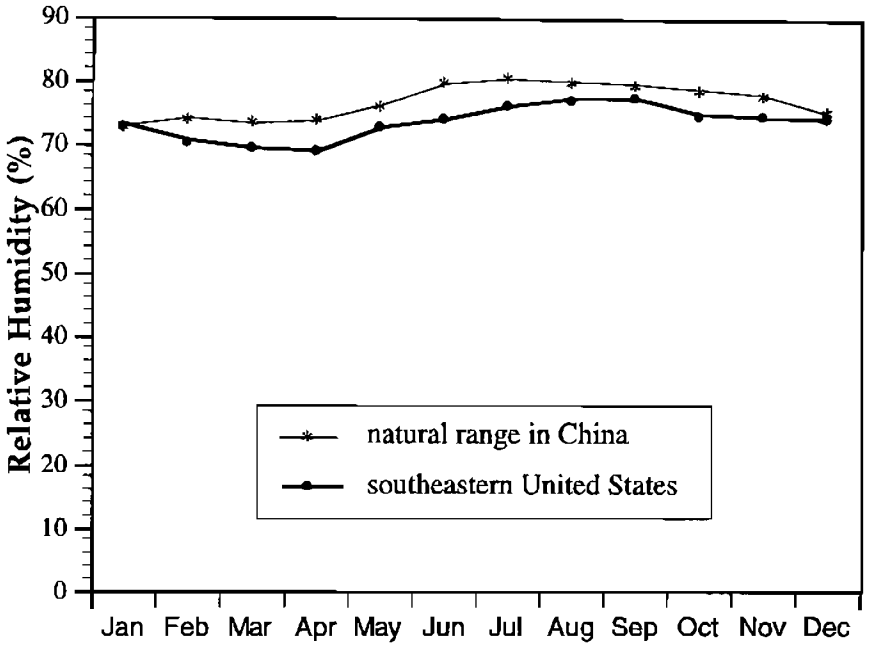


FIGURE 25. **Monthly changes of relative humidity in the natural range of Xi Shu in China and potential cultural range in the southeastern United States** (1961-1990).

The terminal buds of the plant are often damaged at low temperatures of 0°C. In Summerville, South Carolina, however, a tree planted in 1970 has no obvious damage from an overnight low temperature of -13°C (Edmund Cuthbert, pers. comm., August 1994). In Chico California, trees have escaped winter damage from the mean January temperature of 7.3°C and a low temperature of -11.7°C (Perdue et al. 1970). Young plants survived for several years with minimum protection at Glenn Dale, Maryland, where mean January temperature is 1.3°C (Perdue et al. 1970). It was also reported that Xi Shu has withstood temperatures of -12°C without damage in South Korea (Meyer 1991). Such differences in cold tolerance may result from different seed sources (probably different ecotypes).

Xi Shi is a photophilous species. The tree is shade-intolerant, but the seedlings may grow well under the tree. The mean percentage of possible sunshine during June-August reaches 60 to 70 in the southeastern United States (see **Figure 22**) and 70 to 90 over most of the central and western United States (Perdue et al. 1970). The amounts are much more than those of the natural range in China where the percentage is usually less than 50 from June to August. This extra sunshine in the United States should be favorable to the growth of Xi Shu.

Xi Shu is not drought-tolerant, especially during the growing season. In its natural range in China, rainfall is greatest in the summer, and Xi Shu grows well under those natural conditions. But in the southeastern United States, rainfall is evenly distributed among all seasons (see **Figure 24**). Thus, Xi Shu may suffer from lack of adequate available moisture during the growing season. For example, over half of 1,000 seedlings planted in Plaquemines Parish, Louisiana, were lost from dry weather in May 1994 (Tracy Moore, pers. comm., August 1994). Therefore, an irrigation system should be considered when plantations are established in the field (**Figure 26**).

Pure Xi Shu plantations are easily managed and harvested. However, ecologically, it may be better to establish Xi Shu plantations mixed with other hardwoods. For example, there are no large area, healthy, pure Xi Shu plantations in southern China. Studies are needed to determine species that should be associated with Xi Shu. According to the native communities in China, species of *Nyssa*, *Acer*, *Carpinus*, *Aesculus*, and *Liriodendron* appear to be possible associates of Xi Shu.

FIGURE 26. **An irrigation system should be considered when plantations are established in the field** (photo by L. E. Hartman, USDA Forest Service).

11. REPRODUCTION AND GROWTH OF XI SHU

Pollination

Cross-pollination is the major breeding system of Xi Shu, and neither self-fertilization nor agamospermy are observed (Chen et al. 1991). Smith (1969) found that no fruit develops from the terminal flower when it is isolated from other flowers in the same head. But fruit develops normally when the complete head is enclosed in a paper bag. The stamens are shed nearly one week before the stigma of the same flower becomes receptive; this protandry leads to cross-pollination (Chen et al. 1991).

Pollination of Xi Shu is obligatory entomophilous, and fruit production depends on the activities of pollinating insects (Chen et al. 1991). According to L. J. Chen and co-workers (1991), 24 species of visiting insects have been recorded. They belong to Hymenoptera [bees and wasps, such as *Apis cerana* Fabr, *Ceratina hieroglyphica* Sm., *Hylaeus* sp., *Nomia chalybeata* Sm., *Pareumenes quadrisoinosus transitorus* Liu, *Polistes formosanus* Sonan, and *Vespa tronica aucalis* Smith], Lepidoptera [butterflies, including *Argynnis hyperbius* (L.), *Graphium doson postianus* (Fruhstorfer), *G. sarpedon connectens* (Fruhstorfer), *Papilio polytes pasikrates* Fruhstorfer, *P. protenor amaura* Jordan, *Pieris canidia* (L.), *P. almana* (L.), *Polygonia calbum asakurai* Nakahara, *Radena similis* (L.), and *Tacoraea opalina hirayamai* (Matsumura)], Diptera [flies, including *Chrysomyia defixa* (Walker), *Sarcophagidae* sp., and *Syrphidae* sp.], and Coleoptera [beetles, such as *Potosia serata* (Erichson)]. Pollination results in an average fruiting rate of over 60%. Petals of flowers are small and green in color and thus are

inconspicuous. However, stamens have yellow anthers which are very attractive to many insects. Conspicuousness of the stamens is enhanced by their radiate arrangement on a head and by the mass flowering at the same time. Also, nectar and abundant pollen are rewards to insects as full anthesis.

Production of seed is vigorous. In Chico, California, two mature trees (about 30 years old then) produced enough seeds to plant about 4 hectares (10 acres) per year at a rate of 17,780 seedlings per hectare (7,000 seedlings per acre) (Perdue 1968).

Seed Germination

Seed germination can be a problem in the reproduction of Xi Shu by seeds. Seeds of Xi Shu usually do not germinate, or have delayed germination at room temperature (Shao 1989, Zhou 1989). Less than 5% of seeds germinated in 30 days at stable temperatures (e.g., 15°C, 20°C, 25°C, 30°C, and 35°C) (Shao 1989). Studies suggest that inhibitory materials in the seed coat are the main factors influencing this pattern of seed germination (Shao 1989, Zhou 1989). Germination rates exceeding 70% were obtained when the seed was either removed from the fruit or left in fruit that had been dried before planting (Smith 1969).

Germination may be increased either by stratification or by moderate drying with artificial heat. Following stratification at 0-5°C alone for 30 days, the germination rate rose to 83.5% in only 8 days (Shao 1989). The germination rate was 73.5% at temperatures of 20/30°C without stratification. The most satisfactory treatment will probably be a combination of heating and stratification (Perdue 1968, Perdue et al. 1970). The highest germination rates were achieved when seeds were illuminated at a light intensity of 1,000 lumens for 8 hours per day, or subjected to temperature regimes of 30°C during the day and 20°C at night, then stratified at 5°C for 40 days (Zhou 1989).

Presently, reproduction by seeds is a major method of seedling supply in the United States (**Figure 27** and **Figure 28**).

Vegetative Propagation

Xi Shu has great coppice ability and can be propagated vegetatively (**Figure 29** and **30**). In preliminary studies in Chico, propagation by both cutting and budding proved successful (Smith 1969). With "T" budding, the best results were obtained in September when the scion-wood was more mature. Leafy cuttings taken in early summer gave the most satisfactory rooting and produced healthy, vigorous stock.

Trials by the authors at Stephen F. Austin State University show that successful shoot cuttings can be taken from late March to June. Lowrey's experiment at the Anderson Landscape and Nursery, Houston, Texas shows a similar result (L.R. Lowrey, pers. comm., August 1994). Propagating material should be cut from healthy dormant or new shoots. Straight cuttings range from 5 to 20 cm long and 0.5-1.5 cm in diameter. At least two nodes need to be included in each cutting with the basal cut just below a node and the top cut 1-2 cm above a node. Cuttings root well under natural conditions although they may show better results when treated prior to planting with root-promoting substances such as indolebutyric acid (IBA). Cuttings may be planted immediately or kept for several weeks packed in peat moss before planting.

Growth

Xi Shu grows rapidly, especially in the first 10 years in favorable conditions. Two and one-half year old seedlings at Sulphur, and Port Sulphur, Louisiana reached 4 m in height (**Figure 31**). Our observations show that the growth of seedlings produced either by seeds or cuttings under a closed

FIGURE 27. **Seedlings grown from seeds by Anderson Landscape and Nursery, Houston, Texas,** April 1992 (photo by L. R. Lowrey, Anderson Landscape and Nursery).

FIGURE 28. **90-cm tall seedlings in the Columbia Nursery, Columbia, Louisiana on** August 29 1994. **The seeds, from Montana and South Carolina, were sown in the spring of 1994** (photo by S. Y. Li, Tucker Center).

FIGURE 29. **First year coppice regrowth from a 2 year-old seedling cut near ground level in October 1993, SFASU Arboretum, Nacogdoches, Texas** (photo by S. Y. Li, Tucker Center).

FIGURE 30. **Coppice sprouts, Xi Shu,** Port Sulphur, Louisiana (photo by S. Y. Li, Tucker Center).

FIGURE 31. **A two and one-half year-old seedling measuring 4 m in height in Port Sulphur, Louisiana on** August 27, 1994 (photo by T. R. Moore, XyloMed Research Foundation).

canopy started about one month later than those in less shade. The seedlings under full shade usually did not survive while those under full sun grew very fast and averaged about three times taller than those under partial shade. Annual height growth under full sun can average more than one meter in the first 10 years (Saito and Shidei 1968). Mature trees can reach 30 m in height and 100 cm in diameter under favorable conditions.

According to Saito and Shidei's observation in Kyoto, the individual leaf longevity is rather short: 70% of the total leaves in a year will emerge in spring. These leaves are small and usually last only one or two months. None of the leaves that emerged in spring or summer lasted to the end of fall. In East Texas, however, leaves that emerged in the spring were large and lasted the entire growing season. Further studies of the lack of leaf longevity of Xi Shu seem necessary if leaves are to be source of camptothecins.

Maximum leaf biomass was 0.45 kg/m^2 (dry) in July, and maximum gross biomass of the plant (leaf, stem, and root) reached 1.7 kg/m^2 (dry) in September (Kawahara et al. 1968). According to Kawahara and co-workers (1968), nutrient-uptake by trees was relatively large in the early growth period, especially in July, and 50-70% of total nutrient-uptake returned to the soil via leaf-fall by the end of the year. The total dry matter nutrient content was measured in September as: potassium, 19.2 g/m^2; nitrogen, 16.8 g/m^2; calcium, 10.3 g/m^2; magnesium, 8.6 g/m^2; and phosphorus, 12.8 g/m^2. The amount of inorganic nitrogen and available phosphorous in the soils are important to the growth of Xi Shu. Thus, silvicultural practices are needed in the plantation (**Figure 32**).

Biomass of each part, except branches, appeared to be little affected by differences in stand density (Saito 1980). Therefore, seedlings can be planted at higher densities (2,000-7,000 trees/acre) if plantations are managed for drug production.

FIGURE 32. **Laying mulch under Xi Shu in the seed orchard, USDA Forest Service, Chico, California** (photo by L. E. Hartman, USDA Forest Service).

12. PROTECTION OF XI SHU

Diseases

Leaf spot is one of the most common diseases of Xi Shu in China. The primary pathogens for leaf spots are *Cercospora camptothecae* Tai (Dothideaceae, Dothideales, largely in Jiangxi), and *Pseudocercospora camptothecae* Liu et Guo (Dothideaceae, Dothideales, in Zhejiang, Hubei, Hunan, Guangdong, Sichuan, and Yunnan), *Alternaria* spp. (Pleosporaceae, Dothideales, in Hubei and Hunan), *Phyllosticta* spp. (Phacidaceae, Phacidiales, in Hubei, Hunan, and Jiangxi), *Macrophoma* spp. (Sphaerioidaceae, Sphaeropsidales, in Jiangxi). *Cercospora camptothecae* Tai has been recorded in Florida along with *Puccinia* sp. (Basidiomycotina, Uredinales), another fungus host on Xi Shu (Affieri et al. 1984, Farr et al. 1989).

The infected leaves by *Cercospora camptothecae* Tai (Tai 1948) and *Pseudocercospora camptothecae* Liu et Guo (Liu and Guo 1987, **Figure 33)** show brown or black leaf spots. Spots are irregular, many are gray, yellowish brown, or brown with dark dots in the center that denote the mass frucitification of the fungus. They are usually 1-8 mm in diameter. As the disease progresses, the spots enlarge until the entire leaf is affected. The disease reduces the yield and lowers the quality of fruits. Also, fallen leaves from infected plants provide organic matter as a food source for other fungi. This often increases the severity of stem and root rot infections.

About 400 species of *Cercospora* and *Pseudocospora* have been found on a wide variety of crops and trees, particularly in warm, humid regions. Conidia of these fungi vary greatly in size. For example, *Cercospora camptothecae* measures 37.0-60.0 × 3.6–4.3 μm, while *Pseudocercospora camptothecae* Liu et

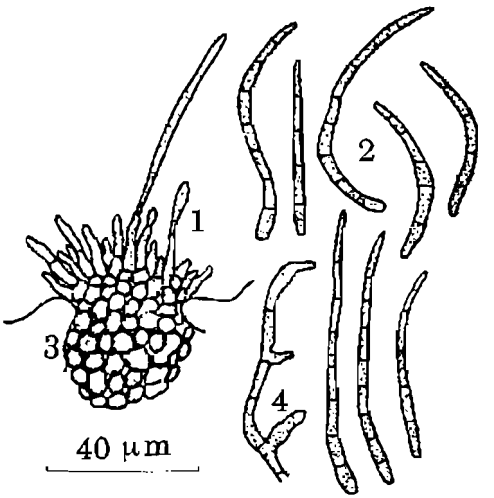


FIGURE 33. ***Pseudocercospora camptothecae*** **Liu et Guo** (specimen HMAS 50504, after Liu and Guo 1987. 1-conidiophores; 2-conidia; 3-stroma; 4-superficial hyphae).

Guo is from 6.0-104.0 × 2.5–4.0 µm (Liu and Guo 1987). The slender, colorless conidia are straight to curved and have several crosswalls. The conidia are borne on brown, septate, knobby, sparingly branched conidiophores borne in clusters. The fungi may overwinter on infected plants and debris and survive from one season to the next on diseased leaves, stems, and seeds. When infected seeds are planted, they may produce weak, stunted seedlings with lesions on the cotyledons; in a few days the growing fungus begins producing conidia and secondary infections (Lucas et al. 1985). The conidia are wind blown or splashed by rain or carried by insects and machinery to nearby plants. They germinate within a few hours and quickly penetrate leaf tissue. The disease spreads rapidly during warm weather, particularly with intermittent rain. It is more severe in pure plantations.

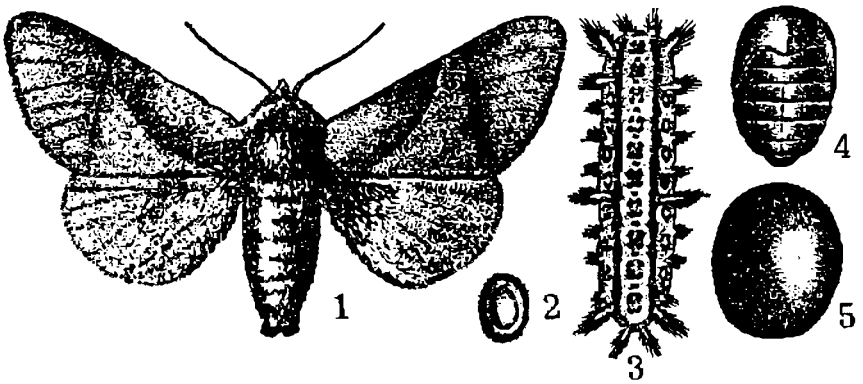


FIGURE 34. *Setora postornata* (Hampson) (after Xiang Zhang, in Cai and Xiao 1983. 1-adult insect; 2-egg; 3-larva; 4-pupa; 5-cocoon).

Fungicides should be applied in the treatment of seeds and regularly in the seedbed and plantation. In the plantation, fallen leaves, branches, and logging debris should be burned as soon as possible to remove the food source for fungi. However, it is also important to use disease-free or disease-resistant seeds to create a disease free forest.

Pests

In China, species of the family Limacodidae (Lepidoptera), including *Setora postornata* (Hampson), *Cnidocampa flavescens* (Walker), and *Parasa* spp. are common leaf pests of Xi Shu. *Setora postornata* (Hampson) (**Figure 34**) is found in almost all provinces in the subtropical region and attacks at least 126 species of plants (Cai and Xiao 1983). The adult moth is 17-20 mm long, brown, with a wing span of 30-40 mm. The full grown larvae are 23-35 mm long, yellowish green with two blue lines and black tubercles along the back. The

body has yellow or purplish red hairs. Two generations occur per year. The larvae often form cocoons in the debris or surface soils (depth < 1 cm). The adult moths show strong phototaxis. Control methods are: (1) Collect overwinter cocoons from the debris and surface and deeply bury them in soils (> 30 cm). (2) Trapping moths attracted to lights in the evening. (3) Biological control by parasitic wasps (*Chrysis shanghaiensis*, *Bracon* sp., and *Trichogramma* sp.). (4) Chemicals applied to control young larvae.

Actias selene ningpoana Felder (Saturniidae, **Figure 35**) is another major leaf pest of Xi Shu. It is largely distributed in the subtropical region of China, Malaysia, India, Sri Lanka, and Burma. It also attacks the species of *Liquidambar*, *Pterocarya*, *Ulmus*, *Populus*, *Salix*, *Sapium*, *Juglans*, and *Malus*. The adult moth has a body 35-40 mm long, with green wings up to 120 mm in length. The body has dense white hairs. The eggs are yellow, 2 mm in diameter. Larvae are black at early stages and become yellow at later stages. The full grown larvae are 73-80 mm long, with yellow hairs. Normally two generations occur per year. Control methods include: biological control by parasitic wasps, destruction of pupae, and trapping moths in flight using lights.

Recently, we found the blackheaded race of the fall webworm [*Hyphantria cunea* (Drury), Actiidae, **Figure 36**] to be a serious insect defoliator on Xi Shu in the United States. A larva can eat 10-15 leaves a day (**Figure 37** and **Figure 38**). This fall webworm is a native of North America and Mexico. It feeds on almost all shade, fruit and ornamental trees except conifers. In the United States, *H. cunea* attacks at least 88 species of trees; in Europe, 230 species of trees, shrubs, ornamentals, and annual plants; in Japan, 317 species are plant hosts; and in China its diet includes at least 50 species of fruit and forest trees (Cai and Xiao 1983, Johnson and Lyon 1991). The adult fall webworms emerge from over-wintering pupae in late spring. They are small white moths with wing spans of 30 to 42 mm. The base of the front legs varies in color from red to orange. The blackheaded race deposit their eggs as single-layer masses in mid-March. When the larvae

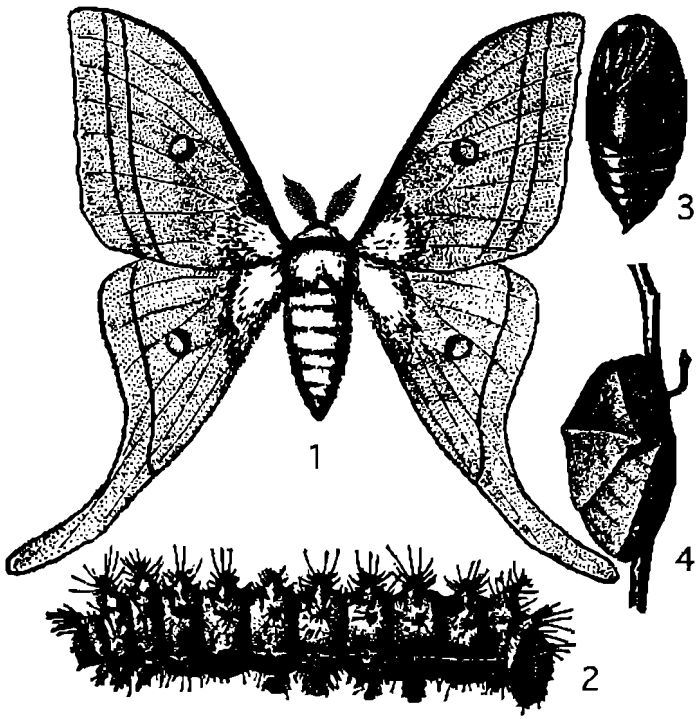


FIGURE 35. ***Actias selene ningpoana* Felder** (after Peiyi Zhang, in Cai and Xiao 1983. 1-adult insect; 2-larva; 3-pupa; 4-cocoon).

hatch, they are yellowish green to pale yellow with two rows of dark tubercles along the back. Their heads are black, and the bodies covered with fine hairs. Groups of larvae cover foliage with webbing and feed inside it through mid-summer. Larvae pass through as many as 11 stages of development. When fully grown, larvae are yellowish or greenish with a broad, dark stripe along the back, and measure about 25 mm in length. Larvae leave webs to pupate in soil debris Generations per year of the fall webworm range from one (in Canada) to four (in East Texas) (Johnson and Lyon 1991).

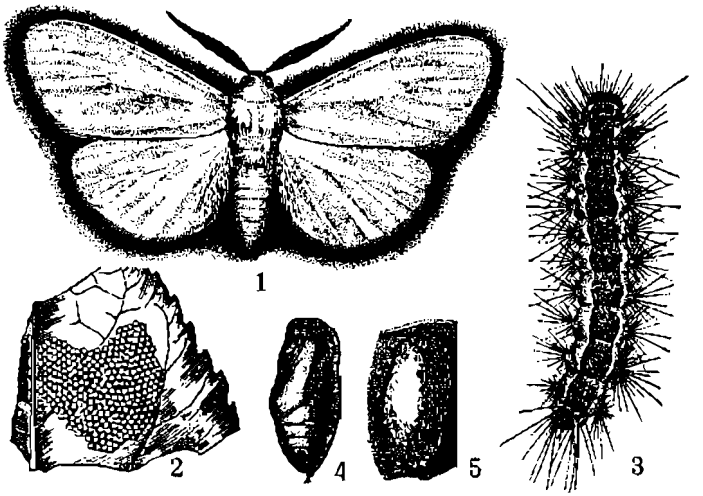


FIGURE 36. ***Hyphantria cunea*** **(Dury)** (after Peiyi Zhang, in Cai and Xiao 1983. 1-adult insect; 2-egg; 3-larva; 4-pupa; 5-cocoon).

Control methods for fall webworm include: (1) Prune and burn branches with webs; (2) Use parasites and predators to control the pest (50 species of parasites and 36 species of predators of the fall webworm are known, Johnson and Lyon 1991). (3) Chemical and microbiological control measures are generally used successfully. The most widely used microbial biological control method is to spray bacterium BTK (*Bacilus thuringiensis* var. *kurstaki*) on leaves around webs when larvae are small or when last stage larvae wander outside of the web (Ellis and Bradley 1992). Parasitic wasps (*Telenomus bifidus* Riley, *Apanteles hyphantriae* Riley, and *Meterorus hyphantriae* Riley) and nuclear polyhedrosis viruses (NPV) are also effective in controlling fall webworms.

In addition, *Phassus sinifer sinensis* Walker (Hepialidae) is relatively common stem pest of Xi Shu in China. It largely attacks deciduous hardwoods. Chemicals are used to control this insect. Other pests such as aphids, scales, and whiteflies also attack Xi Shu and should be controlled if infestation reduces the quantity of leaves available for drug production.

FIGURE 37. **The fall webworm (blackheaded race) is a leaf pest of Xi Shu in the United States** (photo by P. R. Blackwell, Tucker Center).

FIGURE 38. **Larva of the fall webworm can eat 10-15 leaves a day** (photo by S. Y. Li, Tucker Center).

Animals

There are no data available showing that animals feed on Xi Shu. Alternatively, it has been reported that the leaves of Xi Shu poison animals. Goats eating the plant leaves develop hemorrhagic diarrhea, dehydration, muscle tremors, coma, and death (Cao et al. 1992). Regardless of lack of publications on this issue, reports of grazing of Xi Shu by certain species of deer and hogs have been reported and care should be taken to protect young plantations. Further study in this area is needed.

Other Problems

Frost damage is an important factor influencing the growth and distribution of Xi Shu. In the southeastern United States, frost damage is largely restricted to buds and thus limits the height growth of the tree (**Figure 39**). In addition, herbicides should be avoided in Xi Shu plantation management because some herbicides such as 2,4-D [(2,4-dichlorophenoxy)acetic acid] kill the tree.

FIGURE 39. **Frost damage of terminal buds is an important factor influencing the height growth and wood quality of Xi Shu** (photo by T. R. Moore, XyloMed Research Foundation).

13. HARVEST OF XI SHU

Planting at 17,780 seedlings per hectare (7,000 seedlings per acre) yields about 6,750 kg (15,000 pounds) of air-dry woody raw material per acre after three growing seasons (Perdue 1968). Yields can be increased by wider spacing and delayed harvest. Xi Shu has great ability to coppice. This aggressive resprouting may indicate possible multiple harvests during a single season. Plantations are suitable for mechanical harvesting.

Harvesting can also be selective. For example, every other row can be cut to thin the plantation and provide the remaining trees more room for growth.

Harvested seedlings should be cut slightly above ground level and spread on the ground in direct sunlight to dry the leaves. Since they have lower content of camptothecins than other parts, leaves should be dried until they fall off the branches so that they can be separated from the woody parts. Roots are harvested with a hydraulically operated knife attached to a tractor. The roots should be washed to make certain that there are no other roots, clinging rocks or other things that could damage the chipper blades. After chipping, all woody material should be spread out on polyethylene tarps to dry. Dry material can be sacked in bags for shipment and chemical extraction.

Harvest season and age of tree are important factors influencing drug quality. In particular, these two factors plus location constitute three basic conditions of *Daodi* (道地, genuine, optimum) medicine in China and are always emphasized in drug selection by Chinese doctors. Many studies also show that the quantity of extractable chemical compound varies with location, collection season, and age of the tree. This provides scientific support for the *Daodi*

tradition (Nie and Li 1989, Li et al. unpublished). According to T. Kawahara and co-workers (1968), maximum dry weight of the leaves (0.45 kg/m^2) was reached in July, that of the branches, stems, and roots and consequently of the nutrients, in September. However, Perdue and co-workers (1968) claimed that season of collection and age of tree have little or no influence on the yield of CPT. If true, maximum CPT production would be achieved by harvesting trees when they produce maximum yields of dry matter. But the conclusions of Perdue and co-workers (1970) are based on observation of only 20 specimen trees. Thus, both sample size and representiveness seem inadequate for a general picture of the chemogeography of Xi Shu. At a minimum, the influence of collection season, location, and tree age on drug quality should be re-examined based on a large set of samples in order to assure maximum drug recovery.

14. FURTHER RESEARCH

In brief, Xi Shu is a very valuable tree. Camptothecins, the drugs extracted from this tree, have unique mechanisms of action and thus exhibit potent anti-tumor and anti-viral activities. The tree has advantages over Pacific yew in fast growth and use of all plant parts for drugs. Thus, it is expected that Xi Shu will be a favored source of drugs for the treatment of cancers and even some virus diseases in the near future.

Presently, large scale commercial synthesis of CPT and its analogs is not feasible and living plants are the only practical supply source. However, Xi Shu supply is a critical problem in the United States. A three-year-old seedling produces about 1 kg of dry woody material (Perdue 1968) or 50 mg of CPT or its analogs. Each cancer patient is expected to need 1-3 g of drug, which equates to 20-60 three-year-old seedlings of Xi Shu. In 1993, about 1,170,000 people in the United States were diagnosed as having cancer, and the number is increasing. To treat only 30% of these patients, about 7-21 million young trees are needed annually. This requires 4,200-12,600 hectares (about 10,500-31,500 acres) of plantations (5,085 trees/hectare or 2,000 trees/acre, 3 year harvest cycle) to meet the foreseeable demand in the United States alone. If there are 22,200 good seeds per kg (about 10,000 good seeds per pound) of dry fruits and 80% germinate, about 400-1,200 kg (881-2,643 pounds) of dry fruits are needed annually to establish Xi Shu plantations. This requires about 200-600 mature trees to supply these seeds.

Additionally, AIDS is one of the most serious health problems that the United States, or the world, has ever faced. Some 17 million people around the world are infected by the HIV. According to A. C. Novello, Surgeon General of the

United States about one million Americans—1 in every 250—are infected with HIV. In the next 10 years, more Americans of all ages are expected to develop this disease. Between 1981 and 1992, more than 250,000 Americans developed AIDS and more than 170,000 died. In 1994, it is estimated that 47,000 to 66,000 more Americans may die of AIDS and 40,000 to 80,000 will be newly infected with HIV. CPT and its analogs show activity against many viruses including HIV-1. The drugs give a new direction for HIV treatment. If camptothecins prove useful in virus disease clinical trials, the annual need for Xi Shu for treatment of HIV will exceed that for cancer. Probably, up to 40 million young trees will be needed annually for HIV treatment. This is the annual supply needed to treat only 30% of the most seriously ill patients with HIV in the United States. In addition, camptothecins are potent drugs for many other serious diseases, such as psoriasis and DNA viruses, and for plant growth regulation. In total, it is expect that up to 100 million young trees could be needed annually in the United States to meet this demand. This requires up to about 60,000 hectares (about 150,000 acres) of Xi Shu plantations in the United States (in terms of 5,085 trees/hectare or 2,000 trees/acre). However, at present less than 10 acres of plantations exist in the United States.

The establishment of an optimum plant supply system must solve the following problems based on chemical, economic, and ecological principles: Where? In which region and habitat does the tree grows fastest and also contain the highest content of active compounds? What? Which part or parts of the plant are the best for drug production? How and When? How to harvest the plant and in what season. A research model to establish such a production system is as follows (**Figure 40**).

1. **Evaluation and selection of ecotype.** Xi Shu is widely distributed in 12 provinces in China and grows naturally in varied habitats from 200 m to 2,400 m in elevation. This polygamo-monoecious species has great genetic variation among geographic locations, among sites, among stands, and

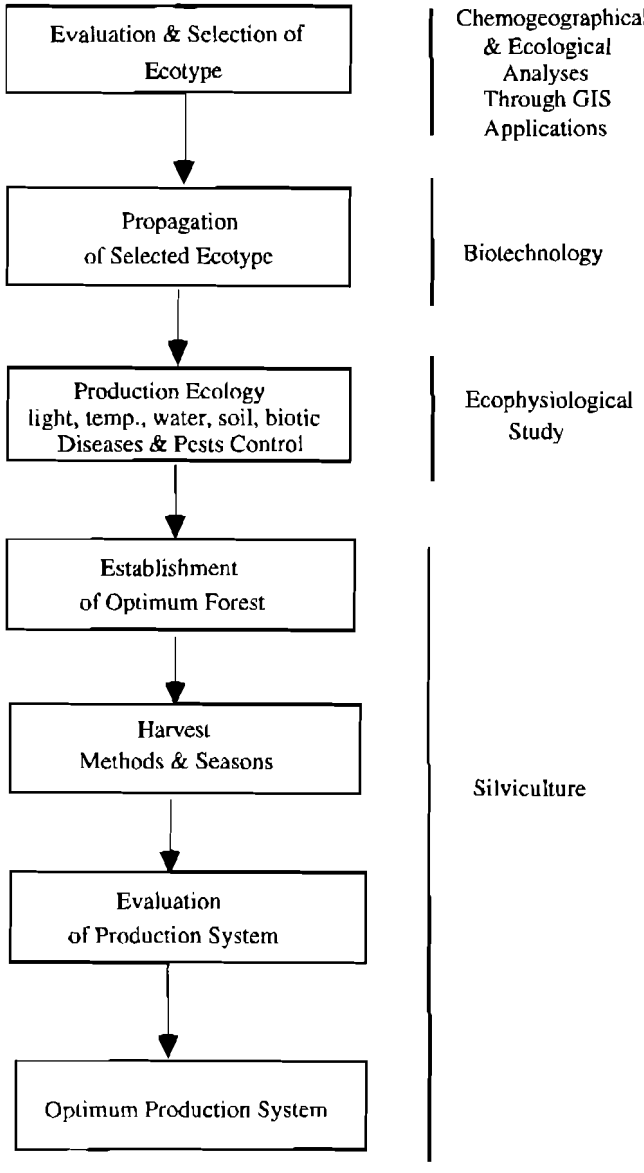


FIGURE 40. **Research steps for establishing an optimum plant supply system for Xi Shu.**

among trees. Current studies on genetic variation within this species are not available. Also, the present seed source in the United States is largely confined to a few parent trees. Such a narrow range of available plant germplasm may limit optimum forest production. Thus, it is advisable to evaluate and select ecotypes or genotypes that display a high content of the active chemical substances, are fast-growing and adapt to cultivation. The primary selection can be conducted within the native range of the tree in China. For long-term study, it will probably be necessary to package all desired qualities into improved individuals through hybridization.

2. **Propagation**. It is not difficult to propagate seedlings from seeds. The seed supply and source is a problem for commercial production in the United States at present and even in the near future. An adequate supply is not available within the United States, and it is doubted that China will want to export seeds of such a valuable tree. On the other hand, reproduction by seed in the absence of broad genetic parental diversity causes filial regression. Vegetative reproduction (by cuttings or micropropagation), however, allows quick and large gains because genetic variation of the selected ecotypes can be captured. According to our studies, it is not difficult for shoot cuttings to produce roots. Tissue culture studies were performed in Japan two decades ago (Sakato and Misawa 1974) and very recently in the Morris Arboretum at the University of Pennsylvania (Meyer 1991, P. White pers. comm., May 1994), Stephen F. Austin State University and Louisiana State University. But these studies are still in the laboratory stage. Thus, reproduction by cuttings (shoot, root, and bud) and micropropagation is needed to produce the optimum forest for drug production.

3. **Production Ecology.** Production ecology of CPT and its analogs of the selected ecotype should be the next step. It is important in growing the tree to know how light, temperature, water, soil nutrition, and biotic factors influence the growth and chemical production of the tree. Camptothecins are nitrogen-bearing compounds. Xi Shu proved responsive to nitrogen fertilizer (Smith 1969).

Therefore, introduction of some nitrogen fixing plants into the Xi Shu plantation can be expected to improve the growth of trees. In addition, this tree is apparently eaten by many insects, and pest control is an important part of production ecology.

4. **Harvest Methods and Seasons.** Studies of drug collection methods and seasons are needed. All parts of the tree can be used for medicine. Fruits may have the highest content of the needed chemical compounds among all parts of the tree, but total production is not as high as in the bark. Bark collection is a good option in drug production. Stripping the bark of a tree will kill the tree. An approach to peel the bark of living trees is needed both economically and ecologically.

5. **Establishment of the optimum plant supply system.** After the establishment of an initial tree supply system, it is important to evaluate all factors in this system and continuously modify the system.

In addition, new approaches for recovery of camptothecins should be considered. First, two species of fungi *Cercospora camptothecae* Tai and *Pseudocercospora camptothecae* Liu et Guo are parasitic on Xi Shu (Liu and Guo 1987). Also, *Dendrobium nobile* cultivated on Xi Shu contains unknown alkaloids not found in wild *D. nobile* (Wang et al. 1985). If these fungi concentrate CPT, as the parasitic fungus on the Pacific yew continues to produce taxol even when it is removed from the tree, it may be possible to grow large quantities of fungi in vats and lower the cost of the drug.

Chemical studies are also needed for species (e.g., *Nyssa* and *Davidia*) related to Xi Shu. Early data from the CCNSC Screening Laboratories of NCI are not promising. However, two problems exist with these studies: (1) most tests used twigs and leaves and usually these parts contain very low concentrations of chemical compounds relative to fruits and root bark; (2) only a limited number of samples were tested. Thus, it may be possible to realize better results if based on a larger number of samples of fruits and root bark of *Nyssa*.

The conclusion is that the Xi Shu is a candidate for further study in the effort to control some cancers and virus diseases.

LITERATURE CITED

Abelson, H.T. and S. Penman. 1972. Selective interruption of high molecular weight RNA synthesis in HeLa cells by camptothecin. *Nat. New Biol.* 237:144-146.

Abelson, H.T. and S. Penman. 1974. Selective interruption of RNA metabolism by chemotherapeutic agents. *Handb. Exper. Pharmako.* 38:571-581.

Abigerges, D., J.P. Armand, G.G. Chabot, et al. 1994. Irinotecan (CPT-11) high-dose escalation using intensive high-dose loperamide to control diarrhea. *J. Natl. Cancer Inst.* 86:446-449.

Affieri, S.A., Jr., K.R. Langdon, C. Wehlburg, et al. 1984. *Index of plant diseases in Florida.* Florida Department of Agriculture and Consumer Services Division of Plant Industry. Bull. No. 11. (Revised, 389 pp.).

Agarwal, J.S. and R.P. Rastogi. 1973. Chemical constituents of *Mappia foetida. Ind. J. Chem.* 11(9):969.

Baillon, H.E. 1877. *Historie des plants.* Paris, London, Leipzig.

Becker, Y. and U. Olshevsky. 1973. Inhibition of herpes simplex virus replication by camptothecin. *Isr. J. Med. Sci.* 9(11-12):15781581.

Beran, M., S. O'Brien, E. Estey, et al. 1992. Topotecan (topo) in patients with refractory and relapsed acute leukemia. In *Proceedings of the Fourth Conference on DNA Topoisomerases in Therapy*, p. 54.

Berry, D.E., L. Mackenzie, E.A. Shultis, et al. 1992. *J. Org. Chem.* 57:420.

Bertrand, R., P. O'Connor, D. Kerrigan, et al. 1992. Sequential administration of camptothecin and etoposide circumvents the antagonistic cytotoxicity of simultaneous drug administration in slowly growing human colon-carcinoma HT-29 cells. *Eur. J. Cancer* 28A:743-748.

Bjornsti, M.A. 1991. DNA topoisomerases. *Curr. Opin. Struct. Biol.* 1:99-104.

Boring, C.C., T.S. Squires, and T. Tong. 1993. Cancer statistics. *Cancer J. Clin.* 43(1):7-26.

Burke, T.G., A.E. Staubus, and A.K. Mishra. 1992. Liposomal stabilization of camptothecin's lactone ring. *J. Am. Chem. Soc.* 114(21):8318-8319.

Burris, H.A. III. 1993. The role of camptothecins in the treatment of lung cancer. *Cancer Investigation* (Chemotherapy Foundation Symposium XI

Innovative Cancer Chemotherapy for Tomorrow, November 10-12, 1993, New York City), pp. 10-12.

Burris, H.A. III, A.R. Hanauske, R.K. Johnson, et al. 1992. Activity of topotecan, a new topoisomerase I inhibitor, against human tumor colony-forming units *in vitro*. *J. Natl. Cancer Inst.* 84:1816-1820.

Burris, H.A. III, M. Rothenberg, J. Kuhn, et al. 1992. Clinical trials with the topoisomerase I inhibitors. *Semin. Oncol.* 19:663-669.

Buta, J.C. and A. Kalinski. 1988. Camptothecin and other plant growth regulators in higher plants with antitumor activity. *ACS Symposium Series* No. 380:294-304.

Buta, J.C. and D.W. Spaulding. 1986. Effect of camptothecin on seedling growth. In *Proceedings of the Plant Growth Regulator Society of America, 13th Annual Meeting*, St. Petersburg Beech, Florida, August 1986. p. 155

Buta, J.G. and J.F. Worley. 1976. Camptothecin, a selective plant growth regulator. *J. Agr. Food Chem.* 24(5):1085-1086.

Cai, B.H. and G.R. Xiao (eds.). 1983. *Forest insects of China*. China Forestry Publishing House, Beijing.

Cai, J.C., M.G. Yin, A.Z. Min, et al. 1977. *Kexue Tongbao* 22:269.

Cai, J.C. and C.R. Hutchinson. 1983. Camptothecin. *Alkaloids* 21:101-137.

Caldas, C. and W.P. McGuire III. 1993. Paclitaxel (taxol) therapy in ovarian carcinoma. *Semin. Oncol.* 20(4, suppl.3):50.

Cao, G.R., J.X. Gao, D.X. Duan, et al. 1992. Studies on *Camptotheca acuminata* leaves: main toxic principle, poisoning, and treatment in goats. In *Poisoning Plants: Proceedings of the Third International Symposium*, pp. 506-508. Iowa State University Press, Ames.

Champoux, J.J. 1992. Topoisomerase I is preferentially associated with normal SV40 replicative intermediates, but is associated with both replicating and nonreplicating SV40 DNAs which are deficient in histones. *Nucleic Acids Res.* 20:3347-3352.

Chang, A., K. Kim, J. Glick, et al. 1992. Phase II study of taxol in patients with stage IV non-small cell-lung cancer (NSCLC): The Eastern Cooperation Oncology Group (ECOG) results. *Proc. Am. Soc. Clin. Oncol.* 11:A981.

Chang, A., K. Kim, J. Glick, et al. 1993. Phase II study of taxol, merbarone, and piroxantrone in stage IV non-small cell-lung cancer: The Eastern Cooperation Oncology Group. *J. Natl. Cancer Inst.* 85(5):388.

Chen, L.J., F.H. Wang, and Y.R. Wu. 1991. The pollination biology of *Camptotheca acuminata* Decne. (Nyssaceae). *Cathaya* 3:45-52.

Cheng, Z.D., S. AbuBakar, M.P. Fons, et al. 1992. Modulation of the frequency of human cytomegalovirus-induced chromosome aberrations by camptothecin. *Virology* 189:397-401.

Chiao, C.Y. and H.S. Li. 1974. Effect of topical use of camptothecine-dimethyl sulfoxide solution in psoriasis. *Chin. Med. J.* 1(5): 355-360.

Chou, Y.L. and S.Y. Li. 1990. *Forests of China.* Science Press, Beijing.

Chu, K.P., L.T. Lin, W.C. Pan, et al. 1979. Study on the microbiol transformation of camptothecin to 10-hydroxycamptothecin. *Kexue Tongbao* 23(12):761-762.

Chuang, H. 1981. Nothapodytes (Icacinaceae). In *Flora Reipublicae Popularis Sinicae* (Vol. 46, ed. by W.P. Fang). Science Press, Beijing.

Clavel, M. A. Mathieu-Bou, A. Duumortier, et al. 1992. Phase I study of CPT-11 administrated as a daily infusion for 3 consecutive days. *Proc. Am. Assoc. Cancer Res.* 33:262.

Covey, J.M., C. Jaxel, K.W. kohn, et al. 1989. Protein-linked DNA strand breaks induced in mammalian cells by camptothecin, an inhibitor of topoisomerase I. *Cancer Res.* 49:5016-5022.

D'Arpa, P. and L.F. Liu. 1989. Topoisomerase-targeting antitumor drugs. *Biochim. Biophys. Acta* 989:163-177.

DeMilo, A.B. and A.B. Borkovec. 1974. Camptothecin, a potent chemosterilant against the house fly. *J. Econom. Entomol.* 67(3):457-458.

Deng, C.Z., S. AbuBakar, M.P. Fons, et al. 1992. Modulation of the frequency of human cytomegalovirus-induced chromosome aberrations by camptothecin. *Virology* 189:397-401.

Dodoens, R. 1090. *Camptotheca acuminata* Dode. *Bull. Soc. Bot. France* IV:650-651.

Eckardt, J.R., H.A. Burris III, J.G. Kuhn, et al. 1994. Activity of intoplicine (RP60475), a new DNA topoisomerase I and II inhibitor, against human tumor colony-forming units *in vitro*. *J. Natl. Cancer Inst.* 86(1):30-33.

Editorial of The Lancet. 1990. Chemotherapy: topoisomerases as targets. *Lancet* 335.

Einzig, A.I., E. Gorowski, J. Sasloff, et al. 1988a. Phase II trial of taxol in patients (pts) with renal cell carcinoma. *Proc. Am. Assoc. Cancer Res.* 29:A884.

Einzig, A.I., E. Gorowski, J. Sasloff, et al. 1988b. Phase II pilot study of taxol in patients with renal cell carcinoma. *Proc. Am. Spc. Clin. Oncol.* 7:249.

Einzig, A.I., P. Wiernik, J. Sasloff, et al. 1990. Phase II study of taxol in patients with advanced ovarian cancer. *Proc. Am. Assoc. Cancer Res.* 31:A1114.

Einzig, A.I., P. Wiernik, J. Sasloff, et al. 1992. Phase II study and long-term follow-up of patients treated with taxol for advanced ovarian adenocarcinoma. *J. Clin. Oncol.* 10(11):1748.

Eisenhauer, E.A. 1993. Taxol in advanced non-small-cell lung cancer: plus Ca change? *J. Natl. Cancer Inst.* 85(5):346.

Ellis, B.W. and F.M. Bradley (eds.). 1992. *The organic gardener's handbook of natural insect and disease control.* Rodale Press, Emmaus, Pennsylvania.

Erdtman, G. 1966. Pollen morphology and plant taxonomy, angiosperms (2nd ed.). Hafner Publishing Company, New York, London.

Fang, W.P. and T.P. Soong. 1975. Praecursores flora Nyssaccarum Sinensium. *Zhiwu Fenlei Xuebao* 13(2):83-89.

Fang, W.P. and Z.R. Zhang. 1983. *Flora Reipublicae Popularis Sinicae* [Vol. 52(2), Nyssaceae]. Science Press, Beijing.

Farnsworth, N.R. 1988. Screening plants for new drugs. In *Biodiversity* (ed. by E.O. Wilson), pp. 83-97. National Academy Press, Washington, D.C.

Farr, D.F., G.F. Bills, G.P. Chamieris, et al. 1989. *Fungi on plants and plant products in the United States.* APS Press, The American Phytopathological Society, St. Paul, Minnesota.

Flam, F. 1994. Race to synthesis taxol ends in a tie. *Science* 263:911.

Forastiere, A.A. 1993. Use of paclitaxel (taxol) in squamous cell carcinoma of the head and neck. *Semin. Oncol.* 20(4, suppl. 3):56.

Franchet, A.R. 1886. *Plantae Davidianae ex Sinarum imperio.* Masson, Paris. (originally published in parts in the Nouvelles Archives du museum d' historic naturelle between 1883 and 1888).

Friedman, H.S., P.J. Houghton, S. C. Schold, et al. 1994. Activity of 9-dimethylaminomethly-10-hydroxycamptothecin against pediatric and adult central nervous system tumor xenografts. *Cancer Chemother. Pharmacol.* 34:171-174.

Fukuoka, M. 1991. A phase II study of CPT-11 for primary lung cancer. *Gan To Kagaku Ryoho* 18:1013-1019.

Fukuoka, M., H. Nittani, and A. Suzuki. 1992. A phase II study of CPT-11, a new derivative of camptothecin for previously untreated non-small cell lung cancer. *J. Clin. Onol.* 10:16-20.

Furuta, T., T. Yokokura, and M. Mutai. 1988. Antitumor activity of CPT-11 against rat Walker 256 carcinoma. *Jpn. J. Cancer Chemother.*15:2757-2760.

Furuta, T. and T. Yokokura. 1991. Combination therapy of CPT-11, a comptothecin derivative, with various antitumor drugs against L1210 leukemia. *Gan To Kagaku Ryoho* 18(3):393-402.

Gallo, R.C., J. Whang-Peng, and R.H. Adamson. 1971. Studies on antitumor activity, mechanism of action, and cell cycle effects of camptothecin. *J. Natl. Cancer Inst.* 46(4):789-795.

Gandia, D., J.P. Armand, G. Chabot, et al. 1992. Phase I study of the new camptothecin analogue CPT-11 administrated every 3 weeks. *Pro. Am. Assoc. Cancer Res.* 33:260.

Giovanella, B.C., H.R. Hinz, A.J. Kozielski, et al. 1991. Complete growth inhibition of human cancer xenografts in nude mice by treatment with 20-(S)-camptothecin. *Cancer Res.* 51:3052-3055.

Giovanella, B.C., J.S. Stehlin, M.E. Wall, et al. 1989. DNA topoisomerase I-targeted chemotherapy of human colon cancer in xenografts. *Science* 246:1046-1048.

Gottlieb, J.A. and J.K. Luce. 1972. Treatment of malignant melanoma with camptothecin (NSC-100880). *Cancer Chemother. Rep.* Part 1, 56(1):103-105.

Gottlieb, J.A., A.M. Guarino, J.B. Call, et al. 1970. Preliminary pharmacologic and clinical evaluation of camptothecin sodium (NSC-100880). *Cancer Chemother. Rep.* Part 1, 54(6):461-470.

Govindachari, T.R. and N. Viswanathan. 1972. 9-Methoxycamptothecin: a new alkaloid from Mappia foetida Miers. *Ind. J. Chem.* 10:453.

Govindachari, T.R., K.R. Ravindranath, and N. Viswanathan. 1974. *J. Chem. Soc. Perkin. Tran.* 1:1215.

Gu, F.L., et al. 1987. Factors influencing the absorption of antineoplastic agents in intravestical instillation treatment of bladder tumors. An experimental and clinical study. *Chin. Med. J.* 100(2):127-31.

Gunsekera, S.P., M.M. Badaw, G.A. Cordell, et al. 1979. *J. Nat. Prod.* 42:475.

Han, J. 1988. Traditional Chinese medicine and the search for new antineoplastic drugs. *J. Ethnopharmaco.* 24:1-17.

Hass, N.B., G.R. Hudes, J. Walczak, et al. 1992. Phase I trial of topotecan on a weekly 24 hour infusional schedule. *Proc. NCI-EORTC Symposium Abstract* 7:a103.

Haas, N.B., F.P. Lacreta, J. Walczak, et al. 1992. Phase I/pharmacokinetic trial of topotecan on a weekly 24-hour infusion schedule. *Proc. Am. Assoc. Cancer Res.* 33:523.

Haas, N.B., F.P. LaCreta, J. Walczak, et al. 1994. Phase I/pharmacokinetic study of topotecan by 24-hour continuous infusion weekly. *Cancer Res.* 54(5):1220-.

Hawkins, M.J. 1992. New Anticancer agents: taxol, camptothecin analogues, and anthrapyrazoles. *Oncology* December:17-23.

Hemsley, W.B. 1896. The flora of Tibet. *Kew Bull. Misc. inf.* 207-216.

Hinz, H.R., N.J. Harris, E.A. Natelon, et al. 1994. Pharmacokinetics of the *in vivo* and *in vitro* conversion of 9-nitro-20(S)-camptothecin to 9-amino-

20(S)-camptothecin in humans, dogs, and mice. *Cancer Res.* 54:3096-3100.

Ho, D.D., T.R. Rota, J.C. Kaplan, et al. 1985. Recombinant human interferon alfa-A-suppresses HTLV III replication *in vitro*. *Lancet* i:602-604.

Holmes, F.A., R.S. Walker, R.L. Theriault, et al. 1991. Phase II trial of taxol: An active drug in metasatic breast cancer. *J. Natl. Cancer Inst.* 83:1797-1805.

Horwitz, M.S. and S.B. Horwitz. 1971. Intracellulardegradation of HaLa and adenovirus type 2 DNA induced by camptothecin. *Biochem. Biophys. Res. Commun.* 45:723-727.

Horwitz, S.B. 1975. In *Antibiotics III Mechanism of Action of Antimicrobial and Antitumor Agents* (eds. by J.W. Corcoran and F.E. Hahn), p. 48. Springer, New York.

Horwitz, S.B. and M.S. Horwitz. 1973. Effects of camptothecin on the breakage and repair of DNA during the cell cycle. *Cancer Res.* 33:2834-2836.

Horwitz S.B., C. Chang, and A.P. Grollman. 1971. Studies on camptothecin: I. Effects on nucleic acid and protein synthesis. *Mol. Pharm.* 7:632-644.

Hsiang, Y.H., R. Hertzberg, S. Hecht, et al. 1985. Camptothecin induces protein-linked DNA breaks via mammalian DNA topoisomerase I. *J. Biol. Chem.* 260:14873-14878.

Hsiang, Y.H., L.F. Liu, M.E. Wall, et al. 1989. DNA topoisomerase I-mediated DNA cleavage and cytotoxicity of camptothecin analogs. *Cancer Res.* 49:4385-4389.

Hsu, J.S., T.Y. Chao, L.T. Lin, et al. 1977. Chemical constituents of the anticancer plant *Camptotheca acuminata* Decne. II. Chemical constituents of the fruits of *Camptotheca acuminata* Decne. *Huaxue Xuebao* 35(3-4):193-200.

Hunan Institute of Forestry. 1978. A preliminary study on the control of *Dendrolimus punctatus* with plant alkaloids. *Kunchong Xuebao* 21(1):108-112.

Hutchinson, C.R. 1981. Camptothecin: Chemistry, biogenesis and medicinal chemistry. *Tetrahedron* 37:1047-1065.

Jaxel, C., K. Kohn, and Y. Pommier. 1988. Topoisomerase I interaction with SV40 DNA in the presence and absence of camptothecin. *Nucleic Acids Res.* 16:11157-11162.

Jaxel, C., G. Capranico, K. Wassermann, et al. 1991. DNA sequence at sites of topoisomerase I cleavage induced by camptothecin in SV40 DNA. In *DNA Topoisomerases Cancer* (eds. by Potmesil, M. and K.W. Kohn), pp. 182-195. Oxford University Press, New York.

Jenks, S. 1994. Camptothecins resurface as promising drugs. *J. Natl. Cancer Inst.* 86(15):1118-1119.

Johnson, J.H. 1992. Forest products, the secret harvest. *Am. For.* 98(3&4):28-31, 65.

Johnson, R.K. 1992a. Treatment of ovarian with camptothecin analogs. *PCT Int. Appl.* 16 pp.

Johnson, R.K. 1992b. Treatment of esophageal cancer with camptothecin analogs. *PCT Int. Appl.* 16 pp.

Johnson, R.K. 1992c. Treatment of non-small-cell lung carcinoma with camptothecin analogs. *PCT Int. Appl.* 17 pp.

Johnson, R.K. 1993. Treatment of colorectal cancer with water-soluble camptothecin analog. *PCT Intl. Appl.* 11 pp.

Johnson, R.K., F.L. McCabe, L.F. Faucette, et al. 1989. SK & F 104864, a water-soluable analog of camptothecin with a broad spectrum of activity in prechemical tumor models. *Proc. Am. Asso. Cancer Res.* 30:623.

Johnson, W.T. and H.H. Lyon. 1991. *Insects that feed on trees and shrubs, an illustrated practical guide.* Cornell University Press, Ithaca, London.

Joyce, C. 1993. Taxol: search for a cancer drug. *BioScience* 43(3):133-136.

Juan, C., J. Hwang, A. Liu, et al. 1988. Human DNA topoisomerase I is encoded by a single-copy gene that maps to chromsome region 20q12-13.2. *Proc. Natl. Acad. Sci. USA* 85:8910-8913.

Kaneda, N. H. Nagata, T. Furuta, et al. 1990. Metabolism and pharmacokinetics of the camptothecin analogue CPT-11 in the mouse. *Cancer Res.* 50:1715-1720.

Kantarjian, H.M., M. Beran, A. Elliis, et al. 1993. Phase I study of Topotecan, a new topoisomerase I inhibitor, in patients with refractory or relapsed acute leukemia. *Blood* 81(5):1146-1151.

Kanzawa, F., H. Kondoh, S.J. Kwon, et al. 1992. Role of carboxylesterase on metabolism of camptothecin analogue (CPT-11) in non-small lung cancer cell line PC-7 cells. *Proc. Am. Assoc. Cancer Res.* 33:427.

Kawahara, T., G. Iwatsubo, T. Nishimura, et al. 1968. Movement of nutrients in a model stand of *Camptotheca acuminata* Decne. *J. Jpn. For.* 50(5):125-134.

Kawato, Y., M. Aonuma, Y. Hirota, et al. 1991. Intracellular roles of SN-38, a metabolite of the camptothecin derivatives CPT-11, in the antitumor effect of CPT-11. *Cancer Res.* 51:4187-4191.

Kawato, Y., T. Furuta, M. Aonuma, et al. 1991. Antitumor activity of a camptothecin derivative CPT-11, against human tumor xenografts in nude mice. *Cancer Chemother. Pharmakol.* 28:192-198.

Kerr, D.A., C.F. Chang, J. Gordon, et al. 1993. Inhibition of human neurotropic virus (JCV) DNA replication in glial cells by camptothecin. *Virology* 196:612-618.

Kessel, D. 1971. Effects of camptothecin on RNA synthesis in leukemia L1210 cells. *Biochim. Biophys. Acta* 246(2):225-232.

Kessel, D., H.B. Bosmann, and K. Lohr. 1972. Camptothecin effects on DNA synthesis in murine leukemia cells. *Biochim. Biophys. Acta* 269(2):210-216.

Kieber, J.J., M.F. Lopez, A.F. Tissier, et al. 1992. Purification and properties of DNA topoisomerase I from broccoli. *Plant Mol. Bol.* 18(5):865-871.

Kingsbury, W.D., J.C. Boehm, D.R. Kakas, et al. 1991. Synthesis of water-soluble (aminoalkyl)camptothecin analogues: inhibition of topoisomerase I and antitumor activity. *J. Med. Chem.* 34:98-107.

Ku, K.Y. and T.C. Tang. 1980. Several botanical sources of camptothecine-an antitumor alkaloid. *Zhong Cao Yao* 11(10):476-479.

Kuhn, J., H. Burris, J. Wall, et al. 1990. Pharmacokinetics of the topoisomerase I inhibitor, SK & F 104864. *Proc. Am. Soc. Clin. Oncol.* 9:70.

Kunimoto, T. K. Nitta, T. Tanaka, et al. 1987. Antitumor activity of 7-ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxy-camptothecin, a novel water-soluble derivative of camptothecin, against murine tumors. *Cancer Res.* 47:5944-5947.

Larsen, N.S. 1994. Study confirms high rates of adult T-cell leukemia in N.Y.C. *J. Natl. Cancer Inst.* 86(2):85-87.

Legha, S.S., S. Ring, N. Papadopoulos, et al. 1990. Phase II trial of taxol in metastatic melanoma. *Cancer* 65:2478-2481.

Li, C.J., L. Averboukh, and A.B. Pardee. 1993. ß-Lapachone, a novel DNA topoisomerase I inhibitor with a mode of action different from camptothecin. *J. Biol. Chem.* 268(30):22463-22468.

Li, C.J., C.L. Wang, and A.B. Pardee. 1994a. Camptothecin inhibits Tat-mediated transactivation of type 1 human immunodeficiency virus. *J. Biol. Chem.* 269(10):7051-7054.

Li, C.J., B.J. Deznbe, D.K. Biswas, et al. 1994b. Inhibitors of JIV-1transcription. *Trends in Microbiol.* 2(5):164-169.

Li, S.Y., S.Q. Nie, and K.T. Adair. 1994. Geographical gradients and production ecology of berberine in traditional Chinese medicine Guan Huang Bai (*Phellodendron amurense* Rupr.). (unpublished).

Lin, L.Z. and G.A. Cordell. 1989. Quinoline alkaloids from *Camptotheca acuminata*. *Phytochemistry* 28(4):1295-1297.

Lin, L.Z. and G.A. Cordell. 1990a. 19-o-methylangustoline from *Camptotheca acuminata*. *Phytochemistry* 29(8):2744-2746.

Lin, L.Z. and G.A. Cordell. 1990b. Further Studies on the alkaloids of *Camptotheca acuminata*. *Pl. Med.* 56(1990):519.

Lin, L.Z., T.Y. Chao, and J.S. Hsu. 1977. Chemical constituents of the anticancer plant *Camptotheca acuminata* Decne. I. Chemical constituents of the roots of *Camptotheca acuminata* Decne. *Huaxue Xuebao* 35(3-4):227-231.

Lin, L.Z., C.C. Sung, and R.S. Hsu. 1979. A new anticancer alkaloid 11-hydroxycamptothecin. *Kexue Tongbao* 24(10):478-479.

Lin, X.R. 1987. Effect of camptothecin in the treatment of psoriasis. *Zhonghua Yixue Zhazhi* 67(1):4-6.

Lin, X.R., et al. 1988a. Clinical trials and experimental study on treating psoriasis with camptothecine. *Chin. Med. J.* 101(6):427-430.

Lin, X.R., et al. 1988b. Topical camptothecine in treatment of psoriasis. *Int. J. Dematol.* 27(7):475-476.

Liu, L.F. 1989. DNA topoisomerase poisons as anti-tumor drugs. *Ann. Rev. Biochem.* 58:351-375.

Liu, X.J. and Y.L. Guo. 1987. Three undescribed species of the genus *Pseudocercospora*. *Zhenjun Xuebao* 6(4):219-224.

Liu, L.F. and K.G. Miller. 1981. Eukaryotic DNA topoisomerases: two forms of type I DNA topoisomerases from HeLa cell nuclei. *Proc. Natl. Acad. Sci. U.S.A* . 78:3487-3491.

Lucas, G.B., C.L. Campbell, and L.T. Lucas. 1985. *Introduction to plant diseases, dentification and management.* The AVI Publishing Company, Inc., Westport, Connecticut.

Lynch, Jr., T.T., L. Kalish, G. Strauss, et al. 1994. Phase II study of topotecan in metastatic non-small-cell lung cancer. *J. Clin. Oncol.* 12(2):347-.

Masuda, N., M. Fukuoka, Y. Kusunoki, et al. 1992. CPT-11: A new derivative of camptothecin for the treatment of refractory or relapsed small cell lung cancer. *J. Clin. Oncol.* 10:1225-1229.

Masuda, N., M. Fukuoka, K. Nakagawa, et al. 1993. Phase I and pharmacologic study of irinotecan in combination with cisplatin for advanced lung cancer. *Br. J. Cancer* 68(4):777-.

Masuda, N., M. Fukuoka, M. Takada, et al. 1992. CPT-11 in combination with cisplain for advanced non-small cell lung cancer. *J. Clin. Oncol.* 10:1775-1780.

McGuire, W.P., E.K. Rowinsky, et al. 1989. Taxol: an unique antineoplastic agent with significant in advanced ovarian celial neoplasms. *An. Intl. Med.* 111:273-279.

Meyer, P.W. 1991. *Camptotheca acuminata. Publ. Gard.* April:39.

Moertel, C.G., A.J. Schutt, R.J. Reitemeier, et al. 1972. Phase II study of camptothecin (NSC-100880) in the treatment of advanced gastrointestinal cancer. *Cancer Chemother. Rep.* 56(1):95-101.

Muggia, F.M., P.J. Creaven, H. Hansen, et al. 1972. Phase I clinical trial of weekly and daily treatment with camptothecin (NSC-100880): correlation with preclinical studies. *Cancer Chemother. Rep.* 56:515-521.

Murray, M. 1991. The tree that fights cancer. *Am. For.* July/Aug:52-54.

Murphy, W.K., R.J. Winn, F.V. Fossella, et al. 1992. Phase II study of taxol (NSC 125973) in patients (pts) with non-small cell lung cancer (NSCLC). *Proc. Am. Soc. Clin. Oncol.* 11:A985.

Murphy, W.K., R.J. Winn, F.V. Fossella, et al. 1993. Phase II study of taxol in patients with untreated advanced non-small cell lung cancer. *J. Natl. Cancer Inst.* 85(5):384.

Negoro, S., M. Fukuoka, N. Masuda, et al. 1991. Phase I study of camptothecin, in the treatment of advanced non-small-cell lung cancer. *J. Natl. Cancer Inst.* 83:1164-1168.

Negoro, S., et al. 1991. A phase II study of CPT-11, a camptothecin derivative, in patients with primary lung cancer, CPT-11 cooperative study group. *Gan To Kagaku Ryoho* 18(6):1013-1019.

Nie, S.Q. and S.Y. Li. 1989. Studies on the traditional Chinese medicine Guan Huang Bai (*Phellodendron amurense* Rupr.). *J. NEFU* 1989(1):1-10.

Niitani, H. 1991. An early phase II study of CPT-11 for primary lung cancer. *Gan To Kagaku Ryoho* 18:607-612.

Noriyuki, M., M. Fukuoka, S. Kudoh, et al. 1994. Phase I study of irinotecan and cisplatin with granulocyte colony-stimulating factor support for advanced non-small-cell lung cancer. *J. Clin. Oncol.* 12(1):90.

Ohe, Y., Y. Sasaki, T. Shinkai, et al. 1992. Phase I study and pharmacokinetics of CPT-11 with 5-day continuous infusion. *J. Natl. Cancer Inst.* 84:972-974.

Ohno, R., K. Okada, T. Masako, et al. 1990. An early phase II study of CPT-11: a new derivative of camptothecin for the treatment of leukemia and lymphoma. *J. Clin. Oncol.* 8:1907-1912.

Pantazis, P., J.A. Early, A.J. Kozielski, et al. Regression of human breast carcinoma tumors in immunodeficient mice treated with 9-nitrocamptothecin: differential response of nontumorigenic and tumorigenic human breast cells *in vitro*. *Cancer Res.* 53:1577-1582.

Perdue, R.E. 1968. *Camptotheca acuminata*—Source of promising cancer drug. *Lasca Leaves* September:55-59.

Perdue, R.E., R.L. Smith, M.E. Wall., et al. 1970. *Camptotheca acuminata* Decaisne (Nyssaceae) source of camptothecin, and antileukemic alkaloid. *Agr. Res. Ser. USDA Techn. Bull.* No. 1415.

Perdue, R.E., M.E. Wall, J.L. Hartwell, et al. 1968. Comparison of the activity of crude *Camptotheca acuminata*, ethanolic extracts against lymphoid leukemia L-1210. *Lioydia* 31: 229.

Pommier, Y., C. Jaxel, C.R. Heise, et al. 1991. Structure-activity relationship of topoisomerase I inhibition by camptothecin derivatives: evidence for the existence of a ternary complex. In *DNA Topoisomerases Cancer* (eds. by Potmesil, M. and K.W. Kohn), pp. 121-132. Oxford University Press, New York.

Pommier, Y., K.W. Kohn, G. Capranico, et al. 1993. Base sequence selectivity of topoisomerase inhibitors suggests a common model for drug action. In *Molecular biology of DNA topoisomerase and its application to chemotherapy* (eds. by T. Andoh, H. Ikeda, and M. Oguro), pp. 215-227. CRC Press, Boca Raton, Florida.

Postlethwait, J.H., J.L. Hopson, and R.C. Veres. 1991. *Biology, bringing science to life*. McGraw-Hill, Inc., New York, St. Louis, San Francisco, Aukland, Bogota, Garacas, Hamburg, Lisbon, London, Madrid, Mexico, Milan, Montreal, New Delhi, Paris, San Juan, Sao Paulo, Singapore, Sydney, Tokyo, Toronto.

Potmesil, M., B.C. Giovanella, M.E. Wall, et al. 1993. Preclinical and clinical development of DNA topoisomerase I inhibitors in the United States. In *Molecular biology of DNA topoisomerases and its application to chemotherapy* (eds. by T. Andoh, H. Ikeda, and M. Oguro), pp. 301-311. CRC Press, Bosca Raton, Florida.

Priel, E., S.D. Showalter, M. Roberts, et al. 1990. Topoisomerase I activity associated with human immunodeficiency virus (HIV): particles and equine infectious anemia virus core. *EMBO J.* 9:4167-4172.

Priel, E., , E. Aflalo, G. Chechelnitsky, et al. 1993. Inhibition of retrovirus-induced disease in mice by camptothecin. *J. Virology* 67(6):3624-3629.

Priel, E., S.D. Showalter, and D.G. Blair. 1991. Inhibition of human immunodeficiency virus (HIV-1) replication *in vitro* by noncytotoxic does of camptothecin, a topoisomerase I inhibitor. *AIDS Res. Hum. Retroviruses* 7(1):65-72.

Priel, E., S.D. Showalter, M. Roberts, et al. 1991. The topoisomerase I inhibitor, camptothecin, inhibits Equine infectious anemia virus replication in chronically infected CF2th cells. *J. Virology* 65(8):4137-4141.

Rangel, C., H. Niell, A. Miller, et al. 1994. Taxol and taxotere in bladder cancer: *in vitro* activity and urine stability. *Cancer Chemoth. pharm.* 33(6):460-.

Ratain, M.J., R. Mick, R.L. Schilsky, et al. 1993. Statistical and ethical issues in the design and conduct of phase I and II clinical trials of new anticancer agents. *J. Natl. Cancer Inst.* 85(20):1637-1646.

Roja, G. and M.R. Heble. 1994. The quinoline alkaloids camptothecin and 9-methoxycamptothecin from tissue cultures and mature trees of *Nothapodytes foetida*. *Phytochemistry* 36(1):65-66.

Roth, B., B. Yeap, G. Wilding, et al. 1992. Taxol (NSC 125973) in advanced, harmone-refactory prostate cancer:An ECOG, phase II trial. *Proc. Am. Soc. Clin. Oncol.* 11:A598.

Rowinsky, E.K., L.B. Grochow, D. Ettinger, et al. 1992. Phase I and pharmacologic study of CPT-11, a semisynthetic topoisomerase I-targeting agent, on a single dose schedule. *Proc. Am. Soc. Clin. Oncol.* 11:115.

Rowinsky, E.K., L.B. Grochow, C.B. Hendricks, et al. 1992. Phase I and pharmacologic study of topotecan: a novel topoisomerase I inhibitor. *J. Clin. Oncol.* 10:647-656.

Saito, H. 1980. Studies on dry matter production in sapling stands of deciduous broad-leaved tree, *Camptotheca acuminata* Decne. *Sci. Rep. Kyoto Perfect. Univ.* 32:94-100.

Saito, H. and T. Shidei. 1968. The leaf longevity of a young stand of *Camptotheca acuminata*. *Jpn. J. Ecol.* 18(5):230-234.

Sakato, K. and M. Misawa. 1974. Effects of chemical and physical conditions on growth of *Camptotheca acuminata* cell cultures. *Agr. Biol. Chem.* 38(3):491-497.

Sakato, K., H. Tanaka, N. Mukai, and M. Misawa. 1974. Isolation and identification of camptothecin from cells of *Camptotheca acuminata* suspension cultures. *Agr. Biol. Chem.* 38(1):217-218.

Saltz, L., M. Sirott, C. Young, et al. 1993. Phase I clinical and pharmacology study of Topotecan given daily for 5 consecutive days to patients with advanced solid tumors, with attempt at dose intensification using recombinant granulocyte colony-stimulating factor. *J. Natl. Cancer Inst.* 85(18):1499-1507.

Sasaki, Y., A. Ohtsu, Y. Shimada, et al. 1994. Simultaneous administration of CPT-11 and Fluorouracil: alteration of the pharmacokinetics of CPT-11 and SN-38 in patients with advanced colorectal cancer. *J. Natl. Cancer Inst.* 86(14):1096-1098.

Scanlon, E.F. 1991. The evolution of breast cancer treatment. *JAMA* 266(9):1280-1281.

Schaeppi, U., R.W. Fleischman, and D.A. Connev. 1974. Toxicity of camptothecin (NSC-100880). *Cancer Chemother. Rep.* 5:25-36.

Schultz, A.G. 1973. Camptothecin. *Chem. Rev.* 73(4):385-405.

Seidman, A., B. Reichman, J. Crown, et al. 1992. Activity of taxol with recombinant granulocyte colony stimulating factor (GCSF) as first chemotherapy (C) of patients (pts) with metastatic breast cancer (MBC). *Proc. Am. Soc. Clin. Oncol.* 11:A64.

Shanghai Institute of Materia Medica. 1975. *Chin. Med. J.* 55:274.

Shanghai Institute of Materia Medica. 1978. Studies on the anticancer action of 10-hydroxy camptothecin. *Chin. Med. J.* 58(10):598-602.

Shao, B.B. 1989. Effects of stratification and temperature variation on the germination of seeds of ten different trees. *Linye Keji* 1989(2):4-7.

Shimada, Y., M. Yoshino, A. Wakui, et al. 1993. Phase II study of CPT-11, a new camptothecin derivative, in metastatic colorectal cancer. *J. Clinl. Oncol.* 11(5):909-.

Shinkai, T., H. Arioka, and H. Kunikane. 1994. Phase I clinical trial of irinotecan (CPT-11), 7-ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxy-camptothecin, and Cisplatin in combination with fixed dose of vindesine in advanced non-small cell lung cancer. *Cancer Res.* 54(10):2636.

Sirott, M.N., L. Saltz, C. Young, et al. 1991. Phase I and clinical pharmacologic study of intravenous topotecan (T). *Proc. Am. Soc. Clin. Oncol.* 10:104.

Slichenmyer, W.J., E.K. Rowinsky, R.C. Donehower, et al. 1993. The current status of camptothecin analogues as antitumor agents. *J. Natl. Cancer Inst.* 85(4):271-291.

Smith, R.L. 1969. *Camptotheca acuminata*, biography of camptothecin, a promising cancer drug. *Lasca Leaves* September-December: 55-59.

Stehlin, J.S., E.A. Natelson, H.R. Hinz, et al. 1994 (in press). Phase I trials and pharmacokinetic results of oray administration of 20(S)-camptothecin. In the *Third Conference on DNA Topoisomerases in Therapy* (ed. by M. Potmesil), CDC.

Stehlin Foundation for Cancer Research, 1993. Camptothecin clinical trials continue. *HOPE* 4(1):1, 3, 7.

Stork, G. and A.G. Schultz. 1971. The total synthesis of dl-camptothecin. *J. Am. Chem. Soc.* 93:4074-4075.

Suzuki, M. 1976. Two new species of nyssaxeous fossil woods from the palaeogene of Japan. *J. Jpn. Bot.* 50(8):228-238.

Tafur, S., J.D. Nelson, D.C. DeLong, et al. 1976. Antiviral components of *Ophiorrhiza mungos*. Isolation of camptothecin and 10-methoxycamptothecin. *Lioydia* 39(4):261-262.

Tai, F.L. 1948. Cercosporae of China—II. Lloydia.

Takeuchi, S., et al. 1991a. An early phase II study of CPT-11 in gynecologic cancers. Research Group of CPT-11 in Gynecologic Cancers. *Gan To Kagaku Ryoho* 18(4):579-584.

Takeuchi, S., et al. 1991b. A late phase II study of CPT-11 on uterine cervical cancer and ovarian cancer. Research Groups of CPT-11 in Gynecologic Cancers. *Gan To Kagaku Ryoho* 18(10):1681-1689.

Takeuchi, S., K. Noda, and M. Yakushui. 1992. Late phase II study of CPT-11, topoisomerase I inhibitor, in advanced cervical carcinoma. *Proc. Am. Soc. Clin. Oncol.* 11:224.

Tanai, T. 1977. Fossil leaves of the Nyssaceae from the Miocene of Japan. *J. Fac. Sci. Hokkaido Univ. IV. Geol. Mineral.* 17(3):505-516.

Tanizawa, A., A. Fujimori, Y. Fujimori, et al. 1994. Comparison of topoisomerase I inhibition, DNA damage, and cytotoxicity of camptothecin derivatives presently in clinical trials. *J. Natl. Cancer Inst.* 86(11):836-842.

Tao, K.L.J. and J.G. Buta. 1986. Differential effects of camptothecin and interactions with plant hormones on seed germination and seedling growth. *Pl. Growth Reg.* 4(3):219-226.

Thigren, T., J. Blessing, H. Ball, et al. 1990. Phase I clinical of taxol as second-line therapy for ovarian carcinoma: A Gynecologic Oncology Group Study. *Proc. Am. Soc. Clin. Oncol.* 9:604.

Tien, H.J., J.M. Tien, M.Y. Yeh, et al. 1977. Studies on the constituents of *Camptotheca acuminata* Done (I). The constituents of leaves. *Hua Hsueh* 1977(2):51-54.

Titman, P.W. 1949. Studies in the woody anatomy of the family Nyssaceae. *Elisha Mitchell Sci. Soc. J.* 65:245-261.

Tsiang, Y. and P.T. Li (eds.). 1977. *Flora Reipublicae Popularis Sinicae.* (Vol. 63, Apocynaceae and Asclepiadaceae). Science Press, Beijing.

Tsuda, H., K. Takatsuki, R. Ohno, et al. 1992. A late phase II trial of a potent topoisomerase I inhibitor, CPT-11, in malignant lymphoma. *Proc. Am. Soc. Clin. Oncol.* 11:316.

U.S. Department of Agriculture (USDA). 1915. *Inventory of seeds and plants imported by the office of foreign seed and plant introduction during the period from October 1 to December 31, 1912*, Washington, D.C.

U.S. Department of Agriculture (USDA). 1929. *Plant material introduced by the Office of Foreign Plant Introduction, Bureau of Plant Industry, January 1 to March 31, 1927* (Nos. 70868 to 73049), Washington, D.C.

U.S. Department of Agriculture (USDA). 1950. *Plant materials introduced by the Division of Plant Exploration and Introduction, Bureau of Plant Industry, April 1 to June 30, 1939* (Nos. 132271 to 133381). Plant Inventory No. 139, Washington, D.C.

U.S. Department of Agriculture (USDA). 1969. *Plant materials introduced January 1 to December 31, 1966* (Nos. 310336 to 317903). Plant Inventory No. 174, Washington, D.C.

U.S. Department of Agriculture (USDA). 1974. *Plant material introduced January 1 to December 31, 1971* (Nos. 355921 to 368260). Plant Inventory No. 179, Washington, D.C.

Verweij, J., B. Lund, J. Beynen, et al. 1992. Clinical studies with topotecan: The EORTC experience. In *Proceedings of the Seventh NCI-EORTC Symposium on New Drugs in Cancer Therapy*, Amsterdam.

Verweij, J., et al. 1993. Phase I and pharmacokinetics study of topotecan, a new topoisomerase I inhibitor. *Ann. Oncol.* 4(8):673-678.

Wall, M.E. 1977. Natural products: chemistry, pharmaconogy, and medical applications. In *Oral contraceptives and steroid chemistry in the People's Republic of China* (eds. by Fried, J., K.J. Ryan, and P.J. Tsuchitani), Pp. 62-72. National Academy of Science, Washington, D.C.

Wall, M.E. 1993. Camptothecin and Taxol. In *Chronicles of Drug Discovery* 327-348.

Wall, M.E. and M.C. Wani. 1993. Camptothecin and analogs: synthesis, biological *in vitro* and *in vivo* activities, and clinical possibilities. *ACS Symp. Ser.* 534 (*Human medicinal agents from plants*), pp. 149-169.

Wall, M.E., M.C. Wani, C.E. Cook, et al. 1966. Plant antitumor agents. I. The isolation and structure of Camptothecin, a novel alkaloidal leukemia and tumor inhibitor from *Camptotheca acuminata. J. Am. Chem. Soc.* 88:3888-3890.

Wall, M.E. M.C. Wani, A.W. Nicholas, et al. 1993. Plant Antitumor agents. 30. Synthesis and structure activity of novel camptothecin analogs. *J. Med. Chem.* 36:2689-2700.

Wang, J.C. 1988. DNA topoisomerases. *Ann. Rev. Biochem.* 54:665-697.

Wang, X.K., T.F. Zhao, and M. Wang. 1985. Gas chromatographic-mass spectroscopic investigation of the alkaloids of *Dendrobium nobile* cultivated on eleven trees. *Zhongyao Tongbao* 10(8):367-369, 371.

Wang, X.W., Z.M. Shen, J.L. Yang, et al. 1986. Inhibitory effect of hydroxy-camptothecin on colony formation of KB cells and DNA damage. *Yaoxue Xuebao* 21(7):492-497.

Wani, M.G. and M.E. Wall. 1969. Plant antitumor agents. II. The structure of two new alkaloids from *Camptotheca acuminata. J. Org. Chem.* 34:1364-1367.

Wani, M.C., A.W. Nicholas, G. Manikumar, et al. 1987. Plant antitumor agents. 25. Total synthesis and antileukemic activity of ring A substituted camptothecin analogues. Structure-activity correlations. *J. Med. Chem.* 30(10):1774-1779.

Wani, M.C., P.E. Ronman, J.T. Lindley, et al. 1980. Plant antitumor agents. 18. Synthesis and biological activity of camptothecin analogues. *J. Med. Chem.* 23:554-560.

White, D.O. and F. Fenner. 1986. *Medical virology* (3rd. ed.). Academic Press, Inc., Orlando, San Diego, New York, Austin, London, Montreal, Sydney, Tokyo, Toronto.

Wilson, E.H. 1914. Nyssaceae. In *Plantae Wilsonianae* (ed. by C.S. Sargent), pp. 254-257. The University Press, Cambridge.

Worley, J.F., D.W. Spaulding, and J.G. Buta. 1979. Inhibition of Xanthi Tobacco sucker growth by camptothecin. *Tobacco Inter.* 181(8):26-27.

Wu, C.C. 1848. *Zhiwu Mingshi Tukao.* Reprinted in 1973, Beijing.

Xu, B., J.T. Chang, J.L. Yang, et al. 1979. New results in parmacologic research of some anticancer ;agents. In *Proceedings of US-China Pharmacology Symposium, Commuttee on Scholarly Communication with the People's Republic of China* (eds. by J.J. Burns and P.J. Tsuchitani), pp. 151-158.

Yang, B.M. and L.D. Duan. 1988. One new plant of Nyssaceae from Hunan. *Nat. Sci. J. Hunan Norm. Univ.* 11(3):63-64.

Yeap, B.Y. and G. Wilding. 1993. Taxol in advanced, harmone-refractory carcinoma of the prostate: a phase II trial of the Eastern Cooperative Oncology Group. *Cancer* 72(8):2457.

Ying, T.S., Y.L. Zhang, and D.E. Boufford. 1993. *The Endemic genera of seed plants of China.* Science Press, Beijing.

Zeng, Y.L. 1982. The development of plant-derived drugs in China. *Pharmaceutisch Weekblad* 117:1037-1043.

Zhou, Y.X. 1989. Study on the characteristics of seed dormancy and germination of *Camptotheca acuminata. Linye Keji* 1989(8):22-25.

BIBLIOGRAPHY

BOTANY OF XI SHU

Baillon, H.E. 1877. *Historie des plants*. Paris, London, Leipzig. (French).

Bean, W.J. 1950. *Trees and shrubs hardy in the British Isles* (7th ed. 3 vol). John Murray, London.

Chun, W.Y. 1922. *Chinese economic trees.* Commercial Press, Ltd., Shanghai. (Chinese).

Decaisne, J. 1873. Caracteres et descriptions de trois genres nouveaux de plants recueilles en Chine par L'abbe A. David. *Soc. Bot. de France Bul.* 20:155-160. (French).

Dodoens, R. 1090. *Camptotheca acuminata* Dode. *Bull. Soc. Bot. France* IV:650-651. (French).

Editorial Committee of Flora of Anhui. 1988. *Flora of Anhui,* vol. 3. Zhong Guo Zhan Wang Press, Beijing. (Chinese).

Editorial Committee of Flora Sichuanica. 1981. *Flora Sichuanica.* Sichuan People Press, Chengdu. (Chinese).

Eyde, R.H. 1963. Morphological and paleobotanical studies of the Nyssaceae. I. A survey of the modern species and their fruits. *J. Arnold Arb.* 44:1-54.

Eyde, R.H. 1988. Comprehending *Cornus*: puzzles and progress in the systematics of the dogwoods. *Bot. Rev.* 54(3):233-351.

Eyde, R.H. and E.S. Barghoorn. 1963. Morphological and paleobotanical studies of the Nyssaceae. II. *J. Arnold. Arb.* 44:328-370.

Fang, W.P. 1981. *Flora Reipublicae Popularis Sinicae.* (Vol. 46, Aceraceae, Hippocastanaceae, Hippocrateaceae, Icacinaceae, Salvadoraceae, and Staphyleaceae). Science Press, Beijing. (Chinese).

Fang, W.P. and T.P. Soong. 1975. Praecursores flora Nyssacearum Sinensium. *Zhiwu Fenlei Xuebao* 13(2):83-89. (Chinese with English abstract).

Fang, W.P. and Z.R. Zhang. 1983. *Flora Reipublicae Popularis Sinicae* [Vol. 52(2), Nyssaceae]. Science Press, Beijing. (Chinese).

Franchet, A.R. 1884-1888. *Plantae Davidianae ex Sinarum imperio.* Masson, Paris. (Originally published in parts in the Nouvelles Archives du museum d' historic naturelle between 1883 and 1888, reprinted with independent pagination and new tables in 1884 and 1888). (French).

Gunasekera, S.P., M.M. Badawi, G.A. Cordell, et al. 1979. Plant anticancer agents. X. Isolation of camptothecin and 9-methoxycamptothecin from *Ervatamia heneana. J. Nat. Prod.* 42(5):475-477.

Hemsley, W.B. 1896. The flora of Tibet. *Kew Bull. Misc. Inf.* 207-216.

Hohn, M.E. and W.G. Meinschein. 1976. Seed oil fatty acids: evolutionary significance in the Nyssaceae and Cornaceae. *Syst. Ecol.* 4(3):193-199.

Hsu, J.S., T.Y. Chao, L.T. Lin, et al. 1977. Chemical constituents of the anticancer plant *Camptotheca acuminata* Decne. II. Chemical constituents of the fruits of *Camptotheca acuminata* Decne. *Huaxue Xuebao* 35(3-4):193-200. (Chinese with English abstract).

Kirchheimer, F. 1938. Cornaceae. Fossilium Catalogues II. *Plantae.* 23:1-210.

Ku, K.Y. and T.C. Tang. 1980. Several botanical sources of camptothecine-an antitumor alkaloid. *Zhong Cao Yao* 11(10):476-479. (Chinese).

Lee, S.C. 1935. *Forest botany of China.* Commercial Press, Ltd., Shanghai.

Lewandowski, R.J. and R. Gutowski. 1993. Case studies from the Morris Arboretum. *Publ. Gard.* 8(1):16-18, 35.

Li, L.C. and P.S. Hsu. 1986. Chromosome observations of eight species endemic to China. *Zhiwu Fenlei Xuebao* 24(2):157-160. (Chinese with English abstract).

Lin, L.T.(Z.), C.Q. Song (Sung), and R.S. Hsu (Xu). 1978. Chemical constituents of the anticancer plant *Camptotheca acuminata* Decne. V. Other constituents of its fruits. *Huaxue Xuebao* 6:327-328. (Chinese with English abstract).

Lin, L.T.(Z.), C.Q. Song (Sung), and R.S. Hsu (Xu). 1979. Chemical constituents of the anticancer plant *Camptotheca acuminata* Decne. III. Ellagic acids from the fruits of *Camptotheca acuminata* Decne. *Huaxue Xuebao* 37(3):207-214. (Chinese with English abstract).

Lin, L.Z., T.Y. Chao, and J.(R.)S. Hsu. 1977. Chemical constituents of the anticancer plant *Camptotheca acuminata* Decne. I.

Chemical constituents of the roots of *Camptotheca acuminata* Decne. *Huaxue Xuebao* 35(3-4):227-231. (Chinese with English abstract).

Meyer, P.W. 1991. *Camptotheca acuminata. Publ. Gard.* 6(4):39.

Ming, Z. 1986. *Chin. J. Vet. Sci. Techn.* 12(3):17. (Chinese).

Murrell, Z.E. 1993. Phylogenetic relationships in *Cornus* (Cornaceae). *Syst. Bot.* 18(3):469-495.

Nanjing College of Pharmacology. 1974. *Yaoxue Zhiliao* 49(2). (Chinese).

Perdue, R.E. 1968. *Camptotheca acuminata*—Source of promising cancer drug. *Lasca Leaves* September:55-59.

Perdue, R.E., R.L. Smith, M.E. Wall., et al. 1970. *Camptotheca acuminata* Decaisne (Nyssaceae) source of camptothecin, and antileukemic alkaloid. *Agr. Res. Ser. USDA Techn. Bull.* No. 1415. 26 pp.

Perdue, R.E., M.E. Wall, J.L. Hartwell, et al. 1968. Comparison of the activity of crude *Camptotheca acuminata,* ethanolic extracts against lymphoid leukemia L-1210. *Lioydia* 31:229.

Shanghai Institute of Materia Medica. 1975. *Zhong Cao Yao Tong Xun* 273. (Chinese).

Smith, R.L. 1969. *Camptotheca acuminata*, biography of camptothecin, a promising cancer drug. *Lasca Leaves* September-December: 55-59.

Sohma, K. 1963. Pollen morphology of the Nyssaceae. I. *Nyssa* and *Camptotheca*. *Sci. Rep. Tôhoku Univ. Ser.* IV (Biol.) 29:389-392.

Steward, A.N. 1958. *Manual of vascular plants of the lower Yangtze Valley.* Oregon State College, Corvallis.

Sun, X.J., N.Q. Du, and M.H. Chen. 1981. The paleo-vegetation and paleo-climate during the time of the Homudu people. *Zhiwu Xuebao* 23(2):146-151. (Chinese with English abstract).

Tanai, T. 1977. Fossil leaves of the Nyssaceae from the Miocene of Japan. *J. Fac. Sci. Hokkaido Univ. IV. Geol. Mineral.* 17(3):505-516. (Japanese with English abstract).

Tang, Y. 1932. Identification of some important hardwoods of south China by their gross structure. *Fan. Mem. Inst. Biol. Bull.* 3:253-338.

Tien, H.J., J.M. Tien, M.Y. Yeh, et al. 1977. Studies on the constituents of *Camptotheca acuminata* Done. I. Constituents of leaves. *Hua Hsueh* 1977(2):51-54. (Chinese with English abstract).

Titman, P.W. 1949. Studies in the woody anatomy of the family Nyssaceae. *Elisha Mitchell Sci. Soc. J.* 65:245-261.

Tsiang, Y. and P.T. Li (eds.). 1977. *Flora Reipublicae Popularis Sinicae.* (Vol. 63, Apocynaceae and Asclepiadaceae). Science Press, Beijing. (Chinese).

U.S. Department of Agriculture (USDA). 1915. *Inventory of seeds and plants imported by the office of foreign seed and plant introduction during the period from October 1 to December 31, 1912.* Washington, D.C.

U.S. Department of Agriculture (USDA). 1929. *Plant material introduced by the Office of Foreign Plant Introduction, Bureau of Plant Industry, January 1 to March 31, 1927* (Nos. 70868 to 73049), Washington, D.C.

U.S. Department of Agriculture (USDA). 1950. *Plant materials introduced by the Division of Plant Exploration and Introduction, Bureau of Plant Industry, April 1 to June 30, 1939* (Nos. 132271 to 133381). Plant Inventory No. 139. Washington, D.C.

U.S. Department of Agriculture (USDA). 1969. *Plant materials introduced January 1 to December 31, 1966* (Nos. 310336 to 317903). Plant Inventory No. 174. Washington, D.C.

U.S. Department of Agriculture (USDA). 1974. *Plant material introduced January 1 to December 31, 1971* (Nos. 355921 to 368260). Plant Inventory No. 179. Washington, D.C.

Van Hengel, A.J., M.P. Harkes, H.J. Wichers, et al. 1992. Characterization of callus formation and camptothecin production by cell lines of *Camptotheca acuminata. Pl. Cell. Tiss. Org. Cult.* 28(1):11-.

Wang, C.W. 1961. *The forests of China.* Harvard Univ., Maria Moors Cabot Found. Pub. No.5.

Wang, F.H. 1993. *Selected works of Wang Fuhsiung.* Esperanto Press, Beijing. 462 pages. (Chinese and English)

Wangerin, W. 1910. Nyssaceae. Das Pflanzenr. IV:1-20.

Wilson, E.H. 1913. *A naturalist in western China.* Methuen & Co. Ltd., London.

Wilson, E.H. 1914. Nyssaceae. In *Plantae Wilsonianae* ed. by C.S. Sargent, Pp. 254-257. The University Press, Cambridge.

Wu, C.C. 1848. *Zhiwu Mingshi Tukao* (Illustrated investigation of the names and natures of plants). Reprinted in 1973, Beijing. (Chinese).

Wu, T.S., H.J. Tien, and M.Y. Yeh. 1980. Studies on the constituents of Formosan folk medicine. VII. Constituents of the flowers of

Vanilla somai Hayata and the roots of *Camptotheca acuminata* Dcne. *Ch'eng-kung Ta Hsueh Hsueh Pao* 15:65-67. (Chinese with English abstract).

Wu, Z.M. 1984. Studies on chromosome number of *Camptotheca acuminata* and *Toona sinensis. Anhui Linye Keji* (3):21-23. (Chinese).

Xiang, Q.Y., D.E. Soltis, D.R. Morgan, et al. 1993. Phylogenetic relationships of *Cornus* L. sensu lato and putative relatives inferred from rbcL sequence data. *Ann. Missouri Bot. Gard.* 80(3):723-734.

Xu, Y.C. (ed.). 1990. *Iconographia arborорum Yunnanicorum.* Yunnan Science and Technology Press, Kunming. (Chinese).

Yang, B.M. and L.D. Duan. 1988. One new plant of Nyssaceae from Hunan. *Hunan Shifan Daxue Xuebao (Ziran Kexue Ban)* 11(3):63-64. (Chinese with English abstract).

Ying, T.S., Y.L. Zhang, and D.E. Boufford. 1993. *The endemic genera of seed plants of China.* Science Press, Beijing.

Zhao, J.H., Y.X. Chen, et al. 1985. Electron microscope study on witches' broom of *Camptotheca acuminata. Nanjing Nongye Daxue Xuebao* 1985(1):95. (Chinese with English abstract).

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OF XI SHU

Andersson, H.C., et al. 1992. Induction of chromosomal aberrations by camptothecin in root-tip cells of *Vicia faba*. *Mutat. Res.* 268(2):167-181.

Brookes, R.R., J.A. McCleave, and E.K. Schofield. 1977. Cobalt and nickel uptake by the Nyssaceae. *Taxon* 20(2-3):197-201.

Burnett, R.J., I.E. Maldonado-Mendoza, T.D. McKnight, et al. 1993. Expression of a 3-hydroxy-3-methylglutaryl coenzyme A reductase gene from *Camptotheca acuminata* is differently regulated by wounding and methyl jasmonate. *Pl. Physiol.* 103(1):41-48.

Buta, J.G. and A. Kalinski. 1988. Camptothecin and other plant growth regulators in higher plants with antitumor activity. *ACS Symposium Series* No. 380:294-304.

Buta, J.G. and D.W. Spaulding. 1986. Effects of camptothecin on seedling growth. In *Proceedings of the Plant Growth Regulator Society of America*, 13th Annual Meeting, St Petersburg Beech, Florida, August 1986, P. 155.

Buta, J.G. and J.F. Worley. 1976. Camptothecin, a selective plant growth regulator. *J. Agr. Food Chem.* 24(5):1085-1086.

Cai, B.H. and G.R. Xiao (eds.). 1983. *Forest insects of China.* China Forestry Publishing House, Beijing. (Chinese).

Cao, G.R., J.X. Gao, D.X. Duan, et al. 1992. Studies on *Camptotheca acuminata* leaves: main toxic principle, poisoning, and treatment in goats. In *Poisonous plants: Proceedings of the Third International Symposium* (eds. by L.F. James, R.F. Keeler, E.M. Bailey, P.R. Cheeke, and M.P. Hegarty), Pp. 506-508. Iowa State University Press, Ames.

Chen, L.J., F.H. Wang, and Y.R. Wu. 1991. The pollination biology of *Camptotheca acuminata* Decne. (Nyssaceae). *Cathaya* 3:45-52.

Chou, Y.L. and S.Y. Li. 1990. *Forests of China.* Science Press, Beijing. (Chinese).

DeMilo, A.B. and A.B. Borkovec. 1974. Camptothecin, a potent chemosterilant against the house fly. *J. Econom. Entomol.* 67(3):457-458.

He, G.H., C.Z. Zhang, et al. 1991. Nonpolluting insecticide compositions containing camptothecin. *Faming Zhuanli Shenqing Gongkai Shuomingshu, P.R. China,* 6 pp. (Chinese).

Hunan Institute of Forestry. 1978. A preliminary study on the control of *Dendrolimus punctatus* with plant alkaloids. *Kunchong Xuebao* 21(1):108-112. (Chinese).

Jacobson, M., R.E. Redfern, and G.D. Mills, Jr. 1975. Naturally occurring insect growth regulators. II. Screening of insect and plant extracts as insect juvenile hormone mimics. *Lioydia* 38(6):455-472.

Kawahara, T. 1971. The return of nutrients with litter fall in the forest ecosystem: II. The amount of organic matter and nutrients. *J. Jpn. For. Soc.* 53(8):231-238. (Japanese with English abstract).

Kawahara, T., G. Iwatsubo, T. Nishimura, et al. 1968. Movement of nutrients in a model stand of *Camptotheca acuminata* Decne. *J. Jpn. For.* 50(5):125-134. (Japanese with English abstract).

Liu, X.J. and Y.L. Guo. 1987. Three undescribed species of the genus *Pseudocercospora. Zhenjun Xuebao* 6(4):219-224. (Chinese with English abstract).

Northeast Forestry College (ed.). 1977. *Forest entomology.* Northeast Forestry College Press, Harbin. (Chinese).

Perdue, R.E. 1968. *Camptotheca acuminata*—source of promising cancer drug. *Lasca Leaves* September:55-59.

Perdue, R.E., M.E. Wall, J.L. Hartwell, et al. 1968. Comparison of the activity of crude *Camptotheca acuminata* Ethanolic extracts against lymphoid leukemia L-1210. *Lioydia* 31: 229.

Perdue, R.E., R.L. Smith, M.E. Wall., et al. 1970. *Camptotheca acuminata* Decaisne (Nyssaceae) source of camptothecin, and antileukemic alkaloid. *Agr. Res. Ser. USDA Techn. Bull.* No.1415. 26 pp.

Saito, H. 1980. Studies on dry matter production in sapling stands of deciduous broad-leaved tree, *Camptotheca acuminata* Decne. *Sci. Rep. Kyoto Perfect. Univ.* 32:94-100. (Japanese with English abstract).

Saito, H. and T. Shidei. 1968. The leaf longevity of a young stand of *Camptotheca acuminata*. *Jpn. J. Ecol.* 18(5):230-234. (Japanese with English abstract).

Sakato, K. and M. Misawa. 1974. Effects of chemical and physical conditions on growth of *Camptotheca acuminata* cell cultures. *Agr. Biol. Chem.* 38(3):491-497.

Shandong Forestry School (ed.). *Forest entomology*. China Forestry Publishing House, Beijing. (Chinese).

Shao, B.B. 1989. Effects of stratification and temperature variation on the germination of seeds of ten different trees. *Linye Keji* 1989(2):4-7. (Chinese with English abstract).

Steffens, G.L., J.G. Buta, L.E. Gregory, et al. 1979. New plant growth regulators isolated from higher plants. In *Adv. Pestic. Sci. (Plenary Lect. Symp. Pap. Int. Congr. Pestic. Chem., 4th*, 1978, ed. by H. Geissbuehler), Vol. 2:343-346. Pergamon, Oxford.

Tai, F.L. 1948. Cercosporae of China-II. *Lioydia* 11:36-56.

Tang, M.Z. 1983. Effect of light and heat on assay of camptothecin. *Yaoxue Tongbao* 18(1):8-9. (Chinese with English abstract).

Tao, K.L.J. and J.G. Buta. 1986. Differential effects of camptothecin and interactions with plant hormones on seed germination and seedling growth. *Pl. Growth Regul.* 4(3):219-226.

Van Hengel, A.J., M.P. Harkes, H.J. Wichers, et al. 1992. Characterization of callus formation and camptothecin production by cell lines of *Camptotheca acuminata*. *Pl. Cell Tiss. Org. Cult.* 28(1):11-18.

Wang, C.Y., J.G. Buta, and H.W. Hruschka. 1980. Effect of camptothecin on the storage quality of radishes. *HortScience* 15(1):72-73.

Wang, C.Y., J.G. Buta, H.E. Moline, et al. 1980. Potato sprout inhibition by camptothecin, a naturally occurring plant growth regulator. *J. Am. Soc. Hortic. Sci.* 105(1):120-124.

Wang, X.K., T.F. Zhao, and M. Wang. 1985. Gas chromatographic-mass spectroscopic investigation of the alkaloids of *Dendrobium nobile cultivated* on eleven trees. *Zhongyao Tongbao* 10(8):367-369, 371. (Chinese with English abstract).

Worley, J.F. and J.G. Buta. 1978. Growth regulating activity of an extract of *Camptotheca acuminata*. In *Proceedings of Annual Meeting of Northeast Weed Science Society*, 32d, P. 100.

Worley, J.F., D.W. Spaulding, and J.G. Buta. 1979. Inhibition of Xanthi tobacco sucker by camptothecin. *Tobacco Intl.* 181(8):26-27.

Zhou, Y.X. 1989. Study on the characteristics of seed dormancy and germination of *Camptotheca acuminata*. *Linye Keji* 1989(8):22-25. (Chinese).

MECHANISMS OF ACTION

OF CAMPTOTHECINS

Abelson, H.T. and S. Penman. 1972. Selective interruption of high molecular weight RNA synthesis in HeLa cells by camptothecin. *Nat. New Biol.* 237:144-146.

Abelson, H.T. and S. Penman. 1974. Selective interruption of RNA metabolism by chemotherapeutic agents. *Handb. Exper. Pharmako.* 38:571-581.

Adamietz, P. 1987. Poly(ADP-ribose) synthase is the major endogenous nonhistone acceptor for poly(ADP-ribose) in alkylated rat hepatoma cells. *Eur. J. Biochem.* 169:365-372.

Aichi, T. 1991. DNA topoisomerase inhibitors. *Farumashia* 27(12):1264-1268. (Japanese).

Akimoto, K., A. Goto, K. Ohya, et al. 1991. Selective and sensitive determination of lactone and hydroxy acid forms of camptothecin and two derivatives by high-performance liquid chromatography with fluorescence detection. *J. Chromat.* 588(1/2):165-170.

Aller, P., C. Rius, F. Mata, et al. 1992. Camptothecin induces differentiation and stimulates the expression of differentiation-related genes in U-937 human promonocytic leukemia cells. *Cancer Res.* 52(5):1245-1251.

Andersson, H.C. and B.A. Kihlman. 1992. Induction of chromosomal aberrations by camptothecin in root-tip cells of *Vicia faba*. *Mut. Res.* 268(2):167-181.

Andoh, T., K. Okaeda, and M. Oguro. 1988. Biological function of DNA topoisomerases and its implication in cancer chemotherapy. *Gan To Kagaku Ryoho* 15:1-14.

Andoh, T., K. Ishii, Y. Suzuki, et al. 1987. Characterization of a mammalian mutant with a camptothecin-resistant DNA topoisomerase I. *Pro. Natl. Acad. Sci. U.S.A.* 84(16):5565-5569.

Andoh, T., K. Ishii, H. Tamura, et al. 1990. DNA topoisomerases and drug resistance. Camptothecin resistance and others. *Saibo Kogaku* 92(111-118). (Japanese with English abstract).

Andoh, T., E. Kjeldsen, B.J. Bonven, et al. 1991. Camptothecin-resistant DNA topoisomerase I. In *DNA Topoisomerases Cancer* (eds. by Potmesil, M. and K.W. Kohn), Pp. 249-259. Oxford University Press, New York.

Andoh, T., H. Tamura, C. Kohchi, et al. 1993. In *Proceedings of International Symposium of Molecular Biology of DNA Topoisomerases: Its appl. Chemother*, Boca Raton, Florida (eds. by Anoh, T., H. Ikeda, and M. Oguro), Pp. 229-235.

Andoh, T., Y. Yasui., O. Koiwai, et al. 1993. Molecular basis of resistance to CPT-11, a specific inhibitor of DNA topoisomerase I. *Int. Congr. Ser. -Excepta Med.* Pp. 95-101.

Andrea, J.E., K. Adachi, M. Kazuo, et al. 1991. Fluorometric assays for DNA topoisomerases and topoisomerase-targeted drugs: quantitation of catalytic activity and DNA cleavage. *Mol. Pharmacol.* 40(4):495-501.

Anzai, H., P. Frost, and J.L. Abbruzzese. 1992a. Synergistic cytotoxicity with combined inhibition of topoisomerase (topo) I and II. *Pro. Am. Assoc. Cancer Res.* 33:431.

Anzai, H., P. Frost, and J.L. Abbruzzese. 1992b. Synergistic cytotoxicity with 2'-deoxy-5-azacytidine and topotecan *in vitro* and *in vivo*. *Cancer Res.* 52:2180-2185.

Avemann, K., R. Knippers, T. koller, et al. 1988. Camptothecin, a specific inhibitor of type I DNA topoisomerase, induces DNA breakage at replication forks. *Mol. Cell. Biol.* 8:3026-3034.

Backer, L.C., et al. 1990. Genotoxicity of inhibitors of DNA topoisomerase I (camptothecin) and II (m-AMSA) *in vivo* and *in vitro*. *Mutagenesis* 5(6):541-547.

Badaracco, G., N. Landsberger, and R. Benfante. 1992. Purification and characterization of a proteolytic active fragment of DNA topoisomerase I from the brine shrimp *Artemia franciscana* (*Crustacea anostraca*). *Biochem. J.* 282(1):249-254.

Bae, Y.S., et al. 1991. A shuttle vector for analysis of illegitimate recombination in mammalian cells: effects of DNA topoisomerase inhibitors on deletion frequency. *Gene* 101(2):285-289.

Baranao, J.L., et al. 1991. A DNA topoisomerase I inhibitor blocks the differentiation of rat granulosa cells induced by follicle-stimulating hormone. *Biochem. J.* 277(Part 2):557-560.

Beek, W.T. and H.K. Danks. 1991. Mechanism of resistance to drugs that inhibit DNA topoisomerases. *Cancer Biol.* 2:235-244.

Been, M.D. and J.J. Champoux. 1980. Breakage of single-stranded DNA by rat liver nicking-closing enzyme with the formation of a DNA-enzyme complex. *Nucleic Acids Res.* 8:6129-6142.

Been, M.D. and J.J. Champoux. 1981. DNA breakage and closure by rat liver type I topoisomerase: separation of the half-reactions by using a single-stranded DNA substrate. *Proc. Natl. Acad. Sci. U.S.A.* 78:2883-2887.

Been, M.D. and J.J. Champoux. 1984. Breakage of single-stranded DNA by eukaryotic type I topoisomerase occurs only at regions with the potential for base-pairing. *J. Mol. Biol.* 108:515-531.

Been, M.D., R.R. Burgess, and J.J. Champoux. 1984. Nucleotide sequence preference at rat liver and wheat germ type 1 DNA topoisomerase breakage sites in duplex SV40 DNA. *Nucleic Acids Res.* 12:3097-3114.

Beerman, T.A., J.M. Woynarowski, and M.M. Mchugh. Modulation of topoisomerase-targeted drugs by DNA minor-groove binding agents. In *DNA topoisomerases in Cancer* (eds. by Potmesil, M. and K.W. Kohn), Pp. 172-181. Oxford University Press, New York, Oxford.

Bendixen, C., B. Thomsen, J. Alsner, et al. 1990. Camptothecin-stabilized topoisomerase I-DNA adducts cause premature termination of transcription. *Biochemistry* 29:5613-5619.

Bhuyan, B.K., T.J. Fraser, and L.G. Gray. 1973. Cell-kill kinetics of several S-phase-specific drugs. *Cancer Res.* 33(4):888-894.

Bjornsti, M.A. 1991. DNA topoisomerases. *Curr. Opin. Struct. Biol.* 1(1):99-104.

Bjornsti, M.A., P. Benedetti, G.A. Viglianti, et al. 1989. Expression of human DNA topoisomerase I in yeast cells lacking yeast DNA topoisomerase I: restoration of sensitivity of the cells to the antitumor drug camptothecin. *Cancer Res.* 49:6318-6323.

Bjornsti, M.A., P. Benedetti, G.A. Viglianti, et al. 1992. Expression of human DNA topoisomerase I in yeast cells lacking yeast DNA topoisomerase I: restoration of sensitivity of the cells to the antitumor drug camptothecin. *Cancer Res.* 52:525-532.

Bosmann, H.B. 1970. Camptothecin inhibits macromolecular synthesis in mammalian cells but not in isolated mitochondria or *Escherichia coli*. *Biochem. Biophys. Res. Commun.* 41(6):1412-1420.

Bronshtain, I.B., I.I. Gromova, V.L. Bukhman, et al. 1989. Effect of camptothecin on DNA-relaxing and DNA-cleavage activity of

calf thymus topoisomerase I. *Mol. Biol.* (Mosk) 23(2):491-501. (Russian with English abstract).

Bronshtain, I.B., I.I. Gromova, and S.V. Razin. 1991. Specific cleavage of chicken alpha A-globin and human c-Ha-ras genes by two molecular forms of calf thymus topoisomerase I. *Mol. Cell. Biochem.* 101(2):115-124.

Bruno, S., W. Giaretti, Z. Darzynkiewicz, et al. 1992. Effect of camptothecin on mitogenic stimulation of human lymphocytes: involvement of DNA topoisomerase I in cell transition from G0 to G1 phase of the cell cycle and in DNA replication. *J. Cell Physiol.* 151(3):478-486.

Bullock, P., J. Champoux, and M. Botchan. 1985. Association of crossover points with topoisomerase I cleavage sites: A model for nonhomologous recombination. *Science* 230:954-958.

Burke, T.G., A.E. Staubus, A.K. Mishra, et al. 1992. Liposomal stabilization of camptothecin's lactone ring. *J. Am. Chem. Soc.* 114(21):8318-8319.

Burris, H.A. III, A.R. Hanauske, R.K. Johnson et al. 1992. Activity of topotecan, a new topoisomerase I inhibitor, against human tumor colony-forming units *in vitro*. *J. Natl. Cancer Inst.* 84:1816-1820.

Bushnell, D.E., J.E. Becker, and V.R. Potter. 1974. Role of messenger RNA in tyrosine aminotransferase superinduction. Effects of camptothecin on hepatoma cells in culture. *Biochem. Biophys. Res. Commun.* 56(3):815-821.

Cai, J.C., M.G. Yin, A.Z. Min, et al. 1977. *Kexue Tongbao* 22:269. (Chinese with English abstract).

Cai, J.C. and C.R. Hutchinson. 1983. Camptothecin. *The Alkaloids* 21:101-137.

Capranico, G. and F. Zunino. 1992. DNA topoisomerase-trapping antitumor drugs. *Eur. J. Cancer* 28A:2055-2060.

Carballo, M., R. Gine, M. Santos, et al. 1991. Characterization of topoisomerase I and II activities in nuclear extracts during callogenesis in immature embryos of *Zea mays*. *Plant Mol. Biol.* 16(1):59-70.

Carte, B.K., C. Debrosse, D. Eggleston, et al. 1990. Isolation and characterization of a presumed biosynthetic precursor of camptothecin from extracts of *Camptotheca acuminata*. *Tetrahedron* 46(23):7661. [Erratum to document cited in CA 113(21):187998y].

Champoux, J.J. 1990. Mechanistic aspects of type-1 topoisomerases. In *DNA topology and its biological effects* (eds. by Cozzarelli, N.

and J.C. Wang), Pp. 217-242. Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York.

Champoux, J.J. and R. Aronoff. 1989. The effects of camptothecin on reaction and the specificity of the wheat germ type I topoisomerase. *J. Biol. Chem.* 264:1010-1015.

Chang, A.Y., Z. Gu, R. Keng, et al. 1991. Radiation (XRT)-sensitizing effects of topoisomerase (topo) I and II inhibitors. *Proc. Am. Assoc. Cancer Res.* 32:389.

Chang, A.Y., Z. Gu, R. Keng, et al. 1992. Topotecan (T) and etoposide (E) inhibit radiation (XRT) repair differently than potential lethal damage (PLD) repair or sublethal damage repair. *Proc. Am. Assoc. Cancer Res.* 33:437.

Chatterjee, S., M.F. Cheng, D. Trivedi, et al. 1989. Camptothecin hypersensitivity in poly(adenosine diphosphate-ribose) polymerase deficient cell lines. *Cancer Commun.* 1:389-394.

Chatterjee, S., M.F. Cheng, D. Trivedi, et al. 1990. Camptothecin hypersensivity mediated by interference with poly (adenosine diphosphate-ribose) polymerase. *Proc. Am. Assoc. Cancer Res.* 31:440.

Chatterjee, S., M.F. Cheng, and N.A. Berger. 1990. Hypersensivity to clinically useful alkylating agents and radiation in poly(ADP-ribose) polymerase-deficient cell lines. *Cancer Commun.* 2:401-407.

Chen, A.Y., C. Yu, C.C. Cheng, et al. 1993. In *Proceedings of International Symposium of Molecular Biology of DNA Topoisomerases: Its appl. Chemother,* Boca Raton, Florida (eds. by Anoh, T., H. Ikeda, and M. Oguro), Pp. 247-254.

Chen, G.L. and L.F. Lie. 1986. DNA topoisomerases as therapeutic targets in cancer chemotherapy. *Ann. Rep. Med. Chem.* 21:257-262.

Chow, K.C., T.L. Johnson, and G.D. Pearson. 1985. A novel method for the detection and quamtitation of eukaryotic topoisomerase I. *Biotechniques* 3:290-296.

Coderoni, S., M. Paparelli, and G.L. Gianfranceschi. 1993. Effect of CPT on the calf thymus topoisomerase I-mediated DNA breakage-reunion reaction: optimal conditions for the formation and reversal of the CPT trapped topoisomerase I cleavable complex. *Mol. Biol. Rep.* 17(2):129-134.

Cole, A.D., S. Heath-Pagliuso, A. Baich, et al. 1992. *In vitro* analysis of a type I type DNA topoisomerase activity from cultured tobacco cells. *Plant Mol. Biol.* 19(2):265-276.

Cortes, F., J. Pinero, and T. Ortiz. 1993. Importance of replication fork progression for the induction of chromosome damage and SCE by inhibitors of DNA topoisomerases. *Mutat. Res.* 303(2):71-76.

Covey, J.M., C. Jaxel, K.W. kohn, et al. 1989. Protein-linked DNA strand breaks induced in mammalian cells by camptothecin, an inhibitor of topoisomerase I. *Cancer Res.* 49:5016-5022.

Creasy, W.A., M. Richards, D. Gil, et al. 1983. Action of (s)-10-hydroxycamptothecin on P388 leukemia and distribution of the drug in mice. *Cancer Treat. Rep.* 67:179-182.

Creemers, G.J., B. Lund, J. Verweij, et al. 1994. Topoisomerase I inhibitors: topotecan and irinotecan. *Cancer Treat. Rev.* 20(1):73-.

Crow, R.T., et al. 1992. Structural modifications of camptothecin and effects on topoisomerase I inhibition. *J. Med. Chem.* 35(22):4160-4164.

D'Arpa, P. and L.F. Liu. 1989. Topoisomerase-targeting antitumor drugs. *Biochim. Biophys. Acta* 989:163-177.

D'Arpa, P., C. Beardmore, and L.F. Liu. 1990. Involvement of nucleic acid synthesis in cell killing mechanisms of topoisomerase poisons. *Cancer Res.* 50:6919-6924.

D'Arpa, P., P.S. Machlin, H. Ratrie, et al. 1988. cDNA cloning of human DNA topoisomerase I: Catalytic activity at a 67.7 kDa carboxyl-terminal fragment. *Proc. Natl. Acad. Sci. U.S.A.* 85:2543-2547.

Degrassi, F., R. De Salvia, C. Tanzarella, et al. 1989. Induction of chromosomal aberrations and SCE by camptothecin, an inhibitor of mammalian topoisomerase I. *Mutat. Res.* 211:125-130.

Del Bino, G. and Z. Darzynkiewicz. 1991. Camptothecin, teniposide, or 4'-(9-acridinylamino)-3-methanesulfon-m-anisidide, but not mitoxantrone or doxorubicin, induces degradation of nuclear DNA in the S phase of HL-60 cells. *Cancer Res.* 51:1165-1169.

Del Bino, G., P. Lassota, and Z. Darzynkiewicz. 1991. The S-phase cytotoxicity of camptothecin. *Exp. Cell Res.* 193:27-35.

Del Bino, G., J. Skierski, and Z. Darzynkiewicz. 1990. Diverse effects of camptothecin, an inhibitor of topoisomerase I, on the cell cycle of lymphocytic (L1210, MOLT-4) and myelogenous (HL-60, KG1) leukemic cells. *Cancer Res.* 50(18):5746-5750.

Del Bino, G., et al. 1991. The concentration-dependent diversity of effects of DNA topoisomerase I and II inhibitors on the cell cycle of HL-60 cells. *Exp. Cell Res.* 195(2):485-491.

Drlica, K. and R.J. Franco. 1988. Inhibitors of DNA topoisomerases. *Biochemistry* 27:2253-2259.

Editorial of The Lancet. 1990. Chemotherapy: topoisomerases as targets. *Lancet* 335.

Eng, W.K., L. Faucette, R.K. Johnson, et al. 1988. Evidence that DNA topoisomerase I is necessary for the cytotoxic effects of camptothecin. *Mol. Pharmacol.* 34:755-760.

Eng, W.K., F.L. McCabe, K.B. Tan, et al. 1990. Development of a stable camptothecin-resistant subline of P388 leukemia with reduced topoisomerase I content. *Mol. Pharmacol.* 38(4):471-480.

Farabegoli, F., M. Govoni, F. Novello. 1992. Effects of camptothecin, an inhibitor of DNA topoisomerase I on ribosomal gene structure and function in TG cells. *Biol. Cell* 74(3):281-286.

Fassberg, J. and V.J. Stella. 1992. A kinetic and mechanistic study of the hydrolysis of camptothecin and some analogues. *J. Pharm. Sci.* 81(7):676-684.

Fesen, F.L., G. Kohlhagen, K.W. Kohn, et al. 1993. Specific interaction of camptothecin, a topoisomerase I inhibitor, with guanine residues of DNA detected by photoactivation at 365 nm. *Biochemistry* 32(34):8955-8962.

Fostel, J.M., D.A. Montgomery, and L.L. Shen. 1992. Characterization of DNA topoisomerase I from Candida albicans as a target for drug discovery. *Antimicrob. Agents Chemother.* 36(10):2131-2138.

Frosina, G. and O. Rossi. 1992. Effects of topoisomerase poisoning by antitumor drugs VM 26, fostriecin and camptothecin on DNA repair replication by mammalian cell extracts. *Carcinogenesis* 13(8):1371-1377.

Fukada, M. 1980. Interaction between SV40 DNA and camptothecin, an antitumor alkaloid. *J. Biochem.* (Tokyo) 87(4):1089-1096.

Fukada, M. 1985. Action of camptothecin and its derivatives on deoxyibonucleic acid. *Biochem. Pharmacol.* 34(8):1225-1230.

Furue, H. 1993. Topoisomerase inhibitors developing in Japan. *Gan To Kagaku Ryoho* 20(1):42-49. (Japanese with English abstract).

Gajkowska, B., E. Puvion, and W. Bernhard. 1977. Unusual perinucleolar accumulation of ribonucleoprotein granules induced by camptothecin in isolated liver cells. *J. Ultrastruct. Res.* 60(3):335-347.

Gallo, R.C., J. Whang-Peng, and R.H. Adamson. 1971. Studies on antitumor activity, mechanism of action, and cell cycle effects of camptothecin. *J. Natl. Cancer Inst.* 46(4):789-795.

Garg, L.C., S. Diangelo, and S.T. Jacob. 1987. Role of DNA topoisomerase I in the transcription of supercoiled rRNA gene. *Proc. Natl. Acad. Sci. U.S.A.* 84:3185-3188.

Gedik, C.M. and A.R. Collins. 1990. Comparison of effects of fostriecin, novobiocin, and camptothecin, inhibitors of DNA topoisomerases, on DNA replication and repair in human cells. *Nucleic Acids Res.* 18(4):1007-1013.

George, J.W., S. Ghate, S.W. Matson, et al. 1992. Inhibition of DNA helicase II unwinding and ATPase activities by DNA-interacting ligands. Kinetics and specificity. *J. Biol. Chem.* 267(15):10683-10689.

Giaccone, G., A.F. Gazdar, H. Beck, et al. 1992. Multidrug sensitivity phenotype of human lung cancer cells associated with topoisomerase II expression. *Cancer Res.* 52(7):1666-1674.

Gilmour, D.S. and S.C. Elgin. 1987. Localization of specific topoisomerase I interactions within the transcribed region of active heat shock genes by using the inhibitor camptothecin. *Mol. Cell. Biol.* 7:141-148.

Gilmour, D.S., W. Pflugfelder, J.C. Wani, et al. 1986. Topoisomerase I interacts with transcribed regions in *Drosophila* cells. *Cell* 44:401-407.

Giovanella, B.C., H.R. Hinz, A.J. Kozielski, et al. 1993. Water-insoluble (S)-camptothecin of the closed lactone ring form and derivatives thereof. *Can. Pat. Appl.* 25 pp.

Giovanella, B.C., J.S. Stehlin, W.E. Wall, et al. 1989. DNA topoisomerase I targeted chemotherapy of human colon cancer in xenografts. *Science* 246:1046-1048.

Gong, J.P., X. Li, and Z. Darzynkiewicz. 1993. Different patterns of apoptosis of HL-60 cells induced by cycloheximide and camptothecin. *J. Cell Physiol.* 157(2):263-270.

Gorczyca, W., J.P. Gong, and Z. Darzynkiewicz. 1993. Detection of DNA strand breaks in individual apoptotic cells by the in situ terminal deoxynucleotidyl transferase and nick translation assays. *Cancer Res.* 53(8):1945-1951.

Goto, T. and J.C. Wang. 1985. Cloning of yeast TOP 1, the gene encoding DNA topoisomerase I, and construction of mutants defective in both DNA topoisomerase I and DNA topoisomerase II. *Proc. Natl. Acad. Sci. U.S.A.* 82:7178-7182.

Groeger, P.E. and C.R. Thomas. 1991. The role of DNA topoisomerase I and II in *Drosophila* Hsp70 heat-shock gene transcription. In *DNA topoisomerases in Cancer* (eds. by Potmesil, M. and K.W. Kohn), Pp. 52-64. Oxford University Press, New York, Oxford.

Gromova, I.I. 1992. Camptothecin inhibits both the cleavage and religation reactions of eukaryotic DNA topoisomerase I. *J. Mol. Biol.* 228(4):1025-.

Gromova, I.I., V.L. Bukhman, R.A. Abagyan, et al. 1990. Sequence dependent modulating effect of camptothecin on the DNA-cleaving activity of the calf thymus type I topoisomerase. *Nucleic Acids Res.* 18(3):637-645.

Gromova, I.I., V.L. Bukhman, K.A. Kafiani, et al. 1989. Camptothecin effect on DNA relaxation and DNA cleavage activity of calf thymus topoisomerase I. *Mol. Biol.* 23(2):379.

Gromova, I.I., E. Kjeldsen, J.Q. Svejstrup, et al. 1993. Characterization of an altered DNA catalysis of a camptothecin-resistant eukaryotic topoisomerase I. *Nucleic Acids Res.* 21(3):593-600.

Gupta, R.S., R. Gupta, B. Eng, et al. 1988. Camptothecin-resistant multants of Chinese hamster ovary cells containing a resistant form of topoisomerase I. *Cancer Res.* 48:6404-6410.

Habelson, H.T. and S. Penman. 1973. Introduction of alkali labile links in cellular DNA by camptothecin. *Biochem. Biophys. Res. Commun.* 50:1048-1054.

Halligan, B., J. Davis, K. Edwards, et al. 1982. Intra- and inter-molecular strand transfer by HaLa DNA topoisomerase I. *J. Biol. Chem.* 257:3995-4000.

Haseltine, W.A. and C.M. Farnet. 1992. Assays for factors that affect circularization and integration of DNA and purification and use of these factors. *PCT Int. Appl.* 124 pp.

Hawkins, M.J. 1992. New anticancer agents: taxol, camptothecin analogs, and anthrapyrazoles [Erratum appears in *Oncology* (Huntingt) 1993 March, 7(3):105]. *Oncology* (Huntingt) 6(12):17-23; discussion 27-30.

He, J.J., Y. Ren, and W.Y. Zhang. 1993. Studies on fluorescence property of camptothecin alkaloids by three dimensional synchronous fluorescence spectrophotometry. *Fenxi Huaxue* 21(8):900-904. (Chinese with English abstract).

Heckendorf, A.H. 1976. *The biosynthesis of camptothecin.* Dissertation of University of Connecticut, Storrs, Connecticut,

130 pp. Avail. Xerox Univ. Microfilms, Ann Arbor, Mich. Order No. 77-4274. Diss. Abstr. Int. B 1977, 37(9):4475-4476.

Heckendorf, A.H. and C.R. Hutchinson. 1977. Biosynthesis of camptothecin. II. Confirmation that isovincoside, not vincoside, is the penultimate biosynthetic precursor of indole alkaloids. *Tetrahedron Lett.* (48):4153-4154.

Hennequin, C., N. Giocanti, and J. Baloso. 1994. Interaction of ionizing radiation with the topoisomerase I poison camptothecin in growing V-79 and HeLa cells. *Cancer Res.* 54(7):1720-1728.

Hertzberg, R.P., M.J. Caranfa, and S.M. Hecht. 1989. On the mechanism of topoisomerase I inhibition by camptothecin: evidence for binding to an enzyme-DNA complex. *Biochemistry* 28:4629-4638.

Hertzberg, R.P., R.W. Busby, M.J. Caranfa, et al. 1990. Irreversible trapping of the DNA-topoisomerase I covalent complex. Affinity labeling of the camptothecin binding site. *J. Bio. Chem.* 265(31):19287-19295.

Hertzberg, R.P., M.J. Caranfa, K.G. Holden, et al. 1989. Modification of hydroxy lactone ring of camptothecin: inhibition of mammalian topoisomerase I and biological activity. *J. Med. Chem.* 32(3):715-720.

Hertzberg, R.P., M.J. Caranfa, W.D. Kingsbury, et al. 1991. The biochemistry of camptothecin-topoisomerase I interaction. In *DNA Topoisomerases Cancer* (eds. by Potmesil, M. and K.W. Kohn), Pp. 103-120. Oxford University Press, New York.

Hertzberg, R.P., K.G. Holden, S.M. Hecht, et al. 1987. Characterization of the structural features of camptothecin essential for topoisomerase I interaction and for induction for protein-linked DNA breaks in cells. *Proc. Am. Assoc. Cancer Res.* 28:27.

Hirabayashi, N., R. Kim, M. Nishiyama, et al. 1992. Tissue expression of topoisomerase I and II in digestive tract cancers and adjacent normal tissues. *Proc. Am. Assoc. Cancer Res.* 33:436.

Holm, C., J.M. Covey, D. Kerrigan, et al. 1989. Differential requirement of DNA replication for the cytotoxicity of DNA topoisomerase I and II inhibitors in Chinese hamster DC3F cells. *Cancer Res.* 49(22):6365-6368.

Horwitz, M.S. and C. Brayton. 1972. Camptothecin. Mechanism of inhibition of adenovirus formation. *Virology* 48(3):690-698.

Horwitz, M.S. and S.B. Horwitz. 1971. Intracellulardegradation of HaLa and adenovirus type 2 DNA induced by camptothecin. *Biochem. Biophys. Res. Commun.* 45:723-727.

Horwitz, S.B. 1974. Novel inhibitors of RNA synthesis. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* 33(11):2281-2287.

Horwitz, S.B. and M.S. Horwitz. 1973. Effects of camptothecin on the breakage and repair of DNA during the cell cycle. *Cancer Res.* 33:2834-2836.

Horwitz, S.B., C. Chang, and A.P. Grollman. 1971. Studies on camptothecin: I. Effects on nucleic acid and protein synthesis. *Mol. Pharm.* 7(6):632-644.

Hsiang, Y.H. and L.F. Liu. 1988. Identification of mammalian DNA topoisomerase I as an intracellular target of the anticancer drug camptothecin. *Cancer Res.* 48:1722-1726.

Hsiang, Y.H., M.G. Lihou, and L.F. Liu. 1989. Arrest of replication forks by drug-stabilized topoisomerase I-DNA cleavable complexes as a mechanism of cell killing by camptothecin. *Cancer Res.* 49(18):5077-5082.

Hsiang, Y.H., H.Y. Wu, and L. Liu. 1988. Proliferation-dependent regulation of DNA topoisomerase II in cultured human cells. *Cancer Res.* 48:3230-3235.

Hsiang, Y.H., R. Hertzberg, S. Hecht, et al. 1985. Camptothecin induces protein-linked DNA breaks via mammalian DNA topoisomerase I. *J. Biol. Chem.* 260:14873-14878.

Hsiang, Y.H., L.F. Liu, M.E. Wall, et al. 1989. DNA topoisomerase I-mediated DNA cleavage and cytotoxicity of camptothecin analogues. *Cancer Res.* 49(16):4385-4389.

Hu, C.J., X.Y. Zhou, X.Q. Gu, et al. 1991. Pharmacokinetics of polyphase liposome of procamptothecin. *Shenyang Yaoxueyuan Xuebao* 8(1):4-8. (Chinese with English abstract).

Huang, C., C.S. Han, X.F. Yue et al. 1983. Cytotoxicity and sister chromatid exchanges induced *in vitro* by six anticancer drugs developed in the People's Republic of China. *J. Natl. Cancer Inst.* 71:841-847.

Hutchinson, C. R. 1981. Camptothecin: Chemistry, biogenesis and medicinal chemistry. *Tetrahedron* 37:1047-1065.

Hutchinson, C.R., A.H. Heckendorf, J.L. Straughn, et al. 1979. Biosynthesis of camptothecin. 3. Definition of strictosamide as the penultimate biosynthetic precursor assisted by carbon-13 and deuterium NMR spectroscopy. *J. Am. Chem. Soc.* 101(12):3358-3369.

Hwang, B.D., S.J. Oh, G.R. Kweon, et al. 1992. Comparative studies on the DNA topoisomerase I from normal and cancer tissue of human colon. *Kor. J. Biochem.* 24(1):53-62.

Hwang, J.L., S.H. Shyy, A.Y. Chen, et al. 1989. Studies of topoisomerase-specific antitumor drugs in human lymphocytes using rabbit antisera against recombinant human topoisomerase II polypeptide. *Cancer Res.* 49:958-962.

Imamura, N., Y. Kusunoki, C. Kohchi, et al. 1987. Mechanism of camptothecin resistance-decreased uptake of SN-38 by resistant cell lines, CPT-T 4-9 and CPT-K 5. *Igaku no Ayumi* 143(9):721-722. (Japanese with English abstract).

Inaba, M., J. Mitsuhashi, S. Kawada, et al. 1994. Different modes of cell-killing action between DNA topoisomerase I and II inhibitors revealed by kinetic analysis. *Jpn. J. Cancer Res.* 85(2):187-193.

Ishimi, Y., M. Nishizawa, T. Andoh, et al. 1991. Characterization of a camptothecin-resistant human DNA topoisomerase I in an *in vitro* system for Simian virus 40 DNA replication. *Eur. J. Biochem.* 202(3):835-839.

Isoe, T., M. Naito, R. Hirai, et al. 1991. Inhibition of ubiquitin-ATP-dependent proteolysis and ubiquitination by cisplatin. *Anticancer Res.* 11(5):1905-1909.

Jaxel, C. K.W. Kohn, M.C. Wani, et al. 1989. Structure-activity study of the actions of camptothecin derivatives on mammalian topoisomerase I: evidence for a specific receptor site and a relation to antitumor activity. *Cancer Res.* 49:1465-1469.

Jaxel, C., G. Carpanico, D. Kerrigan, et al. 1991. Effect of local DNA sequence on topoisomerase I cleavage in the presence or absence of camptothecin. *J. Biol. Chem.* 266:20418-20423.

Johnson, R.K. 1993. Camptothecin analogs and platinum coordination compounds as synergistic neoplasm inhibitors. *PCT Int. Appl.* 15 pp.

Jonstra-Bilen, J., M.E. Ittel, C. Niedergang, et al. 1983. DNA topoisomerase I from calf thymus is inhibited *in vitro* by poly (ADP-ribosylation). *Eur. J. Biochem.* 136:391-396.

Juan, C., J. Hwang, A. Liu, et al. 1988. Human DNA topoisomerase I is encoded by a single-copy gene that maps to chromosome region 20q12-13.2. *Proc. Natl. Acad. Sci. U.S.A.* 85:8910-8913.

Kagel., J.R., V. Stella, and C.M. Riley. 1993. A liquid chromatographic method for the determination of the enantiomeric purity of the anticancer drug, 9-amino-20(S)-camptothecin. *J. Pharm. Biomed. Anal.* 11(9):793-802.

Knab, A.M., et al. 1993. Mechanisms of camptothecin resistance in yeast DNA topoisomerase I mutants. *Biol. Chem.* 268:22322-22330.

Kaneda, N. and T. Yokokura. 1990. Nonlinear pharmacokinetics of CPT-11 in rats. *Cancer Res.* 50(6):1721-1725.

Kaneda, N., H. Nagata, T. Furuta, et al. 1990. Metabolism and pharmacokinetics of the camptothecin analogue CPT-11 in the mouse [Erratum appears in Cancer Res. 1990 July 15, 50(14):4451]. *Cancer Res.* 50(6):1715-1720.

Kanzawa, F., Y. Sugimoto, K. Minato, et al. 1990. Establishment of a camptothecin analogue (CPT-11)-resistant cell line of human non-small cell lung cancer. *Cancer Res.* 50(18):5919-5924.

Kasid, U., B. Olivera, L.F. Liu, et al. 1989. Poly (ADP-ribose)-mediated post-translational modification of chromatin-associated human topoisomerase I. Inhibitory effects on catalytic activity. *J. Biol. Chem.* 264:18687-18692.

Kaufmann, S.H. 1989. Induction of endonucleolytic DNA cleavage in human acute myelogenous leukemia cells by etoposide, camptothecin, and other cytotoxic anticancer drugs. A cautionary note. *Cancer Res.* 49:5870-5878.

Kaufmann, S.H. 1991. Antagonism between camptothecin and topoisomerase II-directed chemotherapeutic agents in a human leukemia cell line. *Cancer Res.* 51:1129-1136.

Kaufmann, S.H., S. McLaughlin, M. Kastan, et al. 1991. Topoisomerase II levels during granulocytic maturation *in vitro* and *in vivo*. *Cancer Res.* 51:3534-3543.

Kaufmann, W.K., J. Boyer, and L.L. Estabrooks. 1991. Inhibition of replication initiation in human cells following stabilization of topoisomerase-DNA cleavable complexes. *Mol. Cell. Biol.* 11(7):3711-3718.

Kerrigan, D. and Y. Pommier. 1990. Protein kinase C activity influences camptothecin-mediated DNA strand breaks and cytotoxicity in DC3F/9-OHE, Chinese hamster cells resistant to topoisomerase II inhibitors. *Proc. Am. Assoc. Cancer Res.* 31:437.

Kessel, D. 1971a. Effects of camptothecin on RNA synthesis in leukemia L1210 cells. *Biochim. Biophys. Acta* 246:225-232.

Kessel, D. 1971b. Some determinants of camptothecin responsiveness in leukemia L1210 cells. *Cancer Res.* 31(12):1883-1887.

Kessel, D. and R. Dysard. 1973. Effects of camptothecin on RNA synthesis in L1210 cells. *Biochim. Biophys. Acta* 312(4);716-721.

Kessel, D., H.B. Bosmann, and K. Lohr. 1972. Camptothecin effects on DNA synthesis in murine leukemia cells. *Biochim. Biophys. Acta* 246:225-232.

Kharbanda, S., E. Rubin, H. Gunji, et al. 1991. Camptothecin and its derivatives induce expression of the c-jun protooncogene in human myeloid leukemia cells. *Cancer Res.* 51:6636-6642.

Kieber, J.J., M.F. Lopez, A.F. Tissier, et al. 1992. Purification and properties of DNA topoisomerase I from broccoli. *Plant Mol. Biol.* 18(5):865-871.

Kihlman, B.A. and H.C. Andersson. 1992. Enhancement and reduction by methylated oxypurines of the frequencies of chromatid aberrations induced by camptothecin in root-tip cells of *Vicia faba*. *Mutat. Res.* 269(2):259-267.

Kim, R. and J.C. Wang. 1989. A subthreshold level of DNA topoisomerases leads to the excision of yeast rDNA as extrachromosomal rings. *Cell* 57:975-985.

Kim, R., N. Hirabayashi, M. Nishiyama, et al. 1992. Experimental studies on biochemical modulation targeting topoisomerase I and II in human tumor xenografts in nude mice. *Int. J. Cancer* 50:760-766.

Kirkegaard, K. and J.C. Wang. 1985. Bacterial DNA topoisomerase I can relax positively supercoiled DNA containing a single-stranded loop. *J. Mol. Biol.* 185:625-637.

Kjeldsen, E., S. Mollerup, B. Thomsen, et al. 1988. Sequence-dependent effect of camptothecin on human topoisomerase I DNA cleavage. *J. Mol. Biol.* 202(2):333-342.

Kjeldsen, E., B.J. Bonven, T. Andoh, et al. 1988. Characterization of a camptothecin-resistant human DNA topoisomerase I. *J. Biol. Chem.* 263(8):3912-3916.

Kjeldsen, E., C. Bendixen, B. Thomsen, et al. 1991. The influence of camptothecin on topoisomerase I interaction with genomic sequences. In *DNA Topoisomerases Cancer* (eds. by Potmesil, M. and K.W. Kohn), Pp. 148-160. Oxford University Press, New York.

Kjeldsen, E., J.Q. Svejstrup, I.I. Gromova, et al. 1992. Camptothecin inhibits both the cleavage and religation reactions of eukaryotic DNA topoisomerase I. *J. Mol. Biol.* 228(4):1025-1030.

Knab, A.M., J. Fertala, and M.A. Bjornsti. 1993. Mechanisms of camptothecin resistance in yeast DNA topoisomerase I mutants. *J. Biol. Chem.* 268(30):22322-22330.

Kohn, K.W. 1979. DNA as a target in cancer chemotherapy: measurements of macromolecular DNA damage produced in

mammalian cells by anticancer agents and carcinogens. *Meth. Cancer Res.* 16:291-345.

Kotoh, S., S. Naito, A. Yokomizo, et al. 1994. Increased expression of DNA topoisomerase I gene and collateral sensitivity to camptothecin in human cisplatin-resistant bladder cancer cells. *Cancer Res.* 54(12):3248-.

Kovacic, P., J.R. Ames, J.W. Grogan, et al. 1988. Anticancer quinones and quinolines: mode of action via electron transfer and oxidative stress. *Redox Chem. Interfacial Behav. Biol. Mol., (Proc. Int. Symp. Redox Mech. Interfacial Prop. Mol. Biol. Importance*, eds. by G. Dryhurst and K. Niki), Pp. 295-307. New York.

Kowalska-Loth, B., K. Staron, I. Buraczewska, et al. 1993. Reduced sensitivity to camptothecin of topoisomerase I from a L5178Y mouse lymphoma subline sensitive to X-radiation. *Biochim. Biophys. Acta* 1172(1/2):117-123.

Krupitza, G. and P. Gerutti. 1989. ADP-ribosylation of ADPR-transferase and topoisomerase I in intact mouse epidermal cells JB16. *Biochemistry* 28:2034-2040.

Kubota, N., et al. 1992. Detection of topoisomerase I gene point mutation in CPT-11 resistant lung cancer cell line. *Biochem. Biophys. Res. Commun.* 188(2):571-577.

Kuhn, J., H. Burris, J. Wall, et al. 1990. Pharmacokinetics of the topoisomerase I inhibitor, SK & F 104864. *Proc. Am. Soc. Clin. Oncol.* 9:70.

Kuhn, J., H. Burris, R. Irvin, et al. 1992. Pharmacokinetics of topotecan following a 30 min infusion or 3 days continuous infusion. In *Proceedings of NCI-EORTC Symposium on New Drugs in Cancer Therapy*, Amsterdam.

Kusumoto, I.T., M. Hattori, Y. Miyaichi, et al. 1991. Effects of flavonoids and alkaloids on reverse transcriptase. *Shoyakugaku Zasshi* 45(3):240-254. (Japanese with English abstract).

Kuwahara, J., T. Suzuki, and Y. Sugiura. 1985. Studies on antitumor drugs targeting DNA: photosensitive DNA cleavage of copper-camptothecin. *Nucleic Acids Symposium Ser.* 16 (*Symp. Nucleic Acids Chem., 13 th*), 201-204.

Kuwahara, J., T. Suzuki, K. Funakoshi, et al. 1986. Photosensitive DNA cleavage and phase inactivation by copper(II)-camptothecin. *Biochemistry* 25(6):1216-1221.

Lau, C. and A. Pardee. 1982. Mechanism by which caffeine potentiates lethality of nitrogen mustard. *Proc. Natl. Acad. Sci. U.S.A.* 79:2942-2946.

Lee, J.B., G.R. Kweon, K. Lim, et al. 1992. Studies on DNA topoisomerase I from human term placenta. *Han'guk Saenghwa Hakhoechi* 25(4):300-309. (Korean with English abstract).

Leteutre, F., M. Fesen, G. Kohlhagen, et al. 1993. Specific interaction of camptothecin, a topoisomerase I inhibitor, with guanine residues of DNA detected by photoactivation at 365 nm. *Biochemistry* 32:8955-8962.

Levin, N.A., M.A. Bjornsti, and G.R. Fink. 1993. A novel mutation in DNA topoisomerase I of yeast cause DNA damage and RAD9-dependent cell cycle arrest. *Genetics* 108(3):799-814.

Li, C.J., L. Averboukh, and A.B. Pardee. 1993. β-Lapachone, a novel DNA topoisomerase I inhibitor with a mode of action different from camptothecin. *J. Biol. Chem.* 268(30):22463-22468.

Li, L.H., T.J. Fraser, E.J. Olin, et al. 1972. Action of camptothecin on mammalian cells in culture. *Cancer Res.* 32(12):2643-2650.

Lim, M., L.F. Liu, D. Jacobson-Kram, et al. 1986. Induction of sister chromatid exchanges by inhibitors of topoisomerases. *Cell Biol. Toxicol.* 2(4):485-494.

Ling, Y.H., B.S. Andersson, and J.A. Nelson. 1990. DNA topoisomerase I as a site of action for 10-hydroxycamptothecin in human promyelocytic leukemia cells. *Cancer Biochem. Biophys.* 11(1):23-30.

Ling, Y.H., C.Y. Shen, and Q.L. Shi. 1987. Effects of four antitumor agents on DNA circular dichroism. *Zhongguo Yaoli Xuebao* 8(4):374-377. (Chinese with English abstract).

Ling, Y.H., M.T. Tseng, and J.A. Nelson. 1991. Differentiation induction of human promyelocytic leukemia cells by 10-hydroxycamptothecin, a DNA topoisomerase I inhibitor. *Differentiation* 46:135-141.

Ling, Y.H., W.J. Yu, and B. Xu. 1984. Effects of 10-hydroxycamptothecin on nuclear RNA polymerase activity in hepatomacells in mice. *Zhongguo Yaoli Xuebao* 5(3):211-214. (Chinese with English abstract).

Ling, Y.H., L.S. Zhao, and B. Xu. 1986. Effects of 10-hydroxycamptothecin on chromatin protein synthesis in murine hepatoma cells. *Zhongguo Yaoli Xuebao* 7(3):285-288. (Chinese with English abstract).

Ling, Y.H., et al. 1993. Effect of DNA topoisomerase I inhibitor, 10-hydroxycamptothecin, on the structure and function of nuclei and nuclear matrix in bladder carcinoma MBT-2 cells. *Anticancer Res.* 13(5A):1613-1617.

Liu, L.F. 1989. DNA topoisomerase poisons as anti-tumor drugs. *Ann. Rev. Biochem.* 58:351-375.

Liu, L.F. and P. D'Arapa. 1992. Topoisomerase targeting antitumor drugs: Mechanisms of cytotoxicity and resistance. *Important Advances Oncol.* 79-89.

Liu, L.F. and K.G. Miller. 1981. Eukaryotic DNA topoisomerases: two forms of type I DNA topoisomerases from HeLa cell nuclei. *Proc. Natl. Acad. Sci. U.S.A.* 78:3487-3491.

Liu, L.F. and J.C. Wang. 1987. Supercoiling of the DNA template during RNA transcription. *Proc. Natl. Acad. Sci. U.S.A.* 84:7024-7027.

Liu, L.F. and J.C. Wang. 1991. Biochemistry of DNA topoisomerases and their poisons. In *DNA topoisomerases in cancer* (eds. by Potmesil, M. and K.W. Kohn), Pp. 13-22. Oxford University Press, New York, Oxford.

Liu, L.F., R.E. Depew, and J.C. Wang. 1976. Knotted single-stranded DNA rings: A novel topological isomer of single-stranded circular DNA formed by *E. coli* omega protein treatment. *J. Mol. Biol.* 106:439-452.

Liversidge, G.G., E. Liversidge, and P. Sarpotdar. 1994. Surface-modified anticancer nanoparticles. *Eur. Pat. Appl.* 15 pp.

Lock, R. 1992. Inhibition of P34cdc2 kinase activation, p34cdc2 dephosphorylation, and mitotic progression in Chinese hamster ovary cells exposed to etoposide. *Cancer Res.* 52:1817-1822.

Lock, R. and W. Ross. 1990. Inhibition of p34cdc2 kinase activity by etoposide or irradiation as a mechanism of G2 arrest in Chinese hamster ovary cells. *Cancer Res.* 50:3761-3766.

Lown, J.W. and H.H. Chen. 1980. Studies related to antitumor antibiotics. XIX. Studies on the effects of the antitumor agent camptothecin and derivatives on deoxyribonucleic acid. Mechanism of the scission of deoxyribonucleic acid by photoactivated camptothecin. *Biochem. Pharmacol.* 29(6):905-915.

Lown, J.W., H.H. Chen, and J.A. Plambeck. 1981. Effects of the antitumor agent camptothecin and derivatives on DNA camptothecin potentiated cleavage of DNA by bleomycin in-vitro. *Chem. Biol. Interact* 35(1):55-70.

Luethy, J.D. and N.J. Holbrook. 1992. Activation of the gadd153 promoter by genotoxic agents: a rapid and specific response to DNA damage. *Cancer Res.* 52(1):5-10.

Luo, J.D., Z.Q. Ma, and X.Q. Gu. 1984. Studies on polyphase liposome of camptothecin, PL-CSA. *Yaoxue Xuebao* 19(1):63-68. (Chinese with English abstract).

Madden, K.R. and J. Champoux. 1992. Overexpression of human topoisomerase I in baby hamster kidney cells: Hypersensitivity of colonal isolates to camptothecin. *Cancer Res.* 52:525-532.

Madelaine, I., S. Prost, A. Naudin, et al. 1993. Sequential modifications of topoisomerase I activity in a camptothecin-resistant cell line established by progressive adaptation. *Biochem. Pharmacol.* 45(2):339-348.

Matsumoto, Y., T. Fujiwara, Y. Honjo, et al. 1993. Quantitative analysis of DNA topoisomerase I activity in human and rat glioma: characterization and mechanism of resistance to antitopoisomerase chemical, camptothecin-11. *J. Surg. Oncol.* 53(2):97-103.

Mattern, M.R., S.M. Mong, H.F. Bartus, et al. 1987. Relationship between the intracellular effects of camptothecin and the inhibition of DNA topoisomerase I in cultural L1210 cells. *Cancer Res.* 47:1793-1798.

Mattern, M.R., K.B. Tan, J.P. Zimmerman, et al. 1989. Evidence for the participation of topoisomerase I and II in cadmium-induced metallothionein expression in Chinese hamster ovary cells. *Anticancer Drug Des.* 4(2):107-124.

Mattern, M.R., S. Mong, S.M. Mong, et al. 1990. Transient activation of topoisomerase I in leukotriene D4 signal transduction in human cells. *Biochem. J.* 265:101-107.

Mattern, M.R., G.A. Hofmann, F.L. McCabe, et al. 1991. Synergistic cell killing by ionizing radiation and topoisomerase I inhibitor topotecan (SK & F 104864). *Cancer Res.* 51:5813-5816.

Maxwell, A. and M. Gellert. 1986. Mechanistic aspects of DNA topoisomerases. *Adv. Protein Chem.* 38:69-107.

McCoubrey, W.K., Jr. and J.J. Champoux. 1986. The role of single-strand breaks in the catenation reaction catalyzed by the rat type I topoisomerase. *J. Biol. Chem.* 261:1081-1083.

McHugh, M.M., R.D. Sigmund, T.A. Beerman, et al. 1990. Effects of minor groove binding drugs on camptothecin-induced DNA lesions in L1210 nuclei. *Biochem. Pharmacol.* 39(4):707-.

Mi, Z.H. and T.G. Burke. 1994. Differential Interactions of camptothecin lactone and carboxylate forms with human blood components. *Biochemistry* 33(34):10325.

Mirabell, C.K., F.H. Drake, K.B. Tan, et al. 1991. Topoisomerase heterogeneity: implications for the discovery of novel antitumor

drugs. In *DNA topoisomerases in Cancer* (eds. by Potmesil, M. and K.W. Kohn), Pp. 133-147. Oxford University Press, New York, Oxford.

Morais, R. 1977. Protein content and enzyme levels of cultured chick embryo cells treated with camptothecin and actinomycin D. *Can. J. Biochem.* 55(11):1180-1185.

Morham, S.G. and S. Shuman. 1992. Covalent and noncovalent DNA binding by mutants of vaccinia DNA topoisomerase I. *J. Biol. Chem.* 267(22):15984-15992.

Motta, S., C. Grazioso, M.C. Pisano, et al. 1993. Effects of antitopoisomerase drugs on chromosome recombination and segregation in grasshopper. In *Chromosome Segregation and Aneuploidy (Proceedings of the NATO advanced research workshop on chromosome segregation and aneuploidy*, October 10-15, 1992, Aghia Pelagia, Greece, ed. by B.K. Vig), Pp. 321-336.

Muggia, F.M. and P.S. Gill. 1991. Implications of topoisomerase mechanisms in the therapy of hematologic neoplasms. In *DNA topoisomerases in Cancer* (eds. by Potmesil, M. and K.W. Kohn), Pp. 312-318. Oxford University Press, New York, Oxford.

Mukherjee, S.K., M.K. Reddy, D. Kumar, et al. 1994. Purification and characterization of a eukaryotic type 1 topoisomerase from pea chloroplast. *J. Biol. Chem.* 269(5):3793-3801.

Musk, S.R. and G. Steel. 1990. The inhibition of cellular recovery in human tumor cells by inhibitors of topoisomerase. *Br. J. Cancer* 62:364-367.

Nakaya, K., et al. 1991. Topoisomerase inhibitors have potent differentiation-inducing activity for human and mouse myeloid leukemia cells. *Jpn. J. Cancer Res.* 82(2):184-191. (Japanese with English abstract).

Nambi, P. M. Mattern, J.O. Bartus, et al. 1989. Stimulation of intracellular topoisomerase I activity by vasopressin and thrombin. Differential regulation by pertussis toxin. *Biochem. J.* 262:485-489.

Neale, J.H., P.D. Klinger, and B.W. Agranoff. 1973. Camptothecin blocks memory of conditioned avoidance in the goldfish. *Science* 179(4079):1243-1246.

Nelson, W.G. and M.B. Kastan. 1994. DNA strand breaks: the DNA template alterations that trigger p53-dependent DNA damage response pathways. *Mol. Cell. Biol.* 14(3):1815-1823.

Nimi, S. K. Nakagawa, Y. Sugimoto, et al. 1992. Mechanism of cross-resistance to a camptothecin analogue (CPT-11) in a

human ovarian cancer cell line selected by cisplatin. *Cancer Res.* 50:5919-5924.

Nitiss, J. and J.C. Wang. 1988. DNA topoisomerase-targeting antitumor drugs can be studied in yeast. *Proc. Natl. Acad. Sci. U.S.A.* 85:7501-7505.

O'Connor, P.M., D. Kerrigan, R. Bertrand, et al. 1990. 10,11-Methylenedioxycamptothecin, a topoisomerase I inhibitor of increased potency: DNA damage and correlation to cytotoxicity in human colon carcinoma (HT-29) cells. *Cancer Commun.* 2(12):395-400.

O'Connor, P.M., W. Nieves-Neira, D. Kerrigan, et al. 1991. S-shape population analysis does not correlate with the cytotoxicity of camptothecin and 10,11-methylenedioxycamptothecin in human colon carcinoma HT-29 cells. *Cancer Commun.* 3:233-240.

O'Connor, P.M., D. Perris, G. White, et al. 1992. Relationships between cdc2 kinase, DNA cross-linking, and cell cycle perturbations induced by nitrogen mustard. *Cell growth Differ.* 3:43-52.

Oda, T., Y. Sato, M. Koshihiro, et al. 1993. Inhibition of DNA topoisomerase I activity by diethylstilbestrol and its analogs. *Biol. Pharm. Bull.* 16(7):708-710.

Okada, K. and T. Andoh. 1991. Separation of camptothecin-resistant mutant. *Tanpakushitsu Kakusan Koso* 36(13):2155-2157. (Japanese with English abstract).

Okada, K., et al. 1991. Mechanisms of acquired resistance to DNA topoisomerase I inhibitors. *Gan To Kagaku Ryoho* 18(10):1562-1567. (Japanese with English abstract).

Oomori, S., Y. Kanakubo, R. Atsumi, et al. 1991. Effects of camptothecin analog CPT-11 on the activities of drug metabolizing enzymes in liver microsomes of rats. *Yakubutsu Dotai* 6(2):185-190. (Japanese with English abstract).

Orengo, G., E. Noviello, G. Cimoli, et al. 1992. Potentiation of topoisomerase I and II inhibitors cell killing by tumor necrosis factor: relationship to DNA strand breakage formation. *Jpn. J. Cancer Res.* 83(11):1132-1136.

Osheroff, N. 1989. Biochemical basis for the interactions of type I and type II topoisomerases with DNA. *Pharmacol. Ther.* 41:223-241.

Palitti, F. 1993. Mechanism of induction of chromsomal aberrations by inhibitors of DNA topoisomerases. *Environ. Mol. Mutagen.* 22(4):275-277.

Palitti, F., F. Cortes, L. Bassi, et al. 1993. Higher G2 sensitivity to the induction of chromosomal damage in the CHO mutant EM9 than in its parental line AA8 by camptothecin, an inhibitor of DNA topoisomerase I. *Mutat. Res.* 285(2):281-285.

Pezzuto, J.M., C.T. Che, D.D. McPherson, et al. 1991. DNA as an affinity probe useful in the detection and isolation of biologically active natural products. *J. Nat. Prod.* 54(6):1522-1530.

Poddevin, B., J.F. Riou, F. Lavelle, et al. 1992. Dual topoisomerase I and II inhibition by RP 60475, an intercalating agent in early clinical trials. *Proc. Am. Assoc. Cancer Res.* 33:437.

Poehland, B.L., N. Troupe, B.K. Carte, et al. 1989. Reversed-phase high-performance liquid chromatographic assay for camptothecin and related alkaloids. *J. Chromatogr.* 481:421-427.

Pommier, Y., C. Jaxel, J.M. Covey, et al. 1988. Structure-activity study of the relation between topoisomerase I inhibition and antitumor activity of camptothecin. *Proc. Am. Assoc. Cancer Res.* 29:1080.

Pommier, Y., C. Jaxel, C.R. Heise, et al. 1991. Structure-activity relationship of topoisomerase I inhibition by camptothecin derivatives: evidence for the existence of a ternary complex. In *DNA Topoisomerases Cancer* (eds. by Potmesil, M. and K.W. Kohn), Pp. 121-132. Oxford University Press, New York.

Pommier, Y., D. Kerrigan, K.D. Hartmsn, et al. 1990. Phosphorylation of mammalian DNA topoisomerase I and activation by protein kinase C. *J. Biol. Chem.* 265(16):9418-9422.

Pommier, Y., K.W. Kohn, G. Capranico, et al. 1993. Base sequence selectivity of topoisomerase inhibitors suggests a common model for drug action. In *Molecular biology of DNA topoisomerase and its application to chemotherapy* (eds. by T. Andoh, H. Ikeda, and M. Oguro), Pp. 215-227. CRC Press, Boca Raton, Florida.

Popanda, O. and H.W. Thielmann. 1992. The function of DNA topoisomerases in UV-induced DNA excision repair: studies with specific inhibitors in permeabilized human fibroblasts. *Carcinogenesis* (London) 13(12):2321-2328.

Porter, S.E. and J. Champoux. 1989. The basis for camptothecin enhancement of DNA breakage by eukaryotic topoisomerase I. *Nucleic Acids Res.* 17:8521-8532.

Porter, S.E. 1990. Use of the drug camptothecin *in vitro* and *in vivo* to study the mechanism and specificity of the eukaryotic type I topoisomerase. *Dissertation of University of Washington.* 123

pp. Available from University Microfilms Int., Order No. DA9104287. Diss. Abstr. Int. B. 1991, 51(9):4180-4181.

Potmesil, M., B.C. Giovanella, L.F. Liu, et al. 1991. Preclinical studies of DNA topoisomerase I-targeted 9-amino and 10,10-methylenedioxy camptothecins. In *DNA Topoisomerases Cancer* (eds. by Potmesil, M. and K.W. Kohn), Pp. 299-311. Oxford University Press, New York.

Potmesil, M., Y.H. Hsiang, L.F. Liu, et al. 1988a. Topoisomerase I (topo I) and topoisomerase II (top II) levels in high and low grade lymphomas. *Proc. Am. Assoc. Cancer Res.* 29:176.

Potmesil, M., Y.H. Hsiang, L.F. Liu, et al. 1988b. Resistance of human leukemic and normal lymphocytes to drug-induced DNA cleavage and low levels of DNA topoisomerase II. *Cancer Res.* 48(12):3537-3543.

Prell, B. and H.P. Vosberg. 1980. Analysis of covalent complexes formed between calf thymus DNA topoisomerase and single-stranded DNA. *Eur. J. Biochem.* 108:389-398.

Rajalakshmi, S. and D.S.R. Sarma. 1973. Rapid repair of hepatic DNA damage induced by camptothecin in the intact rat. *Biochem. Biophys. Res. Commun.* 53(4):1268-1272.

Raju, U., et al. 1991. Alteration of the phase and period of a circadian oscillator by a reversible transcription inhibitor. *Science* 253(5020):673-675.

Raisz, L.G., C.L. Trummel, and H. Simmons. 1972. Induction of bone resorption in tissue culture: Prolonged response after brief exposure to parathyroid hormone or 25-hydrocholecalciferol. *Endocrinology* 90(3):744-751.

Recher, L., H. Chan, L. Briggs, et al. 1972. Ultrastructural changes inducible with the plant alkaloid camptothecin. *Cancer Res.* 32(11):2495-2501.

Riou, J.F., L. Grondard, O. Pettigenet, et al. 1993. Altered topoisomerase I activity and recombination activating gene expression in a human leukemia cell line resistant to doxorubican. *Biochem. Pharmacol.* 46(5):851-861.

Riou, J.F., P. Helissey, L. Grondard, et al. 1991. Inhibition of eukaryotic DNA topoisomerase I and II activities by indoloquinolinedione derivatives. *Mol. Pharmacol.* 40:699-706.

Rowe, T.C., et al. 1987. Camptothecin inhibits hsp 70 heat-shock transcription and induces DNA strand breaks in hsp 70 genes in *Drosophila*. *NCI monogr.* 1987(4):49-53.

Rubin, Eric, P. Pantazis, and A. Bharti. 1994. Identification of a mutant human topoisomerase I with intact catalytic activity and

resistance to 9-nitro-camptothecin. *J. Biol. Chem.* 269(4):2433-2439.

Rukenstein, A., R.E. Rydel, and L.A. Greene. 1991. Multiple agents rescue PC12 cells from serum-free cell death by translation- and transcription-independent mechanisms. *J. Neurosci.* 11(8):2552-2563.

Ryan, A.J., S. Squires, H.L. Strutt, et al. 1991. Camptothecin cytotoxicity in mammalian cells is associated with the induction of persistent double strand breaks in replicating DNA. *Nucleic Acids Res.* 19(12):3295-3300.

Ryan, A.J., S. Squires, and H.L. Strutt. 1994. Different fates of camptothecin-induced replication fork-associated double-strand DNA breaks in mammalian cells. *Carcinogenesis* 15(5):823.

Saijo, M., T. Enomoto, F. Hanaoka, et al. 1990. Purification and characterization of type II DNA topoisomerase from mouse FM3A cells: phosphorylation of topoisomerase II and modification of its activity. *Biochemistry* 29(2):583-590.

Satoh, M. and T. Lindahl. 1992. Role of poly(ADP-ribose) formation in DNA repair. *Nature* 356:356-358.

Sausville, E.A. 1979. *Camptothecin, neocarzinostatin, and bleomycin: effects of DNA and DNA synthesis.* Dissertation of Yeshiva University, New York, N.Y., 277 pp. Avail. Univ. Microfilms Int., Order No. 7905577. Diss. Abstr. Int. B 1979, 39(9):4302.

Sausville, E.A. and S.B. Horwitz. 1979. Inhibition of SV40 DNA synthesis by camptothecin and neocarzinostatin. *Mol. Pharmacol.* 14(6):1156-1166.

Scanlon, K.J., L. Jiao, T. Funato, et al. 1991. Ribozyme-mediated cleavage of c-fos mRNA reduces gene expression of DNA synthesis enzymes and metallothionein. *Proc. Natl. Acad. Sci. U.S.A.* 88(23):10591-10595.

Schaack, J., et al. 1990. Transcription of adenovirus and HeLa cell genes in the presence of drugs that inhibit topoisomerase I and II function. *Nucleic Acids Res.* 18(6):1499-1508.

Schaeppi, U., D.A. Conney, and R.D. Davis. 1967. *Toxic effects of treatment with camptothecin sodium salt* (NSC-100880). U.S. Clearinghouse Fed. Sci. Tech. Inform., PB Rep. PB-180549, 13 pp. Avail. CFSTI. U.S. Govt. Res. Develop. Rep. 1969, 69(4):54.

Schaeppi, U., H. Rosenkrantz, M.M. Mason, et al. 1968. *Toxic effects of the intravenous administration of camptothecin sodium salt (NSC-100880) in dogs and monkeys. Toxic effects of the intravenous and oral administration in mice.* U.S. Clearinghouse

Fed. Sci. Tech. Inform., PB Rep. PB-179993, 1358 pp. Avail. CFSTI. U.S. Govt. Res. Develop. Rep. 1969, 69(1):46-47.

Schaeppi, U., R.W. Fleischman, and D.A. Cooney. 1974. Toxicity of camptothecin (NSC-100880). *Cancer Chemother. Rep.* part 3 5(1):25-36.

Schneider, E., Y.H. Hsiang, and L. Liu. 1990. DNA topoisomerases as anticancer drug targets. *Adv. Pharnacol.* 21:149-183.

Scott, D.O., D.S. Bindra, and V.J. Stella. 1993. Plasma pharmacokinetics of the lactone and carboxylate forms of 20(S)-camptothecin in anesthetized rats. *Pharm. Res.* 10(10):1451-1457.

Scott, D.O., D.S. Bindra, and S.C. Sutton. 1994. Urinary and biliary disposition of the lactone and carboxylate forms of 20(S)-camptothecin in rats. *Drug Metab. Dispos.* 22(3):438.

Sekiguchi, J.A.M. and E.B. Kmiec. 1988. Studies on DNA topoisomerase activity during *in vitro* chromatin assembly. *Mol. Cell. Biochem.* 83(2):195-205.

Shamma, M. and V.S. Georgiev. 1974. Camptothecin. *J. Pharm. Sci.* 63(2):163-168.

Sheriha, G.M. and H. Rapoport. 1976. Biosynthesis of *Camptotheca acuminata* alkaloids. *Phytochemistry* 15(4):505-508.

Shimizu, T., M. Kubota, S. Adachi, et al. 1992. Pre-treatment of a human T-lymphoblastoid cell line with L-asparaginase reduces etoposide-induced DNA strand breakage and cytotoxicity. *Int. J. Cancer* 50(4):644-648.

Sitailo, L.A. 1991. Effect of antibiotics and antitumor agents on the relaxational activity of pea chloroplast DNA topoisomerase I. *Mol. Biol.* 25(3, part 1):509-516.

Slichenmyer, W.J., E.K. Rowinsky, R.C. Donehower, et al. 1993. The current status of camptothecin analogues as antitumor agents. *J. Natl. Cancer Inst.* 85(4):271-291.

Smith, P.J., T.A. Makison, and J.V. Watson. 1989. Enhanced sensitivity to camptothecin in ataxia-telangiectasia cells and its relationship with the expression of DNA topoisomerase I. *Int. J. Radiat. Biol.* 55(2):217-31.

Smith, P.J., P.G. Debenham, and J.V. Watson. 1989. A role of DNA topoisomerases in the active dissociation of DNA minor groove-ligand complexes. A flow cytometric study of inhibitor effects. *Mutat. Res.* 217(2):163-172.

Snapka, R.M. 1992. Gene amplification as a target for cancer chemotherapy. *Oncol. Res.* 4:145-150.

Snapka, R.M., et al. 1993. SV40 DNA replication intermediates: analysis of drugs which target mammalian DNA replication. *Bioessays.* 15(2):121-127.

Spataro, A.C. 1974. *Mechanism of inhibition of nucleic acid synthesis by camptothecin.* Dissertation of University of Rochester, Rochester, New York, 143 pp. Avail. Xerox Univ. Microfilms, Ann Arbor, Mich., Order No. 75-1318. Diss. Abstr. Int. B 1975, 35(7):3493-3494.

Spataro, A.C. and Kessel, D. 1972. Camptothecin-induced degradation and apparent reaggregation of DNA from L1210 cells. *Biochem. Biophys. Res. Commun.* 48(3):643-648.

Spataro, A.C. and Kessel, D. 1973. The effects of camptothecin on mammalian DNA. *Biochim. Biophys. Acta* 331:194-201.

Squiress, S., A.J. Ryan, H.L. Strutt, et al. 1991. Deoxyguanosine enhances the cytotoxicity of the topoisomerase I inhibitor camptothecin by reducing the repair of double-strand breaks induced in replicating DNA. [Erratum appears in *J. Cell Sci.* 1992 March 101 (Pt3):preceding table of contents]. *J. Cell Sci.* 100 (Part 4):883-893.

Squires, S., A.J. Ryan, H.L. Strutt, et al. 1993. Hypersensitivity of cockayne's syndrome cells to camptothecin is associated with the generation of abnormally high levels of double strand breaks in nascent DNA. *Cancer Res.* 53(9):2012-2019.

Spataro, A. and D. Kessel. 1973. The effects of camptothecin on mammalian DNA. *Biochim. Biophys. Acta* 331:194-201.

Stevnsner, T., et al. 1993. Studies on the role of topoisomerases in general, gen- and strand-specific DNA repair. *Carcinogenesis* 14(9):4613-4618.

Stewart, A.F. and G. Schutz. 1987. Camptothecin-induced *in vivo* topoisomerase I cleavages in the transcriptionally active tyrosine aminnotransferase gene. *Cell* 50:1109-1117.

Stewart, A.F., R.E. Herrera, and A. Nordheim. 1990. Rapid induction of c-fos transcription reveals quantitative linkage of RNA polymerase II and DNA topoisomerase I enzyme activities. *Cell* 60:141-149.

Sugimori, M., A. Ejima, S. Ohsuki, et al. 1994. Antitumor agents. VI. Synthesis and antitumor activity of ring A-, ring B-, and ring C-modified derivatives of camptothecin. *Heterocycles* 38(1):81-86.

Sugimoto, Y., S. Tskahara, T. Oh-hara, et al. 1990. Decreased expression of DNA topoisomerase I in camptothecin-resistant

tumor cell lines as determined by a monoclonal antibody. *Cancer Res.* 50(2):6925-6930.

Sugimoto, Y., S. Tsukahara, T. Ohhara, et al. 1990. Elevated expression of DNA topoisomerase II in camptothecin-resistant human tumor cell lines. *Cancer Res.* 50(24):7962-7965.

Sugiura, T., et al. 1992. DNA topoisomerase inhibitor. *Gan To Kagaku Ryoho* 19(13):2140-2145. (Japanese with English abstract).

Sullivan, D.M., L.A. Eskildsen, K.R. Groom, et al. 1993. Topoisomerase II activity involved in cleaving DNA into topological domains is altered in a multiple drug-resistant Chinese hamster ovary cell line. *Mol. Pharmacol.* 43(2):207-216.

Sumner, A.T. 1992. Inhibitors of topoisomerases do not block the passage of human lymphocyte chromosomes through mitosis. *J. Cell Sci.* 103(1):105-115.

Supko, J.G. and L. Malspeis. 1991. A reversed-phase HPLC method for determining camptothecin in plasma with specificity for the intact lactone form of the drug. *J. Liq. Chromat.* 14(9):1779-1803.

Suzuki, H. and S. Nakane. 1994. Differential induction of chromosomal aberrations by topoisomerase inhibitors in cultured Chinese hamster cells. *Biol. Pharm. Bull.* 17(2):222-226.

Svejstrup, J., K. Christiansen, I. Gromova, et al. 1991. New technique for uncoupling the cleavage and religation reactions of eukaryotic topoisomerase I. The mode of action of camptothecin at a specific recognition site. *J. Mol. Biol.* 222:669-678.

Tamura, H., C. Kohchi, R. Yamada, et al. 1991. Molecular cloning of a cDNA of a camptothecin-resistant human DNA topoisomerase I and identification of mutation sites. *Nucleic Acids Res.* 19(1):69-75.

Tan, K.B., M.R. Mattern, W.K. Eng, et al. 1989. Nonproductive rearrangement of DNA topoisomerase I and II genes: correlation with resistance to topoisomerase inhibitors. *J. Natl. Cancer Inst.* 81(22):1732-1735.

Tanizawa, A. and Y. Pommerier. 1992. Topoisomerase I alteration in a camptothecin-resistant cell line derived from Chinese hamster DC3F cells in culture. *Cancer Res.* 52:1848-1854.

Tanizawa, A., R. Bertrand, G. Kohlhagen, et al. 1993. Cloning of Chinese hamster DNA topoisomerase I cDNA and identification

of a single point mutation responsible for camptothecin resistance. *J. Biol. Chem.* 268(34):25463-25468.

Tanizawa, A., K.W. Kohn, and Y. Pommier. 1993. Induction of cleavage in topoisomerase I c-DNA by topoisomerase I enzymes from calf thymus and wheat germ in the presence and absence of camptothecin. *Nucleic Acids Res.* 21(22):5157-5166.

Taudou, G., C. Portemer, C. Jaxel, et al. 1993. Inhibition of DNA synthesis and DNA fragmentation in stimulated splenocytes by the concerted action of topoisomerase I and II poisons. *Biochem. Pharmacol.* 45(2):331-337.

Tewey, K., T. Rowe, T. Yang, et al. 1984. Adriamycin-induced DNA damage mediated by mammalian topoisomerase II. *Science* 226:760-766.

Thacker, J. and A.N. Ganesh. 1990. DNA-break repair, radioresistance of DNA synthesis, and camptothecin sensitivity in the radiation-sensitive irs mutants: comparisons to ataxia-telangiectasia cells. *Mutat. Res.* 235(2):49-58.

Thielmann, H.W., O. Popanda, H. Gersbach, et al. 1993. Various inhibitors of DNA topoisomerases diminish repair-specific DNA inclusion in UV-irradiated human fibroblasts. *Carcinogenesis* 14(11):2341-2351.

Thomsen, B., S. Mollerup, B.J. Bonven, et al. 1987. Sequence specificity of DNA topoisomerase I in the presence and absence of camptothecin. *EMBO J.* 6(6):1817-1823.

Tishler, R.B., S.K. Calderwood, C.N. Coleman, et al. 1993. Increase in sequence-specific DNA binding by p53 following treatment with chemotherapeutic and DNA damaging agents. *Cancer Res.* 53(10):2212-2216.

Tobey, R.A. 1972. Effects of cytosine, arabinoside, daunomycin, mithramycin, azacytidine, adriamycin, and camptothecin on mammalian cell cycle traverse. *Cancer Res.* 32:2720-2775.

Tobey, R.A. 1975. Different drugs arrest cells at a number of distinct stages in G2. *Nature* 254:245-247.

Traganos, F., J. Kapuscinski, J.P. Gong, et al. 1993. Caffeine prevents apoptosis and cell cycle effects induced by camptothecin or topotecan in HL-60 cells. *Cancer Res.* 53(19):4613-4618.

Trask, D.K. and M.T. Muller. 1988. Stabilization of type I topoisomerase-DNA covalent complexes by actinomycin D. *Proc. Natl. Acad. Sci. U.S.A.* 85(5):1417-1421.

Tsao, Y.P., P. D'Arpa, and L.F. Liu. 1992. The involvement of active DNA synthesis in camptothecin-induced G2 arrest: Altered regulation of P34cd2/cyclin B1. *Cancer Res.* 52:1823-1829.

Tsao, Y.P., A. Russo, G. Nyamuswa, et al. 1993. Interaction between replication forks and topoisomerase I-DNA cleavable complexes: studies in cell-free SV40 DNA replication system. *Cancer Res.* 53(24):5908-5914.

Tsuji, T., et al. 1991. CPT-11 converting enzyme from rat serum: purification and some properties. *J. Pharmacobiodyn* 14(6):341-349.

Utsugi, T., S. Demuth, and N. Hanna. 1989. Synergistic antitumor effects of topoisomerase inhibitors and natural cell-mediated cytotoxicity. *Cancer Res.* 49:1429-1433.

Utsugi, T., M.R. Mattern, C.K. Mirabelli, et al. 1990. Potentiation of topoisomerase inhibitor-induced DNA strand breakage and cytotoxicity by tumor necrosis factor: enhancement of topoisomerase activity as a mechanism of potentiation. *Cancer Res.* 50:2636-2640.

Van der Zee, A.G.J., H. Hollema, S. de Jong, et al. 1991. Polycorprotein expression and DNA topoisomerase I and II activity in benign tumors of the ovary and in malignant tumors of the ovary, before and after platinum/cyclophosphamide chemotherapy. *Cancer Res.* 51:5915-5920.

Van der Zee, A.G.J., S. de Jong, W.N. Keith, et al. 1994. Quantitative and qualitative aspects of topoisomerase I and II alpha. and beta. in untreated and platinum/cyclophosphamide treated malignant ovarian tumors. *Cancer Res.* 54(3):749-755.

Von Hoff, D., T. Waddelow, B. Foresth, et al. 1991. Hydroxyurea accelerates loss of extrachromosomally amplified genes from tumor cells. *Cancer Res.* 51:6273-6279.

Wall, M.E. and M.C. Wani. 1985. Antineoplastic structure activity relationships of camptothecin and related analogs. In *Advances in Chinese Medical Materials Research (Int. Symp.*, 1984, ed. by H.M. Chang), Pp. 391-405. World Science, Singapore.

Wall, M.E. and M.C. Wani. 1991. Chemistry and antitumor activity of camptothecins. In *DNA topoisomerases Cancer* (eds. Potmesil, M. and K.W. Kohn), Pp. 93-102. Oxford University Press, New York.

Wall, M.E. and M.C. Wani. 1993. Camptothecin and analogs: synthesis, biological *in vitro* and *in vivo* activities, and clinical possibilities. *ACS Symp. Ser.* 534 (*Human medicinal agents from plants*), Pp. 149-169.

Wang, J.C. 1985. DNA topoisomerases. *Ann. Rev. Biochem.* 54:665-697.

Wang, J.C. 1987. Recent studies of DNA topoisomerases. *Biochim. Biophys. Acta* 909:1-9.

Wang, J.C. and L.F. Liu. 1979. DNA topoisomerases. Enzymes that catalyze the concerted breaking and rejioning of DNA bonds. In *Molecular Genetics* (ed. by H. Taylor), Pp. 65-88, Academic Press, New York.

Wang, L.K., R.K. Johnson, and S.M. Hecht. 1993. Inhibition of topoisomerase I function by nitidine and fagaronine. *Chem. Res. Toxicol.* 6(6):813-818.

Wang, X.W., X.F. Yue, J.X. Han, et al. 1984. Studies on cytotoxicity and induction of sister chromatid exchanges in V79 cells with three antitumor agents. *Kexue Tongbao* (Foreign Lang. Ed.) 29(9):1268-1271.

Wang, X.W., W.J. Yu, Z.M. Shen, et al. 1987. Cytotoxicity of hydroxycamptothecin and four other antineoplastic agents on KB cells. *Zhongguo Yaoli Xuebao* 8(1):86-90. (Chinese with English abstract).

Wani, M.A. and R.M. Snapka. 1990. Drug-induced loss of unstably amplified genes. *Cancer Invest.* 8:587-593.

Wani, M.A., J.M. Strayer, and R.M. Snapka. 1990. Hypersensitivity to low level cytotoxic stress in mouse cells with high levels of DHFR gene amplification. *Anticancer Drugs* 1:67-75.

Wani, M.C., P.E. Ronman, J.T. Lindley, et al. 1980. Plant antitumor agents. 18. Synthesis and biological activity of camptothecin analogues. *J. Med. Chem.* 23:554-560.

Weisenberger, D., U. Scheer, and R. Benavente. 1993. The DNA topoisomerase I inhibitor camptothecin blocks postmitotic reformation of nucleoli in mammalian cells. *Eur. J. Cell Biol.* 61(1):189-192.

Wittig, B., T. Dorbic, and A. Rich. 1990. Measurement of left-handed Z-DNA in permeabilized, metabolically active mammalian nuclei. In *Structure and methods proceedings of the sixth conversation in the discipline biomolecular stereodynamics* (eds. by R.H. Sarma and M.H. Sarma), Pp. 1-23. Adenine Press , New York,

Wong, M.L. 1990. Involvement of topoisomerase in replication, transcription, and packaging of the linear adenovirus genome. *J. Virol.* 64(2):691-699.

Wu, R.S., A. Kumor, and J.R. Warner. 1971. Ribosome formation is blocked by Camptothecin, a reversible inhibitor of RNA synthesis. *Proc. Natl. Acad. Sci. U.S.A.* 68(12):3009-3014.

Xu, B. and Y.H. Ling. 1985. The effects of hydroxycamptothecin in the activity of RNA and DNA polymerases prepared from murine hepatoma cells. *Am. J. Chin. Med.* 13(1-4):23-31.

Yamashita, Y., N. Fujii, C. Murakata, et al. 1992. Induction of mammalian DNA topoisomerase I mediated DNA cleavage by antitumor indolocarbazole derivatives. *Biochemistry* 31(48):12069-12075.

Yamashita, Y., S. Kawada, N. Fujii, et al. 1991. Induction of mammalian DNA topoisomerase I and II mediated DNA cleavage by saintopin, a new antitumor agent from fungus. *Biochemistry* 30:5838-5845.

Yamazaki, H., A. Dilworth, C.E. Myers, et al. 1993. Suramin inhibits DNA damage in human prostate cancer cells treated with topoisomerase inhibitors *in vitro*. *Prostate* (N.Y.) 23(1):25-36.

Yoshida, T., T. Nakata, and E. Ichishima. 1991. DNA topoisomerase I from rice: enzyme synthesis in germination, and partial purification from cultured cells. *Phytochemistry* 30(12):3885-3887.

Zhang, H., P. D'Arpa, and L.F. Liu. 1990. A model for tumor cell killing by topoisomerase poisons. *Cancer Cells* 2:23-27.

Zhang, H., J. Wang, and L.F. Liu. 1988. Involvement of DNA topoisomerase I in transcription of human ribosomal RNA genes. *Proc. Natl. Acad. Sci. U.S.A.* 85:1060-1064.

Zhang, Q.M. and X.Q. Gu. 1990. Leakage kinetics of camptothecin from polyphase liposomes. *Shenyang Yaoxueyuan Xuebao* 7(2):113-117. (Chinese with English abstract).

Zhang, Q.M., P. Wang, and X.Q. Gu. 1991. Three-wavelength spectrophotometry determination of camptothecin in polyphase liposomes. *Shenyang Yaoxueyuan Xuebao* 8(1):48-51. (Chinese with English abstract).

Zhang, Q.M., et al. 1987. A method for determining the encapsulation ratio of camptothecin in polyphase lipsome and studies on its leakage property. *Yaoxue Xuebao* 22(12):918-922. (Chinese with English abstract).

Zucker, R.M. and K.H. Elstein. 1991. A new action for topoisomerase inhibitors. *Chem. Biol. Interact.* 79:31-40

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Atherton, K.T. and D.C. Burke. 1975. Interferon induction by viruses and polynucleotides: a differential effect of camptothecin. *J. Gen. Virol.* 29(3):297-304.

Becker, Y. and U. Olshevsky. 1973. Inhibition of herpes simplex virus replication by camptothecin. *Isr. J. Med. Sci.* 9(11-12):15781581.

Billich, A., M. Schauer, S. Frank, et al. 1992. HIV-1 integrase: high-level production and screening assay for the endonucleolytic activity. *Antiviral Chem. Chemother.* 3(2):113-119.

Bjornsti, M.A. 1991. DNA topoisomerases. *Curr. Opin. Struct. Biol.* 1:99-104.

Cai, J.C. and C.R. Hutchinson. 1983. Camptothecin. *The Alkaloids* 21:101-137.

Carteau, S., J.F. Mouscadet, and H. Goulaouis. 1993. Effect of topoisomerase inhibitors on the *in vitro* HIV DNA integration reaction. *Biochem. Biophys. Res. Commun.* 192(3):1409-1414.

Champoux, J.J. 1988. Topoisomerase I is preferentially associated with isolated replicating simian virus 40 molecules after treatment of infected cells with camptothecin. *J. Virol.* 62(10):3675-3683.

Champoux, J.J. 1992a. Topoisomerase I is preferentially associated with normal SV40 replicative intermediates, but is associated with both replicating and nonreplicating SV40 DNAs which are deficient in histones. *Nucleic Acids Res.* 20:3347-3352.

Champoux, J.J. 1992b. Topoisomerase I is preferentially associated with isolated replicating Simian virus 40 molecules after treatment of infected cells with camptothecin. *J. Virology* 62(10):3675-3683.

Cheng, Z.D., S. AbuBakar, M.P. Fons, et al. 1992. Modulation of the frequency of human cytomegalovirus-induced chromosome aberrations by camptothecin. *Virology* 189:397-401.

Civitico, G., Y.Y. Wang, C. Luscombe, et al. 1990. Antiviral strategies in chronic hepatitis B virus infection: II. Inhibition of duck hepatitis B virus *in vitro* using conventional antiviral agents and supercoiled-DNA active compounds. *J. Med. Virol.* 31(2):90-97.

Deng, C.Z., S. AbuBaker, M.P. Fons, et al. 1992. Modulation of the frequency of human cytomegalovirus-induced chromsome aberrations by camptothecin. *Virology* 189(1):397-.

Fishman, J.A., S.F. Queener, R.S. Roth, et al. 1993. Activity of topoisomerase inhibitors against *Pneumocystis carinii in vitro* and in an inoculated mouse model. *Antimicrob. Agents Chemother.* 37(7):1543-1546.

Gupta, M., C.X. Zhu, Y.C. Tse-Dinh, et al. 1992. An Engineered mutant of vaccinia virus DNA topoisomerase I is sensitive to the anti-cancer drug camptothecin. *J. Biol. Chem.* 267(34):24177-24180.

Horwitz, M.S. and C. Brayton. 1972. Camptothecin. Mechanism of inhibition of adenovirus formation. *Virology* 48(3):690-698.

Horwitz, M.S. and S.B. Horwitz. 1971. Intracellulardegradation of HaLa and adenovirus type 2 DNA induced by camptothecin. *Biochem. Biophys. Res. Commun.* 45:723-727.

Horwitz S.B. 1975. In *Antibiotics III Mechanism of Action of Antimicrobial and Antitumor Agents* (eds. by J.W. Corcoran and F.E. Hahn), P. 48. Springer, New York.

Horwitz, S.B., C.K. Chang, and A.P. Grollman. 1972. Antiviral action of camptothecin. *Antimicrob. Agents Chemother.* 2(5):395-401.

Ishimi, Y., M. Nishizawa, T. Andoh, et al. 1991. Characterization of a camptothecin-resistant human DNA topoisomerase I in an *in vitro* system for Simian Virus 40 DNA replication. *Eur. J. Biochem.* 202(3):835-839.

Jang, L., H.S. Wold, J.J. Li, et al. 1987. Roles of DNA topoisomerases in simian virus 49 DNA replication *in vitro*. *Proc. Natl. Acad. Sci. U.S.A.* 84:950-954.

Jaxel, C., K.W. Kohn, and Y. Pommier. 1988. Topoisomerase I interaction with SV40 DNA in the presence and absence of camptothecin. *Nucleic Acids Res.* 16:11157-11170.

Jaxel, C., G. Capranico, K. Wassermann, et al. 1991. DNA sequence at sites of topoisomerase I cleavage induced by camptothecin in SV40 DNA. In *DNA Topoisomerases Cancer* (eds. by Potmesil, M. and K.W. Kohn), Pp. 182-195. Oxford University Press, New York.

Kelly, D.C., R.J. Avery, and N.J. Dimmock. 1974. Camptothecin. Inhibitor of influenza virus replication. *J. Gen. Virol.* 25 (pt.3):427-432.

Kerr, D.A., C.F. Chang, J. Gordon, et al. 1993. Inhibition of human neurotropic virus (JCV) DNA replication in glial cells by camptothecin. *Virology* 196:612-618.

Kusumoto, I.T., M. Hattori, Y. Miyaichi, et al. 1991. Effects of flavonoids and alkaloids on reverse transcriptase. *Shoyakugaku Zasshi* 45(3):240-254. (Japanese with English abstract).

Leblond-Larouche, L., R. Morais, and M. Zollinger. 1979. Studies of the effect of chloramphenicol, ethidium bromide and camptothecin on the reproduction of *Rous sarcoma* virus in infected chick embryo cells. *J. Gen. Virol.* 44(2):323-331.

Li, C.J., C.L. Wang, and A.B. Pardee. 1994a. Camptothecin inhibits Tat-mediated transactivation of type I human immunodeficiency virus. *J. Biol. Chem.* 269(10):7051-7054.

Li, C.J., B.J. Deznbe, D.K. Biswas, et al. 1994b. Inhibitors of JIV-1transcription. *Trends in Microbiol.* 2(5):164-169.

Li, C.J., et al. 1993. Three inhibitors of type 1 human immunodeficiency virus long terminal repeat-directed gene expression and virus replication. *Proc. Natl. Acad. Sci. U.S.A.* 90(5):1839-1842.

Liu, L.F. 1989. DNA topoisomerase poisons as anti-tumor drugs. *Ann. Rev. Biochem.* 58:351-375.

Maschera, B., E. Ferrazzi, M. Rassu, et al. 1993. Evaluation of topoisomerase inhibitors as potential antiviral agents. *Antiviral Chem. Chemother.* 4(2):85-91.

Minor, P.D. and N.J. Dimmock. 1975. Inhibition of synthesis of influenza virus proteins. Evidence for two host-cell-dependent events during multiplication. *Virology* 67(1):114-123.

Priel, E., D.G. Blair, and S.D. Showalter. 1991. Method of treating retroviral infections in mammals using camptothecin and compounds inhibiting retroviral topoisomerase I. *U.S. Pat. Appl.* 31 pp.

Priel, E., S.D. Showalter, and D.G. Blair. 1991. Inhibition of human immunodeficiency virus (HIV-1) replication *in vitro* by noncytotoxic does of camptothecin, a topoisomerase I inhibitor. *AIDS Res. Hum. Retroviruses* 7(1):65-72.

Priel, E., E. Aflalo, G. Chechelnitsky, et al. 1993. Inhibition of retrovirus-induced disease in mice by camptothecin. *J. Virology* 67(6):3624-3629.

Priel, E., S.D. Showalter, M. Roberts, et al. 1990. Topoisomerase I activity associated with human immunodeficiency virus (HIV): particles and equine infectious anemia virus core. *EMBO J.* 9:4167-4172.

Priel, E., S.D. Showalter, M. Roberts, et al. 1991. The topoisomerase I inhibitor, camptothecin, inhibits Equine infectious anemia virus replication in chronically infected CF2th cells. *J. Virology* 65(8):4137-4141.

Rainwater, R. and K. Mann. 1991. Association of topoisomerase I and II with the chromatin in SV40-infected monkey cells. *Virology* 181:408-411.

Rubinstein, L. and A. Rein. 1974. Effect of camptothecin on simian virus 40 DNA. *Nature* 248(5445):226-228.

Schaack, J., P. Schedl, and T. Shenk. 1990. Topoisomerase I and II cleavage of adenovirus DNA *in vivo*: both topoisomerase activities appear to be required for adenovirus DNA replication. *J. Virology* 64:78-85.

Shin, C.G. and R.M. Snapka. 1990a. Exposure to camptothecin breaks leading and lagging strand simian virus 40 DNA replication forks. *Biochem. Biophys. Res. Commun.* 168:135-140.

Shin, C.G. and R.M. Snapka. 1990b. Patterns of strongly protein-associated simian virus 40 DNA replication intermediates resulting from exposures to specific topoisomerase poisons. *Biochemistry* 29(49):10934-10939.

Shuman, S., M. Golder, and B. Moss. 1988. Characterization of vaccinia virus DNA topoisomerase I expressed in *Escherichia coli*. *J. Biol. Chem.* 263(31):16401-16407.

Snapka, R.M. 1986. Topoisomerase inhibitors can selectively interfere with different stages of simian virus 40 DNA replication. *Mol. Cell. Biol.* 6:4221-4227.

Snapka, R.M. 1987. Topoisomerase inhibitors can selectively interfere with different stages of simian virus 40DNA replication. *NCI Monogr.* 1987(4):55-60.

Snapka, R.M., M.A. Powelson, and J.M. Strayer. 1988. Swiveling and decatenation of replicating simian virus 40 genomes *in vivo*. *Mol. Cell Biol.* 6:4221-4227.

Tachedjian, G., D. Tyssen, S. Locarnini, et al. 1990. Investigation of topoisomerase inhibitors for activity against human immunodeficiency virus: inhibition by coumermycin A1. *Antiviral Chem.* 1(2):131-138.

Tafur, S., J.D. Nelson, D.C. DeLong, et al. 1976. Antiviral components of *Ophiorrhiza mungos*. Isolation of camptothecin and 10-methoxycamptothecin. *Lioydia* 39(4):261-262.

Tan, G.T., J.F. Miller, A.D. Kinghorn, et al. 1992. HIV-1 and HIV-2 reverse transcriptases: a comparative study of sensitivity to inhibition by selected natural products. *Biochem. Biophys. Res. Commun.* 185(1):370-378.

Yang, L., L.F. Liu, and J.J. Li, et al. 1986. The roles of DNA topoisomerase in SV40 DNA replication. *UCLA Symposia Mol. Cell. Biol.* 47:315-326.

Yang, L., M.S. Wold, J.J. Li, et al. 1987. Roles of DNA topoisomerases in simian virus 40 DNA replication *in vitro*. *Proc. Natl. Acad. Sci. U.S.A.* 84:950-954.

PHARMACOLOGY

OF CAMPTOTHECINS

Abigerges, D., J.P. Armand, G.G. Chabot, et al. 1994. Irinotecan (CPT-11) high-dose escalation using intensive high-dose loperamide to control diarrhea. *J. Natl. Cancer Inst.* 86(6):446-449.

Adamovics, J.A. and J.A. Cina. 1979. Minor alkaloids of *Camptotheca acuminata*. *Phytochemistry* 18(6):1085-1086.

Adamovics, J.A. and C.R. Hutchinson. 1979. Prodrug analogs of the antitumor alkaloid camptothecin. *J. Med. Chem.* 22(3):310-314.

Agarwal, J.S. and R.P. Rastogi. 1973. Chemical constituents of *Mappia foetida* Miers. *Ind. J. Chem.* 11(9):969.

Aimi, N., H. Hoshino, M. Nishimura, et al. 1990. Chaboside, first natural glycocamptothecin found from *Ophiorrhiza pumila*. *Tetrahedron Lett.* 31(36):5169-5172.

Aimi, N., M. Nishimura, A. Miwa, et al. 1989. Pumiloside and deoxypumiloside; plausible intermediates of camptothecin biosynthesis. *Tetrahedron Lett.* 30(37):4991-4994.

Aimi, N., T. Tsuyuki, H. Murakami, et al. 1990. Studies on the beta-carboline type glucosidic alkaloids of *Ophiorrhiza* spp. *Tennen Yuki Kagobutsu Tornkai Koen Yoshishu* 28:129-36. (Japanese with English abstract).

Aiyama, R., K.Satake, and S. Sawada. 1988. Conformational analysis of camptothecin: application of molecular orbital caculation to simple lactone model. *Yakuruto Kenkyusho Kenkyu Hokokushu,* Volume Date 1985-1986, (13):13-17. (Japanese with English abstract).

Aiyama, R., H. Nagai, K. Nokata, et al. 1988. A camptothecin derivative from *Nothapodytes foetida*. *Phytochemistry* 27(11):3663-3664.

Aiyama, R., H. Nagai, S. Sawada, et al. 1992. Determination of self-association of irinotecan hydrochloride (CPT-11) in aqueous solution. *Chem. Pharm. Bull.* 40(10):2810.

Akimoto, H., K. Ootsu, and N. Kawamura. 1993. Preparation of dioxolopyranoindolizinoquinolines as antitumor agents. *Can. Pat. Appl.* 38 pp.

Akimoto, K., A. Goto, and K. Ohya. 1991. Selective and sensitive determination of lactone and hydroxy acid forms of camptothecin and two derivatives (CPT-11 and SN-38) by high-performance liquid chromatography with fluorescence detection. *J. Chromatogr.* 588(1/2):165-170.

Allaudeen, H.S., D.A. Berges, R.P. Hertzberg, et al. 1992. Preparation of substituted indolizinol[1,2-b]quinolinones. *PCT Int. Appl.* 93 pp.

Aller, P., C. Rius, F. Mata, et al. 1992. Camptothecin induces differentiation and stimulates the expression of differentiation-related genes in U-937 human promonocytic leukemia cells. *Cancer Res.* 52(5):1245-1251.

Andoh, T. and K. Ishii. 1991. Camptothecin and its derivatives as inducers of tumor necrosis factor. *Jpn. Kokai Tokkyo Koho* 18 pp. (Japanese with English abstract).

Andoh, T., Y. Yasui., O. Koiwai, et al. 1993. Molecular basis of resistance to CPT-11, a specific inhibitor of DNA topoisomerase I. *Int. Congr. Ser. -Excepta Med.* 1026 (Mechanism and new approach on drug resistance of cancer cells) 95-101.

Anzai, H., P. Frost, and J.L. Abbruzzese. 1992a. Synergistic cytotoxicity with combined inhibition of topoisomerase (topo) I and II. *Pro. Am. Assoc. Cancer Res.* 33:431.

Anzai, H., P. Frost, and J.L. Abbruzzese. 1992b. Synergistic cytotoxicity with 2'-deoxy-5-azacytidine and topotecan *in vitro* and *in vivo*. *Cancer Res.* 52:2180-2185.

Araki, E., M. Ishikawa, M. Iigo, et al. 1993. Relationships between development of diarrhea and the concentration of SN-38, an active metabolite of CPT-11, in the intestine and the blood plasma of athymic mice following intraperitoneal administration of CPT-11. *Jpn. J. Cancer Res.* 84(6):697-702.

Arisawa, M., S.P. Gunasekera, G.A. Cordell, et al. 1981. Plant anticancer agents. XXI. Constituents of *Merrilliodendron megacarpum*. *Planta Med.* 43(4):404-407.

Atherton, K.T. and D.C. Burke. 1978. The effects of some different metabolic inhibitors on interferon superinduction. *J. Gen. Virol.* 41(2):229-237.

Atsumi, R., W. Suzuki, H. Hakusui, et al. 1991. Identification of the metabolites of irinotecan, a new derivative of camptothecin, in rat bile and its biliary excretion. *Xenobiotica* 21(9):1159-1169.

Balandrin. M.F., A.D. Kinghorn, and N.R. Farnsworth. 1993. Plant-derived natural products in drug discovery and development: an overview. *ACS Symp. Ser.* 534:2-12.

Baloch, Z., S. Cohen, and P.D. Coffman. 1990. Synergistic interactions between tumor necrosis factor and inhibitors of DNA topoisomerase I and II. *J. Immunol.* 145(9):2908-2913.

Beijnen, J.H., H. Rosing, W.W. ten Bokkel Huinink, et al. 1993. High-performance liquid chromatographic analysis of the antitumor drug camptothecin and its lactone ring-opened form in rat plasma. *J. Chromatogr.* 617(1):111-117.

Beisler, J.A. 1971. Potential anti-tumor agents Part 1. Analogs of camptothecin. *J. Med. Chem.* 14(11):1116-1118.

Benedetti, P. and G.A. Viglianti. 1989. Expression of human DNA topoisomerase I in yeast cells lacking yeast DNA topoisomerase I: restoration of sensitivity of the cells to the antitumor drug camptothecin. *Cancer Res.* 49(22):6318.

Benedetti, P., P. Fiorani, L. Capuani, et al. 1993. Camptothecin resistance from a single mutation changing glycine 363 of human DNA topoisomerase I to cysteine. *Cancer Res.* 53(18):4343-4348.

Bertrand, R., D. Kerrigan, M. Sarang, et al. 1991. Cell death induced by topoisomerase inhibitors. Role of calcium in mammalian cells. *Biochem. Pharmacol.* 42(1):77-85.

Bertrand, R., E. Solary, J. Jenkins, et al. 1993. Apoptosis and its modulation in human promyelocytic HL-60 cells treated with DNA topoisomerase I and II inhibitors. *Exp. Cell Res.* 207(2):388-397.

Betcher, D.L. and N. Burnham. 1992. Pharmacology: topotecan. *J. Pediatric Oncol. Nurs.* 9(1):31-32.

Bever, B.O. and G.R. Zahnd. 1979. Plants with oral hypoglycaemic action. *Quart. J. Crude Drug. Res.* 17(3 & 4):139-196.

Bhakuni, D.S. 1973. Alkaloids as anticancer drugs. *J. Scient. Ind. Res.* 32:382-393.

Bhuyan, B.K., T.J. Fraser, and L.G. Gray. 1973. Cell-kill kinetics of several S-phase-specific drugs. *Cancer Res.* 33(4):888-894.

Bhuyan, B.K., L.G. Scheidt, and T.J. Fraser. 1972. Cell cycle phase specificity of antitumor agents. *Cancer Res.* 32(2):398-407.

Blaney, S.M., et al. 1993. Plasma and cerebrospinal fluid pharmacokinetic study of topotecan in nonhuman primates. *Cancer Res.* 53(4):725-727.

Boehm, J.C., R.K. Johnson, S.M. Hecht, et al. 1989. Preparation, testing, and formation of water soluble camptothecin analogs as antitumor agents. *Eur. Pat. Appl.* 46 pp.

Boothman, D.A., M.Z. Wang, R.A. Schea, et al. 1992. Posttreatment exposure to camptothecin enhances the lethal effects of x-rays on radioresistant human malignant melanoma cells. *Int. J. Radiat. Oncol. Biol. Phys.* 24(5):939-948.

Boscia, R.E., T. Korbut, S.A. Holden, et al. 1993. Interaction of topoisomerase I inhibitors with radiation in cis-diamminedichloroplatinum (II)-sensitive and -resistant cells *in vitro* and in the FSAIIC fibrosarcoma *in vivo*. *Int. J. Cancer* 53(1):118-123.

Bosmann, H.B. 1972. Antineoplastic drug activity in the mitotic cycle: Effects of six agents on macromolecular synthesis in synchronous mammalian leukemic cells. *Biochem. Pharmacol.* 21(14):1977-1988.

Boxenbaum, H. and J.B. Fertig. 1984. Scaling of camptothecin plasma protein binding in 24 species. *Biopharm. Drug Dospos.* 5(4):405-408.

Bristol, J.A., D.L. Commins, R.W. Davenport, et al. 1975. Analogs of camptothecin. *J. Med. Chem.* 18(5):535-537.

Bruno, S., P. Lassota, W. Giaretti, et al. 1992. Apoptosis of rat thymocytes triggered by prednisolone, camptothecin, or teniposide is selective to G0 cells and is prevented by inhibitors of proteases. *Oncol. Res.* 4(1):29-35.

Bruno, S., et al. 1992. Inhibitors of proteases prevent endonucleolysis accompanying apoptotic death of HL-60 leukemic cells and normal thymocytes. *Leukemia* 6(11):1113-1120.

Bruno, S., W. Giaretti, Z. Darzynkiewicz, et al. 1992. Effect of camptothecin on mitogenic stimulation of human lyphocytes: involvement of DNA topoisomerase I in cell transition from G0 to G1 phase of the cell cycle and in DNA. *J. Cell. Physiol.* 151(3):478-486.

Burke, T.G. and Z.H. Mi. 1993a. Preferential binding of the carboxylate form of camptothecin by human serum albumin. *Anal. Biochem.* 212(1):285-287.

Burke, T.G. and Z.H. Mi. 1993b. Ethyl substitution at the 7 position extends the half-life of 10-hydroxycamptothecin in the presence of human serum albumin. *J. Med. Chem.* 36(17):2580-2582.

Burke, T.G. and Z. Mi. 1994a. The structural basis of camptothecin interactions with human serum albumin: impact on drug stability. *J. Med. Chem.* 37(1):40-46.

Burke, T.G. and Z. Mi. 1994b. Preferential binding of the carboxylate form of camptothecin by human serum albumin. *Anal. Biochem.* 212(1):285-.

Burke, T.G., A.K. Mishra, M.C. Wani, et al. 1993. Lipid bilayer partitioning and stability of camptothecin drugs. *Biochemistry* 32(20):5352-5364.

Burke, T.G., A.E. Staubus, A.K. Mishra, et al. 1992. Liposomal stabilization of camptothecin's lactone ring. *J. Am. Chem. Soc.* 114:8318-8319.

Burris, III, H.A., A.R. Hanauske, R.K. Johnson, et al. 1992. Activity of topotecan, a new topoisomerase I inhibitor, against human tumor colony-forming units *in vitro*. *J. Natl. Cancer Inst.* 84(23):1816-1820.

Buta, J.G. and M.J. Noval. 1978. Isolation of camptothecin and 10-hydroxycamptothecin from *Camptotheca acuminata* by gel permeation chromatography. *Ind. Eng. Chem. Prod. Res. Dev.* 17(2):160-161.

Cai, J.C. and C.R. Hutchinson. 1983. Camptothecin. *The Alkaloids* 21:101-137.

Caldecott, K. and P. Jeggo. 1991. Cross-sensitivity of gamma-ray-sensitive hamster mutants to cross-linking agents. *Mutat. Res.* 255(2):111-121.

Campain, J.A., R. Padmanabham, J.L. Hwang, et al. 1993. Characterization of an unusual mutant of human melanoma cells resistant to anticancer drugs that inhibit topoisomerase II. *J. Cell. Physiol.* 155(2):414-425.

Chabner, B.A. 1992. Camptothecins (editorial). *J. Clin. Oncol.* 10(1):3-4.

Chabot, G., D. Abigerges, D. Gandia, et al. 1992. Pharmacokinetic-pharmacopdynamic relationships in patients administrated with CPT-11, a new camptothecin analogue. *Proc. Am. Assoc. Cancer Res.* 33:266.

Chabot, G., M. De Forni, D. Gandi, et al. 1992. Comparative pharmacokinetics of the camptothecin analogue CPT-11 and its active metabolite SN-38, using three different schedule in phase I trials. In *Proceedings of NCI-EORTC Symposium on New Drugs in Cancer Therapy*, Amsterdam, P. 82.

Chan, P.K. 1992. Characterization and cellular localization of nucleophosmin/B23 in HeLa cells treated with selected cytotoxic

agents (studies of B23-translocation mechanism). *Exp. Cell Res.* 203(1):174-181.

Chang, J.Y., L.A. Dethlefsen, L.R. Barley, et al. 1992. Characterization of camptothecin-resistant Chinese hamster lung cells. *Biochem. Pharmacol.* 43:2443-2452.

Chang, J.Y., L.A. Dethlefsen, L.R. Barley, et al. 1993. Characterization of camptothecin-resistant Chinese hamster lung cells. *Biochem. Pharmacol.* 45(3):787. [Erratum to document cited in CA117(7):62514p].

Chatterjee, S., M.F. Cheng, and N.A. Nathan. 1990. Hypersensitivity to clinically useful alkylating agents and radiation poly(ADP-ribose)polymerease-deficient cell lines. *Cancer Commun.* 2(12):401-407.

Chatterjee, S., M.F. Cheng, S.J. Berger, et al. 1991. Alkylating agent hypersensitivity in poly (adenosine diphosphate-ribose) polymerase deficient cell lines. *Cancer Commun.* 3(3):71-75.

Chatterjee, S., M.F. Cheng, D. Trivedi, et al. 1989. Camptothecin hypersensivity in poly(adenosine diphosphate-ribose) polymerase-deficient cell lines. *Cancer Commun.* 1(6):389-394.

Chen, A.Y., C. Yu, M. Potmesil, et al. 1991. Camptothecin overcomes MDRI-mediated resistance in human KB carcinoma cells. *Cancer Res.* 51(22):6039-6044.

Chen, J.P. and B. Xu. 1991. Inhibitory effects of hydroxycamptothecin on three types of human tumor xenografts. *Zhonghua Zhongliu Zazhi* 18(suppl.):313-315. (Chinese with English abstract).

Chen, R.T., Z, Hua, Z.X. Lu, et al. 1980. Distribution and excretion of camptothecin suspension and sodium camptothecin in mice. *Zhongguo Yaoli Xuebao* 1(2):109-112. (Chinese with English abstract).

Chou, S., M. Kaneko, K. Nakaya, et al. 1990. Induction of differentiation of human and mouse myeloid leukemia cells by camptothecin. *Biochem. Biophys. Res. Commun.* 166:160-167.

Chu, K.P., L.T. Lin, W.C. Pan, et al. 1979. Study on the microbiol transformation of camptothecin to 10-hydroxycamptothecin. *Kexue Tongbao* 23(12):761-762. (Chinese with English abstract).

Clavel, M., A. Mathieu-Bou, A. Duumortier, et al. 1992. Phase I study of CPT-11 administrated as a daily infusion for 3 consecutive days. *Proc. Am. Assoc. Cancer Res.* 33:262.

Clive, D. and R. Krehl. 1991. Stability of tk-/-mutants of L5178Y mouse lymphoma cells in Fischer's medium. *Mutat. Res.* 260(4):409-413.

Comins, D.L. and M.F. Baevsky. 1992. Preparation of camptothecin and analogs. *PCT Int. Appl.* 38 pp.

Cotter, T.G., et al. 1992. Microfilament-disrupting agents prevent the formation of apoptic bodies in tumor cells undergoing apoptosis. *Cancer Res.* 52(4):997-1005.

Cotter, T.G., J.M. Glynn, F. Echeverri, et al. 1992. The induction of apoptosis by chemotherapeutic agents occurs in all phases of the cell cycle. *Anticancer Res.* 12(3):773-779.

Creemers, G.J., B. Lund, J. Verweij, et al. 1994. Topoisomerase I inhibitors: topotecan and irinotecan. *Cancer Treat. Rev.* 20(1):73-.

Del Bino, G., S. Bruno, P.N. Yi, et al. 1992. Apoptotic cell death triggered by camptothecin or teniposide. The cell cycle specificity and effects of ionizing radiation. *Cell Prolif.* 25(6):537-548.

Deng, C.Z., S. AbuBarkar, M.P. Fons, et al. 1992. Modulation of the frequency of human cytomegalovirus-induced chromosome aberrations by camptothecin. *Virology* 189(1):397-401.

Di Leonardo, A., A. Maddalena, and P. Cavolina. 1992. Nalidixic acid-resistant V79 cells with reduced DNA topoisomerase II activity and amplification prone phenotype. *Mutat. Res.* 269(2):319-327.

Division of Cancer Treatment, National Cancer Institute. 1988. *Guidelines for reporting of adverse drug reactions.* Bethesda, Md.

Dixit, R., R.Kovatch, M. Stoltz, et al. 1992. 72-Hour continuous intravenous infusion of 9-amino-20(S)-camptothecin (NSC-603071) in Fischer 344 rats. *Gov. Rep. Announce. Index* (U.S.) 92(20), Abstract 257:270.

Dixit, R., M. Stedham, R. Lopez, et al. 1991. Toxicity of multiple subcutaneous injections of 9-amino-20(S)-camptothecin (NSC-603071) in male mice. *Gov. Rep. Announce. Index* (U.S.) 92(20), Abstract 257:265.

Dixit, R., M. Stedham, R. Lopez, et al. 1992a. Repeated dose toxicity of subcutaneous injections of 9-amino-(20R,S)-camptothecin (NSC-629971) in male mice. *Gov. Rep. Announce. Index* (U.S.) 92(20), Abstract 257:264.

Dixit, R., M. Stedham, R. Lopez, et al. 1992b. Toxicity of multiple subcutaneous injections of suspensions of 9-amino-20(S)-

camptothecin (NSC-603071) in mice. *Gov. Rep. Announce. Index* (U.S.) 92(20), Abstract 257:265.

Dixit, R., M. Stedham, R. Lopez, et al. 1992c. Pharmacokinetics study of 9-amino-20(S)-camptothecin (NSC-603071) in beagle dogs. *Gov. Rep. Announce. Index* (U.S.) 92(20), Abstract 257:268.

Dixit, R., M. Stedham, R. Lopez, et al. 1992d. 48-Hour continuous intravenous infusion dose range-finding study of 9-amino-20(S)-camptothecin (NSC-603071) in beagle dogs. *Gov. Rep. Announce. Index* (U.S.) 92(20), Abstract 257:269.

Dixit, R., M. Stoltz, C. Fanska, et al. 1992. Pharmacokinetics study of 9-amino-20(S)-camptothecin (NSC-603071) in rats. *Gov. Rep. Announce. Index* (U.S.) 91(20), Abstract 156:232.

Dixit, R., M. Stoltz, R. Lopez, et al. 1992. Pharmacokinetics study of 9-amino-20(S)-camptothecin (NSC-603071) in CD2F1 mice. *Gov. Rep. Announce. Index* (U.S.) 92(20), Abstract 257:263.

Drewinko, B., E.J. Freireich, and J.A. Gottlieb. 1974. Lethal activity of camptothecin sodium on human lymphoma cells. *Cancer Res.* 34:747-750.

Earl, R.A. 1983. *Approaches to the indolizine and quinolizine ring systems via thermal and metal-mediated methods: the synthesis of camptothecin.* Dissertation of University of California at Berkeley, Berkeley, California. 209 pp. Avail. Univ. Microfilms Int., Order No. 8413369. Diss. Abstr. Int. B 1984 45(3):874.

Earl, R.A. and K.P.C. Vollhardt. 1984. The preparation of 2(1H)-pyridinones and 2,3-dihydro-5(1H)-indolizinones via transition metal mediated cocyclization of alkynes and isocyanates. A novel construction of the antitumor agent camptothecin. *J. Org. Chem.* 49(25):4786-4800.

Ejima, A., H. Terasawa, M. Sugimori, et al. 1990. Preparation of camptothecin analogs as antitumor agents. *Jpn. Kokai Tokkyo Koho* 16 pp. (Japanese with English abstract).

Erdelmeier, C.A.J., I. Erdelmeier, and A.D. Kinghorn. 1986. Use of overpressure layer chromatography (OPLC) for the separation of natural products with antineoplastic activity. *J. Nat. Prod.* 49(6):1133-1137.

Evans, H.H., M. Ricanati, M.F. Horng, et al. 1989. Relationship between topoisomerase II and radiosensitivity in mouse L5178Y lymphoma strains. *Mutat. Res.* 217(1):53-63.

Ezell, E.L. and L.L. Smith. 1991. ^{1}H- and ^{13}C-NMR spectra of camptothecin and derivatives. *J. Nat. Prod.* 54(6):1645-1650.

Falk, S.J. and P.J. Smith. 1992. DNA damaging and cell cycle effects of the topoisomerase I poison camptothecin in irradiated human cells. *Int. J. Radiat. Biol.* 61(6):749-757.

Fortunak, J.M., M. Mellinger, and J.L. Wood. 1992. Method for making certain pyranol[3',4':6,7]indolizino[1,2-b]quinolinones by decarboxylation of camptothecins. *PCT Int. Appl.* 7 pp.

Fortunak, J.M., J.L. Wood, A.R. Mastrocola, et al. 1992. Water-soluble camptothecin analogs, processes and methods. *PCT Int. Appl.* 50 pp.

Fortunak, J.M., A.R. Mastrocola, J.L. Wood, et al. 1994. Preparation of mappicine ketones from camptothecins: chemistry of the camptothecin E ring. *Tetrahedron Lett.* 35(32):5763.

Fukuoka, M., H. Nittani, and A. Suzuki 1992. A phase II study of CPT-11, a new derivative of camptothecin for previously untreated non-small cell lung cancer. *J. Clin. Onol.* 10:16-20.

Furuta, T., T. Yokokura, and M. Mutai. 1988. Antitumor activity of CPT-11 against rat Walker 256 carcinoma. *Gan To Kagaku Ryoho* 15:2757-2760.

Gabriel, S.K. 1969. *Sterochemistry of bicyclic epoxidations. Studies in the synthesis of some natural products.* Dissertation of Georgia Institute of Technology, Atlanta, Georgia, 124 pp. Avail. 69-19,646. Diss. Abstr. Int. B 1969, 30(6):2571.

Gallo, R.C., J. Whang-Peng, and R.H. Adamson. 1971. Studies on antitumor activity, mechanism of action, and cell cycle effects of camptothecin. *J. Natl. Cancer Inst.* 46(4):789-795.

Gao, Y.S. 1982. A selected review of recent chemical studies of Chinese medicinal plants and synthetic studies related to camptothecins and their modifications. In *Proceedings of Sino-American Symposium of Chemistry of Natural Products* (1980, ed. by Y. Wang), Pp. 83-93. Science Press, Beijing.

Geroni, C., E. Pesenti, G. Tagliabue, et al. 1993. Establishment of L1210 leukemia cells resistant to the distamycin-A derivative (FCE 24517): characterization and cross-resistance studies. *Int. J. Cancer* 53(2):308-314.

Glynn, J.M., et al. 1992. Apoptosis induced by actinomycin D, camptothecin or aphidicolin can occur in all phases of the cell cycle. *Biochem. Soc. Trans.* 20(1):84S.

Gong, J.P., X. Li, Z. Darzynkiewicz, et al. 1993. Different patterns of apoptosis of HL-60 cells induced by cycloheximide and camptothecin. *J. Cell. Physiol.* 157:263-270.

Gorczyca, W., M.R. Melamed, and Z. Darzynkiewicz. 1993. Apoptosis of S-phase HL-60 cells induced by DNA

topoisomerase inhibitors: Detection of DNA strand breaks by flow cytometry using the in situ nick translation assay. *Toxicol. Lett.* 67(1-3):249-258.

Gorczyca, W., S. Bruno, M.R. Melamed, et al. 1992. Cell cycle-related expression of p120 nucleolar antigen in normal human lymphocytes and in cells of HL-60 and MOL-4 leukemic lines: effects of methotrexate, camptothecin, and teniposide. *Cancer Res.* 52(12):3491-3494.

Gorczyca, W., J.P. Gong, B. Ardelt, et al. 1993. The cell cycle related differences in susceptibility of HL-60 cells to apoptosis induced by various antitumor agents. *Cancer Res.* 53(13):3186-3189.

Gottlieb, J.A. and J.K. Luce. 1972. Treatment of malignant melanoma with camptothecin (NSC-100880). *Cancer Chemother. Rep.* Part 1, 56(1):103-105.

Gottlieb, J.A., A.M. Guarino, J.B. Call, et al. 1970. Preliminary pharmacologic and clinical evaluation of camptothecin sodium (NSC-100880). *Cancer Chemother. Rep.* Part 1, 54(6):461-470.

Govindachari, T.R. and N. Viswanathan. 1972a. 9-Methoxycamptothecin: a new alkaloid from *Mappia foetida* Miers. *Ind. J. Chem.* 10:453-454.

Govindachari, T.R. and N. Viswanathan. 1972b. Alkaloids of *Mappia foetida*. *Phytochemistry* 11(12):3529-3531.

Govindachari, T.R., K.R. Ravindranath, and N. Viswanathan. 1974. *J. Chem. Soc. Perkin. Tran.* 1:1215.

Grochow, L.B., E.K. Rowinsky, R. Johnson, et al. 1992. Pharmacokinetics and pharmacodynamics of topotecan in patients with advanced cancer. *Drug Metab. Dispos.* 20(5):706-710.

Gu, X.Q., Y.H. Zhang, and M.J. Gu. 1990. Preparation of antitumor camptothecin arginine salt. *Faming Zhuanli Shenqing Shuomingshu, P.R. China,* 9 pp. (Chinese).

Guarino, A.M., J.B. Anderson, D.K. Starkweather, et al. 1973. Pharmacologic studies of camptothecin (NSC-100880): distribution, plasma protein binding, and biliary excretion. *Cancer Chemother. Rep.* 57:125-140.

Guarino, A.M., L.G. Hart, J.B. Call, et al. 1969. Studies of the physiologic disposition of the antitumor agent, camptothecin sodium (NSC-100880), in rodents. *Proc. Am. Assoc. Cancer Res.* 10:33.

Han, J. 1988. Traditional Chinese medicine and the search for new antineoplastic drugs. *J. Ethnopharmaco.* 24 (1):1-18.

Han, R. 1994. Highlight on the studies of anticancer drugs derived from plants in China. *Stem. Cells* (Dayt) 12(1):53-63.

Hart, L.G., J.B. Call, and V.T. Oliverio. 1969. A fluorometric method for determination of camptothecin in plasma and urine. *Cancer Chemother. Rep.* 53:211-214.

Hartwell, J.L. and B.J. Abbott. 1969. *Advances in pharmacology and chemotherapy* (Vol. 7). Academic Press, New York.

Hatano, T., T. Yasuhara, and T. Okuda. 1989. Tannins of cornaceous plants. II. Cornusiins D, E, and F, new dimeric and trimeric hydrolyzable tannins from *Cornus officinalis*. *Chem. Pharm. Bull.* 37(10):2665-2669.

Hatano, T., Y. Ikegami, T. Shingu, et al. 1988. Camptothecins A and B, new dimeric hydrolyzable tannins from *Camptotheca acuminata* Decne. *Chem. Pharm. Bull.* 36(6):2017-2022.

Hatano, T., N. Ogawa, R. Kira, et al. 1989. Tannins of cornaceous plants. I. Cornusiins A,B, and C, dimeric monomeric and trimerica hydrolyzable tannins from *Cornus officinalis*, and orientation of valoneoyl group in related tannins. *Chem. Pharm. Bull.* 37(8):2083-2090.

Hawkins, M.J. 1992. New anticancer agents: taxol, camptothecin analogs, and anthrapyrazoles [published erratum appears in *Oncology* (Huntingt) 1993 March, 7(3):105]. *Oncology* (Huntingt) 6(12):17-23; discussion 27-30.

He, X.G., F.X. Jiang, and Q.R. Zhou. 1978. Examples of the use of high-speed liquid chromatography in phytochemistry. *Zhiwu Xuebao* 20(1):76-83. (Chinese with English abstract).

Heckendorf, A.H. and C.R. Hutchinson. 1977. Biosynthesis of camptothecin. II. Confirmation that isovincoside, not vincoside, is the penultimate biosynthetic precursor of indole alkaloids. *Tetrahedron Lett.* 48:4153-4154.

Hendricks, C.B., E.K. Rowinsky, L.B. Grochow, et al. 1992. Effect of P-glycoprotein expression on the accumulation and cytotoxicity of topotecan (SK & F 104864), a new camptothecin analogues. *Cancer Res.* 52(8):2268-2278.

Hennequin, C., N. Giocanti, J. Baloso, et al. 1994. Interaction of ionizing radiation with the topoisomerase I poison camptothecin in growing V-79 and HeLa cells. *Cancer Res.* 54(7):1720-1728.

Hikiike, M. and T. Yaegashi. 1987. Preparation of camptothecin derivatives as antitumor agents. *Jpn. Kokai Tokkyo Koho* 3 pp. (Japanese with English abstract).

Hinz, H.R., N.J. Harris, E.A. Natelson, et al. 1994. Pharmacokinetics of the *in vivo* and *in vitro* conversion of 9-nitro-20(S)-

camptothecin to 9-amino-(S)-camptothecin in humans, dogs, and mice. *Cancer Res.* 54(12):3096-.

Holm, C., J.M. Covey, D. Kerrigan, et al. 1989. Differential requirement of DNA replication for the cytotoxicity of DNA topoisomerase I and II inhibitors in Chinese hamster DC3F cells. *Cancer Res.* 49(22):6365-6368.

Holmstrom, M. and V. Winters. 1992. Micronucleus induction by camptothecin and amsacrine in bone marrow of male and female CD-1 mice. *Mutagenesis* 7(3):189-193.

Horwitz, M.S. and S.B. Horwitz. 1971. Intracellular degradation of HeLa and adenovirus type 2 DNA induced by camptothecin. *Biochem. Biophys. Res. Commun.* 45(3):723-727.

Horwitz, S.B. 1975a. Camptothecin. In *Antibiotics* (eds. by Gottlieb, D., P.D. Shaw, and J.W. Corcoran), Vol. 3:48-57. Springer, New York.

Horwitz, S.B. 1975b. Camptothecin. *Handb. Exp. Pharmakol.* 38 (Antineoplast. Immunosuppr. Agents, Part 2):649-656.

Horwitz, S.B., C.K. Chang, and A.P. Grollman. 1972. Antiviral action of camptothecin. *Antimicrob. Agen. Chemother.* 2(5):395-401.

Hsu, J.S., T.Y. Chao, L.T. Lin, et al. 1977. Chemical constituents of the anticancer plant *Camptotheca acuminata* Decne. II. Chemical constituents of the fruits of *Camptotheca acuminata* Decne. *Huaxue Xuebao* 35(3-4):193-200. (Chinese with English abstract).

Hu, C.J., X.Y. Zhou, X.Q. Gu, et al. 1990. Antitumor pharmacokinetics of poly-phase liposomes of pro-camptothecin. *Shenyang Yaoxueyuan Xuebao* 7(2):118-122. (Chinese with English abstract).

Hu, C.J., X.Y. Zhou, Q.M. Zhang, et al. 1990. Pharmacokinetics of pro-camptothecin. *Shenyang Yaoxueyuan Xuebao* 7(1):24-30. (Chinese with English abstract).

Hu, C.J., X.Y. Zhou, Q.M. Zhang, et al. 1990. Tissue distribution of poly-phase liposome of pro-camptothecin. *Shenyang Yaoxueyuan Xuebao* 7(3):189-193. (Chinese with English abstract).

Huang, C., C.S. Han, X.F. Yue, et al. 1983. Cytotoxicity and sister chromatid exchanges induced *in vitro* by six anticancer drugs developed in the People's Republic of China. *J. Natl. Cancer Inst.* 71:841-847.

Huang, R.W., K. Takatsuki, and H. Tsuda. 1993. A new derivative of camptothecin, irinotecan hydrochloride (CPT-11) induces

programmed cell death in leukemia/lymphoma cell lines. *Int. J. Oncol.* 3(4):679-685.

Hui, E.K.W. and B.Y.M. Yung. 1993. Cell cycle phase-dependent effect of retinoic acid on the induction of granulocytic differentiation in HL-60 promyelocytic leukemia cells. Evidence for sphinganine potentiation of retinoic acid-induced differentiation. *FEBS Lett.* 318(2):193-199.

Hunter, G.R., G.F. Kalf, and H.P. Morris. 1973. Partial characterization of the DNA-dependent DNA polymerases of rat liver and hepatoma. *Cancer Res.* 33(5):987-992.

Hutchinson, C.R. 1981. Camptothecin: Chemistry, biogenesis and medicinal chemistry. *Tetrahedron* 37:1047-1065.

Hutchinson, C.R., A.H. Heckendorf, P.E. Daddona, et al. 1974. Biosynthesis of camptothecin. I. Definition of the overall pathway assisted by carbon-14 nuclear magnetic resonance analysis. *J. Am. Chem. Soc.* 96(17):5609-5611.

Hutchinson, C.R., G.J. O'Loughlin, T.T. Brown, et al. 1974. Biomimetic chemistry of camptothecin. Involvement of isovincoside lactam (strictosamide). *J. Chem. Soc. Chem. Commun.* 22:928.

Ikeda, Y., M. Matsui, and M. Ozaki. 1993. Enhancers for anticancer agents. *Jpn. Kokai Tokkyo Koho* 6 pp. (Japanese).

Ishida, R., M. Nishizawa, F. Kohtani, et al. 1989. Biochemical and genetic analysis of toxic effect of HOE 15030 in mammalian cells. *Somatic Cell Mol. Genet.* 15(4):279-288.

Janavs, J.L., M.E. Pierce, and J.S. Takahashi. 1994. RNA synthesis inhibitors increase melatonin production in Y79 human retinoblastoma cells. *Mol. Brain Res.* 23(1-2):47-56.

Jensen, P.B., I.J. Christensen, M. Sehested, et al. 1993. Differential cytotoxicity of 19 anticancer agents in wild type and etoposide resistant small cell lung cancer cell lines. *Br. J. Cancer* 67(2):311-320.

Jiang, T.L., S.E. Sydney, and R.M. Liu. 1983. Activity of camptothecin, harringtonin, cantharidin and curcumae in the human tumor stem cell assay. *Eur. J. Cancer Clin. Oncol.* 19(2):263-270.

Jones, N.J., S. Ellard, R. Waters, et al. 1993. Cellular and chromosomal hypersensivity to DNA crosslinking agents and topoisomerase inhibitors in the radiosensitive Chinese hamster irs mutants: phenotypic similarities to ataxia telangiectasia and Fanconi's anemia cells. *Carcinogenesis* 14(12):2487-2494.

Johnson, R.K., F.L. McCabe, and Y. Yu. 1992. Combination regimens with topotecan in animals tumor models. In Proceedings on the *Seventh NCI-EORTC Symposium on New Drugs in Cancer Therapy*, Amsterdam, P. 85.

Johnson, R.K., F.L. McCabe, L.F. Faucette, et al. 1989. SK & F 104864, a water-soluable analog of camptothecin with a broad spectrum of activity in prechemical tumor models. *Proc. Am. Asso. Cancer Res.* 30:623.

Jovtchev, G., M. Stergios, R. Rieger, et al. 1993. Wirkungen des topoisomerase I-inhibitors camptothecin auf die durch hitzeschock ausgeloste adaptive antwort gegenuber maleinsaurehydrazid (MH) bei *Hordeum vulgare.* [Effects of the topoisomerase I inhibitor camptothecin on the heat shock-triggered adaptive response to maleic hydrazide (MH) in *Hordeum vulgare.*] *Biol. Zentralbl.* 112(4):365-372. (German with English abstract).

Kamataki, T. 1993. Pharmaceuticals containing beta-glucuronidase inhibitors for the control of side effects of an antitumor agent. *PCT Int. Appl.* 22 pp.

Kaneda, N. and T. Yokokura. 1990. Nonlinear pharmacokinetics of CPT-11 in rates. *Cancer Res.* 50:1721-1725.

Kaneda, N., H. Nagata, T. Furuta, et al. 1990. Metabolism and pharmacokinetics of the camptothecin analogue CPT-11 in the mouse [Erratum appears in *Cancer Res.* 1990 July 15, 50(14):4451]. *Cancer Res.* 50(6):1715-1720.

Kann, H.E., Jr. and K.W. Kohn. 1972. Effects of deoxyribonucleic acid-reactive drugs on ribonucleic acid synthesis in leukemia L1210 cells. *Mol. Pharmacol.* 8(5):551-560.

Kano, Y., S. Sakamoto, T. Kasahara, et al. 1991. Effects of amsacrine in combination with other anticancer agents in human acute lymphoblastic leukemia cells in culture. *Leuk. Res.* 15(11):1059-1066.

Kano, Y., K. Suzuki, M. Akutsu, et al. 1992. Effects of CPT-11 in combination with other anti-cancer agents in culture. *Int. J. Cancer* 50(4):604-610.

Kashiki, H., E. Takahashi, and T. Takemoto. 1987. Antitumor substances from *Putterlichia* or other plant tissue cultures. *Jpn. Kokai Tokkyo Koho* 5 pp. (Japanese with English abstract).

Kawato, Y., M. Aonuma, Y. Hirota, et al. 1991a. Intracellular roles of SN-38, a metabolite of the camptothecin derivatives CPT-11, in the antitumor effect of CPT-11. *Cancer Res.* 51:4187-4191.

Kawato, Y., T. Furuta, M. Aonuma et al. 1991b. Antitumor activity of a camptothecin derivative CPT-11, against human tumor xenografts in nude mice. *Cancer Chemother. Pharmakol.* 28:192-198.

Kawato, Y., M. Aonuma, K. Matsumoto, et al. 1991. Production of SN-38, a main metabolite of the camptothecin derivative CPT-11, and its species and tissue specificities. *Yakubutsu Dotai* 6(6):899-907. (Japanese).

Kawato, Y., M. Sekiguchi, K. Akahane, et al. 1993. Inhibitory activity of camptothecin derivatives against acetylcholinesterase in dogs and their binding activity to acetylcholine receptors in rats. *J. Pharm. Pharm.* 45(5):444-448.

Kerr, D.A., C.F. Chang, J. Gordon, et al. 1993. Inhibition of human neuotropic virus (JCV) DNA replication in glial cells by camptothecin. *Virology* 196:612-618.

Kessel, D. 1971a. Effects of camptothecin on RNA synthesis in leukemia L1210 cells. *Biochim. Biophys. Acta* 246(2):225-232.

Kessel, D. 1971b. Some determinants of camptothecin responsiveness in leukemia L1210 cells. *Cancer Res.* 31(12):1883-1887.

Kessel, D., H.B. Bosmann, and K. Lohr. 1972. Camptothecin effects on DNA synthesis in murine leukemia cells. *Biochim. Biophys. Acta* 269(2):210-216.

Kharbanda, S., E. Rubin, H. Gunji, et al. 1991. Camptothecin and its derivatives induce expression of c-jun protooncogene in human myeloid leukemia cells. *Cancer Res.* 51(24):6636-6642.

Kihlman, B.A. and H.C. Andersson. 1992. Enhancement and reduction by methylated oxypurines of the frequences of chromated aberrations induced by camptothecin in root-tip cells of *Vicia faba*. *Mutat. Res.* 269(2):259-267.

Kim, J.H., S.H. Kim, A. Kolozsvary, et al. 1992. Potentiation of radiation response in human carcinoma cells *in vitro* and murine fibrosarcoma *in vivo* by topotecan, an inhibitor of DNA topoisomerase I. *Int. J. Radiat. Oncol. Phys.* 22:515-518.

Kingsbury, W.D. 1988. The chemical rearrangement of camptothecin to mappicine ketone. *Tetrahedron Lett.* 29(52):6847-6850.

Kjeldsen, E., B.J. Bonven, T. Andoh, et al. 1988. Characterization of a camptothecin-resistant human DNA topoisomerase I. *J. Biol. Chem.* 263:3912-3916.

Kobayashi, I., S. Owada, M. Takeshita, et al. 1992. The effect of CPT-11 in combination with interferon-alpha against human

colon carcinoma heterotransplanted in nude mice. *Nippon Geka Gakkai Zasshi* 93(12):1507. (Japanese).

Koch, M. 1992. Major anticancer agents from plants. *C.R. Seances Soc. Biol. Ses Fil.* 186(5):441-457. (French).

Kohno, K., J. Kuniichi, and M. Kuwano. 1988. Vincristine-resistant human cancer KB cell line and increased expression of multidrug-resistance gene. *Jpn. J. Cancer Res.* 79(11):1238-1246.

Kondo, O., H. Sudo, Y. Hasegawa, et al. 1993. Manufacture of plant metabolites for pharmaceutical preparation. *Jpn. Kokai Tokkyo Koho*, 8 pp. (Japanese with English abstract).

Kowalska-Loth, B., K. Staron, I. Buraczewska, et al. 1993. Reduced sensitivity to camptothecin of topoisomerase I from a L5178Y mouse lymphoma subline sensitive to X-radiation. *Biochim. Biophys. Acta* 1172(1/2):117-123.

Krohn, K. and E. Winterfeldt. 1975. Reactions with indole derivatives. XXVIII. Alkylation of camptothecin intermediates. New approach to camptothecin. *Chem. Ber.* 108(9):3030-3042. (German).

Kroll, D.J., C.J. Christopher, T.W. Wiedmann, et al. 1990. Drug sensitivity of heat-resistant mouse B16 melanoma variants. *Radiat. Res.* 124(1):15-21.

Ku, K.Y. and T.C. Tang. 1980. Several botanical sources of camptothecine-an antitumor alkaloid. *Zhong Cao Yao* 11(10):467-479. (Chinese).

Kudoh, S., M. Takada, N. Masuda, et al. 1993. Enhanced antitumor efficacy of a combination of CPT-11, a new derivative of camptothecin, and cisplatin against human lung tumor xenografts. *Jpn. J. Cancer Res.* 84(2):203-207.

Kunimoto, T., K. Nitta, T. Tanaka, et al. 1987a. Antitumor activity of 7-ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxy-camptothecin, a novel water-soluble derivative of camptothecin, against murine tumors. *Cancer Res.* 47:5944-5947.

Kunimoto, T., K. Nitta, T. Tanaka, et al. 1987b. Antitumor activity of a new camptothecin derivatives, SN-22, against various murine tumors. *J. Pharmacobio-Dyn.* 10(3):148-151.

Kurono, Y., M. Miyajima, and K. Ikeda. 1993. Interaction of camptothecin derivatives with human plasma proteins *in vitro*. *Yakugaku Zasshi* 113(2):167-175. (Japanese with English abstract).

Lanza, A., S. Tornaletti, M. Stefanini, et al. 1993. The sensitivity to DNA topoisomerase inhibitors in L5178Y lymphoma strains is

not related to a primary defect of DNA topoisomerases. *Carcinogenesis* 14(9):1759-1763.

Lee, M.H. and F.C. Chen. 1984. The antitumor activity of several Chinese medical herbs. *Form. Sci.* 38(1):49-74.

Lee, S. and J. Inselburg. 1993. In vitro sensitivity of plasmodium falciparum to drugs that bind DNA or inhibit its synthesis. *J. Parasitol.* 79(5):780-782.

Leteurtre, F., M. Fesen, G. Kohlhagen, et al. 1993. Specific interaction of camptothecin, a topoisomerase I inhibitor, with guanine residues of DNA detected by photoactivation at 365 nm. *Biochemistry* 32(34):8955-8962.

Li, L.H., T.J. Fraser, E.J. Olin, et al. 1972. Action of camptothecin on mammalian cells in culture. *Cancer Res.* 32:2643-2650.

Li, M., D.H. Li, X. Gu, et al. 1988. Cytokinetics of cancer cells and molecular pharmacology of polyphase liposome of camptothecin. *Shenyang Yaoxueyuan Xuebao* 5(3):161-167. (Chinese with English abstract).

Liebeskind, D., S.B. Horwitz, M.S. Horwitz, et al. 1974. Immunoreactivity to antinucleoside antibodies in camptothecin treated HeLa cells. *Exper. Cell Res.* 86(1):174-178.

Lin, L.T.(Z.), C.C. Sung, and R.S. Hsu. 1979. 11-Hydroxycamptothecin, a new anticancer alkaloid. *Kexue Tongbao* 24(10):478-479. (Chinese with English abstract).

Lin, L.Z. and G.A. Cordell. 1989. Quinoline alkaloids from *Camptotheca acuminata*. *Phytochemistry* 28(4):1295-1297.

Lin, L.Z. and G.A. Cordell. 1990a. 19-O-methylangustoline from *Camptotheca acuminata*. *Phytochemistry* 29(8):2744-2746.

Lin, L.Z. and G.A. Cordell. 1990b. Further Studies on the alkaloids of *Camptotheca acuminata*. *Pl. Med.* 56:519.

Lin, L.Z. and G.A. Cordell. 1990c. 13C-NMR assignments of camptothecine and 10-hydroxycamptothecine. *J. Nat. Prod.* 53(1):186-189.

Lin, L.Z., T.Y. Chao, and J.(R.)S. Hsu. 1977. Chemical constituents of the anticancer plant *Camptotheca acuminata* Decne. I. Chemical constituents of the roots of *Camptotheca acuminata* Decne. *Huaxue Xuebao* 35(3-4):227-231. (Chinese with English abstract).

Lin, L.Z., C.Q. Song, and R.S. Xu. 1982. Chemical constituents of the anticancer plant *Camptothecin acuminata* Decne. IV. Isolation and identification of 11-hydroxycamptothecin and other four compounds. *Huaxue Xuebao* 40(1):85-89. (Chinese with English abstract).

Lin, L.Z., et al. 1988. A new alkaloid-18-hydroxycamptothecin. *Yaoxue Xuebao* 23(3):186-188. (Chinese with English abstract).

Ling, Y.H., C.Y. Shen, and Q.L. Shi. 1986. Effects of 10-hydroxycamptothecin in chromatin protein synthesis in murine hepatoma cells. *Zhongguo Yaoli Xuebao* 7(3):285-288. (Chinese with English abstract).

Ling, Y.H., C.Y. Shen, and Q.L. Shi. 1987. Effects of four antitumor agents on DNA circular dichroism. *Zhongguo Yaoli Xuebao* 8(4):374-377. (Chinese with English abstract).

Loh, J.P. and A.E. Ahmed. 1990. Determination of camptothecin in biological fluids using reversed-phase high-performance liquid chromatography with fluorescence detection. *J. Chromatogr.* 530(2):367-376.

Luzzio, M.J., J.M. Besterman, M.G. Evans, et al. 1993. Preparation of 7-(aminomethyl)camptothecins as neoplasm inhibitors. *Eur. Pat. Appl.* 35 pp.

McCabe, F.L. and R.K. Johnson. 1994. Comparative activity of oral and parenteral topotecan in murine tumor models: efficacy of oral topotecan. *Cancer Investig.* 12(3):308-313.

Madden, K.R. and J.J. Champoux. 1992. Overexpression of human topoisomerase I in baby hamster kidney cells: hypersensitivity of clonal isolates to camptothecin. *Cancer Res.* 52(3):525-532.

Madelaine, I., S. Prost, A. Naudin, et al. 1993. Sequential modifications of topoisomerase I activity in a camptothecin-resistant cell line established by progressive adaptation. *Biochem. Pharm.* 45(2):339-348.

Martin, D.S., R.L. Stolfi., J.R. Colofiore, et al. 1993. Chemotherapeutic drug combinations. *PCT Int. Appl.* 79 pp.

Masuda, N., M. Fukuoka, K. Nakagawa, et al. 1993. Phase I and pharmacologic study of irinotecan in combination with cisplatin for advanced lung cancer. *Br. J. Cancer* 68(4):777-.

Matsuo, K., K. Kohno, H. Takano, et al. 1990. Reduction of drug accumulation and DNA topoisomerase II activity in acquired teniposide-resistant human cancer KB cell lines. *Cancer Res.* 50(18):5819-5824.

Matsuoka, H., et al. 1992. Cytotoxic effect of CPT-11 against human recurrent carcinoma cells primarily cultured on contact-sensitive plates: preliminary report. *Nippon Geka Gakkai Zasshi* 93(11):1451. (Japanese).

Matsuzaki, T., T. Yokokura, M. Mutai, et al. 1988. Inhibition of spontaneous and experimental metastasis by a new derivative of

camptothecin, CPT-11, in mice. *Cancer Chemother. Pharmacol.* 21(4):308-312.

Mattern, M.R., G.A. Hofmann, F.L. McCabe, et al. 1991. Synergistic cell killing by ionizing radiation and topoisomerase I inhibitor topotecan (SK & F 104864). *Cancer Res.* 51:5813-5816.

McHugh, M.M., R.D. Sigmund, and T.A. Beerman. 1990. Effects of minor groove binding drugs on camptothecin-induced DNA lesions in L1210 nuclei. *Biochim. Biophys. Res. Commun.* 168(1):135-140.

McHugh, M.M., R.D. Sigmund, and T.A. Beerman. 1990. Effects of minor groove binding drugs on camptothecin-induced DNA lesions in L1210 nuclei. *Biochem. Pharmacol.* 39(4):707-714.

McPhail, A.T. and G.A. Sim. 1968. Structure of camptothecin: x-ray analysis of camptothecin iodoacetate. *J. Chem. Soc.* B 8(923-928.

McSheehy, P.M., M. Gervasoni, V. Lampasona, et al. 1991. Studies of the differentiation properties of camptothecin in the human leukaemic cells K562. *Eur. J. Cancer* 27:1406-1411.

Miyasaka, T., M. Tadashi, S. Sawada, et al. 1981. Camptothecin derivatives. *Ger. Offen.* 103 pp. (German).

Miyasaka, T., S. Sawada, and K. Nogata. 1981a. A selective one-step introduction of hydroxylic functions at the C-5 and C-7 positions of 20(S)-camptothecin, an alkaloid having antitumor activity. *Heterocycles* 16(10):1713-1717.

Miyasaka, T., S. Sawada, and K. Nogata. 1981b. Chemical modification of antitumor alkaloid camptothecin. Acid-catalyzed conversion of 17-hydroxymethylcamptothecin into the aldehyde and its acetals. *Heterocycles* 16(10):1719-1721.

Miyasaka, T., M. Mutai, S. Sawada, et al. 1982. 7-Substituted camptothecin derivatives. *Eur. Pat. Appl.* 43 pp.

Miyasaka, T., S. Sawada, K. Nogata, et al. 1983a. Camptothecin derivatives formulations containing such derivatives and their use. *Eur. Pat. Appl.* 53 pp.

Miyasaka, T., S. Sawada, K. Nogata, et al. 1983b. Camptothecin 1-oxide derivatives, formulations comprising these derivatives and their use in producing an antitumor effect. *Eur. Pat. Appl.* 19 pp.

Miyasaka, T., S. Sawada, K. Nogata, et al. 1983c. Camptothecin derivatives. *Eur. Pat. Appl.* 26 pp.

Miyasaka, S., S. Sawada, K. Nogata, et al. 1986. Camptothecin derivatives. *Jpn. Kokai Tokkyo Koho* 10 pp. (Japanese with English abstract).

Zhang, X. and R.Q. Ding. 1984. Preparation of tritium-labeled camptothecin, 10-hydroxycamptothecin and nevadensin. *Hejishu* (2):47-48. (Chinese with English abstract).

Zhang, X.D., M.M. Ke, Z.F. Huang, et al. 1990. Treatment of yellow residue from camptothecin production. *Faming Zhuanli Shenqing Gongkai Shuomingshu, P.R. China,* 5 pp. (Chinese).

Zhang, X.D, J.C. Bao, et al. 1990. Extracting camptothecin from *Nothapodytes*. *Faming Zhuanli Shenqing Gongkai Shuomingshu, P.R. China,* 4 pp. (Chinese).

Zhu, G.P. 1986. 10-Hydroxycamptothecin manufacture by *Aspergillus flavus* T-419. *Faming Zhuanli Shenqing Gongkai Shuomingshu, P.R. China.* 10 pp. (Chinese).

Yokokura, T., T. Furuta, S. Sawada, et al. 1986. (Carbamoyloxy)camptothecins as anticancer agents. *Jpn. Kokai Tokkyo Koho* 23 pp. (Japanese with English abstract).

Yoshida, A., T. Ueda, Y. Wano, et al. 1993. DNA damage and cell killing by camptothecin and its derivative in human leukemia HL-60 cells. *Jpn. J. Cancer Res.* 84(5):566-573.

Yoshikawa-Fukada, M., K. Yoshikawa, and K. Notake. 1980. Effects of camptothecin on leukemia cells. *Aichi Ika Daigaku Igakkai Zasshi* 8(1):40-47. (Japanese with English abstract).

Yoshikazu, A., O. Kikoh, O. Yasuo, et al. 1992. Preparation of (fluoroethyl) camptothecin derivatives as neoplasm inhibitors. *Eur. Pat. Appl.* 59 pp.

Yu, Z.J. 1993. Chinese material medica combined with cisplatin and lipiodol through transcatheter arterial embolization in the treatment of primary hepatomal. *Zhong Xi Yi Jiehe Zazhi* 13(6):327-329. (Chinese with English abstract).

Zee-Cheng, K.Y. and C.C. Cheng. 1970. Common receptor-complement feature among some antileukemic compounds. *J. Pharm. Sci.* 59(1):1630-1634.

Zeng, Y.L. 1982. The development of plant-derived drugs in China. *Pharmaceutisch Weekblad* 117:1037-1043.

Zhao, J.H., H. Tohda, A. Oikawa, et al. 1992. Camptothecin-induced sister-chromatid exchange dependent on the presence of bromodeoxyuridine and the phase of the cell cycle. *Mutat. Res.* 282(1):49-54.

Zhang, Q.M., X.Q. Gu, and Y.H. Zhang. 1988. Chemical stability of S-CPT in phosphate buffer (pH=7.6). *Shenyang Yaoxueyuan Xuebao* 5(4):243-246. (Chinese with English abstract).

Zhang, Q.M., P. Wang, and X.Q. Gu. 1991. Three-wavelength spectrophotometry determination of camptothecin in polyphase liposomes. *Shenyang Yaoxueyuan Xuebao* 8(1):48-51. (Chinese with English abstract).

Zhang, Q.M., X.Q. Gu, Y. Sha, et al. 1987. A method for determining the encapsulation ratio of camptothecin in polyphase liposome and studies on its leakage property. *Yaoxue Xuebao* 22(12):918-922. (Chinese with English abstract).

Zhang, Q.M., D.S. Su, X.Q. Gu, et al. 1988. Microelectrophoresis of camptothecin polyphase liposome (139-10). *Shenyang Yaoxueyuan Xuebao* 5(3):157-160. (Chinese with English abstract).

Yakult Co. 1983b. 5-substituted-5-hydroxycamptothecins. *Jpn. Kokai Tokkyo Koho* 4 pp. (Japanese with English abstract).

Yakult Honsha Co., Ltd. 1981. Camptothecin choline salt. *Jpn. Kokai Tokkyo Koho* 3 pp. (Japanese with English abstract).

Yakult Honsha Co., Ltd. 1982a. Antitumor formulations containing camptothecin derivatives. *Jpn. Kokai Tokkyo Koho* 5 pp. (Japanese with English abstract).

Yakult Honsha Co., Ltd. 1982b. Camptothecin derivatives. *Jpn. Kokai Tokkyo Koho* 6 pp. (Japanese with English abstract).

Yakult Honsha Co., Ltd. 1984a. 9-Nitrocamptothecin. *Jpn. Kokai Tokkyo Koho* 5 pp. (Japanese with English abstract).

Yakult Honsha Co., Ltd. 1984b. Camptothecin derivatives. *Jpn. Kokai Tokkyo Koho* 5 pp. (Japanese with English abstract).

Yakult Honsha Co., Ltd. 1984c. 9-Substituted camptothecin derivatives. *Jpn. Kokai Tokkyo Koho* 5 pp. (Japanese with English abstract).

Yakult Honsha Co., Ltd. 1984d. 7-Hydroxycamptothecin derivatives. *Jpn. Kokai Tokkyo Koho* 7 pp. (Japanese with English abstract).

Yakult Honsha Co., Ltd. 1985a. 10-Bromo-1,2,6,7-tetrahydroxycamptothecin. *Jpn. Kokai Tokkyo Koho* 3 pp. (Japanese with English abstract).

Yakult Honsha Co., Ltd. 1985b. Camptothecin derivatives. *Jpn. Kokai Tokkyo Koho* 8 pp. (Japanese with English abstract).

Yakult Honsha Co., Ltd. 1986a. Camptothecin derivatives. *Jpn. Kokai Tokkyo Koho* 4 pp. (Japanese with English abstract).

Yakult Honsha Co., Ltd. 1986b. Camptothecin derivatives. *Jpn. Kokai Tokkyo Koho* 6 pp. (Japanese with English abstract).

Yang, J.L., J.X. Han, and B. Xu. 1979. Effect of sodium camptothecin on concomitant tumor immunity in mice. *Yaoxue Xuebao* 14(1):12-17. (Chinese with English abstract).

Yang, S.D., Z.R. Guo, and J.Y. Guo. 1979. Determination of camptothecin in its hemi-ketal compound by the IR method. *Yaoxue Xuebao* 14(2):96-100. (Chinese with English abstract).

Yang, Y.M., M.L. Dai, and Z.H. Huang. 1984. Mass spectrometric study of camptothecin and related compounds. *Huaxue Xuebao* 42(1):42-50. (Chinese with English abstract).

Yao, P.H. 1994. Determination of camptothecin by HPLC method. *Zhongguo Yaoxue Zazhi* 29(3):165-166. (Chinese).

Yeh, S.D.J. 1979. Nuclear medicine and cancer research in the People's Republic of China. *Am. J. Chin. Med.* 7(2)::149-155.

Woo, W.S. and H.J. Chi. 1973. Anti-cancer elements of higher plants. *J. Pharm. Soc. Korea* 17(2):55-70. (Korean with English abstract).

Wu, C.Y. (ed.). 1991. *Xin Hua Ben Cao Gang Yao.* Shanghai Science and Technology Press, Shanghai. (Chinese).

Wu, T.S., M.T. Chen, C.S. Kuoh, et al. 1985. Studies on the constituents of *Camptotheca acuminata* Decne. II. The constituents of fresh fruits. *J. Chin. Chem. Soc.* (Taipai) 32(2):173-175.

Wu, T.S., H.J. Tien, and M.Y. Yeh. 1980. Studies on the constituents of Formosan folk medicine. VII. Constituents of the flowers of *Vanilla somai* Hayata and the roots of *Camptotheca acuminata* Dcne. *Ch'eng-kung Ta Hsueh Hsueh Pao* 15:65-67. (Chinese with English abstract).

Wu, X.J. 1989. The effect of drug-microsphere embolization of hepatic artery on normal liver and experimental hepatic tumor in rates. *Chung Hua Fang She Hsueh Tsa Chih* 23(6):326-329. (Chinese with English abstract).

Wu, X.J. 1990. An experimental study of the basic properties of drug microspheres and target treatment of rates with liver tumor. *Chung Hua Wai Ko Tsa Chih* 28(4):241-243. (Chinese with English abstract).

Xu, B., J.T. Chang, J.L. Yang, et al. 1979. New results in parmacologic research of some anticancer agents. In *Proceedings of US-China Pharmacology Symposium, Commuttee on Scholarly Communication with the People's Republic of China*, eds. by J.J. Burns and P.J. Tsuchitani. Pp. 151-158.

Xu, B. 1981. Pharmacology of some natural products of China. *Trends Pharmacol. Sci.* 2(10):271-272.

Xu, B. 1990. Anticancer study of several new plant drugs. Presented in the *XIth International Congress of Pharmacology*, Amsterdam, Netherlands, July 1-6, 1990. *Eur. J. Pharmacol.* 183(2):243-244.

Yaegashi, T., S. Sawada, S. Okajima, et al. 1988. 10-Hydroxycamptothecin glycosides as antitumor agents. *Jpn. Kokai Tokkyo Koho* 17 pp. (Japanese with English abstract).

Yaegashi, T., S. Okajima, S. Sawada, et al. 1989. Preparation and testing of camptothecin derivatives as neoplasm inhibitors with enhanced solubility and activity. *Eur. Pat. Appl.* 47 pp.

Yakult Co. 1983a. 7-Hydroxycamptothecin derivatives. *Jpn. Kokai Tokkyo Koho* 6 pp. (Japanese with English abstract).

Wang, X.W. 1987. Cytotoxicity of hydroxycamptothecin and four other antineoplastic agents on KB cells. *Zhongguo Yaoli Xuebao* 8(1):86-90. (Chinese with English abstract).

Wani, M.C. and M.E. Wall. 1969. Plant antitumor agents. II. The structure of two new alkaloids from *Camptotheca acuminata*. *J. Org. Chem.* 34:1364-1367.

Wani, M.C., A.W. Nicholas, and M.E. Wall. 1987. Plant antitumor agents. 28. Resolution of a key tricyclic synthon, 5'(RS)-1,5-dioxo-5'-hydroxy-2'H,5'H,6'H-6'-oxopyrano[3',4'-f]EDLTA 6,8-tetrahydroindolizine: total synthesis and antitumor activity of 20(S)- and 20(R)-camptothecin. *J. Med. Chem.* 30(12):2317-2319.

Wani, M.C., A.W. Nicholas, and M.E. Wall. 1991. Preparation of 20(S)- and 20(R)-camptothecin derivatives. *U.S.* 10 pp. Cont. of U.S. Ser. No. 38, 157, abandoned.

Wani, M.A., J.M. Strayer, and R.M. Snapka. 1990. Hypersensitivity to low level cytotoxic stress in mouse cells with high levels of DHFR gene amplification. *Anticancer Drugs* 1(1):67-75.

Waraneke, J. and E. Winterfeldt. 1972a. Reaktionen an indolderivaten: XVI. Die autoxydative indo-chinolom umwandlung eines camptothecin-modells. (Reactions with indole derivatives L XVI. The autoxidative indole-quinolone rearrangement of a camptothecin model compound. *Chem. Ber.* 105(7):2120-2125. (German).

Waraneke, J. and E. Winterfeldt. 1972b. Reaktionen an indolderivaten: XVI. Die autoxydative indo-chinolom umwandlung eines camptothecin-modells. (Reactions with indole derivatives L XVI. The autoxidative indole-quinolone rearrangement of a camptothecin model compound. *Izv. Akad. Nauk. Turkm. Ser. Biol. Nauk.* 4:83-87. (Turkmen with English abstract).

Webb, C.D., M.D. Latham, R.B. Lock, et al. 1991. Attenuated topoisomerase II content directly correlates with a low level of drug resistance in a Chinese hamster ovary cell line. *Cancer Res.* 51(24):6543-6549.

Winterfeldt, E. and H. Radunz. 1971. Convenient route to the camptothecin chromophore. *J. Chem. Soc. D.* (7):374-375.

Woessner, R.D., W.K. Eng, G.A. Holfmann, et al. 1992. Camptothecin hyper-resistant P388 cells: drug-dependent reduction in topoisomerase I content. *Oncol. Res.* 4(11-12):481-488.

Wall, M.E. and M.C. Wani. 1980a. Anticancer agents based on natural product models. Camptothecin. *Med. Chem.* (Academic) 16(Anticancer Agents Based on Nat. Models):417-436.

Wall, M.E. and M.C. Wani. 1980b. Structure activity relationships of plant antitumor agents related to camptothecin and the quassinoids (*Camptotheca acuminata*, Simaroubeacae). Presented at International Research Congress on Medical Plant Research (Strasboug, France), published in *Natural products as medicinal agents*, 1981., Pp. 125-149. Stuttgart, Hippokrates Verlag.

Wall, M.E. and M.C. Wani. 1991. Chemistry and antitumor activity of camptothecins. In *DNA topoisomerases Cancer* (eds. by Potmesil, M. and K.W. Kohn), Pp. 93-102. Oxford University Press, New York.

Wall, M.E., and M.C. Wani. 1991. Camptothecin analogs as potent inhibitors of human colorectal cancer. *PCT Int. Appl.* 49 pp.

Wall, M.E., C. Mansukh, and C.A. Tele. 1992. Preparation of reduced camptothecin analogs. *S. African*, 20 pp.

Wall, M.E., A.W. Nicholas, G. Manikumar, et al. 1991. Preparation of 10,11-methylenedioxy-20(RS)-camptothecin and 10,11-methylenedioxy-20(S)-camptothecin analogs as antitumor agents. *Eur. Pat. Appl.* 21 pp.

Wall, M.E., M.C. Wani, C.E. Cook, et al. 1966. Plant antitumor agents. I. The isolation and structure of Camptothecin, a novel alkaloidal leukemia and tumor inhibitor from *Camptotheca acuminata*. *J. Am. Chem. Soc.* 88:3888-3890.

Wall, M.E., M.C. Wani, A.W. Nicholas, et al. 1991. Preparation of camptothecin analogs as antitumor agents. *PCT Int. Appl.* 45 pp.

Wall, M.E. M.C. Wani, A.W. Nicholas, et al. 1993. Plant Antitumor agents. 30. Synthesis and structure activity of novel camptothecin analogs. *J. Med. Chem.* 36:2689-2700.

Walton, M.I., D. Whysong, P.M. O'Connor, et al. 1993. Constitutive expression of human bcl-2 modulates nitrogen mustard and camptothecin induced apoptosis. *Cancer Res.* 53(8):1853-1861.

Wang, X.W., Z.M. Shen, J.L. Yang, et al. 1986. Inhibitory effect of hydroxy-camptothecin on colony formation of KB cells and DNA damage. *Zhongguo Yaoli Xuebao* 21(7):492-497. (Chinese with English abstract).

Wang, X.K., T.F. Zhao, and M. Wang. 1985. Gas chromatographic-mass spectroscopic investigation of the alkaloids of *Dendrobium nobile cultivated* on eleven trees. *Zhongyao Tongbao* 10(8):367-369, 371. (Chinese with English abstract).

Tezuka, K., S. Sawada, T. Furuta, et al. 1986. 7-Ethylcamptothecin quaternary amomonium salts. *Jpn. Kokai Tokkyo Koho* 6 pp. (Japanese with English abstract).

Tien, H.J., J.M. Tien, M.Y. Yeh, et al. 1977. Studies on the constituents of *Camptotheca acuminata* Dcne. I. Constituents of leaves. *Hua Hsueh* 2:51-54. (Chinese with English abstract).

Tobey, R.A. 1972. Effects of cytosine arabinoside, daunomycin, mithramycin, azacytidine, adriamycin, and camptothecin on mammalian cell cycle traverse. *Cancer Res.* 32(12):2720-2725.

Tobey, R.A. and H.A. Crissman. 1972. Use of flow microfluorometry in detailed analysis of effects of chemical agents or cell cycle progression. *Cancer Res.* 32(12):2726-2732.

Traganos, F., J. Kapuscinski, J.P. Gong, et al. 1993. Caffeine prevents apoptosis and cell cycle effects induced by camptothecin or topotecan in HL-60 cells. *Cancer Res.* 53(19):4613-4618.

Trask, D. and M. Muller. 1988. Stabilization of type I topoisomerase-DNA covalent complexes by actinomycin D. *Proc. Natl. Acad. Sci. U.S.A.* 85:1417-1421.

Tsuruo, T., T. Matsuzaki, M. Matsushita, et al. 1988. Antitumor effect of CPT-11, a new derivative of camptothecin, against pleiotropic drug-resistant tumors *in vitro* and *in vivo*. *Cancer Chemother. Pharmacol.* 21(1):71-74.

Tu, Z.H., M.Y. Wang, W.Q. Xiao, et al. 1990. Effects of 10-hydroxycamptothecin on induced chromosome aberrations in Chinese hamster ovary cells and micronuclei in mouse bone marrow and fetal liver. *Zhongguo Yaoli Xuebao* 11(4):378-381. (Chinese with English abstract).

Vaughan, W., J. Karp, and P. Burke. 1980. Long chemotherapy-free remissions after single-cycle timed-sequential chemotherapy for acute myelocytic leukemia. *Cancer* 45:859-865.

Vishnvvajjala, R. and A. Garzon-Aburbey. 1990. Preparation of water-soluble derivatives of camptothecin and their use as prodrugs in cancer therapy. *U.S. Pat. Appl.* 21 pp.

Wall, M.E. 1977. Natural products: chemistry, pharmaconogy, and medical applications. In Fried, J., K.J. Ryan, and P.J. Tsuchitani (eds), *Oral contraceptives and steroid chemistry in the People's Republic of China*. Pp. 62-72. National Academy of Sciences, Washington, D.C.

Wall, M.E. and M.C. Wani. 1977. Antineoplastic agents from plants. *Ann. Rev. Pharmacol. Toxicol.* 17:117-132.

Takeda, S., T. Shimazoe, H. Kuga, et al. 1992. Camptothecin analog (CPT-11)-sensitive human pancreatic tumor cell line QGP-1N shows resistance to SN-38, an active metabolite of CPT-11. *Biochim. Biophys. Res. Commun.* 188(1):70-77.

Takeda, S., T. Shimazoe, K. Sato, et al. 1992. Differential expression of DNA topoisomerase I gene between CPT-11 acquired- and native-resistant human pancreatic tumor cell lines: detected by RNA/PCR-based quantiation assay. *Biochem. Biophys. Res. Commun.* 184(2):618-625.

Tamura, H., C. Kohchi, R. Yamada, et al. 1991. Molecular cloning of a cDNA of a camptothecin-resistant human DNA topoisomerase I and identification of mutation sites. *Nucleic Acids Res.* 19:69-75.

Tan, K.B., M.R. Mattern, W.K. Eng, et al. 1989. Nonproductive rearrangement of DNA topoisomerase I and II genes: correlation with resistance to topoisomerase inhibitors. *J. Natl. Cancer Inst.* 81:1732-1735.

Tanaka, T., K. Mashimo, and M. Wagatsuma. 1971. Reactions of 1H-pyrrolo[3,4-b]quinoline derivatives. *Tetrahedron Lett.* (30):2803-2806.

Tang, M.Z. 1983. Effect of light and heat on assay of camptothecin. *Yaoxue Tongbao* 18(1):8-9. (Chinese with English abstract).

Tanizawa, A. and Y. Pommier. 1992. Topoisomerase I alternation in a camptothecin-resistant cell line derived from Chinese hamster DC3F cells in culture. *Cancer Res.* 52:1848-1854.

Teague, H.J. 1970. *Thiapyrone chemistry. Reaction of 2,6-dimethylthio-3,5-diphenylthiapyrone with hydroxide ion. Attempted preparation of naphthalene A/B camptothecin.* Dissertation of North Carolina State University, Raleigh, North Carolina, 79 pp. Avail. Xerox Univ. Microfilms, Ann Arbor, Mich., Order No. 7-18,983. Diss. Abstr. Int. B 1970, 31(4):1844.

Terasawa, H., A. Ejima, and M. Sugimori. 1991. Synthesis and antitumor activity of camptothecin analogs. *Yuki Gosei Kagaku Kyokaishi* 49(11):1013-1020. (Japanese).

Terasawa, H., A. Ejima, S. Ohsuki, et al. 1992. Hexacyclic compounds, e.g., (9S)-1-amino-9-ethyl-2,3-dihydro-9-hydroxy-1H,2H-benzol[de]pyranol[3',4':6,7]indolizino[1,2-b]quinoline-10,13(9H,15H)-dione, methods for their preparation and their use as neoplasm inhibitors. *Eur. Pat. Appl.* 77 pp.

Terasawa, H., M. Sugimori, A. Ejima, et al. 1989. Antitumor agents. III. A novel procedure for inversion of the configuration of a tertiary alcohol related to camptothecin. *Chem. Pharm. Bull.* 37(12):3382-3385.

Sorensen, B.S., P.B. Jensen, M. Schested, et al. 1994. Antagonistic effect of aclarubicin on camptothecin induced cytotoxicity: role of topoisomerase I. *Biochem. Pharm.* 47(11):2105.

Sudo, H., Y. Hasegawa, and J. Matsunaga. 1991. Extraction of camptothecin from *Camptotheca acuminata* and *Nothapodytes foetida*. *Jpn. Kokai Tokkyo Koho* 7 pp. (Japanese).

Sugawara, I., T. Iwahashi, K. Okamoto, et al. 1991. Characterization of an etoposide-resistant human K562 cell line. *Jpn. J. Cancer Res.* 82(9):1035-1043. (Japanese with English abstract).

Sugisawa, A. M. Yamamoto, Y. Nomura, et al. 1986. Bacterial polysaccharide. *Jpn. Kokai Tokkyo Koho* 5 pp. (Japanese with English abstract).

Sugimori, M., A. Ajima, S. Ohsuki, et al. 1994. Antitumor agents. VI. Synthesis and antitumor activity of ring A-, ring B-, and ring c-modified derivatives of camptothecin. *Heterocycles* 38(1):81-86.

Sugimoto, Y., S. Tsukahara, T. Oh-Hara, et al. 1990. Decreased expression of DNA topoisomerase I in camptothecin-resistant tumor cell lines as determined by a monoclonal antibody. *Cancer Res.* 50:6925-6930.

Supino, R., M. Binaschi, G. Capranico, et al. 1993. A study of cross-resistance pattern and expression of molecular markers of multidrug resistance in a human small-cell lung-cancer cell line selected with doxorubicin. *Int. J. Cancer* 54(2):309-314.

Supko, J.G. and L. Malspeis. 1991. A reversed-phase HPLC method for determining camptothecin in plasma with specificity for the intact lactone form of the drug. *J. Liq. Chromatogr.* 14(9):1779-1803.

Supko, J.G. and L. Malspeis. 1993. Pharmacokinetics of the 9-amino and 10,22-methylenedioxy derivatives of camptothecin in mice. *Cancer Res.* 53(13):3062-3062.

Tafur, S., J.D. Nelson, D.C. DeLong, et al. 1976. Antiviral components of *Ophiorrhiza mungos*. Isolation of camptothecin and 10-methoxycamptothecin. *Lioydia* 39(4):261-262.

Tagawa, H., H. Terasawa, and A. Ejima. 1987. Preparation of pyranoindolizines as intermediates for anticancerous camptothecin derivatives. *Eur. Pat. Appl.* 30 pp.

Tagawa, H., M. Sugimori, H. Terasawa, et al. 1988. Camptothecin derivatives useful as antitumor medicines. *Eur. Pat. Appl.* 44 pp.

Takayanagi, I., et al. 1989. Some pharmacological properties of a new antitumor drug, CPT-11, in isolated muscle preparations. *Gen. Pharmacol.* 20(6):763-766.

Schneider, E., J.K. Horton, C.H. Yang, et al. 1994. Multidrug resistance-associated protein gene overexpression and reduced drug sensitivity of topoisomerase II in a human breast carcinoma MCF7 cell line selected for etoposide resistance. *Cancer Res.* 54(1):152-158.

Schwartz, G.N., B.A. Teicher, J.P. Eder, Jr., et al. 1993. Modulation of antitumor alkylating agents by novobiocin, topotecan, and lonidamine. *Cancer Chemoth. Pharm.* 32(6):455-462.

Scott, D.O., D.S. Bindra, V.J. Stella, et al. 1993. Plasma pharmacokinetics of lactone and carboxylate forms of 20(S)-camptothecin in anesthetized rats. *Pharm. Res.* 10(10):1451-1457.

Scott, D.O., D.S. Bindra, and S.C. Sutton. 1994. Urinary and biliary disposition of the lactone and carboxylate forms of 20(S)-camptothecin in rats. *Drug Metab. Dispos.* 22(3):438.

Shamma, M. 1968. Numbering system for camptothecin based on its biogenesis. *Experientia* 24(2):107.

Shamma, M. and V.S. Georgiev. 1974. Camptothecin. *J. Pharm. Sci.* 63(2):163-168.

Shamma, M. and L. Novak. 1970. Preparation of some tricyclic analogs of camptothecin. *Collect. Czech. Chem. Commun.* 35(11):3280-3286.

Shanghai Institute of Materia Medica. 1978. Studies on the anticancer action of 10-hydroxy camptothecin. *Chinese Med. J.* 58(10):598-602. (Chinese with English abstract).

Shin, C.G., J.M. Strayer, M.A. Wani, et al. 1990. Rapid evaluation of topoisomerase inhibitors: caffeine inhibition of topoisomerases *in vivo*. *Teratog. Carcinog. Mutagen.* 10(1):41-52.

Skove, K., H.B. Zhou, and B. Marples. 1994. The effect of two topoisomerase inhibitors on low-dose hypersensitivity and increased radioresistance in Chinese hamster V79 cells. *Radiat. Res.* 138 (1, suppl.), S117-S120.

Slichenmyer, W.J., E.K. Rowinsky, R.C. Donehower, et al. 1993. The current status of camptothecin analogues as antitumor agents. *J. Natl. Cancer Inst.* 85(4):271-291.

Smit, J.A. and J.H. Stark. 1994. Inhibiting the repair of DNA damage induced by gamma irradiation in rat thymocytes. *Radiat. Res.* 137(1):84-88.

Smith, P.L., J.G. Liehr, S. Jacob, et al. 1992. Pharmacokinetics of tritium labeled camptothecin in nude mice. *Proc. Am. Assoc. Cancer Res.* 33:342.

Rothenberg, M.L., J. Kuhn, and H.A. Burris. 1992. A phase I pharmacokinetic trial of CPT-11 in patients with refractory solid tumors. *Proc. Am. Soc. Clin. Oncol.* 11:113.

Sainsbury, M., R.H. Strange, P.R. Woodward, et al. 1993. The intramolecular 1,3-dipolar cyclization of mesoionic species generated by the thermolysis of the mixed anhydrides of acetic and N-alkynoyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acids. *Tetrahedron* 49(10):2065-2076.

Sakato, K., H. Tanaka, N. Mukai, et al. 1974. Isolation and identification of camptothecin from cells of *Camptotheca acuminata* suspension cultures. *Agr. Biol. Chem.* 38(1):217-218.

Sartiano, G.P., M.L. Coetzee, K. Klein, et al. 1977. Effect of camptothecin and adriamycin on bleomycin-induced tritiated thymidine triphosphate incorporation in a rat nuclear system. *J. Natl. Cancer Inst.* 58(5):1357-1364.

Sasaki, Y., M. Morita, T. Miya, et al. 1992. Pharmacokinetic and pharmacodynamic analysis of CPT-11 and its active metabolite SN-38. *Proc. Am. Soc. Clin. Oncol.* 11:111.

Sato, S., H. Sato, and M. Fujita. 1986. Preparation of camptothecin tetraalkylammonium salts. *Jpn. Kokai Tokkyo Koho* 3 pp. (Japanese with English abstract).

Sawada, S. and T. Yaegashi. 1991. Preparation of anticancer water-soluble camptothecins. *Jpn. Kokai Tokkyo Koho*, 4 pp. (Japanese with English abstract).

Sawada, S. and K. Muraji. 1992. Preparation of camptothecin derivatives as antitumor agents. *Jpn. Kokai Tokkyo Koho*, 4 pp. (Japanese with English abstract).

Sawada, S., R. Aiyama, and H. Nagai. 1989. Isolation of dehydroxycamptothecin from *Nothapodytes foetida* as an antitumor and intermediate for pharmaceuticals. *Jpn. Kokai Tokkyo Koho* 3 pp. (Japanese with English abstract).

Sawada, S., K. Nokata, S. Okajima, et al. 1988. Preparation of 7-ethylcamptothecin (aminoethl)amide derivatives as antitumor prodrugs. *Eur. Pat. Appl.* 30 pp.

Schaack, J., et al. 1990. Topoisomerase I and II cleavage of adenovirus DNA *in vivo*: both topoisomerase activities appear to be required for adenovirus DNA replication. *J. Virol.* 64(1):78-85.

Schmitt, B., U. Bruce, and H.P. Vosberg. 1984. Characterization of size variants of type I DNA topoisomerase isolated from calf thymus. *Eur. J. Biochem.* 144:127-134.

Perlman, S., H.T. Abelson, and S. Penman. 1973. Mitochondrial protein synthesis: RNA with the properties of eukaryotic messenger RNA. *Proc. Natl. Acad. Sci. U.S.A.* 70(2):350-353.

Pettit, G.R., R.J. Quinn, T.H. Smith, et al. 1972. Antineoplastic agents. XXVIII. Camptothecin delta-lactone. *J. Org. Chem.* 37(17):2789-2791.

Poehland, B.L., N. Troupe, B.K. Carte, et al. 1989. Reversed-phase high-performance liquid chromatographic assay for camptothecin and related alkaloids. *J. Chromatogr.* 481:421-427.

Poot, M., B. Epe, H. Hoehn, et al. 1992. Cell cycle effects of the DNA topoisomerase inhibitors camptothecin and m-AMSA in lymphoblastoid cell lines from patients with Fanconi anemia. *Mutat. Res.* 270(2):185-189.

Poot, M., H. Hoehn, T.M. Ruenger, et al. 1992. Impaired S-phase transit of Werner syndrome cells expressed in lymphoblastoid cell lines. *Exp. Cell Res.* 202(2):267-273.

Potmesil, M. 1994. Camptothecins: from bench research to hospital wards. *Cancer Res.* 54(6):1431-1439.

Qiao, L., J.G. Pizzolo, W. Corczyca, et al. 1993. P145 expression during the cell in HL-60 cell line and normal human lymphocytes: effects of camptothecin, vinblastine, cycloheximide, antinomtycin D., retinoic acid and DMSO. *Leukemia Res.* 17(11):991-997.

Quick, J. 1977. A new route to pyridones via imines of pyruvic esters. *Tetrahedron Lett.* (4):327-330.

Recher, L., H. Chan, L. Briggs, et al. 1972. Ultrastructural changes inducible with the plant alkaloid camptothecin. *Cancer Res.* 32(11):2495-2501.

Riou, J.F., A. Naudin, and F. Lavelle. 1992. Effects of taxotere on murine and human tumor cell lines. *Biochem. Biophys. Res. Commun.* 187(1):164-170.

Roffler, S.R., J. Chan, and M.Y. Yeh. 1994. Potentiation of radioimmunotherapy by inhibition of topoisomerase I. *Cancer Res.* 54(5):1276-1285.

Roja, G. and M.R. Heble. 1994. The quinoline alkaloids camptothecin and 9-methoxycamptothecin from tissue cultures and mature trees of *Nothapodytes foetida*. *Phytochemistry* 36(1):65-66.

Ronman, P.E., M.C. Wani, and M.E. Wall. 1981. The preparation of tritium- and deuterium-labeled camptothecin. *J. Labelled Compd. Radiopharm.* 18(3):319-329.

growth of mammalian cells in culture. *Aichi Ika Daigaku Igakkai Zasshi* 11(3):286-293. (Japanese with English abstract).

Nagata, H., et al. 1987. Action of 7-ethylcamptothecin on tumor cells and its disposition in mice. *Cancer Treat Rep.* 71(4):341-348.

Naito, M., H. Hamada, and T. Tsuruo. 1988. ATP/magnesium-dependent binding of vincristine to the plasma membrane of multidrug-resistant K562 cells. *J. Biol. Chem.* 263(24):11887-11891.

Nakaya, K., S. Chou, M. Kaneko, et al. 1991. Topoisomerase inhibitors have potent differentiation-inducing activity for human and mouse myeloid leukemia cells. *Jpn. J. Cancer Res.* 82(2):184-191.

Neil, G.L. and E.R. Homan. 1973. The effect of dose interval on the survival of L1210 leukemic mice treated with DNA synthesis inhibitors. *Cancer Res.* 33(4):895-901.

Nitta, K., T. Yokokura, S. Sawada, et al. 1985. Antitumor activity of a new derivative of camptothecin. In *Recent advances in chemotherapy (Proc. Int. Congr. Chemother., 14th*, ed. by J. Ishigami), Vol. Anticancer Sect. 1:28-30. University of Tokyo Press, Tokyo.

Nitta, K., T. Yokokura, S. Sawada, et al. 1987. Antitumor activity of new derivatives of camptothecin. *Gan To Kagaku Ryoho* 14(3):850-857. (Japanese with English abstract).

Nivasaka, T., S. Sawada, and K. Nokata. 1981. A selective one-step introduction of hydroxylic functions at the C-5 and C-7 positions of 20(S)-camptothecin, an alkaloid having antitumor activity. *Heterocycles* 16(10):1713-1717.

Palitti, F., F. Cortes, L. Bassi, et al. 1993. Higher G2 sensitivity to the induction of chromosomal damage in the CHO mutant EM9 than in its parental line AA8 by camptothecin, an inhibitor of DNA topoisomerase I. *Mutant. Res.* 285(2):281-285.

Pan, P.C., S.Y. Pan, Y.H. Tu, et al. 1975. Studies on the derivatives of camptothecin. *Huaxue Xuebao* 33(1):71-74. (Chinese).

Perdue, R.E., M.E. Wall, J.L. Hartwell, et al. 1968. Comparison of the activity of crude *Camptotheca acuminata* Ethanolic extracts against lymphoid leukemia L-1210. *Lioydia* 31:229.

Perdue, R.E., R.L. Smith, M.E. Wall., et al. 1970. *Camptotheca acuminata* Decaisne (Nyssaceae), source of camptothecin, and antileukemic alkaloid. *Agr. Res. Ser. USDA Techn. Bull.* No.1415. 26 pp.

Miyasaka, T., S. Sawada, K. Nogata, et al. 1987a. Preparation of hydroxycamptothecin sulfate ester salts as water-soluble anticancer agents. *Jpn. Kokai Tokkyo Koho* 6 pp. (Japanese with English abstract).

Miyasaka, T., S. Sawada, K. Nogata, et al. 1987b. Preparation of camptothecin derivatives as antitumor agents. *Jpn. Kokai Tokkyo Koho* 13 pp. (Japanese with English abstract).

Moore, M.M. and C.L. Doerr. 1990. Comparison of chromosome aberration frequency and small-colony TK-deficient mutant frequency in L5178Y/TK+/-3.7.2C mouse lymphoma cells. *Mutagenesis* 5(6):609-614.

Mori, H., et al. 1991. Augmentation of antiproliferative activity of CPT-11, a new derivative of camptothecin, by tumor necrosis factor against proliferation of gynecologic tumor cell lines. *Anticancer Drugs* 2(5):469-474.

Miyadera, A. and A. Imura. 1992a. Optical resolution of indolizines with Bacillus species. *Jpn. Kokai Tokkyo Koho*, 4 pp. (Japanese with English abstract).

Miyadera, A. and A. Imura. 1992b. Enzymic optical resolution of indolizines. *Jpn. Kokai Tokkyo Koho*, 4 pp. (Japanese with English abstract).

Miyadera, A. and A. Imura. 1993. Optically active 20-acylcamptothecins and their enzymic manufacture. *Jpn. Kokai Tokkyo Koho* 4 pp. (Japanese).

Miyadera, A. and A. Imura. 1993. Optically active indolizines and their enzymic manufacture. *Jpn. Kokai Tokkyo Koho* 4 pp. (Japanese).

Nagao, Y. 1989. Preparation of camptothecin analogs as anticancer agents. *Jpn. Kokai Tokkyo Koho* 3 pp. (Japanese with English abstract).

Nagao, Y. 1989. 20-O-Acylcamptothecins as antitumor agents and their preparations. *Jpn. Kokai Tokkyo Koho* 4 pp. (Japanese with English abstract).

Nagao, Y., S. Takagi, K. Inoe, et al. 1991. Preparation of furanoindolizinoquinolines. *Jpn. Kokai Tokkyo Koho* 8 pp. (Japanese with English abstract).

Nagata, M. 1987. Flow-cytometric analysis of the effect of the antitumor alkaloid camptothecin on cell cycle progression. *Aichi Ika Daigaku Igakkai Zasshi* 15(4):683-699. (Japanese with English abstract).

Nagata, H., M. Fukada, K. Noasako, et al. 1983. Effects of an antitumor alkaloid, camptothecin and its derivatives on cell

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Abigerges, D., J.P. Armand, G.G. Chabot, et al. 1993. High-dose intensity of CPT-11 administered as a single dose every 3 weeks: The institut Gustave Roussy Experience. *Proc. Am. Soc. Clin. Oncol.* 12:133.

Abigerges, D., J.P. Armand, G.G. Chabot, et al. 1994. Irinotecan (CPT-11) high-dose escalation using intensive high-dose loperamide to control diarrhea. *J. Natl. Cancer Inst.* 86:446-449.

Andoh, T., K. Ishii, Y. Suzuki, et al. 1987. Characterization of a mammalian mutant with a camptothecin-resistant DNA topoisomerase I. *Proc. Natl. Acad. Sci. Sci. U.S.A.* 84:5565-5569.

Anzai, H., P. Frost, and J.L. Abbruzzese. 1992. Synergistic cytotoxicity with combined inhibition of topoisomerase (topo) I and II. *Pro. Am. Assoc. Cancer Res.* 33:431.

Anzai, H., P. Frost, and J.L. Abbruzzese. 1992. Synergistic cytotoxicity with 2'-deoxy-5-azacytidine and topotecan *in vitro* and *in vivo*. *Cancer Res.* 52:2180-2185.

Barilero, I., D. Gandia, J.P. Armand, et al. 1992. Simultaneous determination of the camptothecin analogue CPT-11 and its active metabolite SN-38 by high-performance liquid chromatography: application to plasma pharmacokinctic studies in cancer patients. *J. Chromatography* 575(2):275-280.

Beijner, J.H., B.R. Smith, W.J. Keijer, et al. 1990. High-performance liquid chromatographic analysis of the new antitumor drug SK & F 104864-a (NSC-609699) in plasma. *J. Pharm. Biomed. Anal.* 8:789-794.

Beran, M., S. O'Brien, E. Estey, et al. 1992. Topotecan (topo) in patients with refractory and relapsed acute leukemia. In *Proceedings of the Fourth Conference on DNA Topoisomerases in Therapy*, P. 54.

Bertrand, R., P. O'Connor, D. Kerrigan, et al. 1992. Sequential administration of camptothecin and etoposide circumvents the antagonistic cytotoxicity of simultaneous drug administration in slowly growing human colon-carcinoma HT-29 cells. *Eur. J. Cancer* 28A:743-748.

Bissery, M.C., A. Mathieu-Boue, and F. Lavelle. 1991. Preclinical evaluation of CPT-11, a camptothecin derivative. *Proc. Am. Assoc. Cancer Res.* 32:402.

Bissery, M.C., A. Mathieu-Boue, and F. Lavelle. 1992. Experimental anti-tumor activity of CPT-11 *in vitro* and *in vivo*. In *Proceedings of the Seventh NCI-EORTC Symposium on New Drugs in Cancer Therapy*, Amsterdam, P. 82.

Blaney, S.M., F.M. Balis, D.E. Cole, et al. 1993. Pediatric phase I trial and pharmacokinetic study of topotecan administrated as a 24-hour continuous infusion. *Cancer Res.* 53(5);1032-1036.

Boothman, D.A., M. Wang, R.A. Schea, et al. 1992. Posttreatment exposure to camptothecin enhances the lethal effects of x-rays on radioresistant human malignant melanoma cells. *Int. J. Radiat. Oncol. Biol. Phys.* 24(5):939-948.

Burke, T.G., A.K. Mishra, M.C. Wani, et al. 1993. Lipid bilayer partitioning and stability of camptothecin drugs. *Biochemistry* 32(20):5352-5364.

Burke, T.G., A.E. Staubus, A.K. Mishra, et al. 1992. Liposomal stabilization of camptothecin's lactone ring. *J. Am. Chem. Soc.* 114(21):8318-8319.

Burris, H.A. 1993. The role of camptothecins in the treatment of lung cancer. *Cancer Investigation* (Chemotherapy Foundation Symposium XI Innovative Cancer Chemotherapy for Tomorrow, November 10-12, 1993, New York City), Pp. 10-12.

Burris, H.A., J. Kuhn, J. Wall, et al. 1992. Early clinical trials of topotecan, a new topoisomerase I inhibitor. In *Proceedings of the Seventh NCI-EORTC Symposium on New Drugs in Cancer Therapy*, Amsterdam, P. 118.

Burris, H.A., M. Rothenberg, J. Kuhn, et al. 1992. Clinical trials with the topoisomerase I inhibitors. *Semin. Oncol.* 19(6):663-669.

Chabot, G., D. Abigerges, D. Gandia, et al. 1992. Pharmacokinetic-oharmacopdynamic relationships in patients administrated with CPT-11, a new camptothecin analogue. *Proc. Am. Assoc. Cancer Res.* 33:266.

Chabot, G., M. De Forni, D. Gandi, et al. 1992. Comparative pharmacokinetics of the camptothecin analogue CPT-11 and its active metabolite SN-38, using three different schedule in phase I

trials. In *Proceedings of NCI-EORTC Symposium on New Drugs in Cancer Therapy*, Amsterdam, P. 82.

Chen, A.Y., C. Yu, M. Potmesil, et al. 1991. Camptothecin overcomes MDR1-mediated resistance in human KB carcinoma cells. *Cancer Res.* 51:6039-6044.

Cheson, B.D., et al. 1993. Clinical trials referral resource. Clinical trials with topotecan. *Oncology* (Huntingt) 7(2):49-51.

Chiao, C.Y. and H.S. Li. 1974a. Effect of topical use of camptothecine-dimethyl sulfoxide solution in psoriasis. *Chin. Med. J.* 4:208-210. (Chinese).

Chiao, C.Y. and H.S. Li. 1974b. Effect of topical use of camptothecine-dimethyl sulfoxide solution in psoriasis. *Chin. Med. J.* 1(5): 355-360.

Clavel, M. A. Mathieu-Bou, A. Duumortier, et al. 1992a. Phase I study of the camptothecin analog CPT-11, administrated daily for 3 consecutive days. In *Proceedings of the 7th NCI-EORTC Symposium on New Drugs in Cancer Therapy*, Amsterdam, P.83.

Clavel, M. A. Mathieu-Bou, A. Duumortier, et al. 1992b. Phase I study of CPT-11 administrated as a daily infusion for 3 consecutive days. *Proc. Am. Assoc. Cancer Res.* 33:262.

Cole, D. S. Blaney, F. Balis, et al. 1992. A phase I and pharmacokinetic study of topotecan in pediatric patients. *Proc. Am. Soc. Clin. Oncol.* 11:116.

Cordon-Cardo, C. and J.P. O'Brien. 1991. The multidrug resistance phenotype in human cancer. In *Important advances in oncology* (eds. by DeVita,, V.T. Jr., S. Hellman, and S.A. Rosenberg), Pp. 19-38. Philadelphia.

Creaven, P.J., L.M. Allen, and F.M. Muggia. 1972. Plasma camptothecin (NSC-100880) levels during a 5-day course of treatment: relation to dose and toxicity. *Cancer Chemother. Rep.* 56:573-578.

Creemers, G.J., B. Lund, J. Verweij, et al. 1994. Topoisomerase I inhibitors: topotecan and irenotecan. *Cancer Treat. Rev.* 20(1):73-.

Culine, S., M. De Forni, J.M. Extra, et al. 1992. Phase I study of the camptothecin analogue CPT-11, using a weekly schedule. *Proc. Am. Soc. Clin. Oncol.* 11:110.

Darzynkiewicz, Z., X. Liu, and F. Tragnos. 1994. Simultaneous analysis of DNA replication and apoptosis during treatment of HL-60 cells with camptothecin and hypertermia and Mitogen stimulation of human lymphocytes. *Cancer Res.* 54(16):4289.

Dewys, W.D., S.R. Humphreys, and A. Goldin. 1968. Studies on therapeutic effectiveness of drugs with tumor weight and survival time indices of Walker 256 carcinosarcoma. *Cancer Chemother. Rep.* 52:229-242.

Drewinko, B., C. Green, and T.L. Loo. 1976. Combination chemotherapy *in vitro* with cis-dichlorodiammineplatinum (II). *Cancer Treat Rep.* 60:1619-1625.

Drewinko, B., T.L. Loo, and E.J. Freireich. 1979. Combination chemotherapy *in vitro*. III. BCNU. *Cancer Treat Rep.* 63:373-375.

Eckardt, J.R., H. Burris, J. Kuhn, et al. 1992. Phase I and pharmacokinetic trial of continuous infusion topotecan in patients with refractory solid tumors. *Proc. Am. Soc. Clin. Oncol.* 11:138.

Eckardt, J.R., H. Burris, G.A. Rodriguez, et al. 1993. A phase I study of the topoisomerase I and II inhibitors topotecan (T) and etoposide (E). *Proc. Am. Soc. Clin. Oncol.* 12:137.

Eckardt, J.R., H. Burris, M.L. Rothenberg, et al. 1993. Topoisomerase I inhibitors: promising novel compounds. *Contemp. Oncol.* January:47-60.

Eng, W.K., F.L. McCabe, K.B. Tan, et al. 1990. Development of a stable camptothecin-resistant subline of p388 leukemia with reduced topoisomerase I content. *Mol. Pharmacol.* 38:471-480.

Falk, S.J. and P.J. Smith. 1992. DNA damaging and cell cycle effects of the topoisomerase I poison camptothecin in irradiated human cells. *Int. J. Radiat. Biol.* 61(6):749-757.

Fojo, A., K. Ueda, D. Slamon, et al. 1987. Expression of a multidrug resistance gene in human tumors and tissues. *Proc. Natl. Acad. Sci. U.S.A.* 84:265-269.

Friedman, H.S., P.J. Houghton, S. C. Schold, et al. 1994. Activity of 9-dimethylaminomethly-10-hydroxycamptothecin against pediatric and adult central nervous system tumor xenografts. *Cancer Chemother. Pharmacol.* 34:171-174.

Fukuoka, M. 1991. A phase II study of CPT-11 for primary lung cancer. *Gan To Kagaku Ryoho* 18:1013-1019. (Japanese with English abstract).

Fukuoka, M., H. Nittani, A. Suzuki, et al. 1992. A phase II study of CPT-11, a new derivative of camptothecin for previously untreated non-small cell lung cancer. *J. Clin. Onol.* 10:16-20.

Furue, H. 1993. Topoisomerase inhibitors developing in Japan. *Gan To Kagaku Ryoho* 19(13):2140-2145. (Japanese with English abstract).

Furuta, T., T. Yokokura, and M. Mutai. 1988. Antitumor activity of CPT-11 against rat Walker 256 carcinoma. *Gan To Kagaku Ryoho* 15:2757-2760. (Japanese with English abstract).

Furuta, T. and T. Yokokura. 1990. Effect of administration schedules on the antitumor activity of CPT-11, a camptothecin derivative. *Gan To Kagaku Ryoho* 17(1):121-130. (Japanese with English abstract).

Furuta, T. and T. Yokokura. 1991. Combination therapy of CPT-11, a camptothecin derivative, with various antitumor drugs against L 1210 leukemia. *Gan To Kagaku Ryoho* 18(3):393-402. (Japanese with English abstract).

Gallo, R.C., J. Whang-Peng, and R.H. Adamson. 1971. Studies on antitumor activity, mechanism of action, and cell cycle effects of camptothecin. *J. Natl. Cancer Inst.* 46:789-795.

Gandia, D., J.P. Armand, G. Chabot, et al. 1992a. A phase I study of CPT-11 (camptothecin-11) administered every 3 weeks in advanced cancer patients. In *Proceedings of the 7th NCI-EORTC Symposium on New Drugs in Cancer Therapy*, Amsterdam, P.82.

Gandia, D., J.P. Armand, G. Chabot, et al. 1992b. Phase I study of the new camptothecin analogue CPT-11 administrated every 3 weeks. *Pro. Am. Assoc. Cancer Res.* 33:260.

Gandia, D., et al. 1993. CPT-11-induced cholinergic effects in cancer patients. *J. Clin. Oncol.* 11(1):196-197.

Giantonio, B.J., R. Kosierowsky, H.E. Ramsey, et al. 1993. Phase II study of topotecan (TT) for hormone refractory prostate cancer (HRPC). *Proc. Am. Soc. Clin. Oncol.* 12:247.

Giovanella, B.C., H.R. Hinz, A.J. Kozielski, et al. 1991. Complete growth inhibition of human cancer xenografts in nude mice by treatment with 20-(s)-camptothecin. *Cancer Res.* 51:3052-3055.

Giovanella, B.C., L.F. Liu, M. Potmesil, et al. 1993. Treatment of colon tumors with camptothecin compounds. *U.S.* 14 pp.

Giovanella, B.C., J.S. Stehlin, M.E. Wall, et al. 1989. DNA topoisomerase I—targeted chemotherapy of human colon cancer in xenografts. *Science* 246(4933):1046-1048.

Goldstein, L., H. Galski, A. Fojo, et al. 1989. Expression of a multidrug resistance gene in human cancers. *J. Natl. Cancer Inst.* 81:116-124.

Gottlieb, J.A. and J.K. Luce. 1972. Treatment of malignant melanoma with camptothecin (NSC-100880). *Cancer Chemother. Rep.* Part 1, 56(1):103-105.

Gottlieb, J.A., A.M. Guarino, J.B. Call, et al. 1970. Preliminary pharmacologic and clinical evaluation of camptothecin sodium (NSC-100880). *Cancer Chemother. Rep.* Part 1, 54(6):461-470.

Green, M.R. 1993. New directions for chemotherapy in non-small-cell lung cancer. *Chest* 103(4 suppl):370s-372s.

Gu, F.L., et al. 1987. Factors influencing the absorption of antineoplastic agents in intravestical instillation treatment of bladder tumors. An experimental and clinical study. *Chin. Med. J.* 100(2):127-31.

Haas, N.B., F.P. LaCreta, J. Ealezak, et al. 1994. Phase I/pharmacokinetic study of topotecan by 24-hour continuous infusion weekly. *Cancer Res.* 54(5):1220-.

Hass, N.B., G.R. Hudes, J. Walczak, et al. 1992. Phase I trial of topotecan on a weekly 24 hour infusional schedule. *Proc. NCI-EORTC Symposium Abstract* 7:a103.

Haas, N.B., F.P. Lacreta, J. Walczak, et al. 1992. Phase I/pharmacokinetic trial of topotecan on a weekly 24-hour infusion schedule. *Proc. Am. Assoc. Cancer Res.* 33:523.

Hartwell, J.L. and B.J. Abbott. 1969. *Advances in pharmacology and chemotherapy* (Vol. 7). Academic Press, New York.

Hawkins, M.J. 1992. New anticancer agents: taxol, camptothecin analogs, and anthrapyrazoles [published erratum apears in *Oncology* (Huntingt) 1993 March, 7(3):105]. *Oncology* (Huntingt) 6(12):17-23; discussion 27-30.

Hendricks, C.B., E.K. Rowinsky, L.B. Grochow, et al. 1992. Effects of P-glycoptein expression on accumulation and cytotoxicity of topotecan (SK & F 104864), a new camptothecin analog. *Cancer Res.* 52:2268-2278.

Herman, T.S., V. Khandakar, T. Korbut , et al. 1992. Cytotoxicity, tumor cell survival and tumor growth delay with camptothecin or topotecan under hyperthermic conditions alone or with cisplain. *Proc. Am. Assoc. Cancer Res.* 33:499.

Hinz,.H.R., N.J. Harris, E.A. Natelson, et al. 1994. Pharmacokinetics of the *in vivo* and *in vitro* conversion of 9-nitro-20(S)-camptothecin to 9-amino-20(S)-camptothecin in humans, dogs, and mice. *Cancer Res.* 54:3096-3100.

Hirano, A., M. Funakoshi, S. Mizunuma, et al. 1993. An investigation of optimal dose schedules of CPT-11, a camptothecin derivative in human carcinoma cell lines. *Proc. Am. Assoc. Cancer Res.* 34:420.

Hochster, H., J. Speijer, R. Oratz, et al. 1993. Topotecan 21 day continuous infusion excellent tolerance of novel schedule. *Proc. Am. Soc. Clin. Oncol.* 12:139.

Hollstein, M., D. Sidransky, B. Vogelstein, et al. 1991. p53 Mutations in human cancers. *Science* 253:49-53.

Houghton, P.J., P.J. Cheshire, J.C. Hallman, et al. 1993. Therapeutic efficacy of the topoisomerase I inhibitor 7-ethyl-10-(4-[1-piperidino]-1-piperidino)-carbonyloxy-camptothecin against human tumor xenografts. *Cancer Res.* 53(12):2823-2829.

Houghton, P.J., P.J. Cheshire, L. Myers, et al. 1992a. Evaluation of 9-dimethylaminomethyl-10-hydroxycamptothecin (topotecan) against xenografts derived from adult and childhood tumors. In *Proceedings of the Seventh NCI-EORTC Symposium on New Drugs in Cancer Therapy*, Amsterdam, P. 89.

Houghton, P.J., P.J. Cheshire, L. Myers, et al. 1992b. Evaluation of 9-dimethylaminomethyl-10-hydroxycamptothecin against xenografts derived from adult and childhood solid tumors. *Cancer Chemother. Pharmacol.* 31(3):229-239.

Hutchinson, C.R. 1981. Camptothecin: Chemistry, biogenesis and medicinal chemistry. *Tetrahedron* 37:1047-1065.

Iison, D., R.J. Motzer, P. O'Moore, et al. 1993. A phase II study of topotecan in advanced renal cell carcinoma. *Proc. Am. Soc. Clin. Oncol.* 12:248.

Investigational Drug Branch. 1989. *Topotecan clinical brochure.* National Cancer Institute, Bethesda, MD.

Janik, J., L. Miller, I.I. Smith, et al. 1993. Prechemotherapy granulocyte macrophage colony stimulating factor (GM-CSF) prevents topotecan induced neutropenia. *Proc. Am. Soc. Clin. Oncol.* 12:437.

Johnson, R.K. 1991. Preclinical profile of SKF-104864, a water soluble camptothecin analog. *Cancer Investig.* 9(3):346-347.

Johnson, R.K. 1992a. Treatment of ovarian with camptothecin analogs. *PCT Int. Appl.* 16 pp.

Johnson, R.K. 1992b. Treatment of esophageal cancer with camptothecin analogs. *PCT Int. Appl.* 16 pp.

Johnson, R.K. 1992c. Treatment of non-small-cell lung carcinoma with camptothecin analogs. *PCT Int. Appl.* 17 pp.

Johnson, R.K. 1993. Treatment of colorectal cancer with water-soluble camptothecin analog. *PCT Int. Appl.* 11 pp.

Johnson, R.K., F.L. McCabe, and Y. Yu. 1992. Combination regimens with topotecan in animals tumor models. In

Proceedings on the *7th NCI-EORTC Symposium on New Drugs in Cancer Therapy*, Amsterdam.

Johnson, R.K., M.P. Chitnis, W.M. Embey, et al. 1978. In vivo characteristics of resistance and cross-resistance of an adriamycin-resistant subline of P388 leukemia. *Cancer Treat. Rep.* 62:1535-1547.

Johnson, R.K., R.P. Hertzberg, W.D. Kingsburg, et al. 1991. Preclinical profile of SK and F 104864, a water-soluble analog of camptothecin. In *the 6h NCI-EORTC Symposium on New Drugs in Cancer Therapy*, Amsterdam.

Johnson, R.K., F.L. McCabe, L.F. Faucette, et al. 1989. SKF 104864, a water soluble analog of camptothecin with a broad spectrum of activity in preclinical models. *Proc. Am. Assoc. Cancer Res.* 30:623.

Johnson, R.K., F.L. McCabe, G. Gallagher, et al. 1992. Comparative efficacy of topotecan, irinotecan, camptothecin and 9-aminocamptothecin in preclinical tumor models. In Proceedings on the *7th NCI-EORTC Symposium on New Drugs in Cancer Therapy*, Amsterdam, P. 85.

Kambe, M., A. Wakui, T. Nakao, et al. 1993. A late phase II study of irenotecan (CPT-11) in patients with advanced gastric cancer. *Proc. Am. Soc. Clin. Oncol.* 12:198.

Kano, Y., S. Sakamoto, T. Kasahara, et al. 1991. Effects of amsacrine in combination with other anticancer agents in human acute lymphoblastic leukemia cells in culture. *Leuk. Res.* 15(11):1059-1066.

Kantarjian, H.M., M. Beran, A. Elliis, et al. 1993. Phase I study of Topotecan, a new topoisomerase I inhibitor, in patients with refractory or relapsed acute leukemia. *Blood* 81(5):1146-1151.

Kanzawa, F., H. Kondoh, S.J. Kwon, et al. 1992. Role of carboxylesterase on metabolism of camptothecin analogue (CPT-11) in non-small lung cancer cell line PC-7 cells. *Proc. Am. Assoc. Cancer Res.* 33:427.

Kanzawa, F., Y. Sugimoto, K. Minato, et al. 1990. Establishment of a camptothecin analogue (CPT-11)-resistant cell line of human non-small cell lung cancer: characterization and mechanism of resistance. *Cancer Res.* 50(18):5919-5924.

Karato, A., Y. Sasaki, T. Shinkai, et al. 1993. Phase I study of CPT-11 and etoposide in patients with refractory tumors. *J. Clin. Oncol.* 11:2030-2035.

Kastan, M., O. Onyekwere, D. Sidransky, et al. 1991. Participation of p53 protein in the cellular response to DNA damage. *Cancer Res.* 51:6304-6311.

Katz, E.J., J.S. Vick, K.M. Kling, et al. 1990. Effect of topoisomerase modulators on cisplatin cytotoxicity in human ovarian carcinoma cells. *Eur. J. Cancer* 26:724-727.

Kawato, Y., T. Furuta, M. Aonuma, et al. 1991. Antitumor activity of a camptothecin derivative, CPT-11, against human tumor xenografts in nude mice. *Cancer Chemother. Pharmacol.* 28:192-198.

Kessel, D. 1971. Some determinants of camptothecin responsiveness in leukemia L1210 cells. *Cancer Res.* 31:1883-1887.

Kharabanda, S., E. Rubin, H. Gunji, et al. 1991. Camptothecin and its derivatives induce expression of the c-*jun* protooncogene in human Myeloid leukemia cells. *Cancer Res.* 52:6636-6642.

Kim, J.H., S.H. Kim, A. Kolozsvary, et al. 1992. Potentiation of radiation response in human carcinoma cells *in vitro* and murine fibrosarcoma *in vivo* by topotecan, an inhibitor of DNA topoisomerase I. *Int. J. Radiat. Oncol. Phys.* 22:515-518.

Kono, A., et al. 1991. Conversion of CPT-11 into SN-38 in human tissues. *Gan To Kagaku Ryoho* 18(12):2175-2178. (Japanese with English abstract).

Kroll, D.J., C.J. Borgert, T.W. Wiedmann, et al. 1990. Drug sensitivity of heat-resistant mouse B16 melanoma variants. *Radiat. Res.* 124:15-21.

Kudelka, A., C. Edwards, R. Freedman, et al. 1993. An open phase II study to evaluate the efficacy and toxicity of topotecan administered intravenously as 5 daily infusions every 21 days to women with advanced epithelial ovarian carcinoma. *Proc. Am. Soc. Clin. Oncol.* 12:259.

Kudoh, S., M. Fukuoka, N. Masuda, et al. 1993. Relationship between CPT-11 pharmacokinetics and diarrhea in the combination chemotherapy of irenotecan (CPT-11) and cisplatin (CDDP). *Proc. Am. Soc. Clin. Oncol.* 12:141.

Kuhn, J., H. Burris, R. Irvin, et al. 1992. Pharmacokinetics of topotecan following a 30 minute infusion or 3 day continuous infusion. In *Proceedings of the Seventh NCI-EORTC Symposium on New Drugs in Cancer Therapy*, Amsterdam.

Kuhn, J., H. Burris, J. Wall, et al. 1990. Pharmacokinetics of the topoisomerase I inhibitor, SK & F 104864. *Proc. Am. Soc. Clin. Oncol.* 9:70.

Lai, S.L., L. Goldstein, M. Gottesman, et al. 1989. MDRI gene expression in lung cancer. *J. Natl. Cancer Inst.* 81:1144-1150.

Lin, X.R. 1987. Effect of camptothecin in the treatment of psoriasis. *Zhonghua Yixue Zazhi* 67(1):4-6. (Chinese with English abstract).

Lin, X.R., et al. 1988a. Clinical trials and experimental study on treating psoriasis with camptothecine. *Chin. Med. J.* 101(6):427-430.

Lin, X.R. and T. Huang. 1988. Topical camptothecine in treatment of psoriasis. *Int. J. Dematol.* 27(7):475-476.

Lynch, Jr., T.T., L. Kalish, G. Strauss, et al. 1994. Phase II study of topotecan in metastatic non-small-cell lung cancer. *J. Clin. Oncol.* 12(2):347-.

Masuda, N., M. Fukuoka, Y. Kusunoki, et al. 1992. CPT-11: A new derivative of camptothecin for the treatment of refractory or relapsed small cell lung cancer. *J. Clin. Oncol.* 10:1225-1229.

Masuda, N., M. Fukuoka, K. Nakagawa, et al. 1993. Phase I and pharmacologic study of irinotecan in combination with cisplatin for advanced lung cancer. *Br. J. Cancer* 68(4):777-.

Masuda, N., M. Fukuoka, M. Takada, et al. 1992. CPT-11 in combination with cisplain for advanced non-small cell lung cancer. *J. Clin. Oncol.* 10:1775-1780.

Mathieu-Boue, A., M. de Forni, and R. Bugat. 1994. Phase I and pharmacokinetic study of the camptothecin derivative irinotecan, administered on a weekly schedule in cancer patients. *Cancer Res.* 54(16):4347.

Matsuzaki, T., T. Yokokura, M. Mutai, et al. 1988. Inhibition of spontaneous and experimental metastasis by a new derivative of camptothecin, CPT-11, in mice. *Cancer Chemother. Pharmacol.* 21:308-312.

McCabe, F.L. and R.K. Johnson. 1994. Comparative activity of oral and parenteral topotecan in murine tumor model: efficacy of oral topotecan. *Cancer Invest.* 12(3):308-.

Miller, A.B., B. Hoogstraten, M. Sequet, et al. 1981. Reporting of cancer treatment. *Cancer* 47:206-214.

Miller, A.A., J.B. Hargis, S. Fields, et al. 1993. Phase I study of topotecan and cisplatin in patients with adavanced cancer (GALGB 9261). *Proc. Am. Soc. Clin. Oncol.* 12:399.

Moertel, C.G., A.J. Schutt, R.J. Reitemeier, et al. 1972. Phase II study of camptothecin (NSC-100880) in the treatment of advanced gastrointestinal cancer. *Cancer Chemother. Rep.* 56:95-101.

Mori, H. and N. Itoh. 1992. Treatment of recurrent gynaecologic malignancies with a new camptothecin derivative. *Eur. J. Cancer* 28(2/3):613-.

Muggia, F.M., P.J. Creaven, H. Hansen, et al. 1972. Phase I clinical trial of weekly and daily treatment with camptothecin (NSC-100880): correlation with preclinical studies. *Cancer Chemother. Rep.* 56:515-521.

Murphy, B., L. Saltz, M. Sirott, et al. 1992. Granulocyte-colony stimulating factor (G-CSF) does not increase the maximum tolerated dose (MTD) in a phase I study of topotecan. *Proc. Am. Soc. Clin. Oncol.* 11:139.

Nagai, S., et al. 1993. Growth inhibition of human gastrointestinal cancer xenograft lines by treatment with CPT-11 and VP-16. *J. Sur. Oncol.* 54(4):211-215.

Nakai, H., et al. 1991. An early phase II study of CPT-11 in primary lung cancer. *Gan To Kagaku Ryoho* 18(4):607-612. (Japanese with English abstract).

Negoro, S., M. Fukuoka, N. Masuda, et al. 1991. Phase I study of camptothecin, in the treatment of advanced non-small-cell lung cancer. *J. Natl. Cancer Inst.* 83:1164-1168.

Negoro, S., et al. 1991. A phase II study of CPT-11, a camptothecin derivative, in patients with primary lung cancer, CPT-11 cooperative study group. *Gan To Kagaku Ryoho* 18(6):1013-1019. (Japanese with English abstract).

Negoro, S., M. Fukuoka, N. Masuda, et al. 1993. Phase I study of irenotecan (CPT-11) and etoposide (E) with G-CSF in advanced lung cancer. *Proc. Am. Soc. Clin. Oncol.* 12:133.

Negoro, S., M. Fukuoka, H. Niitani, et al. 1991. Phase II study of CPT-11, a new camptothecin derivative, in small cell lung cancer (SCLC). *Proc. Am. Soc. Clin. Oncol.* 10:241.

Ng, C.E., A.M. Bussey, G.P. Raaphorst, et al. 1994. Inhibition of potentially lethal and sublethal damage repair by camptothecin and etoposide in human melanoma cell lines. *Int. J. Rad. Biol.* 66(1):49.

Niitani, H. 1991. An early phase II study of CPT-11 for primary lung cancer. *Gan To Kagaku Ryoho* 18:607-612. (Japanese with English abstract).

Noriyuki, M., M. Fukuoka, S. Kudoh, et al. 1994. Phase I study of irinotecan and cisplatin with granulocyte colony-stimulating factor support for advanced non-small-cell lung cancer. *J. Clin. Oncol.* 12(1):90-.

Oguro, M. 1990. A topoisomerase I inhibitor, CPT-11: its enigmatic antitumor activity in combination with other agents *in vitro*. In *Proceedings of the Third Conference on Topoisomerases* P. 35.

Oguro, M., Y. Seki, K. Okada, et al. 1990. Collateral drug sensitivity induced in CPT-11 (a novel derivative of camptothecin)-resistant cell lines. *Biomed. Pharmacother.* 44(4):209-216.

Oguro, M., et al. 1991. Combination cancer chemotherapy using a DNA topoisomerase inhibitor CPT-11, as a core agent—the *in vitro* evaluation. *Gan To Kagaku Ryoho* 18(10):1556-1561. (Japanese with English abstract).

Ohe, Y., Y. Sasaki, T. Shinkai, et al. 1991. Pharmacokinetics with a 5-day continuous-infusion of a camptothecin derivative, CPT-11. *Proc. Am. Soc. Clin. Oncol.* 10:117.

Ohe, Y., Y. Sasaki, T. Shinkai, et al. 1992. Phase I study and pharmacokinetics of CPT-11 with 5-day continuous infusion. *J. Natl. Cancer Inst.* 84:972-974.

Ohno, R., K. Okada, T. Masaoka, et al. 1990. An early phase II study of CPT-11: A new derivative of camptothecin, for the treatment of leukemia and lymphoma. *J. Clin. Oncol.* 8:1907-1912.

Ohno, R., et al. 1994. An early phase II study of CPT-11 (irinotecan hydrochloride) in patients with hematological malignancies. *Gan To Kagaku Ryoho* 21(1):75-82. (Japanese with English abstract).

Okamoto, H. and S. Saijo. 1991. Preclinical trial from standpoint of clinical trials. *Gan To Kagaku Ryoho* 18:1467-1475. (Japanese with English abstract).

Okamoto, A., M. Okabe, and K. Gomi. 1993. Analysis of DNA fragmentation in human uterine cervix carcinoma HeLa S3 cells treated with duocarmycins or other antitumor agents by pulse field gel electrophoresis. *Jpn. J. Cancer Res.* 84(1):93-98.

Oonishi, T., T. Machida, and H. Hagiwara. 1992. Camptothecin derivatives as synergistic antitumor agents. *Jpn. Kokai Tokkyo Koho* 8 pp. (Japanese with English abstract).

Oravec, M., A. Kumar, and R.S. Wu. 1972. Inhibition of labeling of messenger and nucleoplasmic RNA of HaLa cells by camptothecin. *Biochim. Biophys. Acta* 272(4):607-611.

Oshita, F., Y. Fujiwara, and N. Saijo. 1992. Radiation sensitivities in various anticancer-drug-resistant human lung cancer cell lines and mechanism of radiation cross-resistance in a cisplatin-resistant cell line. *J. Cancer Res. Clin. Oncol.* 119(1):28-34.

Owens. J.K., R. Schea, M. Wang et al. 1992. Camptothecin sensitizes radioresistant human melanoma cells to X-irradiation. *Proc. Am. Assoc. Cancer Res.* 33:437.

Oyama, H., et al. 1992. Intracellular distribution of CPT-11 in CPT-11-resistant cells with confocal laser scanning microscopy. *Jpn. J. Clin. Oncol.* 22(5):331-334. (Japanese with English abstract).

Pantazis, P., J.A. Early, A.J. Kozielski, et al. 1993. Regression of human breast carcinoma tumors in immunodeficient mice treated with 9-nitrocamptothecin: differential response of nontumorigenic and tumorigenic human breast cells *in vitro*. *Cancer Res.* 53(7):1577-1582.

Pantazis, P., J.A. Early, J.T. Mendoza, et al. 1994. Cytotoxic efficacy of 9-nitrocamptothecin in the treatment of human malignant melanoma cells *in vitro*. *Cancer Res.* 54:771-776.

Pantazis, P., N. Harris, J. Mendoza, et al. 1994 (in press). Conversion of 9-nitro-camptothecin to 9-amino-camptothecin by human blood cells *in vitro*. *Eur. J. Haematology* (3 pp.).

Pantazis, P., H.R. Hinz, J.T. Mendoza, et al. 1992. Complete inhibition of growth followed by death of human malignant melanoma cells *in vitro* and regression of human melanoma xenografts in immunodeficient mice induced by camptothecins. *Cancer Res.* 52(14):3980-3987.

Pantazis, P., A.J. Kozielski, J.T. Mendoza, et al. 1993. Camptothecin derivatives induce regression of human ovarian carcinomas grown in nude mice and distinguish between non-tumorigenic and tumorigenic cells *in vitro*. *Int. J. Cancer* 53(5):863-871.

Pantazis, P., A.J. Kozielski, R. Rodriguez, et al. 1994. Therapeutic efficacy of camptothecin derivatives against human malignant melanoma xenografts. *Melanoma Res.* 4:5-10.

Pantazis, P., A.J. Kozielski, D.M. Vardeman, et al. 1993. Efficacy of camptothecin congeners in the treatment of human breast carcinoma xenografts. *Oncol. Res.* 5(8):273-281.

Pantazis, P., J.T. Mendoza, J.A. Early, et al. 1993. 9-Nitro-camptothecin delays growth of U-937 leukemia tumors in nude mice and is cytotoxic or cytostatic for human myelomonocytic leukemia lines *in vitro*. *Eur. J. Haematology* 50(2):81-89.

Pantazis, P., J.T. Mendoza, A. DeJesus, et al. 1995 (in press). Development of resistance to 9-nitro-camptothecin by human leukemia U-937 cells *in vitro* correlates with altered sensitivities to several anticancer drugs. *Anticancer Drugs.*

Pantazis, P., J.T. Mendoza, A. DeJesus, et al. 1995 (in press). Partial characterization of human leukemia U-937 cell sublines resistant to 9-nitro-camptothecin. *Eur. J. Haematology.*

Pantazis, P., D. Vardeman, J. Mendoza, et al. in press. Sensitivity of camptothecin-resistant human leukemia cells and tumors to

anticancer drugs with diverse mechanisms of action. *Leukemia Res.*

Poddevin, B., J.F. Riou, F. Lavelle, et al. 1992. Dual topoisomerase I and II inhibition by RP 60475, an intercalating agent in early clinical trials. *Proc. Am. Assoc. Cancer Res.* 33:437.

Poddevin, B., J.F. Riou, F. Lavelle, et al. 1993. Dual topoisomerase I and II inhibition by intoplicine (RP 60475), an new antitumor agent in early clinical trials. *Mol. Pharmacol.* 44(4):767-774.

Pommier, Y. 1993. DNA topoisomerase I and II in cancer chemotherapy: update and perspectives. *Cancer Chemother. Pharmacol.* 32(2):103-108.

Potmesil, M., B.C. Giovanella, L.F. Liu, et al. 1991. Preclinical studies of DNA topoisomerase I-targeted 9-amino and 10,10-methylenedioxy camptothecins. In *DNA topoisomerases cancer* (eds. by Potmesil, M. and K.W. Kohn), Pp. 299-311. Oxford University Press, New York.

Potmesil, M., B.C. Giovanella, M.E. Wall, et al. 1993. Preclinical and clinical development of DNA topoisomerase I inhibitors in the United States. In *Molecular biology of DNA topoisomerases and its application to chemotherapy* (eds. by T. Andoh, H. Ikeda, and M. Oguro), Pp. 301-311. CRC Press, Bosca Raton, Florida.

Pratt, C.B., C. Stewart, V.M., Santana, et al. 1993. Phase I study of topotecan for pediatric patients with drug resistant solid tumors. *Proc. Am. Soc. Clin. Oncol.* 12:410.

Pratt, C.B., C. Stewart, V.M., Santana. 1994. Phase I study of topotecan for pediatric patients with malignant solid tumors. *J. Clin. Oncol.* 12(3):539-.

Recondo, G., J. Abbruzzese, B. Newman, et al. 1991. A phase I trial of topotecan (topo) administered by a 24-hr infusion. *Proc. Am. Assoc. Cancer Res.* 32:206.

Riou, J.F., P. Helissey, L. Grondard, et al. 1991. Inhibition of eukaryotic DNA topoisomerase I and II activities by indoloquinolinedione derivatives. *Mol. Pharmacol.* 40:699-706.

Rothenberg, M.L., J. Kuhn, and H.A. Burris. 1992. A phase I pharmacokinetic trial of CPT-11 in patients with refractory solid tumors. *Proc. Am. Soc. Clin. Oncol.* 11:113.

Rothenberg, M.L., H.A. Burris, J.R. Eckhardt, et al. 1993. Phase II study of topotecan + cisplatin in patients with non-small cell lung cancer (NSCLC). *Proc. Am. Soc. Clin. Oncol.* 12:156.

Rothenberg, M.L., J. Kuhn, H.A. Burris, et al. 1992. CPT-11: phase I experience using a weekly schedule. In *Proceedings of the*

Fourth Conference on DNA Topoisomerases in Therapy, Amsterdam, P. 119.

Rothenberg, M.L., et al. 1993. Phase I and pharmacokinetic trial of weekly CPT-11. *J. Clin. Oncol.* 11(11):2194-2204.

Rowinsky, E.K., S. Sartorius, and L.B. Grochow. 1992. Phase I and pharmacologic study of topotecan, an inhibitor of topoisomerase I, with granulocyte colony stimulating factor (G-CSF): Toxicologic differences between concurrent and post-treatment G-CSF administration. *Proc. Am. Soc. Clin. Oncol.* 11:116.

Rowinsky, E.K., L.B. Grochow, D. Ettinger, et al. 1992. Phase I and pharmacologic study of CPT-11, a semisynthetic topoisomerase I-targeting agent, on a single dose schedule. *Proc. Am. Soc. Clin. Oncol.* 11:115.

Rowinsky, E.K., L.B. Grochow, C.B. Hendricks, et al. 1992. Phase I and pharmacologic study of topotecan: a novel topoisomerase I inhibitor. *J. Clin. Oncol.* 10:647-656.

Rowinsky, E.K., et al. 1994. Phase I and pharmacological study of the novel topoisomerase I inhibitor 7-ethyl-10[4-(1-piperidino)-1-piperidino] carbonyloxycamptothecin (CPT-11) administrated as a ninety-minute infusion every 3 weeks. *Cancer Res.* 54(2):427-436.

Rubin, E., P. Pantazis, A. Bharti, et al. 1994. Identification of a mutant human topoisomerase I with intact catalytic activity and resistance to 9-nitro-camptothecin. *J. Biol. Chem.* 269(4):2433-2439.

Sabiers, J.H., N.A. Beijer, S.J. Berger, et al. 1993. Phase I trial of topotecan administered as a 72 hour infusion. *Proc. Am. Assoc. Cancer Res.* 34:426.

Sakata, Y., A. Wakui, I. Nakao, et al. 1993. A late phase II study of irenotecan (CPT-11) in advanced pancreatic cancer. *Proc. Am. Soc. Clin. Oncol.* 12:211.

Saltz, L., M. Sirott, C. Young, et al. 1993. Phase I clinical and pharmacology study of Topotecan given daily for 5 consecutive days to patients with advanced solid tumors, with attempt at dose intensification using recombinant granulocyte colony-stimulating factor. *J. Natl. Cancer Inst. 85*(18):1499-1507.

Sasaki, Y., A. Ohtsu, Y. Shimada, et al. 1994. Simultaneous administration of CPT-11 and Fluorouracil: alteration of the pharmacokinetics of CPT-11 and SN-38 in patients with advanced colorectal cancer. *J. Natl. Cancer Inst.* 86(14):1096-1098.

Scanlon, E.F. 1991. The evolution of breast cancer treatment. *JAMA* 266(9):1280-1281.

Schaeppi, U., R.W. Fleischman, and D.A. Conney. 1974. Toxicity of camptothecin (NSC-100880). *Cancer Chemother. Rep.* 5:25-36.

Shanghai Institute of Materia Medica. 1975. *Chin. Med. J.* 55:274.

Shanghai Institute of Materia Medica. 1978. Studies on the anticancer action of 10-hydroxy camptothecin. *Chin. Med. J.* 58(10):598-602. (Chinese with English abstract).

Shimada, Y., M. Yoshino, A. Wakui, et al. 1991. Phase II study of CPT-11, a new camptothecin derivative, in patients with metastatic colorectal cancer. *Proc. Am. Soc. Clin. Oncol.* 10:135.

Shimada, Y., M. Yoshino, A. Wakui, et al. 1993. Phase II study of CPT-11, a new camptothecin derivative, in metastatic colorectal cancer. *J. Clinl. Oncol.* 11(5):909-.

Shinkai, T., H. Arioka, and H. Kunikane. 1994. Phase I clinical trial of irinotecan (CPT-11), 7-ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxy-camptothecin, and Cisplatin in combination with fixed dose of vindesine in advanced non-small cell lung cancer. *Cancer Res.* 54(10):2636-.

Sirott, M.N., L. Saltz, C. Young, et al. 1991. Phase I and clinical pharmacologic study of intravenous topotecan (T). *Proc. Am. Soc. Clin. Oncol.* 10:104.

Silber, R., M. Potmesil, and B.B. Bank. 1989. Studies on drug resistance in chronic lymphocytic leukemia. *Adv. Enzyme Regul.* 29:267-276.

Slichenmyer, W.J., et al. 1990. New natural products in cancer chemotherapy. *J. Clin. Pharmacol.* 30(9):770-788.

Slichenmyer, W.J., E.K. Rowinsky, R.C. Donehower, et al. 1993. The current status of camptothecin analogues as antitumor agents. *J. Natl. Cancer Inst.* 85(4):271-291.

Smmada, Y., M. Yoshino, A. Wakui, et al. 1991. Phase II study of CPT-11, a new camptothecin derivative with metastatic colorectal cancer. *Proc. Am. Soc. Clin. Oncol.* 10:a408.

Staubus, A.E., M. Rutherford, P. Snuffer, et al. 1992. Kinetics of ring opening of camptothecin analogs and topotecan in plasma and whole blood. *Proc. Am. Assoc. Cancer Res.* 33:531.

Stewart, C.F., S.D. Baker, W.R. Crom, et al. 1993. Clinical pharmacokinetics of topotecan (T) in children with cancer. *Proc. Am. Assoc. Cancer Res.* 34:395.

Suminage, M., H. Furue, and T. Taguchi. Phase I study of CPT-11, a derivative of camptothecin. In *16th International Congress on Chemotherapy*, Jerusalem, Israel, P.82.

Taguchi, S., K. Noda, and M. Yakushiji. 1992. Late phase II study of CPT-11, topoisomerase I inhibitor, in advanced cervical carcinoma (cc). *Proc. Am. Soc. Clin. Oncol.* 11:224.

Takeuchi, S., H. Takamizawa, Y. Takeda, et al. 1991. Clinical study of CPT-11 camptothecin derivative on gynaecological malignancy. *Proc. Am. Soc. Clin. Oncol.* 10:189.

Taguchi, T. 1991. DNA topoisomerase inhibitor as chemotherapeutic drug—clinical point of view. *Gan To Kagaku Ryoho* 18(10):1574-1578. (Japanese with English abstract).

Taguchi, T., A. Wakui, K. Hasegawa, et al. 1990. Phase I clinical study of CPT-11. *Gan To Kagaku Ryoho* 17:115-120. (Japanese with English abstract).

Taguchi, T., et al. 1990. Phase I clinical study of CPT-11. Research group of CPT-11. *Gan To Kagaku Ryoho* 17(1):115-120. (Japanese with English abstract).

Taguchi, T., et al. 1994. An early phase II study of CPT-11 (irinotecan hydrochloride) in patients with advanced breast cancer. *Gan To Kagaku Ryoho* 21(1):83-90. (Japanese with English abstract).

Takeda, S., et al. 1990. Inhibitory effects of CPT-11 on liver metastases in nude mice injected with human pancretaic tumor cells into their spleens. *Gan To Kagaku Ryoho* 17(12):2433-2436. (Japanese with English abstract).

Takeuchi, S., H. Takamizawa, Y. Takeda, et al. 1991. Clinical study of CPT-11, camptothecin derivative, on gynecological malignancy. *Proc. Am. Soc. Clin. Oncol.* 10:189.

Takeuchi, S. 1991a. An early phase II study of CPT-11 in gynecologic cancers. Research Group of CPT-11 in Gynecologic Cancers. *Gan To Kagaku Ryoho* 18(4):579-584. (Japanese with English abstract).

Takeuchi, S., et al. 1991b. A late phase II study of CPT-11 on uterine cervical cancer and ovarian cancer. Research Groups of CPT-11 in Gynecologic Cancers. *Gan To Kagaku Ryoho* 18(10):1681-1689. (Japanese with English abstract).

Takeuchi, S., K. Noda, and M. Yakushui. 1992. Late phase II study of CPT-11, topoisomerase I inhibitor, in advanced cervical carcinoma. *Proc. Am. Soc. Clin. Oncol.* 11:224.

Tanizawa, A., A. Fujimori, Y. Fujimori, et al. 1994. Comparison of topoisomerase I inhibition, DNA damage, and cytotoxicity of camptothecin derivatives presently in clinical trials. *J. Natl. Cancer Inst.* 86(11):836-842.

Teicher, B.A., S.A. Holden., V. Khandakar, et al. 1993. Addition of a topoisomerase I inhibitor to trimodality therapy [cis-diamminedichloroplatinum (II)/heat/radiation] in a murine tumor. *J. Cancer Res. Clin. Oncol.* 119(11):645-651.

Ten Bokkel Huinink, W.W., S. Rodenhuis, J. Beunen, et al. 1992. Phase I study of the topoisomerase I inhibitor topotecan (SK & F 104864). *Proc. Am. Soc. Clin. Oncol.* 11:110.

Tong, W. L. Saltz, M. Sirott, et al. 1991. Rapid HPLC assay for topotecan (T). *Proc. Am. Assoc. Cancer Res.* 32:433.

Tsuda, H., K. Takatsuki, R. Ohno, et al. 1992. A late phase II trial of a potent topoisomerase I inhibitor, CPT-11, in malignant lymphoma. *Proc. Am. Soc. Clin. Oncol.* 11:316.

Tsuruo, T. T. Matsuzaki, M. Matsuzaki, et al. 1988. Antitumor effect of CPT-11, a new derivative of camptothecin, against pleiotropic drug-resistant tumors *in vitro* and *in vivo*. *Cancer Chemother. Pharmacol.* 21:71-74.

Tu, Z.H., M.Y. Wang, W.Q. Xiao, et al. 1990. Effects of 10-hydroxycamptothecin on induced chromosome aberrations in Chinese hamster ovary cells and micronuclei in mouse bone marrow and fetal liver. *Zhongguo Yaoli Xuebao* 11(4):378-381. (Chinese with English abstract).

Venditti, J.M. and B.J. Abbott. 1967. Studies on oncolytic agents from natural sources. Correlation of activity against animal tumors and clinical effectiveness. *Lloydia* 30:332-348.

Venditti, J.M. 1971. Treatment schedule dependency of experimentally active antileukemic (L1210) drugs. *Cancer Chemother. Rep.* 2:35-59.

Verweij, J., B. Lund, J. Beynen, et al. 1992. Clinical studies with topotecan: The EORTC experience. In *Proceedings of the Seventh NCI-EORTC Symposium on New Drugs in Cancer Therapy*, Amsterdam.

Verweij, J., et al. 1993. Phase I and pharmacokinetics study of topotecan, a new topoisomerase I inhibitor. *Ann. Oncol.* 4(8):673-678.

Verweij, J., J. Wanders, F. Calabresi, et al. 1993. Phase II study with topotecan in colorectal cancer. In *Proceedings of EORTC Early Drug Development Meeting*, Rotterdam, P. 31.

Wall, M.E. and M.C. Wani. 1993. Camptothecin and analogs: synthesis, biological *in vitro* and *in vivo* activities, and clinical possibilities. *ACS Symp. Ser.* 534 (*Human medicinal agents from plants*), Pp. 149-169.

Wall, J.G., H. Burris, G. Rodriguez, et al. 1991. Phase I trial of topotecan (SK and F 104864) in patients with refractory solid tumors. *Proc. Am. Soc. Clin. Oncol.* 10:98.

Wall, J.G., K. Havlin, S. Burris, et al. 1990. Phase I study of SK & F 104864, a novel topoisomerase I inhibitor. *Proc. Am. Soc. Clin. Oncol.* 9:336.

Wall, J.G., H. Burris, D. Van Hoff, et al. 1992. A phase I clinical and pharmacokinetic study of the topoisomerase I inhibitor topotecan (SK & F 104864) given as an intravenous bolus every 21 days. *Anticancer Drugs* 3(4):337-342.

Wang, Y., K. Inoue, and H. Shibata. 1987. Preclinical evaluation of a new camptothecin derivative, CPT-11, on the subrenal capsule assay. *Gan To Kagaku Ryoho*14:1264-1270. (Japanese with English abstract).

Waud, W.R., S.D. Harrison, Jr., K.S. Gilbert, et al. 1991. Antitumor drug cross-resistance *in vivo* in a cisplatin-resistant murine P388 leukemia. *Cancer Chemother. Pharmacol.* 27(6):456-463.

Xu, B., J.T. Chang, J.L. Yang, et al. 1979. New results in parmacologic research of some anticancer agents. In *Proceedings of US-China Pharmacology Symposium, Commuttee on Scholarly Communication with the People's Republic of China*, eds. by J.J. Burns and P.J. Tsuchitani. Pp. 151-158.

REVIEW

OF CAMPTOTHECINS

Cai, J.C. and C.R. Hutchinson. 1983. Camptothecin. *The Alkaloids* 21:101-137.

Creemers, G.J., B. Lund, J. Verweij, et al. 1994. Topoisomerase I inhibitors: topotecan and irinotecan. *Cancer Treat. Rev.* 20(1):73-.

Darzynkiewicz, Z., S. Bruno, G. Del Bino, et al. 1992. Features of apoptotic cells measured by flow cytometry. *Cytometry* 13:795-808.

Hutchinson, C. R. 1981. Camptothecin: chemistry, biogenesis and medicinal chemistry. *Tetrahedron* 37:1047-1065.

Jenks, S. 1994. Camptothecins resurface as promising drugs. *J. Natl. Cancer Inst.* 86(15):1118-1119.

Misawa, M., H. Tanaka, and N. Mukai. 1973. Anticarcinogenic camptothecin. *Jpn. Kokai* 14 pp. (Japanese).

Perdue, R.E., R.L. Smith, M.E. Wall., et al. 1970. *Camptotheca acuminata* Decaisne (Nyssaceae) source of camptothecin, and antileukemic alkaloid. *Agr. Res. Ser. USDA Techn. Bull.* No.1415. 26 pp.

Schultz, A.G. 1973. Camptothecin. *Chem. Rev.* 73(4):385-405.

Shamma, M. and V.S. Georgiev. 1974. Camptothecin. *J. Pharm. Sci.* 63(2):163-183.

Slichenmyer, W.J., E.K. Rowinsky, R.C. Donehower, et al. 1993. The current status of camptothecin analogues as antitumor agents. *J. Natl. Cancer Inst.* 85(4):271-291.

Sugasawa, T., T. Toyoda, and K. Sasakura. 1974. Camptothecin. *Jpn. Kokai* 8 pp. (Japanese).

Wall, M.E. 1993. Camptothecin and Taxol. In *Chronicles of Drug Discovery* 327-348.

Wall, M.E. and M.C. Wani. 1993. Camptothecin and analogs: synthesis, biological *in vitro* and *in vivo* activities, and clinical

possibilities. *ACS Symp. Ser.* 534 (*Human medicinal agents from plants*), Pp. 149-169.

SYNTHESIS

OF CAMPTOTHECINS

Aimi, N., M. Ueno, H. Hoshino, et al. 1992. Synthesis and absolute configuration of chaboside, first natural gluco-camptothecin. *Tetrahedron Lett.* 33(37):5403-5404.

Baxmann, E. and E. Winterfeldt. 1978. Total synthesis of 7-methoxycamptothecin. *Chem. Ber.* 111(10):3403-3411.

Boch, M., T. Korth, J.M. Nelke, et al. 1972. Reaktionen an indolderivaten: XVII. Die biogenetisch orientierte totalsynthese Von DL-camptothecin and 7-chlor-camptothecin. [Reactions with indole derivatives: XVII. The biologically oriented total-synthesis of DL-camptothecin and 7-chlorocamptothecin]. *Chem. Ber.* 105(7):2126-2142. (German with English abstract).

Borch, R.F., C.V. Grudzinskas, D.A. Peterson, et al. 1972. New synthesis of substituted 2(1H)-pyridones. Synthesis of a potential camptothecin intermediate. *J. Org. Chem.* 37(8):1141-1145.

Bradley, J.C. and G. Buchi. 1976. The short synthesis of camptothecin [*Camptotheca acuminata*]. *J. Org. Chem.* 41(4):699-701.

Bryson, T.A. 1970. *Total synthesis of camptothecin.* Dissertation of University of Pittsburgh, Pittsburgh, Pennsylvania, 137 pp. Avail. Xerox Univ. Microfilms, Ann Arbor, Mich., Order No. 71-4456. Diss. Abstr. Int. B 1971, 31(8):4567-4568.

Cai, J.C., M.G. Yin, A.Z. Min, et al. 1981. Total synthesis of dl-10-hydroxycamptothecin and dl-10-methoxycamptothecin. *Huaxue Xuebao* 39(2):171-178. (Chinese with English abstract).

Comins, D.L. and M.F. Baevsky. 1993. Methods and intermediates for the assymmetric synthesis of camptothecin and camptothecin analogs. *U.S.*, 15 pp.

Comins, D.L., M.F. Baevsky, and H. Hao. 1992. A 10-step, asymmetric synthesis of (s)-camptothecin. *J. Am. Chem. Soc.* 114:10971-10972.

Comins, D.L., H. Hong, G. Jianhua, et al. 1994. Asymmetric synthesis of camptothecin alkaloids: a nine-step synthesis of (S)-camptothecin. *Tetrahedron Lett.* 35(30):5331.

Corey, E.J., D.N. Crouse, and J.E. Anderson. 1975. Total synthesis of natural 20(S)-camptothecin. *J. Org. Chem.* 40(14):2140-2141.

Crouse, D.N. 1976. *The total synthesis of natural 20-(S)-camptothecin.* Dissertation of Harvard University, Cambridge, Massachusetts, 118 pp. Avail. Xerox Univ. Microfilms, Ann Arbor, Mich., Order No. 76-15,512.

Crow, R.T. and D.H. Crothers. 1992. Structural modifications of camptothecin and effects on topoisomerase I inhibition. *J. Med. Chem.* 35(22):4160-.

Curran, D.P. and H. Liu. 1992. New 4 + 1 radical annulations. A formal total synthesis of (±)-camptothecin. *J. Am. Chem. Soc.* 114:5863-5864.

Curran, D.P., J. Sisko, P.E. Yeske, et al. 1993. Recent applications of radical reactions in natural product synthesis. *Pure Appl. Chem.* 65(6):1153-1159.

Danieli, B. and G. Palmisano. 1974. Sintesi totali della camptothecina [Total synthesis of camptothecin, *Camptotheca acuminata*]. *Fitoterapia* 45(3):87-101. (Italian with English abstract).

Danishefsky, S. and S.J. Etheredge. 1974. Synthesis and biological evaluation of de-AB-camptothecin. *J. Org. Chem.* 39(23):3430-3432.

Danishefsky, S., J. Quick, and S.B. Horwitz. 1973. Synthesis and biological activity in the camptothecine series. *Tetrahedron Lett.* (27):2525-2528.

Earl, R.A. 1983. *Approaches to the indolizine and quinolizine ring systems via thermal and metal-mediated methods: the synthesis of camptothecin.* Dissertation of University of California at Berkeley, Berkeley, California. 209 pp. Avail. Univ. Microfilms Int., Order No. 8413369. Diss. Abstr. Int. B 1984 45(3):874.

Earl, R.A. and K.P.C. Vollhardt. 1983. Chobalt-catalyzed cocyclizations of isocyanato alkynes: a regiocontrolled entry into 5-indolizinones. Application to the total synthesis of camptothecin. *J. Am. Chem. Soc.* 105(23):6991-6993.

Eggler, J.F. 1971. *Total synthesis of camptothecin.* Dissertation of University of Pittsburgh, Pittsburgh, Pennsylvania, 81 pp. Avail. Xerox Univ. Microfilms, Ann Arbor, Mich., Order No. 72-2141. Diss. Abstr. Int. B 1972, 32(7):3848.

Ejima, A., H. Terasawa, M. Sugimori, et al. 1989a. Antitumor agents. 1. Asymmetric synthesis of camptothecin. *Tetrahedron Lett.* 30(20):2639-2640.

Ejima, A., H. Terasawa, M. Sugimori, et al. 1989b. Antitumor agents. 4. Synthesis and antileukemic activity of (±)-20-deoxyaminocamptothecin analogues. *Chem. Pharm. Bull.* (Tokyo) 37(8):2253-2255.

Ejima, A., H. Terasawa, M. Sugimori, et al. 1990. Antitumor agents. 2. Asymmetric synthesis of (S)-camptothecin. *J. Chem. Soc. Perkin. Trans.* 1(1):27-31.

Ejima, A., H. Terasawa, M. Sugimori, et al. 1992. Antitumor agents. 5. Synthesis and antileukemic activity of E-ring-modified (RS)-camptothecin analogues. *Chem. Pharm. Bull.* (Tokyo) 40(3):683-688.

El-Sayad, H.A. 1974. *Investigations of the synthesis of a camptothecine intermediate.* Dissertation of University of North Carolina, Chapel Hill, North Carolina, 53 pp. Avail. Xerox Univ. Microfilms, Ann. Arbor, Mich., Order No. 75-4815. Diss. Abstr. Int. B 1975, 35(8):3827-3828.

French, K.A. 1975. *Circular dichroism study of ketal formation of some steroidal ketones. Synthesis of camptothecin and analogs.* Dissertation of Georgia Institute of Technology, Atlanta, Georgia, 148 pp. Avail. Xerox Univ. Microfilms, Ann Arbor, Mich., Order No. 75-17,488. Diss. Abstr. Int. B 1975, 36(3):1218.

Gao, Y.S. 1982. A selected review of recent chemical studies of Chinese medicinal plants and synthetic studies related to camptothecins and their modifications. In *Proceedings of Sino-American Symposium of Chemistry of Natural Priducts* (1980, ed. by Y. Wang), Pp. 83-93. Science Press, Beijing.

Grudzinskas, C.V. 1971. *Synthesis of the D and E rings of camptothecin.* Dissertation of University of Minnesota, Minneapolis, Minnesota, 44 pp. Avail. Xerox Univ. Microfilms, Ann Arbor, Mich., Order No. 71-22,260. Diss. Abstr. Int. B 1971, 32(3):1449-1450.

Heckendorf, A.H. and C.R. Hutchinson. 1977. Biosynthesis of camptothecin. II. Confirmation that isovincoside, not vincoside, is the penultimate biosynthetic precursor of indole alkaloids. *Tetrahedron Lett.* 48:4153-4154.

Hutchinson, C.R., A.H. Heckendorf, P.E. Duddonu, et al. 1974. Biosynthesis of camptothecin. I. Definition of the overall pathway assisted by carbon-13 nuclear magnetic resource analysis. *J. Am. Chem. Soc.* 96(17):5609-5611.

Hutchinson, C.R., A.H. Heckendorf, J.L. Stranghn, et al. 1979. Biosynthesis of camptothecin. 3. Definition of strictosamide as the penultimate biosynthetic precursor assisted by ^{13}C and ^{2}H HMR spectroscopy. *J. Am. Chem. Soc.* 101(12):3358-3369.

Ihara, M. 1987. Synthesis of heterocyclic natural products by new enamine annulation and sulfeno-cycloamination. *Yakugaku Kenkyu no Shinpo* (3):134-152. (Japanese with English abstract).

Ihara, M., K. Noguchi, T. Ohsawa, et al. 1982. An alternative biomimetic synthesis of (±)-camptothecin. *Heterocycles* 19(10):1835-1838.

Ihara, M., K. Noguchi, T. Ohsawa, et al. 1983. Studies on the synthesis of heterocyclic compounds and natural products. 999. Double enamine annelation of 3,4-dihydro-1-methyl beta-carboline and isoquinoline derivatives with 6-methyl-2-pyrone-3,5-dicarboxylates and its application for the synthesis of (±)-camptothecin. *J. Org. Chem.* 48(19):3150-3156.

Isaac, W. 1972. *Approaches to the synthesis of camptothecin.* Dissertation of University of Michigan, Ann Arbor, Michigan, 143 pp. Avail. Xerox Univ. Microfilms, Ann Arbor, Mich., Order No. 73-6851. Diss. Abstr. Int. B 1973, 33(9):4195.

Kametani, T., T. Ohsawa, and M. Ihara. 1980. A facile synthesis of (±)-camptothecin by enamine annulation. *Heterocycles* 14(7):951-953.

Kametani, T., T. Ohsawa, and M. Ihara. 1981. Studies on the syntheses of racemic heterocyclic compounds:878. Synthesis of racemic-camptothecin and racemic-10-hydroxycamptothecin via enamine annulation. *J. Chem. Soc. Perkin.Trans.* 10(5):1563-1568.

Kametani, T., S. Takano, and H. Takeda. 1972. Syntheses of herterocyclic compounds: CDLXXIV. Synthesis of camptothecin and related compounds: III. Syntheses of 12-ethyl-6,7,10,12,13,13a-hexahydro-12-hydroxy-1H,9H-furano[3,4-g]indolo[3,2-d]quinolizine. *Yakugaku Zasshi* 92(6):743-746. (Japanese with English abstract).

Kametani, T., H. Nemoto, H. Takeda, et al. 1970a. Synthetic approach to camptothecin. *Chem. Ind.* (London) 41:1323-1324.

Kametani, T., H. Nemoto, H. Takeda, et al. 1970b. Syntheses of heterocyclic compounds. CCCLXXI. Synthetic approach to camptothecin. *Tetrahedron* 26(24):5753-5755.

Kametani, T., S. Takano, H. Nemoto, et al. 1971. Studies on the synthesis of heterocyclic compounds: CDXXX. Synthesis of

camptothecin and related compounds: II. A synthesis of 4-ethyl-4-hydroxy-5-mrthoxy-6-methyl-3-oxo-1,2,3,4-tetrahydro-2,7-naphthyricline. *Yakugaku Zasshi* 91(9):966-971. (Japanese with English abstract).

Kametani, T., S. Takano, H. Terasawa, et al. 1972. Synthesis of heterocyclic compounds. CDLXXVI. Synthesis of camptothecin and related compounds. IV. Synthesis of 8-cyano-7ethoxycarbonyl-9,11-dihydro-9,11-dioxoindolizino[1,2-b]quinoline. *Yakugaku Zasshi* 92(7):868-870. (Japanese with English abstract).

Kametani, T., H.Takeda, F. Satoh, et al. 1973. Synthesis of a potential camptothecin intermediate. *J. Heterocycl. Chem.* 10(1):77-78.

Kende, A.S., T.J. Bentley, R.W. Draper, et al. 1973. Total synthesis of DL-camptothecin from furfural. *Tetrahedron Lett.* 16:1307-1310.

Kepler, J.A., M.C. Wani, J.N. McNaull, et al. 1969. Plant antitumor agents. IV. An approach toward the synthesis of camptothecin. *J. Org. Chem.* 34(12):3853-3858.

Kingsbury, W.D., J.C. Boehm, D.R. Jakas, et al. 1991. Synthesis of water-soluable (aminoalkyl) camptothecin analogues: inhibition of topoisomerase I and antitumor activity. *J. Med. Chem.* 34:98-107.

Kingsbury, W.D., R.P. Hertzberg, J.C. Boehm, et al. 1989. Chemical synthesis and structure-activity-relationships related to SK & F 104864, a novel watersoluble analog of camptothecin. *Proc. Am. Soc. Cancer Res.* 30:622.

Liao, T.K., W.H. Nyberg, and C.C. Cheng. 1971. Total synthesis of camptothecin. I. Synthesis of ethyl 8-(alpha-chlorobutyryloxymethyl)-7,9-dioxo-7,8,9,11-tetrahydrpo-indolizino [1,2-a]quinoline-8-carboxylate and related tetracyclic compounds. *J. Heterocycl.* Chem. 8(3):373-377.

Lyle, R.E., J.A. Bristol, M.J. Kane, et al. 1973. Synthesis of an analog of camptothecin by a general method. *J. Org. Chem.* 38(19):3268-3271.

Meyers, A.I., R.L. Nolen, E.W. Collington, et al. 1973. Total synthesis of camptothecin and desethyldesoxycamptothecin. *J. Org. Chem.* 38(11):1974-1983.

Mukherjee, A. and W.C. Agosta. 1993. Concise total synthesis of di-camptothecin and related anticancer drugs. *Chemtracts: Org. Chem.* 6(2):75-78.

Nabors, J. 1970. *Synthesis of diterpenoid alkaloids.* Synthesis of camptothecin. Dissertation of Georgia Institute of Technology, Atlanta, Georgia, 121 pp. Avail. Xerox Univ. Microfilms, Ann Arbor, Mich., Order No. 70-12,973. Diss. Abstr. Int. B 1970, 31(1):125-126.

Nicholas, A.W., M.C. Wani, G. Manikumar, et al. 1990. Plant antitumor agents. 29. Synthesis and biological activity of ring D and ring E modified analogues of camptothecin. *J. Med. Chem.* 33(3):972-978.

Nicholas, A.W., M.C. Wani, M.E. Wall, et al. 1993. Synthesis of position-specific tritium-labeled 20(line under S)-camptothecin, 9-amino-20(S)-camptothecin, and 10,11-methylenedioxy-20(line under S)-camptothecin. *J. Lab. Comp. Radioph.* 33(9):839-848.

Peterson, D.A. 1971. *Studies toward the total synthesis of camptothecin.* Dissertation of University of Minnesota, Minneapolis, Minnesota, 43 pp. Avail. Xerox Univ. Microfilms, Ann Arbor, Mich., Order No. 72-5566. Diss. Abstr. Int. B 1972, 32(10):5697.

Plattner, J.J., R.D. Gless, and G.K. Cooper. 1974. Synthesis of some DE and CDE ring analogs of camptothecin. *J. Org. Chem.* 39(3):303-311.

Plattner, J.J., R.D. Gless, and H. Rapoport. 1972. Synthesis of some DE and CDE ring analogs of camptothecin. *J. Am. Chem. Soc.* 94(24):8613-8615.

Quick, J.E. 1972. *Total synthesis of camptothecin and a D,E-ring analog.* Dissertation of University of Pittsburgh, Pittsburgh, Pennsylvania, 144 pp. Avail. Xerox Univ. Microfilms, Ann Arbor, Mich., Order No. 73-5008. Diss. Abstr. Int. B 1973, 33(9):4201-4202.

Rama, A.V., J.S. Yadav, and V. Muralikrishna. 1994. Regioselective synthesis of camptothecin. *Tetrahedron Lett.* 35(21):3613-.

Raucher, S. 1973. Approach to the synthesis of camptothecin. Dissertation of University of Minnesota, Minneapolis, Minnesota, 56 pp. Avail. Xerox Univ. Microfilms, Ann Arbor, Mich., Order No. 74-10,571. Diss. Abstr. Int. B 1974, 34(12):5912.

Sawada, S., S. Matsuoka, K. Nokata, et al. 1991. Synthesis and antitumor activity of 20(S)-camptothecin derivatives: A-ring modified and 7,10-disubstituted camptothecins. *Chem. Pharm. Bull.* (Tokyo) 39(12):3183-3188.

Sawada, S., K. Nokata, T. Furuta, et al. 1991. Chemical modification of an antitumor alkaloid camptothecin: synthesis and antitumor activity of 7-C-substituted camptothecins. *Chem. Pharm. Bull.* (Tokyo) 39(10):2574-2580.

Sawada, S., S. Okajima, R. Aiyama, et al. 1991. Synthesis and antitumor activity of 20(S)-camptothecin derivatives: carbamate-linked, water-soluble derivatives of 7-ethyl-10-hydroxycamptothecin. *Chem. Pharm. Bull.* (Tokyo) 39(6):1446-1454.

Sawada, S., T. Yaegashi, T. Furuta, et al. 1993. Chemical modification of an antitumor alkaloid, 20(S)-camptothecin: E-lactone ring-modified water soluble derivatives of 7-ethylcamptothecin. *Chem. Pharm. Bull.* 41(2):310-310.

Schultz, A.G. 1973. Camptothecin. *Chem. Rev.* 73(4):385-405.

Shamma, M. and L. Novak. 1969. Synthetic approaches to camptothecine. *Tetrahedron* 25(11):2275-2279.

Shamma, M., D.A. Smithers, and V. St Georgiev. 1973. A total synthesis of (+)-camptothecin. *Tetrahedron* 29(14):1949-1954.

Shanghai No. 5 Pharmaceutical Plant, Shanghai No. 12 Pharmaceutical Plant, and Shanghai Institute of Pharmaceutical Industrial Research. 1978. The total synthesis of dl-camptothecin. *Sci. Sin.* (Engl. Ed.) 21(1):87-98.

Sheriha, G.M. and H. Rapoport. 1976. Biosynthesis of *Camptotheca acuminata* alkaloids. *Phytochemistry* 15(4):505-508.

Shu, A.Y.L., D. Jakas, and J.R. Heys. 1990. Synthesis of tritiated (S)-10-bromoacetamidomethylcamptothecin. *J. Labelled Compd. Radiopharm.* 28(11):1256-1276.

Smith, T.H. 1974. *Synthetic approaches to camptothecin. Synthesis of [Trp8] luteinizing hormone releasing hormone. Synthesis of potentially antineoplastic N-tritroso compounds.* Dissertation of Arizona State University, Tempe, Arizona, 180 pp. Avail. Univ. Microfilms, Ann Arbor, Mich., Order No. 74-20,148. Diss. Abstr. Int. B 1974, 35(3):1210-1211.

Smithers, D.A. 1972. *Synthetic approaches to (±)-camptothecin.* Dissertation of Pennsylvania State University, University Park, Pennsylvania, 128 pp. Avail. Univ. Microfilms, Ann Arbor, Mich., Order No. 72-7482. Diss. Abstr. Int. B 1973, 33(10):4699.

Stork, G. and A.G. Schultz. 1971. The total synthesis of *dl*-Camptothecin. *J. Am. Chem. Soc.* 93:4074-4075.

Sugasawa, T., T. Toyoda, and K. Sasakura. 1972. Total synthesis of dl-camptothecin. *Tetrahedron Lett.* (50):5109-5112.

Sugasawa, T., T. Toyoda, N. Uchida, et al. 1976. Experiments on the synthesis of dl-camptothecin. 4. Synthesis and antileukemic activity of dl-camptothecin analogues. *J. Med. Chem.* 19(5):675-679.

Sugimori, M., A. Ajima, S. Ohsuki, et al. 1994. Antitumor agents. VI. Synthesis and antitumor activity of ring A-, ring B-, and ring c-modified derivatives of camptothecin. *Heterocycles* 38(1):81-86.

Tang, C.F. and H. Rapoport. 1972. A total synthesis of (±)-camptothecin. *J. Am. Chem. Soc.* 94(24):8615-8616.

Tang, C.F., C.J. Morrow, and H. Rapoport. 1975. A total synthesis of *dl*-camptothecin. *J. Am. Chem. Soc.* 97:159-167.

Terasawa, H., A. Ejima, and M. Sugimori. 1991. Synthesis and antitumor activity of camptothecin analogs. *Yuki Gosei Kagaku Kyokaishi* 49(11):1013-1020. (Japanese).

Terasawa, H., M. Sugimori, S. Ohsuki, et al. 1992. Antitumor agents. V. Synthesis and antileukemic activity of E-ring-modified (RS)-camptothecin analogues. *Chem. Pharm. Bull.* 40(3):683-.

Volkmann, R.A. 1972. *Total synthesis of dl-camptothecin.* Dissertation of University of Pittsburgh, Pittsburgh, Pennsylvania, 123 pp. Avail. Xerox Univ. Microfilms, Ann Arbor, Mich., Order No. 73-1659. Diss. Abstr. Int. B 1973, 33(11):5218.

Wall, M.E. and M.C. Wani. 1993. Camptothecin and analogs: synthesis, biological *in vitro* and *in vivo* activities, and clinical possibilities. *ACS Symp. Ser.* 534 (*Human medicinal agents from plants*), Pp. 149-169.

Wall, M.E., H.F. Campbell, and M.C. Wani. 1972. Plant antitumor agents: X. The total synthesis of a ring DE analog of camptothecin. *J. Am. Chem. Soc.* 94(10):3632-3633.

Wall, M.E., M.C. Wani, S.M. Natschke, et al. 1986. Plant antitumor agents. 22. Isolation of 11-hydroxycamptothecin from *Camptotheca acuminata* Decne: total synthesis and biological activity. *J. Med. Chem.* 29(8):1553-1555.

Wall, M.E., M.C. Wani, A.W. Nicholas, et al. 1990a. Synthesis of camptothecin and its analogs as antitumor agents. *PCT Int. Appl.* 51 pp.

Wall, M.E., M.C. Wani, A.W. Nicholas, et al. 1990b. Synthesis of camptothecin and its analogs as neoplasm inhibitors. *U.S.* 14 pp.

Wall, M.E. M.C. Wani, A.W. Nicholas, et al. 1993. Plant Antitumor agents. 30. Synthesis and structure activity of novel camptothecin analogs. *J. Med. Chem.* 36:2689-2700.

Walraven, H.G.M. and U.K. Pandit. 1975. Facile two synthon approach to deethyldeoxycamptothecin. *Tetrahedron Lett.* (50):4507-4510.

Walraven, H.G.M. and U.K. Pandit. 1980. A facile two synthon approach to the camptothecin skeleton. *Tetrahedron* 36(2):321-327.

Wang, S., C.A. Coburn, W.G. Bornmann, et al. 1993. Concise total synthesis of dl-camptothecin and related anticancer drugs. *J. Org. Chem.* 58(3):611-617.

Wani, M.C., A.W. Nicholas, and M.E. Wall. 1986. Plant antitumor agents 23. Synthesis and antileukemic activity of camptothecin analogues. *J. Med. Chem.* 29(11):2358-2363.

Wani, M.C., A.W. Nicholas, and M.E. Wall. 1987. Plant antitumor agents. 28. Resolution of a key tricyclic synthon. 5'(RS)-1,5-dioxo-5'-ethyl-5'-hydroxy-2H', 5'H, 6'H-6'-oxopyrano[3', 4'-f]delta 6,8-tetrahydro-indolizine:total synthesis and antitumor activity of 20(S)- and 20 (R)-camptothecin. *J. Med. Chem.* 30(12):2317-2319.

Wani, M.C., H.F. Campbell, G.A. Kepler, et al. 1972. Plant antitumor agents: IX. The total synthesis of di-camptothecin. *J. Am. Chem. Soc.* 90(10):3631-3632.

Wani, M.C., J.A. Kepler, J.B. Thompson, et al. 1970. Plant antitumor agents: alkaloids: synthesis of a pentacyclic camptothecin precursor. *J. Chem. Soc. D.* (7):404.

Wani, M.C., A.W. Nicholas, G. Manikumar, et al. 1987. Plant antitumor agents. 25. Total synthesis and antileukemic activity of ring A substituted camptothecin analogues. Structure-activity correlations. *J. Med. Chem.* 30(10):1774-1779.

Wani, M.C., P.E. Ronman, J.T. Lindley, et al. 1980. Plant antitumor agents. 18. Synthesis and biological activity of camptothecin analogues. *J. Med. Chem.* 23:554-560.

Weber, L.D. 1972. *Approach to the synthesis of the E ring of camptothecin.* Dissertation of University of Minnesota, Minneapolis, Minnesota, 55 pp. Avail. Xerox Univ. Microfilms, Ann Arbor, Mich., Order No. 73-1073. Diss. Abstr. Int. B 1972, 33(7):3009-3010.

Wenkert, E., K.G. Dave, R.G. Lewis, et al. 1967. General methods of synthesis of indole alkaloids, IV. Synthesis of dl-corynantheidine and a camptothecin model. *J. Am. Chem. Soc.* 89(25):6741-6745.

Winterfeldt, E., T. Korth, D. Pike, et al. 1972. Biogenetically oriented total synthesis of camptothecin and 7-chlorocamptothecin. *Angew. Chem. Int. Ed. Engl.* 11(4):289-290.

Yaegashi, T., S. Sawada, T. Furuta, et al. 1992. Chemical modification of an antitumor alkaloid, 20(S)-camptothecin:

glycosides, phosphates and sulfates of 7-ethyl-10-hydroxycamptothecin. *Chem. Pharm. Bull.* (Tokyo) 40(1):131-135.

Yaegashi, T., S. Sawada, T. Furuta, et al. 1993. Chemical modification of an antitumor alkaloid, 20(S)-camptothecin and 7-ethylcamptothecin: reaction of the E-lactone ring portion with hydrazine hydrate. *Chem. Pharm. Bull.* 41(5):971-974.

Zalkow, L.H., J.B. Nabors, K. French, et al. 1972. Studies in the synthesis of camptothecin: an efficient synthesis of 2,3-dihydro-1H-pyrrolo[3,4-b]quinoline. *J. Chem. Soc. Sect. C. Org. Chem.* 21:3551-3554.

NOTES TO MAJOR NON-ENGLISH JOURNALS

Aichi Ika Daigaku Igakkai Zasshi (Japanese with English abstract);

Anhui Linye Keji (安徽林業科技) = Anhui Forest Science and Technology (Chinese);

Biologisches Zentralblatt (an International Journal of Cell Biology, Genetics, Evolution, and Theoretical Biology, text and abstract in English and German);

Chemistry Berlin (German with English abstract);

Ch'eng-kung Ta Hsueh Hsuch Pao (成功大學學報) = Journal of Ch'eng-kung University (Chinese with English abstract);

Chung Hua Fang She Hsueh Tsa Chih (中華防治學雜誌) (Chinese with English abstract);

Chung Hua Wai Ko Tsa Chih (中華外科雜誌) (Chinese with English abstract);

Faming Zhuanli Shenqing Gongkai Shuomingshu, P.R. China (發明專利申請公開說明書) = Public Manual of Application for P. R. China Patent (Chinese);

Farumashia = Pharmacy (Japanese);

Fenxi Huaxue (分析化學) = Analytical Chemistry (Chinese with English abstract);

Fitoterapia (Italian with English abstract);

Gan To Kagaku Ryoho = Japanese Journal of Cancer Chemotherapy (Japanese with English abstract);

Han'guk Saenghwa Hakhoechi (Korean with English abstract);

Hejishu (核激素) (Chinese with English abstract);

Hua Hsueh (化學) = Chemistry (Chinese with English abstract);

Huaxue Tongbao (化學通報) = Chemistry Bulletin (Chinese with English abstract);

Huaxue Xuebao (化學學報) = Hua Hsueh Hsueh Pao = Acta Chimica Sinica (Chinese with English abstract);

Hunan Shifan Daxue Xuebao (湖南師范大學學報) = Journal of Hunan Normal University (Natural Science Edition) (Chinese with English abstract);

Igaku no Ayumi (Japanese);

Izv. Akad. Nauk. Turkm. Ser. Biol. Nauk. (Turkmen with English abstract);

Japan Kokai (Japanese);

Japanese Journal of Clinical Oncology (Japanese with English abstract);

Japanese Kokai Tokkyo Koho (Japanese with English abstract);

Journal of Faculty of Sciences Hokkaido University (Japanese with English abstract);

Journal of Pharmacological Society of Korean (Korean with English abstract);

Kexue Tongbao (科學通報) = K'o Hsueh T'ung Pao = Science Bulletin (Chinese with English abstract);

Kunchong Xuebao (昆虫學報) = Kun Chung Hsueh Pao = Acta Entomologica Sinica (Chinese with English abstract);

Linye Keji (林業科技) = Forest Science and Technology (Chinese with English abstract);

Nanjing Nongye Daxue Xuebao (南京農業大學學報) = Journal of Nanjing Agricultural University (Chinese with English abstract);

Nippon Geka Gakkai Zasshi (Japanese);

Nippon Steitai Gakkaishi = Japanese Journal of Ecology (English, French, German, and Japanese);

Saibo Kogaku (Japanese);

Scientific Reports of Kyoto Perfectual University (Japanese with English abstract);

Shenyang Yaoxueyuan Xuebao (瀋陽藥學院學報) = Journal of Shenyang College of Pharmacology (Chinese with English abstract);

Shoyakugaku Zasshi = Japanese Journal of Pharmacognosy (Japanese with English abstract);

Tanpakushitsu Kakusan Koso = Protein, Nucleic Acid, Enzyme (Japanese);

Tennen Yuki Kagobutsu Tornkai Koen Yoshishu (Japanese with English abstract);

Yakugaku Zasshi (Japanese with English abstract);

Yakubutsu Dotai = Xenobiotic Metabolism (Japanese);

Yakuruto Kenkyusho Kenkyu Hokokushu (Japanese);

Yaoxue Tongbao (藥學通報) = Chinese Pharmaceutical Bulletin (Chinese with English abstract);

Yaoxue Xuebao (藥學學報) = Acta Pharmaceutica Sinica (Chinese with English abstract);

Yaoxue Zhiliao (藥學資料) = Information of Pharmacology (Chinese);

Yuki Gosei Kagaku Kyokaishi (Japanese with English abstract);

Zhenjun Xuebao (真菌學報) = Acta Mycologica Sinica (Chinese with English abstract);

Zhiwu Fenlei Xuebao (植物分類學報) = Acta Phytotaxonomy Sinica (Chinese with English abstract);

Zhiwu Xuebao (植物學報) = Chih Wu Hsueh Pao = Acta Botanical Sinica (Chinese with English abstract);

Zhong Cao Yao (中草藥) = Chung Ts'ao Yao = Chinese Traditional and Herbal Drugs (Chinese with English abstract);

Zhong Cao Yao Tong Xun (中草藥通訊) = Communication of Traditional and Herbal Drugs (Chinese);

Zhonghua Yixue Zazhi (中華醫學雜誌) = Chung Hua I Hsueh Tsa Xhih = Chinese Journal of Medicine (Chinese with English abstract);

Zhongguo Yaoli Xuebao (中國藥理學報) = Chung-kuo Yao Li Hsueh Pao = Acta Pharmacologica Sinica (Chinese with English abstract);

Zhongguo Yaoxue Zazhi (中國藥學雜誌) (Chinese with English abstract);

Zhonghua Zhongliu Zazhi (中華腫瘤雜誌) = Chinese Journal of Clinical Oncology (Chinese with English abstract);

Zhong Xi Yi Jiehe Zazhi (中西醫結合雜誌) = Chung Kuo Chung Hsi I Chieh Ho Tsa Chih = Chinese Journal of Integrated Traditional and Western Medicine (Chinese with English abstract);

Zhongyao Tongbao (中藥通報) = Bulletin of Chinese Materia Medica (Chinese with English abstract).

APPENDIX

Climatic Factors in the Natural Range of Xi Shu in China and the Potential Range in the Southeastern United States

Data Sources: 1. World-Climates (by B. W. Rudloff, Wissenschaftliche Verlagsgesellschaft mbH Stuttgart, 1981); 2. The Times Books World Weather Guide (by E. A. Pearce and G. Smith, Times Books Random House, 1990); 3. Physical Geography of China (by S. Q. Zhao, Science Press and John Wiley & Sons, 1990); 4. Weather of U.S. Cities (fourth edition, edited by F. E. Bair, Gale Research Inc., 1992).

Temperature: Fahrenheit from Celsius: $°F = 1.8 \times °C + 32$
Precipitation: 1 in = 25.4 mm

Table 1. Mean percentage of possible sunshine in the natural range of Xi Shu in China and potential range in the southeastern United States (1961-1990). (%)

Location	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Ann
CHINA													
Shanghai	45	39	38	30	38	40	57	63	48	50	47	45	45
Wuhan, Hubei	40	36	33	38	42	51	61	67	55	49	45	43	47
Nanchang, Jiangxi	37	25	25	23	26	30	46	67	75	66	58	49	44
Chengdu, Sichuan	24	21	25	28	32	32	39	42	25	19	21	21	28
Guangzhou, Guangdong	42	27	21	25	38	40	56	55	54	66	59	50	44
Guilin, Guangxi	24	13	16	27	28	36	44	54	56	41	38	41	34
Kunming, Yunnan	73	74	76	73	59	37	36	45	47	44	65	68	58
Mean	41	34	33	35	38	38	48	56	51	47	48	45	43

Table 1. (continued).

Location	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Ann
UNITED STATES													
Houston, Texas	43	48	50	54	58	64	66	65	62	61	49	51	56
Corpus Christi, Texas	45	50	55	56	60	73	80	77	68	68	55	45	61
Little Rock, Arkansas	46	54	57	62	68	73	71	73	68	69	56	48	62
Shreveport, Louisiana	50	55	57	59	64	71	74	73	69	69	58	52	63
Lake Charles, Louisiana	59	60	73	76	75	81	80	76	76	71	60	52	70
Tupelo, Mississippi	60	54	62	75	74	74	72	71	69	63	55	50	65
Jackson, Mississippi	49	53	60	65	63	71	65	66	62	66	56	49	60
Montgomery, Alabama	48	53	59	65	64	64	62	64	62	65	56	50	59
Savannah, Georgia	55	58	62	70	68	65	63	62	57	64	62	55	62
Greenville, S. Carolina	57	60	64	67	62	63	61	61	62	66	60	55	62
Columbia, S. Carolina	56	59	64	69	68	67	66	66	64	66	63	59	64
Charleston, S. Carolina	57	60	65	71	69	65	66	63	60	63	59	56	63
Jacksonville, Florida	59	62	67	72	70	64	63	62	57	59	60	56	63
Apalachicola, Florida	58	61	65	74	78	71	64	64	66	74	67	57	67
Mean	53	56	61	67	67	69	68	67	64	66	58	48	63

Table 2. Monthly mean temperature in the natural range of Xi Shu in China and potential range in the southeastern United States (1961-1990). (°C)

Location	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Ann
CHINA													
Nanjing, Jiangsu	2	4	9	15	20	25	28	28	23	18	11	5	16
Shanghai	3	4	8	14	19	23	27	27	23	18	12	6	15
Yichang, Hubei	6	7	11	18	22	26	29	29	24	19	13	8	18
Wuhan, Hubei	4	6	10	17	21	27	30	30	25	19	13	7	17
Jiujiang, Jiangxi	5	6	10	17	22	26	30	29	24	19	13	7	17
Nanchang, Jiangxi	6	7	10	16	21	25	29	30	25	19	14	7	17
Changsha, Hunan	4	6	11	17	23	26	30	30	26	19	16	7	18
Chengdu, Sichuan	6	8	13	18	22	24	26	26	22	18	12	8	17
Chongqing, Sichuan	7	10	15	19	23	25	29	30	25	19	14	11	19
Aiamen, Fujian	14	13	16	17	24	27	29	29	28	25	21	17	22
Guangzhou, Guangdong	14	14	17	22	26	27	28	28	27	24	20	16	22
Guilin, Guangxi	9	10	13	19	24	24	28	28	26	22	16	11	19
Longzhou, Guangxi	14	15	19	23	27	29	29	29	28	24	19	18	23
Kunming, Yunnan	10	11	14	18	20	20	20	20	18	16	12	10	16
Tengchong, Yunnan	8	10	13	16	18	20	20	21	20	17	16	9	16
Mengzi, Yunnan	14	16	19	22	24	24	24	24	23	20	16	14	20
Mean	8	9	13	18	22	25	27	27	24	20	15	10	18

Table 2. (continued).

Location	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Ann
UNITED STATES													
Houston, Texas	11	13	16	20	24	27	28	28	26	21	16	12	20
Corpus Christi, Texas	14	15	19	23	26	28	29	29	28	23	18	15	22
Little Rock, Arkansas	4	7	11	17	21	26	28	27	24	17	11	6	17
Shreveport, Louisiana	8	10	14	19	23	27	28	28	25	19	13	9	19
Lake Charles, Louisiana	11	12	16	20	24	27	28	28	26	21	15	12	20
Baton Rouge, Louisiana	10	12	16	20	24	27	28	27	26	20	15	12	20
Tupelo, Mississippi	5	7	11	17	21	25	27	27	23	17	11	7	17
Jackson, Mississippi	8	10	14	18	23	26	28	27	25	18	12	9	18
Montgomery, Alabama	8	10	14	18	22	26	28	27	25	19	13	9	18
Mobile, Alabama	10	12	16	20	24	27	28	28	26	20	15	12	20
Huntsville, Alabama	5	6	11	16	20	25	26	26	23	16	10	6	16
Savannah, Georgia	10	11	15	19	23	26	27	27	25	19	14	11	19
Athens, Georgia	6	7	11	17	21	24	26	26	23	17	11	7	16
Greenville, S. Carolina	5	6	16	16	20	24	26	25	22	16	11	6	16
Columbia, S. Carolina	7	8	13	18	22	25	27	27	24	17	12	8	17
Charleston, S. Carolina	9	10	14	18	22	25	27	27	24	19	14	10	18
Jacksonville, Florida	12	13	16	20	23	26	27	27	26	21	16	13	20
Gainesville, Florida	13	13	17	20	24	26	27	27	26	21	17	13	20
Apalachicola, Florida	12	13	16	20	24	27	28	27	26	21	16	13	20
Mrean	9	10	14	19	23	26	28	27	25	19	14	10	19

Table 3. Monthly mean precipitation in the natural range of Xi Shu in China and potential range in the southeastern United States (1961-1990). **(mm)**

Location	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Ann
CHINA													
Nanjing, Jiangsu	41	51	76	102	81	183	206	117	94	51	41	30	1073
Shanghai	49	62	85	91	96	177	148	139	132	74	53	38	1144
Yichang, Hubei	23	30	48	99	124	158	208	178	102	74	33	18	1095
Wuhan, Hubei	46	48	96	152	165	244	180	96	71	81	48	28	1255
Jiujiang, Jiangxi	64	84	150	180	175	244	142	132	89	96	69	43	1468
Nanchang, Jiangxi	55	108	192	250	289	295	258	111	109	57	70	70	1864
Changsha, Hunan	48	94	135	145	208	221	112	109	69	76	69	38	1324
Chengdu, Sichuan	7	15	25	56	96	122	304	303	139	53	18	8	1146
Chongqing, Sichuan	15	20	38	99	142	180	142	122	150	112	48	20	1088
Aiamen, Fujian	33	76	89	124	158	178	132	168	109	48	30	33	1178
Guangzhou, Guangdong	27	65	101	185	256	292	264	249	149	49	51	34	1722
Guilin, Guangxi	51	79	161	223	259	370	236	200	101	87	53	47	1867
Longzhou, Guangxi	20	36	48	81	178	216	229	231	142	64	30	20	1295
Kunming, Yunnan	3	18	21	31	99	192	214	220	161	95	31	11	1096
Tengchong, Yunnan	13	38	36	69	128	236	312	282	163	158	41	23	1499
Mengzi, Yunnan	8	18	28	41	127	132	196	198	96	51	56	15	966
Mean	31	53	83	121	161	215	205	178	117	77	46	30	1317

Table 3. (continued).

Location	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Ann
UNITED STATES													
Houston, Texas	82	83	68	108	119	103	85	93	125	93	86	93	1137
Corpus Christi, Texas	41	39	21	51	77	85	50	89	156	81	39	36	767
Little Rock, Arkansas	99	97	119	137	134	93	92	78	108	72	111	107	1250
Shreveport, Louisiana	102	88	96	120	119	90	90	64	84	67	96	98	1114
Lake Charles, Louisiana	108	99	77	103	131	106	141	137	132	88	96	129	1347
Baton Rouge, Louisiana	116	126	117	142	122	79	180	128	112	67	100	127	1417
Tupelo, Mississippi	144	118	176	144	133	94	117	72	92	76	118	142	1425
Jackson, Mississippi	127	114	149	149	123	75	112	94	90	67	106	137	1342
Montgomery, Alabama	107	116	150	111	102	88	121	81	120	58	76	121	1249
Mobile, Alabama	117	125	165	136	139	129	197	171	167	67	93	138	1642
Huntsville, Alabama	131	122	172	125	117	95	129	79	101	74	108	138	1390
Savannah, Georgia	78	81	97	80	117	145	187	169	131	58	48	70	1262
Athens, Georgia	123	106	148	103	121	101	132	92	91	69	84	104	1274
Greenville, S. Carolina	107	112	149	110	107	121	104	93	110	89	82	100	1283
Columbia, S. Carolina	111	101	131	91	98	113	136	141	107	65	64	89	1248
Charleston, S. Carolina	85	86	111	66	112	166	186	165	125	74	55	79	1310
Jacksonville, Florida	78	88	94	84	125	136	166	182	184	87	49	66	1340
Gainesville, Florida	82	100	90	75	105	161	178	205	140	62	52	82	1330
Apalachicola, Florida	89	92	103	83	75	122	180	191	220	81	72	89	1396
Mean	101	100	118	106	115	111	136	122	126	73	81	102	1291

Table 4. Monthly mean relative humidity in the natural range of Xi Shu in China and potential range in the southeastern United States (1961-1990). (%)

Location	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Ann
CHINA													
Shanghai	74	78	78	80	82	84	83	82	81	77	78	77	80
Wuhan, Hubei	76	78	81	81	80	78	79	78	77	77	79	77	79
Chengdu, Sichuan	79	81	78	78	77	81	85	85	85	86	83	83	82
Chongqing, Sichuan	87	88	87	86	87	86	80	76	84	88	91	91	86
Guangzhou, Guangdong	69	78	83	84	85	86	84	83	80	72	69	68	78
Kunming, Yunnan	68	62	58	56	64	78	83	84	82	82	76	73	72
Mengzi, Yunnan	55	53	48	50	57	64	69	70	66	67	67	56	60
Mean	73	74	73	74	76	80	80	80	79	78	78	75	77

Table 4. (continued).

Location	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Ann
UNITED STATES													
Houston, Texas	74	73	72	73	75	75	75	75	77	76	77	75	75
Corpus Christi, Texas	78	76	74	77	80	78	75	75	77	76	77	76	77
Little Rock, Arkansas	70	68	66	67	72	70	72	72	74	71	71	71	70
Shreveport, Louisiana	72	69	67	70	73	73	72	71	73	72	73	74	71
Lake Charles, Louisiana	79	77	77	76	78	78	80	80	80	77	78	80	78
Baton Rouge, Louisiana	74	71	70	71	73	75	77	78	77	74	75	75	74
Tupelo, Mississippi	70	70	65	63	71	70	73	73	73	73	72	72	70
Jackson, Mississippi	76	73	71	72	74	74	77	77	78	77	78	78	76
Montgomery, Alabama	70	67	66	68	71	72	76	77	74	73	73	72	71
Mobile, Alabama	72	70	71	71	72	74	77	78	76	72	74	74	74
Huntsville, Alabama	73	69	67	65	71	72	75	75	76	73	72	72	72
Savannah, Georgia	69	66	67	66	71	74	76	79	79	74	73	71	72
Athens, Georgia	69	66	65	64	70	72	76	77	77	74	71	70	71
Greenville, S. Carolina	66	64	63	62	69	71	74	76	77	72	70	69	70
Columbia, S. Carolina	70	66	66	63	69	71	74	78	78	76	74	72	71
Charleston, S. Carolina	72	70	70	70	74	77	79	81	81	77	75	73	75
Jacksonville, Florida	76	73	71	71	72	76	77	80	81	79	78	78	76
Gainesville, Florida	78	75	76	72	73	79	82	84	84	81	83	82	79
Apalachicola, Florida	78	78	78	77	77	78	80	82	80	77	78	79	79
Mean	73	71	70	69	73	74	76	77	77	75	75	74	74

Table 5. Extreme temperatures in the natural range of Xi Shu in China and potential range in the southeastern United States (1961-1990).

Location	Latitude	Longitude	Highest Temp. (°C)	Lowest Temp. (°C)	Difference (°C)
CHINA					
Nanjing, Jiangsu	32°04'N	118°47'E	43.0	–13.8	56.8
Shanghai	31°12'N	121°26'E	40.2	–12.1	52.3
Wuhan, Hubei	30°33'N	114°17'E	41.3	–13.0	54.3
Nanchang, Jiangxi	28°40'N	115°58'E	39.4	–5.9	45.3
Changsha, Hunan	28°15'N	112°50'E	43.0	–8.1	51.1
Chengdu, Sichuan	30°40'N	104°04'E	40.1	–4.0	44.1
Chongqing, Sichuan	29°30'N	106°33'E	44.0	–2.5	46.5
Wenzhou, Zhejiang	28°01'N	120°49'E	40.5	–3.0	43.5

Table 5. (continued).

Location	Latitude	Longitude	Highest Temp. (°C)	Lowest Temp. (°C)	Difference (°C)
UNITED STATES					
Houston, Texas	29°58'N	95°21'W	41.7	−13.9	55.6
Corpus Christi, Texas	27°46'N	97°30'W	40.0	−10.6	50.6
Little Rock, Arkansas	34°44'N	92°14'W	44.4	−20.5	64.9
Shreveport, Louisiana	32°28'N	93°49'W	41.7	−16.1	57.8
Lake Charles, Louisiana	30°07'N	93°13'W	38.9	−11.7	50.6
Baton Rouge, Louisiana	30°32'N	91°08'W	39.4	−13.3	52.7
Tupelo, Mississippi	34°16'N	88°46'W	40.6	−21.1	61.7
Jackson, Mississippi	32°19'N	90°05'W	41.1	−16.6	57.7
Montgomery, Alabama	32°18'N	86°24'W	40.6	−17.8	58.4
Mobile, Alabama	30°41'N	88°15'W	40.0	−16.1	56.1
Huntsville, Alabama	34°39'N	86°46'W	39.4	−23.9	63.3
Savannah, Georgia	32°08'N	81°12'W	40.6	−16.1	56.7
Athens, Georgia	33°57'N	83°19'W	41.7	−20.0	61.7
Greenville, S. Carolina	34°54'N	82°13'W	39.4	−21.1	60.5
Columbia, S. Carolina	33°57'N	81°07'W	41.7	−18.3	60.0
Charleston, S. Carolina	32°54'N	80°02'W	40.0	−14.4	54.4
Jacksonville, Florida	30°30'N	81°42'W	40.6	−13.9	54.5
Gainesville, Florida	29°41'N	82°16'W	38.9	−12.2	51.1
Apalachicola, Florida	29°44'N	85°02'W	38.9	−12.8	51.7

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