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Tripterygium wilfordii Hook. f. – how a traditional Taiwanese medicinal plant found its way to the West

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Received October 5, 2012, accepted November 15, 2012

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Dedicated to Prof. Dr. Theo Dingermann, Frankfurt, on the occasion of his 65th birthday.

Pharmazie 68: 643–646 (2013) *doi: 10.1691/ph.2013.6506*

Tripterygium wilfordii is regarded as a promising traditional medicinal plant showing several, mainly anti-inflammatory and cytotoxic activities. It contains unusal natural products currently under investigation as lead compounds. The species has been well known in Traditional Chinese Medicine but was recognized in Western science as an insecticide not before the 1930's and as a promising medicinal plant in the 1960's. The name refers to Charles Wilford, employed as a botanical collector at Kew Botanical Gardens, London from 1857–1860. He collected the plant on the island of Taiwan, formerly called Formosa, in June 1858, unfortunately without reporting its medicinal use in the country of origin. The plant was named according to the Linnaean system before 1862 what initially concealed its medicinal properties which had to be re-discovered in the second half of the 20th century.

1. Introduction

Tripterygium wilfordii Hook. f. is a traditional medicinal plant originally found in Taiwan. It has been known in Europe since the late 1850's but has not been widely investigated in the West before the 1970's. In the last few decades increasing efforts have been made to elucidate its value as an anti-inflammatory and imunosuppressive agent (Tao and Lipsky 2000; Pan and Chen 2008; Graziose et al. 2010), in particular for the treatment of rheumatoid arthritis (Jiang et al. 2009; Chen et al. 2009; Bao and Dai 2011; Canter et al. 2006; Werz 2012). It is also regarded to be a cytotoxic drug (Luo et al. 2009; Kannaiyan et al. 2011; Liu 2011; Liu et al. 2011), a male contraceptive (Lopez et al. 2005), a treatment option for idiopathic refractory nephrotic syndrome (Xu et al. 2009), various gynecologic diseases (Luo and Tan 2008) and others. It contains considerably toxic compounds (Zhou et al. 2012) which led to a basically negative benefit-risk ratio (Canter at al. 2006). On the other hand this obstacle might be overcome by structural modification of the constituents which may also serve as lead compounds for further drug development. Scientific interest in this plant continously rose during the last 40 years as did the number of publications on this medicinal plant (Fig. 1). The plant is said to be already mentioned in the Chinese herbal "Dian Nan Ben Cao" written in the 15th century by Mao Lan (1397-1476, Zhou et al. 2012), and, according to Lipsky and Tao (1997), the 'Compendium of Materia Medica" compiled by Li Shi-Zheu in 1578, also reported a variety of medicinal uses (Lipsky and Tao 1997).

The internationally accepted name of the plant is *Tripterygium wilfordii* Hook f., in China the terms "Lei Gong Teng" "and 'Thunder God Vine' are common. The usual German expression is, even though the roots are the source of therapeutically useful extracts, "Wilfords Dreiflügelfrucht" (Werz 2012). This terminology makes the individual lending the species his name unusually prominent. Thus, it might be interesting how this terminology developed and how the plant, which is now an important research object, found its way into the Western botanical classification system.

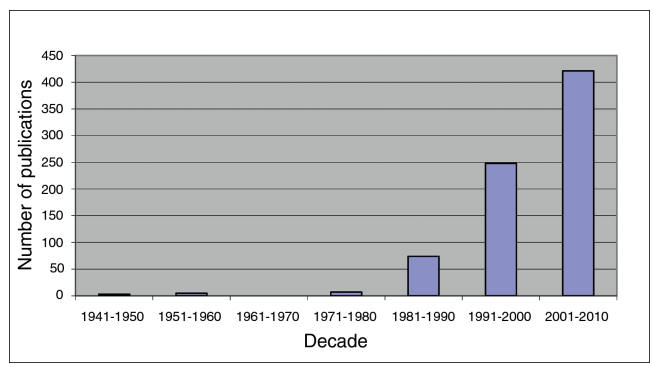

Fig. 1: Number of publications indexed in the „Web of Knowledge" database 1941-2010.

2. Hooker – father and son

The plant got its name before 1862, when it is first mentioned in Bentham and Hooker's "Genera plantarum" (Bentham and Hooker 1862). The authors added a short comment about the region of origin, the island of Taiwan, formerly known as Formosa ("Insulae Formosae incola"). One of the editors, Joseph Dalton Hooker (1817-1911), had graduated as MD from the University of Glasgow in 1839 but started exploring expeditions, initially to Antarctica, soon therafter. He was a close friend to

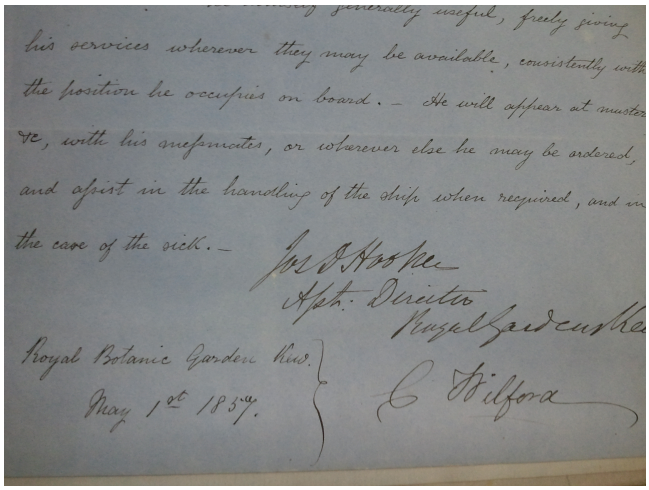

Fig. 2: Image from the contract between Kew and Wilford, signed by the latter and Joseph Dalton Hooker (Reproduced with kind permission of the Board of Trustees of the Royal Botanic Gardens, Kew).

Charles Darwin (Fay 2011). From 1855 he served as assistant director of the Royal Gardens at Kew, Great Britain, under his father, William Jackson Hooker (1785-1865), the first full-time director (Fitzgerald 2004). He moved to his father's position immediately after his death in 1865 and stayed there for the next 20 years. These years, Kew served a something like "the imperial metrological centre of a world-botany" (Bonneuil 2002).

The species later called *Tripterygium wilfordii* had been collected in Taiwan in June 1858 and the name refers on the one hand to the the unusal three-winged shape of the fruits, on the other hand to the man who had harvested the plant. "Pterygium" is said to be the diminutive of "pteryx", the Greek word for "wing" (Genaust 1996). The specific epithet honours Charles Wilford, a botanist working for Kew from 1857 to 1859 under the Hooker's who, on the long run, did not have an easy relationship with him.

3. Wilfords journey

Initially working as a herbarium assistant at Kew, Charles Wilford was sent as botanical collector on the "*splendid steam yacht The Emperor*" to India "*for making botanical researches among the numerous islands of the Japanese territories*" and embarked May 2nd, 1857 to Hong Kong (Bretschneider 1898). In an official letter written one day before the journey started, Hooker granted him the passage and an annual salary of 100 pounds but recommended "*living on an economic scale*". Additionally he was allowed to spend another 60, maximum 80 pounds for necessary expenses (KA, letter Hooker-Wilford, May 1st, 1857, Fig. 2). Wilford worked under general requirements documented in printed instructions including guidelines for handling "*Medicinal substances*: *These latter are of vast importance, and merit the attention of travellers in every country. Of many is not yet known, except to the natives who collect and prepare them, what are the particular plants to afford them, not how they were prepared. It is hoped that the present application may be the means of dispelling this ingnorance and that travellers will endeavour to procure the substances and well-dried flowering specimens of the plants which afford them.*" (KA fol. 12 v).

Eventually, Wilford arrived in Rio de Janeiro July 4th, in Singapore October 10th while "staying only 12 hours in Java" (KA letter Wilford-Hooker, Oct. 10th, 1857) and in Hong-Kong November 10th, 1857 (KA letter Wilford-Hooker, Nov. 13th, 1857). Complaining about very expensive living in Hong-Kong, Wilford started collecting plants the following spring and sent a

Fig. 3: Original herbarium sheet sent by Wilford with additional drawings and remarks about the place of origin (blue label, http://www.kew.org/herbcatimg/301479.jpg, Reproduced with kind permission of the Board of Trustees of the Royal Botanic Gardens, Kew).

"first collection of plants", 350 specimens, from there at the end of March. Hooker wrote April 4th, 1858, that he should concentrate on mosses, algae and lichen (KA Fol. 56). In June, Wilford decided not to continue the journey as initially planned from the city of Amoy (Xiamen) to Shanghai, but to make a detour to Formosa. Wilford left Amoy June 7th and returned July, 1st. During this journey, the later "*Tripterygium wilfordii*" was collected and labelled as has been found "on banks of the river Sanar, Formosa" (Bretschneider 1898, Fig. 3). Botany was not the only reason for Wilford to visit Formosa, so he went there also (or primarily) in order to "*search for two men supposed to have been wrecked nine years ago and kept in slavery by the aborignes* [!]" (KA Fol. 62r, letter to Hooker June 25th, 1858). In fact, the search turned out to be unsuccessful, as had already been supposed by the local authorities: they frankly admitted that foreigners were usually killed by the aborigines but not kept in slavery.

The following months brought a lot of disappointment for Hooker who did not hear from Wilford for a long time, who, however, continously drew out money without carefully justifying his needs. In October, Hooker admitted that "*amongst the Formosa plants are some excellent things*" but expressed that he was "*much disappointed of having had no seeeds, fruits and roots from you*" (KA Fol. 69r, letter Hooker-Wilford October 10th, 1858) and "*not a single object for the museum*" (letter to Wilford November 17th, 1858). Indeed, Wilford had stopped communication almost completely. After having sent a detailed but not completed diary form his Formosa trip in June nothing else followed for months which made Hooker considerably angry: "*Since then not a parcel, not a seed, not a word from you. Yet you continue to draw bills without giving us any account whatever how the money is spent, you cannot truly think this is right*" (KA Fol. 74, letter to Wilford January 4th, 1959). He then

contacted Capt'n Wand, commander of the yacht 'Actaeon', where Wilford was now sailing with complaining about his botanist's "*apparent neglect of duty*". Approximately four weeks later, Wilford wrote a short note pointing out that he had sent plants from Japan and from Shanghai and expressed the he felt "*sure I cannot have made any mistake*" (letter to Hooker April 26th, 1859). The same day, however, commander Wand confirmed Hookers suggestions: "*I had long noticed his conduct as being anything but satisfactory even when with me in the yacht*" (letter Wand-Hooker April 26th, 1859). Nevertheless, Wilford stayed on board and sent more than 100 species in September along with some apologies referring to the fact that they had visited mainly highly cultivated land being not suitable for collection of hitherto unknown botanical species. Capt'n Ward was later honoured by the fact that Hooker named one of Wilfords novelties *Asplenium wardii* in 1860 (Bretschneider 1898).

When the initial contract came to its end in April 1860, Wilford did not return to England but stayed on board the ship "Actaeon" as a botanist, now as employee of the Royal Admiralty. This engangement lasted for more than a year, before Admiral James Hope sent the botanist home to England because of not further specified "misconduct" (letter to Hooker July 17th, 1861). He arrived in Plymouth October 3rd the same year (KA fol. 136) and a long lasting dispute about the approriateness of his expenses as a Kew employee followed. Wilford died in Wimbledon in 1893 (KA, Collectors List)

Despite the controversies about professionalism Wilford was doubtless a productive botanist who sent hundreds of species from the Far East to Europe where they were classified according to the Linnaean system. Most specimens were kept at Kew, duplicates were also sent to other principal herbariums in Europe. So, according to Bretschneider (1898), the botanical Garden in St. Petersburg received 370 species from Kew in 1859, which had been collected by Charles Wilford.

Tripterygium is not the only genus further specified remembering the Kew botanist, others include *Geranium wilfordii*, *Lychnis wilfordii* or *Cynanchum wilfordii*, which is also a promising plant from Traditional Chinese Medicine (Choi et al. 2012a,b).

4. From insecticidal use to medical treatment

Obviously, Wilford did not care a lot about the instructions issued by his employer, according to which the medicinal use of indigenous plants should be carefully monitored and reported.

This might be one of the reasons why the medicinal virtues of *T. wilfordii* remained largely unknown in Western science until the end of the 20th century. Early interest focused on the insecticidal use of *T. wilfordii* root powder in the 1930's following a dispute about culture of *Tripterygium* roots which was, on one hand, blamed for soil erosion but on the other hand was said to be indispensable in agriculture to kill noxius insects. Investigations followed and results were published in Chinese language between 1931 and 1937 (for ref. see Swingle et al. 1941). These papers were translated into English at the 'Division of Plant Exploration and Introduction" in the US. "Several thousand cuttings" were then collected, brought to Washington and cultivated in the 'US Plant Exploration Garden' of that Government agency at Glenn Dale, MD. Investigations revealed that freshly prepared root powder acts a stomach poison against a variety of parasites including larvae of the silkworm, *Bombyx mori* and the Colorado potato beetle, *Leptinotarsa decemlineata* (Swingle et al. 1941). Around 1940 as well, first reports about the chemical nature of active ingredients appeared in the literature (Schechter and Haller 1942), systematic investigations were undertaken at the 'Bureau of Entomology and Plant Quarantine at the Agricultural Research Administration, US Department of Agriculture" and published in the early 1950's. Research was still focused on alkaloids with insecticidal properties and detected compounds were initially named, like the species itself, according to the Kew collector, i.e. wilforine, wilfordine, wilforgine, wilfortrin or wilforzine (Acree and Haller 1950; Beroza 1951, 1952. 1953a,b). Most of the work has been done by Morton Beroza (1917-2011), who did his PhD thesis on the subject and eventually became a member of the Agricultural Research Service's Science Hall of Fame (Washington Post 2011).

Further interest was triggered by the cultural changes taking place in China after the World War II leading – among many other developments – to an integration of Western style medicine into Chinese healthcare. Western-trained and oriented physicians influenced medical practice even in rural areas and *vice versa*, and became familiar with local traditions. As reports on beneficial, but also toxic effects of *T. wilfordii* were manifold, trials in a number of autoimmune and inflammatory diseases were organized and rapidly performed which led to a re-discovery of the plant's medicinal virtues. In 1982 already, experiences with more than 2000 patients with rheumatoid arthritis were reported (Lipsky and Tao 1997).

In the early 1970's researchers became aware of significant anti-leukemic activities of Celestraceae species and also found *T. wilfordii* extracts effective. Investigations led to the discovery of triptolide, tripdiolide and tripronide, three closely related diterpenoid triepoxides (Kupchan et al. 1972). Triptolide is now believed to be responsible for most of the biological activities of *T. wilfordii* extracts (Brinker et al. 2007) and also serves as lead compound in drug development (Zhou et al. 2012).

5. Discussion

Research into the traditional use of medicines is a promising field of drug development (Helmstädter and Staiger 2012) which is in particular true for plants used in Traditional Chinese Medicine and Ayurveda (e.g. the 60-page review on Ayurvedic anti-inflammatory agents by Aggarwal et al. 2011). *T. wilfordii* may serve as an outstanding example of a traditional medicinal plant showing high potential even under the premises of the lead structure concept and evidence based medicine. Knowledge about its medicinal virtues, however, became known relatively late and thus, systematic research could not start before the late 20th century. This is certainly due to the facts that neighter Chinese heritage had spread to the West nor Westerns scientific views and methods were largely known in China before the second half of the 20th century. In the case of *T. wilfordii*, some kind of carelessness may also have contributed. Despite otherwise instructed, the Kew collector did not care about the uses of the plants harvested primarily for botanical classification. There are other examples like *Syzygium cumini*, a medicinal plant known in Europe since the early 19th century and commmercially imported from Java in the 1880's along with information about its use as anti-diabetic remedy in the country of origin. This initially led to extensive clinical and chemical investigations already at the end of the 19th century (Helmstädter 2008). Wilford did also not report local terminology which made it hardly possible to trace the roots back into history. So the medicinal virtues of the plant which was well known in science under its Latin name only needed to be "re-discovered" in the 1960's before further investigations could start.

The obvious "*divorce of Chinese plants from their indigenous settings, names and uses, and the plant's incorporation in the Linnaean system*" which was strictly eurocentric, might be regarded as a late example of the so called "linguistic imperialism in botany" (Cook 2007, 2010). In fact, Linné did not accept other terms than those derived from Latin or Greek, the languages of European science and *expressis verbis* avoided

"*barbarous names*". Some say that he not only erased indigenous names but also indigenous knowledge about plant's uses and habitat, thereby promoting European white male hegemony (Cook 2010 according to Schiebinger 2004). Cook (2010) however, argues that a somewhat artificial system of nomenclature, as chosen by Linné while refering to the "dead" languages Latin and Greek, was necessary to avoid confusion most probably caused by an adoption of traditional, local terminology. A wide variety of synonyms would have made a proper and fair-minded choice hardly possible. However, the Linnaean system, as still adopted by the Hookers in the mid 1860's, cut the tradition of the (from an European point of view) new species which has been known for centuries as useful medicinal plant in the country of origin. This neglection of knowledge about traditonal use caused a considerable delay in research progress, as the relevant species had first to be "re-discovered" as promising sources of therapeutically useful agents. Thus it seems to be time for systematical research into historical literature, which may reveal starting points for further phytochemical research and clinical trials. Studies have to include sources of Traditional Chinese Medicine as well as early reports from visitors, e.g. the detailed reports already made in the 17th century by Christian missionaries like Michael Boym (1612-1659, Anagnostou 2011) and some others.

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