

Expanding The Frontiers of Traditional Medicine: A Case History in Investigating A Prospective Therapy

Michael J. Balick¹ and Roberta Anne Lee²

¹ The New York Botanical Garden, Bronx, New York 10458-5126

² The Continuum Centre for Health & Healing, Beth Israel Medical Center,
245 Fifth Avenue at 28th Street, New York, NY 10016

One of the results of the developing interest in herbal medications in all corners of the world, is that individuals are exploring and experimenting with plant species, particularly those from cultures other than their own, in furtherance of their health care needs. People in Western cultures, where the herbal traditions are largely based upon European herbal teachings, find that the ethnopharmacopoeas of other cultures are of great fascination and use, in the same manner as traditional healers living in, say, tropical America are developing an interest in European herbs. The end result is that there is a great demand for information about many of the tens of thousands of plants used in traditional herbal medical systems throughout the ages. We suggest that in the computer age, information about herbs—both correct and erroneous—is available more than ever before. In this paper we present a case history of a patient's request for information from his physician (R.L.), and the combined botanical/medical response that was provided. We also suggest additional web sites where information may be accessed.

A 43 year old man presented in my (R.L.) office with a diagnosis of rheumatoid arthritis. I could tell by examination that the disease had not progressed too rapidly as his joints were still well intact. He was a person who had spent an enormous amount of time searching for the most natural remedies available—and had found a plant that he was interested in taking for this ailment. He asked me whether I would agree to his taking *Tripterygium wilfordii*, also known as the Thunder God Vine. As I had no clinical experience with this plant, I contacted my co-author (M.B.) to assist in acquiring more data.

Based on the leaflets the patient provided, the scientific, botanical name for this plant was noted as *Tripterygium wilfordii* Hook F. The first stop on this information quest was to ascertain whether the scientific name was the correct one. "The International Plant Names Index" (<http://www.ipni.org>)¹ is excellent for this purpose. When the Latin name provided by the patient (*Tripterygium wilfordii*) was typed into the data base, the index confirmed it to be a legitimate name in botanical circles.

This species was first described in the classic work *Genera Plantarum* by the noted botanists George Bentham and Joseph. D. Hooker in 1862.² It is most commonly found in Southern China and is native of the Hunan Province.

The plant belong to family *Celastraceae*, commonly known as the "Staff-Tree Family," which contains more widely known medicinally used plants such as the American bittersweet (*Celastrus scandens*), once employed externally and internally by Native Americans. A root bark tea of the American bittersweet plant was used internally to induce sweating; as a diuretic and emetic; and for chronic liver and skin ailments, rheumatism, leukorrhea, and suppressed menses. The bark was employed externally to treat burns, scrapes, and skin eruptions.³ This family also contains the strawberry bush (not related to the common fruit), *Euonymus americanus*, which is native to the Eastern and Midwestern United States, where a tea of its roots was used by Native Americans to treat a person who vomited blood or had uterine prolapse, painful urination, or stomachache; it also was used externally for swellings.³ Another member of the *Celastraceae*, *Catha edulis*, is a stimulant known as *khat* in the Middle East. The family *Celastraceae* contains many useful species.

Tripterygium wilfordii is a perennial vine or shrub that grows up to 10 meters in height, especially in moist areas.⁴ Looking at the herbarium specimens and corresponding description in The New York Botanical Garden Herbarium, a reference collection of preserved plants around the world totaling 6.5 million in number, we noted the species to have small greenish flowers and winged fruits. According to one botanical reference, its native range also includes Japan and Korea.⁵ Armed with our botanical background, we decided it was time to dig deeper into the literature. Contemporary textbooks on the Chinese materia medica did not prove particularly enlightening, especially because we were looking for recent scientific information pertinent to patient care in a Western medical practice. According to the Chinese texts, traditional uses include the

treatment of boils, fever, abscesses, and inflammation. A paper published by Lipsky and Tao⁶ on this species noted that the plant has had a long history in Chinese medicine and “stimulates blood circulation, relieves stasis, is anti-inflammatory, relieves edema, purges excess internal warmth, and eliminates toxicity, among other activities.” However, the same reference also notes that the “leaves, stock, flowers, and skin of the roots are poisonous and capable of causing death when ingested. Even ingestion of honey containing the pollen of the plant has been reported to cause death”. Further this species was said to have been valued for its toxic qualities and used in China as an insecticide. During the Maoist Era, clinical trials were carried out involving this plant as part of the program to encourage the use of traditional medicines.⁷

So here we were faced with an interesting plant with both healing and toxic properties, along with a history of traditional use—some of which was to kill insects in agricultural fields! How does one proceed to answer the patient’s question? In September 2001, we contacted by e-mail a well-known practitioner of Chinese medicine, Efrem Korngold, OMD, LAc, coauthor of the book *Between Heaven and Earth* (New York: Ballantine Books; 1992) and one of the first non-Asian practitioners of Chinese medicine in the United States. When asked about his knowledge and use of this plant, he indicated that he was most familiar with a pharmaceutical grade product made in China marketed as “Lu Fan Teng.” He affirmed that the modern indications for the contemporary uses of this plant in China were for conditions such as lupus, multiple sclerosis, rheumatic arthritis, and vitiligo. Interestingly, he noted that on the whole “the product was not very effective except in the mildest of cases—even when using it consecutively for 3 months.”

On the other hand, he admitted that he may have been conservative in his dosing, noting that he was very aware of the potential toxic side effects. In addition, he expressed concern about the practicality and reliability of a product manufactured in China and only sporadically available in the United States. He also felt that, at least within the scope of his practice and that of other practitioners in his community, the plant’s use as an internally ingested product was rare. In many notable Chinese texts, topical applications of the crude herb were more commonly recommended—specifically because of its known toxicity.⁸ Dr Korngold stated that the commercially prepared product, Lu Fan Teng, was typically used in China, and to a much lesser degree in the United States, as a less toxic alternative to other immunosuppressive agents like cyclosporin.⁹

The next step was to query Jim Duke’s database on the phytochemistry and ethnobotany of plants (http://www.ars_grin.gov/duke/).¹⁰ In this database, 23 chemical compounds were linked to this plant. Only 5 had reported activity; 3 compounds had been identified as effective insecticides and pesticides (celabenzine, wilfordine, wilforine), and the other 2 chemicals had antitumor, cytotoxic, or antileukemic activity (tripdiolide, triptolide). It was clear that *T. wilfordii* is not your “run of the mill” plant used in Chinese medicine.

Entering “Thunder God Vine” in the search engine Google (<http://www.google.com>) led to Australian New Crops Listing of Useful Plants of the World (<http://www.newcrops.au>).¹¹ This is a site that evaluates more than 4200 new crops using the AGRICOLA (AGRIcultural Online Access) database from 1970 to 1996—an online database developed by the National Agricultural Library.¹² It contains a wealth of information and is available with only a click of the mouse. This section began with an analysis of papers on *T. wilfordii*, noted annually in the AGRICOLA database. From 1972 to 1988, on the average, between 10 and 20 papers were published each year. The number of research publications exploded in 1991—nearly 90 publications appeared on this plant alone!

Additional web sites that could be accessed include: The Alternative Medicine Foundation (<http://www.herbmed.org>); The American Botanical Council (<http://www.herbalgram.org>); The University of North Carolina, Chapel Hill, School of Pharmacy (<http://www.geocities.com/chadrx/>); Herb Research Foundation (<http://www.herbs.org>); Longwood Herbal Task Force (<http://www.mcp.edu/herbal/default/htm>); The Natural Pharmacist (<http://www.tnp.com/home.asp>)¹³

Looking over the references cited in the various databases, I (R.L.) began to have some concern for my patient’s welfare. In 1995, a study involving 24 men was carried out on a close relative of *T. wilfordii* called *Tripterygium hypoglaucum*.¹⁴ The sperm motility was measured in those receiving 15 mg/d of the root for at least 2 months and for as long as 10 years. On average, sperm motility was noted to be 26% that of normal activity and “incapable of reaching the uterus.”¹⁵ When the study was completed, 8 men ceased treatment of *T. hypoglaucum* and their sperm activity returned to normal, from 6 to 12 months following cessation of the treatment.

At the University of Colorado Health Sciences Center, a study was released in March 2000 looking at the effect of T2, a chloroform/methanol extract of *T. wilfordii* used for the treatment of autoimmune and

inflammatory diseases for many years in China. This *in vitro* study revealed that therapeutic concentrations of T2 exert a significant inhibitory effect on hematopoietic cells, suggesting that blood dyscrasias (leucopenia, thrombocytopenia, and aplastic anemia) can be encountered with the use of this drug.¹⁶

In 1997, at the Showa University in Japan, a case report of an infant born at 38 weeks with severe brain anomalies appeared. The cause was attributed to the mother's use of *T. wilfordii* for her rheumatoid arthritis early in her pregnancy.¹⁷ In 1998, at the University of Texas Southwestern Medical Center, *in vitro* studies of various connective tissue cell lines (fibroblasts, synovial tissue, and so on) were exposed to extracts of *T. wilfordii* or concentrates of singular compounds of this plant. The ability of the compounds to inhibit prostaglandin synthesis or inflammation (PGE₂ synthesis) was measured. The results showed remarkable inhibition of the inflammatory process. In the study, the inhibitory effects were compared to a potent steroid commonly used in prescriptive medicine (dexamethasone) and found to be similar.¹⁸ Admittedly, this is potentially a positive effect, but in realizing that this extract may be bought over the counter without medical guidance (which could be from a Chinese practitioner), we became concerned for the uninformed consumer. A significant review paper on this plant, "A Potential New Treatment for Rheumatoid Arthritis: Thunder God Vine,"⁶ summarizes the clinical experience in China using this plant for an assortment of inflammatory and autoimmune diseases. Although the trials reported were for the most part uncontrolled, many of the conditions were noted to be treated successfully. Adverse effects also were listed and were said to be "dose related and reversible with the cessation of medication"—in this case, the T2 chloroform/methanol extract of *T. wilfordii*.

In September 2001, we spoke with Dr Peter E. Lipsky, lead author on this paper, who is scientific director of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) at the National Institutes of Health. He noted that his lab had undertaken phase I (safety) and phase II (efficacy) tests, and had planned to undertake a multicenter phase III trial on rheumatoid arthritis. He also mentioned that he had identified the active compounds in the plant, studied their mechanism of action, and developed reproducible extracts at his NIH laboratory. We next asked his advice on whether or not to recommend this compound to patients that were seeking relief from arthritis. He replied:

"They should not take it, as of now. The major issue is quality control. Our experience with available extracts that are made by numerous small pharmaceutical

companies in China is that the potency of their products is variable. The products imported into the United States cannot be guaranteed to be efficacious or safe. The amount of active components in these products varies substantially. Some of these products are occasionally found in U.S. health food stores, especially in Chinatown in New York and in San Francisco. Reliable sources of this product are needed, and for the trials we are planning, the plant material will be imported into the United States and reproducible extracts made. We also test the extracts we are making for toxicity before certifying them for use in clinical trials."

Finally, our search led us to a most useful database, NAPRALERT (Natural Products Alert), created by Dr. Norman Farnsworth and his colleagues at the University of Illinois. The information stored in this powerful resource is a "synthesis of information from more than 150,000 scientific journal articles, books, abstracts and patents, collected systematically from the global literature since 1975." This database can be queried along three major lines: ethnomedical use by traditional cultures, chemical composition, and biological activity. In the search of all three areas, the database identified hundreds of citations. We found that the plant is known by several Chinese names: *Chi Hsueh Teng*, *Koikema*, *Lei Gong Teng*, *Lei Ling Ting*, *Lei Kung Teng*, and *Mang cao*, as well as by "Thunder God Vine."¹⁹

Information from NAPRALERT confirmed the use of *T. wilfordii* in China for arthritis, reduction of inflammation and other conditions such as pruritus, and treating ulcers of the waistband as well as leprosy. In Japan, one variety was noted to be used for treating an unspecified cancer (using dried fruit in water extract). There were hundreds of references for studies on biological activity, treatment of humans, treatment of laboratory animals, and *in vitro* screening systems. Finally, there were many pages of references to studies of the plant's chemistry. This database is supported by user fees and can be accessed through the Internet at <http://www.ag.uiuc.edu/~ffh/napra.html>.

After carefully weighing the evidence we uncovered in our cursory search of the literature, search of databases, and various telephone conversations, and despite a rich history of use in China and the existence of human studies to support the plant's efficacy, clinical research in our country is not yet completed, and there are many listed side effects; therefore, I (R.L.) could not in good conscience recommend that my patient take Thunder God Vine at this time. More information is needed on efficacy, side effects, contraindications, and potential interactions with allopathic drugs before I can be

comfortable in suggesting the use of this plant. There are also issues and questions about quality control and sourcing of the product, especially since some of the plant parts are acknowledged toxins. From where do the companies that make this product get their material? How is it treated? How does a patient know it is *T. wilfordii*? Some plants sourced from this region contain heavy metals and other pollutants. Are there any issues of contamination? Admittedly, many of these questions could be answered by a practitioner of Chinese medicine living in China, for example, and such a person might have a long history of clinical experience with this herb. However, from the perspective of a U.S. based physician, a conservative stance was warranted.

Interestingly, the patient did not react well to the advice offered, despite the many hours devoted to his question. He had great hope that he could use and be cured by this herb. However, based on our conversation with Dr Lipsky, I will, at Dr Lipsky's recommendation, tell my patient not to give up, and let him know that a clinical trial with this plant will be underway in the near future. This brief exercise in tracking down a little-known botanical has been useful for my clinical practice as well as a fascinating journey that has taken us from Beijing to the Bronx. At the same time, we offer it to stimulate discussion amongst botanical medicine researchers as to their opinions on the nature of the problem presented in this case history—undertaking a search for clinically useful information on a plant from the traditional medical pharmacopoeia, and advising interested patients.

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