REVIEW

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Traditional use and scientific investigations of the medicinal plant *Simaba cedron* Planch.

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Simaba cedron Planch (Simaroubaceae) has frequently been reported as a traditional remedy against snake bites, malaria, gastrointestinal and other disorders. Starting in the 18th century, European physicians and researchers made several efforts to verify the reported virtues and to isolate active principles. Most important achievements are reviewed her. From modern investigations, an anti-malarial activity seems plausible due to the quassinoids contained. An effect against snake-bites seems questionable, research about the usefulness against gastrointestinal disorders, which is also reported, is missing. Other Simaroubaceae, however, are under current investigation now.

1. Introduction

Among the historical sources regarded as useful tools to identify traditionally used medicinal plants hitherto scarcely investigated, the heritage of exploring botanists moved into the focus of historical research. Knowledge extracted out of these historical sources may help to unveil plant uses forgotten over the centuries and even give some clues for today's phytopharmaceutical research (Helmstädter 2017). As an example, correspondence, diaries and publications of the German-born botanist Berthold Seemann (1825–1871) have been shown to contain valuable information about traditionally used medicinal plants of South America and other regions (Helmstädter 2015). Seemann, an employee of Kew Gardens, London, undertook a voyage of exploration to the American West coast and the Pacific between 1845 and 1851. He corresponded with his employer, wrote an extended diary and published about his botanical experiences after his return to England. Therein, he described the medicinal use of indigenous plants now and then. The most extended description deals with the species *Simaba cedron* Planch., which obviously had a great reputation as a remedy against snake bites and malaria.

2. Early knowledge transmission about cedron and its suggested properties

Many sources (e.g. Seemann 1853) point out that already in 1699, the virtues of what was later called *Simaba cedron* had been described in a report about pirates of South America. Most probably, the following text was interpreted in this way: "*There are a sort of serpents upon this island, whose stinging is so dangerous, that if anyone has not a certain fruit by him, which he is to chew, and presently to apply to the wound, there is no escaping present death for him, as we found by experience, by some of our men whom we lost in this manner, and who, in their dying, endured terrible pains, through the activity and violence of that fire which this poison kindled in their bodies. The tree, on which this fruit grows, is to be found upon the same place, as well as in the other parts of this country, being, as to its leaves and height, very like unto our almond-trees; but its fruit resembles sea-chestnuts, though it is of a grayish color, and of a somewhat bitter taste, enclosing a whitish almond in the midst thereof. It is chewed altogether before the application is made, and is known by no other name than the serpent's seed*" (Exquemelin 1699).

In his diary about the Panama excursion, Seeman wrote that no inhabitant would leave his house without carrying cedron with him. After an animal bite, 3-4 grains of cedron seeds should be taken internally in brandy or water. In addition, a similar mixture should be applied onto the wound. This mode of administration was confirmed by Lindley stating: "*When a person is bitten, a little, mixed with water is applied to the wound, and about two grains scraped into brandy, or, in the absence of it, into water is administered internally*" (Lindley 1853). Seemann himself was never bitten by a snake but stung by scorpions and reported immediate success and complete recovery from initial symptoms like pain and swelling (Seemann 1847-1857, fol. 10). He also reported that he had cured several patients suffering from "fever" with cedron himself.

The Kew directorate, however, became aware of cedron seeds and its reported properties in the 1830s already. In letters to the Kew director Sir William Jackson Hooker sent from Bogota, Colombia, in 1834, W. Turner reported the medicinal use of cedron in Colombia (Kew Archives Directors correspondence 67/182, 183). He referred to newspaper reports dating back to 1829 and sent a clipping out of a local magazine, the *Bogota almanac* from 1833 where the plant has been described as a valuable remedy against snake bites. The *almanac* published about the topic in order to get endangered farm workers informed about this "most effective antivenom". Turner immediately sent seeds to England which, however, could not be cultivated initially. In the 1840s, Colombian authorities tried to explore the origin of the remedy and mandated a commission supervised by Dr. Juan Maria Cespedes, professor of botany in Bogota, with field studies in 1843 (Seemann 1853). They explored the botanical origin of the cedron seeds traditionally derived from the banks of the river Magdalena. Eventually, the true botanical nature of the cedron plant was determined by William Purdie (died 1857), another botanist sent by Kew to field trips in South America. He received detailed information about the nature and habitat of the cedron plant in the Magdalena region. He managed to harvest ripe fruits, leaves and flowers from the respective plant and sent them to England for cultivation and further studies. Purdie described them an useful but rather expensive: "*So highly are the seeds prized here for their powerful medicinal virtues, that they cannot be purchased for less than two reals, or one shilling, each*" (Hooker 1850, p. 378).

Eventually, the botanical name *Simaba cedron* was suggested by the French botanist Jules Emile Planchon (1823–1888) in 1846 according to the botanical classification as Simarubacea and in reminiscence to the vernacular name of the plant (Planchon 1846). In 1850, Kew director William Jackson Hooker published an extensive description of the plant, accompanied by a rather exact drawing of the pant done by William Fitch (Hooker 1850, Fig. 1).

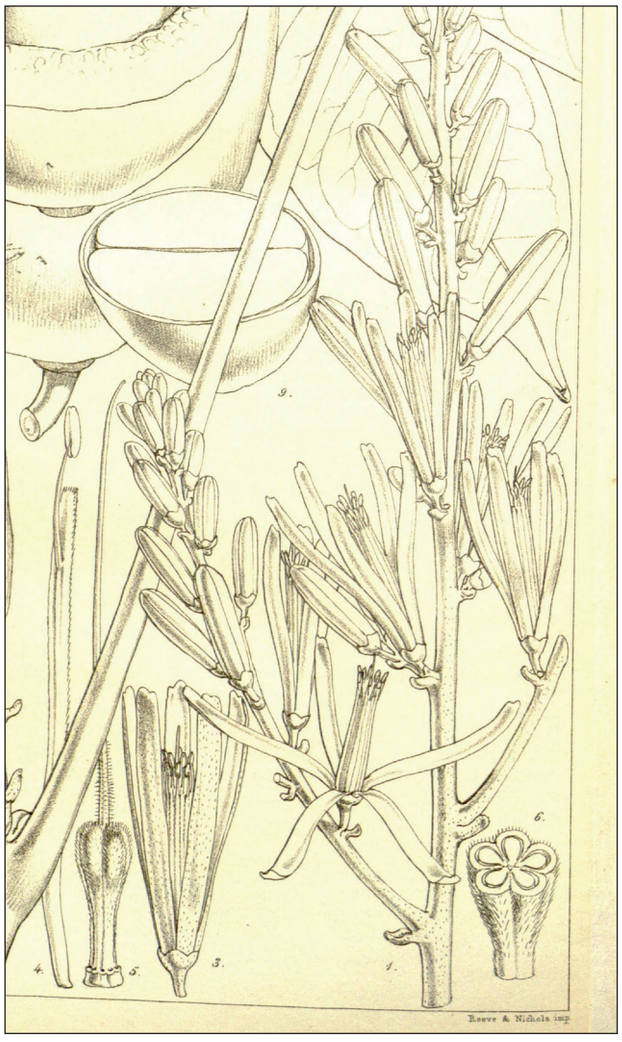

Fig. 1: Early *S. cedron* drawing (Hooker 1950)

The same year, French journals also reported about the cedron seeds. Jomard (1850) mentioned a situation dated back to 1828 where, on a marketplace in Carthagena, natives let themselves bitten by snakes to demonstrate the curative effects of the seeds afterwards and to sell them for high prices. The remedy was also said to be able to cure cases of malaria resistant to quinine. In 1850 as well, a medical congress in France with participants from all over Europe dealed with the cedron seeds and two scientists obviously offered to try the remedy themselves, which means, after voluntarily been bitten by a snake. Cedron was also suggested to cure mental disorders and epilepsy (Hooker 1850). Hooker asked the British pharmacologist Jonathan Pereira (1804–1853) who had received cedron seeds from Panama, for his opinion. He was not aware of any pharmacological experiments done in Europe, and expressed considerable scepticism: "*Notwithstanding the faith of the Panama doctors, I am afraid there is not an antidote against snake-poison: all the reputed antidotes to snake-poisons having hitherto proved unworthy of trust when used under the eye of competent observers*" (Hooker 1850, p. 380). As early as 1853, cedron was shortly mentioned in a German *materia medica* textbook as a remedy against fever (Buchheim 1853) and became part of the standard literature on medicinal plants of the 19th and early 20th centuries (Henkel 1867; Dragendorff 1898; Geissler and Moeller 1909; Thoms 1931; Madaus 1938, pp. 871–872).

Hartwich (1885) refers to Seemann's publications and points out that in Europe, cedron seeds had initially been highly but undeservingly recommended as a remedy against snake bites, what he classified as fantasy. He observed some upturn in the frequency of use, however, against stomach problems. These considerations might have gone back to a presentation about the flora of Costa-Rica given by H. Polakowski in a meeting of the "Botanischer Verein der Provinz Brandenburg" in 1876. He referred to two physicians named Dr. v. Frantzius, who had visited Costa-Rica in 1853 (Frahm and Eggers 2001) and Dr. Ellendorf who also regarded Seemann's reports as far too optimistic. Ellendorf even stated that all the snake bite patients he saw had died before somebody had managed to organize cedron seeds as an antidote (Ascherson and Koehne 1877). In 1883 however, Morse praised the drug as acting specifically ("as if by miracle") against snake bites, and being useful against insect stings, rabies and malaria. He regarded Lowry's cedrine (see below) as the active principle, speculates about the mechanism of action as "that of a cerebral sedative" and mentions camphor, valerian and Asa foetida as antidotes.

In the US, knowledge about cedron use was spread by Samuel S. Purple (1822–1900), the later president of the New York Academy of Medicine. In 1854, he published extensively about the "invaluable specific for the bites of venomous snakes" and reported several cases of cedron treatment in "intermittent fever" (i.e. malaria). Treatment with 10-20 grains of powdered cedron seeds turned out to be successful in most cases, so that Purple concluded: "*There can hardly arise a doubt but that the cotyledons of the Simaba cedron, one of which is here represented, possess decided anti-periodic properties*" (Purple 1854a). He seriously considered cedron seeds as a quinine substitute and regretted short supply. He also recommended to use it as a "tonic" and against gastrointestinal disturbances, which were, however, also observed as side effects of treatment. He denied any effectivity in yellow fever which also had been reported (Purple 1854b). *Simaba cedron* is also mentioned in an overview about American medicinal plants given by Kraemer (1903).

In his Enzyclopedia of medicinal plants, Madaus (1938, pp. 871-872) again reported the use against snake bites and malaria and also stated that an aqueous extract is useful to kill insects in contaminated herbaria. He also mentioned a variety of other indications including Angina tonsillaris, Fluor albus and dysmenorrhea. Externally it is said to help treating ulcers, furunculosis and wounds. Homeopathic indications concentrate on neuralgia.

In 1935, Gauckler botanically investigated a South American preparation recommended against snake bites. He found three *Aristolochia* species (*A. pandurata*, *A. maxima*, *A. ringens*) as well as *S. cedron* contained.

3. Confirmation of traditional uses

The traditional use of *Simaba cedron* has been confirmed by several ethnopharmacological reports and field studies. Duke (1975) points out that "powdered fruits, or tea made of leaves and roots" were "used to protect against snakes or other enemies" by the Cuna Indians. Hirschhorn (1981) assigned botanical names to plants listed in the three-volume Diccionario de Americanismos edited in Francisco Santamariá 1942, including (Simaba) cedron. According to him, seeds were used as a "tonic, fruit and nuts febrifuge and for snake bite, infusion medicinal". Joly et al. (1987) pointed out that the "infusion of ground fruits is used for intermittent fevers, malaria and snake-bites" in Panama. In Mexico, "seed shavings boiled in tea" were described to be used as remedy for "empacho", defined as a form of "cold stomach" comprising a variety of gastrointestinal disturbances like flatulence and diarrhea. With *Aloysia triphylla* (L'HCr.) Britton, an alternative botanical assignment for the vernacular name "cedron" was made

(Messer 1991). De Feo (1992) reported the use of cedron as a part of magical rituals in the Peruvian Andes and says that "it protects from viper bites". The seeds are also included in a list of more than 400 plants traditionally suggested as remedies against snake bites (Selvanayagam et al. 1995). Cedron was also included in a list of phytopharmaceuticals against snakebites in Colombia by Otero et al. (2000a). The authors report the use of a decoction of the whole plant or crushed seeds as drinks and external baths. They should be particularly useful against the haemorrhagic effects of *Bothrops* snake venom (Otero et al. 2000b). Giovannini and Howes (2017) found *Simaba cedron* among the most prominent out of more than 200 plant species recommended against snake bites in Central America. Mojab (2012) reports the traditional use of cedron against malaria as did Oliveira et al. (2015). In mid 19th century France, cedron preparations were unsuccessfully tried against epilepsy (Rabot 1852).

Fig. 2: *S. cedron* seed (©Alex Potovkin, Bahia, Brazil)

3. Phytochemical and pharmacological studies

Already in 1851, Lewy reported on a bitter tasting substance named cédrine which he regarded to be the active principle of the therapeutic actions of the seeds. After defatting the seeds with ether, a crystallizable substance was found in the residue, hardly soluble in cold water, soluble in boiling water and alcohol. Its bitter taste was said to be comparable to that of strychnine but more prolonged. The author points out that at doses above 50 mg serious toxicity has been observed (Lewy 1851; see also Rochleder 1858). However, the isolation procedure described could not be reproduced later, neither by Cloéz in the early 1870s (N.N. 1872), nor by Tanret (1880). Rabot (1852) independently described the isolation of a yellow, bitter tasting fraction from Cedron seeds in detail.

Modern phytochemical investigations started in the early 1960s. Polonsky (1960) reported the isolation of two crystalline components named cédronine and cedronyline from a hot aqueous seed extract. Structures could not fully elucidated (see also Geissman 1964). Krebs and Rüber (1960) published a rather detailed report on the isolation of what they again called

Table: Pharmacological investigations of *S. cedron* and its components

Jahr	Publication	Material studied	Results for S. cedron
Snake bites			
	Bonsmann (1942)	Animal study of a preparation comprising four ethanolic plant extracts (three *Aristolochia* species and *S. cedron*) extract (Gauckler 1935). Tested s.c. against nine different snake venoms injected 5 min before the preparation	Some protective effects in mice against lethal venom doses form *Naja flava* and *Bothrops jarajaca* in mice. No effect against higher venom doses as well as venoms from other species. No effects in rats and guinea pigs.
	Otero et al. (2000b)	In vitro neutralization of *Bothrops atrox* venom haemorrhage	Weak (12 %) neutralisation by whole plant and crushed seed extracts
Antibiotic activity			
	Correia et al. (2008)	Study of different plant (bark and resin) extracts incl. *S. cedron* against multiresistant bacterial strains	No activity was found.
Cytotoxicity of compounds			
	Ozeki et al. (1998), Hitotsuyanagi et al. 2001), see also Guo et al. (2009)	*In vitro* investigations on the antileukemic and antimalarial activity of quassinoids	Cedronolactones A and E show significant resp. weak *in vitro* toxicity against P-338 cells
Antiinflammatory activity			
1963	Hammarlund (1963), see also Geissman (1964)	Different seed extracts tested for anti-inflammatory activity in rats	Only weak, unspecific activity of the ethanolic and aqueous extracts in rats
Antimalarial activity			
	Phillipson and O'Neill (1986)	Chloroform extract of leaves	IC50 5 µg/mL
	Phillipson (1987)	Report on antiplasmodial activity in an avian animal model *In vitro* activity against *P. falciparum*	"Notably active", but toxic Activity due to quassinoids contained
	O'Neill et al. (1985); Mojab (2012)	*In vitro* test of leave and fruit extracts, inhibition of uptake of [G-^{3}H]-hypoxanthin in *Plasmodium falciparum*	Moderate activity of a chloroform leave extract
	Moretti et al. (1994), Muhammad and Samoylenko (2007)	Test for *in vitro* and *in vivo* antimalarial activity of cedronin, derived from *S. cedron* stem bark	Proved activity *in vitro* and *in vivo*
Cytotoxic activity			
	Monks et al. (2002)	Screening of plant extracts against tumor cell lines HT29 and NCI-H460	Cytotoxic activity of organic and aqueous bark extract

cedrin. The bitter tasting substance was identified to be neither glycosidic nor alkaloidal in nature and to contain a lactone ring in its structure. They also suggested a chemical structure somehow related to santonine.

Driven by reports about the use of cedron seeds as an antirheumatic agent in Denmark, Hammarlund (1963) tested a variety of extracts in order to find an antirheumatically active fraction to be further investigated in view of the isolation of an active principle. As none of the extracts proved to be effective, and only a weak unspecific anti-inflammatory activity could be found, he gave up. Additionally, significant toxicity was seen. Hammarlund suggested a low amount of saponin-like substances as ingredients of the foaming extracts and denied the presence of alkaloids.

Polonsky's suggestion of cedronine (Polonksy 1960, 1973, 1985) could be confirmed by Jacobs and Lewis (1987). They published a X-ray crystal structure of the compound and the related 7-epi-cedronine. Courcino Vieira et al. (1997) additionally reported the isolation of nilocitin, glaucorubol and a variety of related compounds out of *Simaba cedron* stem bark. From the bark as well, Ozeki et al. (1998) isolated the hitherto unknown cedronolactones A-D along with several other structures. Three years later, cedronolactone E was discovered (Hitotsuyanagi et al. 2001). These substances belong to the class of quassinoids, widely distributed within the Simaroubaceae. They were initially found in *Quassia* species possibly named according to a slave called Graman Quassi (or Kwasimukamba, ca. 1690 – 1780) who was known in South America for his ability to cure febrile diseases (Mariss 2015; Schiebinger 2004).

Moreira et al. (2006) found additional components contained in *S. cedron*. Barbosa et al. (2011) report 19 quassionoids as ingredients, the alkaloids canthin-6-one, 5-methoxycanthin-6-one, 3-methylcantin-5,6-dione, the coumarin scopoletin, the triterpenes niloticine, piscidinol A, 23,24,25-trihydroxytirucall-7-en-3-one, bourjutinolone A, the steroids sitosterol, stigmasterol, campestrol, and the compounds cedrin, cedrol, and 3',5-dimethoxyamericanin.

Extracts of different plant parts as well as isolated components were also investigated pharmacologically. For an overview of results see Table.

4. Conclusion

Simaba cedron, a plant used traditionally as a medicine, has been known in Europe since at least 1699 and provoked considerable interest among European scientists from the 1830s onwards. Early reports and historical sources mainly concentrate on its use as an antidote against snake bites. Some authors reported rather enthusiastically about its effects, while others were rather sceptic right from the beginning. Albeit some 20th century studies are available, it is certainly true that "*more studies are needed to understand any scientific basis to explain the traditional use of this species against snakebites in Central America*" (Giovannini and Howes 2017). These should, in fact, be done with seeds as the predominantly used plant part in history. More and even more promising studies are available about the use of the drug against malaria, which is also a traditional indication and, of course, much more relevant these days. Activity seems plausible, as the plant is containing a variety of quassinoids, known for their antimalarial and cytotoxic properties (Guo et al. 2005; Vikas et al. 2007; Fiaschetti et al. 2011; Auparakkitanon 2014). There is a lot of research in this direction, although it seems that, in recent years, the focus of research moved to Simaroubaceae species other than the traditional "wonder drug" *Simaba cedron*, for example, *Brucea javanica* (Chen et al. 2013). As *Simaba cedron* has also been reported as a remedy against gastrointestinal disorders and in view of the fact that some Simaroubaceae species are well documented as remedies against gastric complaints (García-Barrantes and Badilla 2011; Sawangjaroen and Sawangjaroen 2005), this indication might be promising for investigation as well.

Conflicts of interest: None declared.

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