

# *Uncaria tomentosa* (Willd.) D.C.: Cat's Claw, Uña de Gato, or Savéntaro

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## ABSTRACT

Recently, *Uncaria tomentosa* (Willd.) D.C. has become known as a healing plant with an ethnomedicinal background. There have been several reports on its constituents, in particular, oxindole alkaloids. It was found that 2 chemotypes of *Uncaria tomentosa* with different alkaloid patterns occur in nature. The roots of one type contain pentacyclic oxindoles and the other contains tetracyclic oxindoles. This difference should be considered when the plant is to be used for medicinal applications. Tetracyclic oxindole alkaloids act on the central nervous system, whereas pentacyclic oxindole alkaloids affect the cellular immune system. recent studies have shown that the tetracyclic alkaloids exert antagonistic effects on the action of the pentacyclic alkaloids. Mixtures of these 2 types of drugs are therefore unsuitable for medicinal uses.

## INTRODUCTION

The Rubiaceae genus *Uncaria* thrives in tropical forests. In the past, it representatives gained a certain economic significance. Also, several species have found application in ethnomedicine. In the Malayan archipelago, *Uncaria gambir* (Hunt.) Roxb. and closely related species provided a polymer tanning mixture, the Gambir catechu, which was extracted from the leaves for the production of the technically important catechins. In folk medicine, leaves and young shoots of this plant are used to treat diarrhea. *Uncaria sinensis* (Oliv.) Havil. served for the treatment of fever. A mildly cytotoxic action was found from *Uncaria perrottetii* (A. Rich.) Merr. *Uncaria homomalla* Miq. has been used as a blood cleansing remedy and *Uncaria longiflora* (Poir.) Merr. was used to treat rheumatism (Phillipson et al., 1978). Negatively inotropic, negatively chronotropic (Zhang and Liu, 1986; Zhu and Guoxiong, 1993), and hypotensive (Aisaka et al., 1985; Shi et al., 1989) actions have been described for the tetracyclic oxindole alkaloids and indole alkaloids of the Japanese *Uncaria rhynchophylla* Miq., which affect the intracellular calcium level of smooth muscle cells. Additionally, the tetracyclic oxindole alkaloids inhibit the aggregation of thrombocytes (Chen et al., 1992; Jin et al., 1991). their sedative

action, which in toxic dosages may lead to respiratory paralysis and ataxia (Kanatani et al., 1985), render them questionable for uncontrolled application. A few years ago, ethnopharmacologist in Austria called attention to a representative of the genus occurring in South America: *Uncaria tomentosa* (Willd.) D.C., a mighty liana of the rain forests of northern South America and continental Central America. Its far-reaching branches carry meter-long shoots, on which are large oval leaves, 10 cm long. In the leaf axils there are paired, sharp, slightly bent thorns, for which the plant was given the Spanish folk name *uña de gato* (cat's claw). During the time of blossoming, panicle-like inflorescences form instead of the claw-shaped thorns. The white- to yellow-colored, small blossoms huddle together in ball-shaped formations and exude a cinnamon-like fragrance (Teppner et al., 1984). The name *uña de gato* is shared with a whole list of plants from the most diverse families, among them *Uncaria guianensis* (Aubl.) Gmel., the leaves of which are applied for wound healing (Ostendorf, 1962), and *Acacia greggii* A. Gray from the Mexican-American border. All share the common feature of curved spines or thorns

The question raised is whether the root of *Uncaria tomentosa* or preparations thereof are of interest to us in our industrialized world. The following elaboration's describe the position of research.

The multitude of plants that are included under the name *uña de gato* is reflected in the large number of drugs that are sold by this name in the street-markets of Peru. All claim to possess actions against viral infections, including human immunodeficiency virus (HIV), tumorous diseases, arthritis, and a long list of other diseases that are considered incurable. Behind these generally false assertions is the statement of Asháninka Indian shamans that their *savéntaro* (*U. tomentosa*) helps against diseases that cannot be influenced by shamanistic practices. Peruvian scientists have pointed out the general falsehood of claims made for the actions of the plant, traditionally held or otherwise, although unaware of the secret knowledge of the Asháninka priests (Cabieses, 1994; Obregón-Vilches, 1994). Yet, on the basis of generally false properties, Peruvian businesses began to export drug materials of *Uncaria tomentosa*, harvested without any controls, under the vernacular of *uña de gato*. In the United States, the *Uncaria tomentosa* products received the corresponding name of Cat's Claw. Today, *Uncaria tomentosa* products have reached the global market under these 2 names. Their use is at least questionable; certainly it does not correspond with the guidelines of traditional application by shamans of the Asháninka tribe, the largest group of indigenous people in Perú.

## PHARMACOGNOSTIC AND PHARMACOLOGICAL RESULTS

Since 1974, and Austrian research group working with Klaus Keplinger has been working on the elucidation of the pharmacological properties of *Uncaria tomentosa*. Keplinger has not only made efforts in pharmacological and biological examinations, but has also deeply involved himself with the spiritual-religious background of the Asháninka Indians (Keplinger, 1993). Eventually, he succeeded

in unveiling a strictly maintained secret of the Asháninka priests concerning their selection of *Uncaria tomentosa*. His group was able to bring the mythological but accurate message of the healers concerning the vine into the light of scientific understanding (Keplinger et al., 1999).

**Table 1. Content of Alkaloids in the Root of an *Uncaria Tomentosa* (Relative to the Fresh Weight of the Root)\***

	<u>June 1983</u>	<u>October 1985</u>	<u>July 1987</u>
		mg alkaloids/g root:	
Pentacyclic oxindole alkaloids:			
Pteropodine	1.29	3.83	0.04
Isopteropodine	0.40	1.66	0.01
Speciophylline	1.72	2.49	0.03
Uncarine F	0.39	0.66	-
Mitraphylline	1.07	3.62	0.07
Isomitraphylline	0.66	1.52	0.08
Tetracyclic oxindole alkaloids:			
Rhynchophylline	20.33	0.09	12.53
Isorhynchophylline	12.39	0.03	8.63

\* At the time of the taking these samples, the plant stood in the native jungle forest at the entry to the valley of Rio Perené in Central Peru. The next plant was found approximately 300 m distance away, so that any confusion regarding the examined root materials is impossible. For unknown reasons, this plant changed its alkaloid pattern from a tetracyclic into a pentacyclic type, and back again. Because the location of the plant was in an area of terrorists, its development could not be further pursued (Source: Immodal Pharmaka, GmbH).

**In nature, *Uncaria tomentosa* occurs in 2 chemical types, which contain in their roots either the tetracyclic oxindole alkaloids rynchophylline and isorynchophylline, or the pentacyclic oxindole alkaloids pteropodine, isopteropodine, speciophylline, uncarine F, as well as mitraphylline and isomitraphylline (Laus et al., 1997; Laus and Keplinger, 1994)(Table 1, above). Chemotypes of a particular species contain different chemical constituents, but are otherwise botanically indistinguishable. In particular, seeds from on mother plant of the pentacyclic type yielded young plants of pentacyclic and tetracyclic types in the 51:59 ratio, whereas seeds from one plant of the tetracyclic type yielded a generation of pentacyclic and tetracyclic type plants in a ratio of 5:15. In addition, seasonal variations in the indole and oxindole alkaloid content of greenhouse-cultivated *Uncaria tomentosa* and related *Mitragyna* species (Shellard and Houghton, 1971, 1972) have been observed. To the Asháninka Indians in the Central Peruvian rain forest, the pentacyclic alkaloid-chemotype of**

*Uncaria tomentosa* is a medicinal plant, the potency of which can be recognized, but only by high-ranking healer-priests. They call it savéntaro (saveshi = plant, antearo = potent) and regard it as being inhabited by the good spirits of the forest. The Asháninka healer-priests have no special name for the tetracyclic alkaloid-chemotype, but they strictly differentiate it.

In recent years, much work has been done on the chemistry of oxindole alkaloids. Oxindole alkaloids isomerize in aqueous solution to give pH-dependent mixtures of isomers. The kinetics of their isomerization in solution has been investigated (Laus, 1998; Laus et al., 1996). The isomer group of pteropodine consists of 4 isomers, ie, pteropodine, isopteropodine, speciophylline and uncarine F. The isomer group of mitraphylline consists of 2 isomers, ie, mitraphylline and isomitraphylline. Of course, this behavior seriously impedes the evaluation of pharmacological properties of single isomers. In consequence, single isomers may be used for quick assays but cannot be used for experiments that last for days. Therefore, equilibrated mixtures of isomeric oxindole alkaloids are used instead of pure compounds in order to guarantee a stable and defined composition. The question of whether *Uncaria tomentosa* could be of interest as a medicinal plant for our industrialized world has possibly been answered by the work of the aforementioned Austrian research group: the root of *Uncaria tomentosa* is a valuable drug only when its pentacyclic chemotype is used without admixture of the tetracyclic chemotype. The pentacyclic oxindole alkaloids act on the cellular immune system. They raise the rate of phagocytosis by granulocytes (Wagner et al., 1985) and they induce the release of a factor from endothelial cells that regulates the proliferation of lymphocytes (Wurm, 1997). Supernatants of EA.hy926 human endothelial cell cultures (Edgell et al., 1983) incubated with  $10^{-6}$  M pentacyclic oxindole alkaloids (POA) increase the proliferation of normal passive or weakly activated human B and T lymphocytes up to 230% ( $p < 0.001$ ), as measured by [ $^3$ H]thymidine uptake. In contrast, the proliferation of normal human B and T lymphoblasts (from peripheral blood or tonsils), Epstein-Barr virus-transformed human lymphoblastoid Raji (ATCC CCL86), and leukemic Jurkat (ATCC E6.1) cell lines is significantly inhibited by up to 85% ( $p < 0.001$ ), whereas the viability of the Raji and Jurkat cells was not impaired ( $> 90\%$  in all cases). The proliferation of the myeloid cell line U-937 was not affected by supernatants of POA-stimulated endothelial cell cultures. It was found that neither the alkaloids alone, nor in combination with a supernatant of untreated endothelial cell, exert an effect on the proliferation of lymphocytes. Thus, it was shown that the pentacyclic isomers do not affect directly the proliferation, but rather induce endothelial cells to release a yet to be identified factor that influences the proliferation of lymphocytes. The secretion of the factor was effected by the pentacyclic alkaloids but not by the tetracyclic alkaloids. Rather, it was shown that the tetracyclic alkaloids act antagonistically on the release of the factor. Admixture of 0.01, 0.1, and 1  $\mu$ M TOA to 1  $\mu$ M POA (pteropodine isomers as well as mirraphylline isomers) as stimulant reduced the effect of the supernatants of Raji and Jurkat cells in a dose-dependent manner (Wurm et al., 1998).

Besides the oxindole alkaloids, some other substances have been identified in *Uncaria tomentosa*, but the plant parts from which they were isolated have been incompletely described. Among these are sitosterol, stigmasterol, campesterol in the steroid fraction of the "bark" (Senatore et al., 1989), and quinovic acid glycosides, for which an inhibitory effect against vesicular stomatitis virus has been shown (Aquino et al., 1989). Another quinovic acid glycoside reduced the inflammatory response of the carageenan-induced rat paw edema (Aquino et al., 1991). Epicatechin and other phenolic compounds have been identified in the bark of uña de gato (Montenegro de Matta et al., 1976; Wirth and Wagner, 1997).

## TOXICOLOGICAL RESULTS AND POSSIBLE SIDE EFFECTS

In the acute oral toxicity test in mice, the freeze-dried aqueous extract of pentacyclic alkaloid-type Radix *Uncariae tomentosae* (containing 35 mg total pentacyclic oxindole alkaloids per gram; 6% yield from crude drug) produced an LD<sub>50</sub> of greater than 16g/kg body (Kynoch and Lloyd, 1975). In an additional test, the aqueous extract of Radix *Uncariae tomentosae* administered orally up to the maximum dosage of 5 g/kg body weight, and intraperitoneally up to a concentration of 2g/kg body weight, was atoxic in mice (Kreutzkamp, 1984). The aqueous-acidic extract of Radix *Uncariae tomentosae* (containing 7.5 mg total oxindole alkaloids per gram; 10% yield from crude drug) also proved atoxic in rats after daily oral administration of 1000mg/kg body weight for 28 days (Svendson and Skydsgaard, 1986). In the mes test for mutagenic properties, the lyophilisate of the aqueous extract was tested up to the maximum concentration of 5000 µg per plate. In none of the tested concentrations was there any hint of a possible mutagenic action. Extracts and fractions of *Uncaria tomentosa* bark showed no mutagenic effect in several strains of *Salmonella typhimurium* but rather a protective antimutagenic activity in vitro against photomutagenesis. A decoction of *Uncaria tomentosa* ingested daily for 15 days by a smoker decreased the mutagenicity of the subject's urine (Rizzi et al., 1993). A double-blind randomized study assessed the effects of a freeze-dried aqueous extract of *Uncaria tomentosa* on the mutagenic activity of urine donated by 12 smokers and 12 nonsmokers. The dose correlated linearly and significantly with the decrease of mutagenic activity in the group of smokers (Leon, 1996).

Sedative effects and circulatory complaints are possible side effects of preparations of *Uncaria tomentosa* that contain larger amounts of tetracyclic oxindole alkaloids. Until now, no such effects have been observed in applications of the Radix *Uncariae tomentosae* chemotype that contains largely pentacyclic oxindole alkaloids. The intake of this chemotype leads to a significant development of a mild lymphocytosis. In HIV-infected patients with full-blown acquired immune deficiency syndrome (AIDS), there have been singular cases of a mild erythrocytosis from the supplementary intake of preparations made from the pentacyclic chemotype. During the early ingestion of such a preparation, clinicians observed occasional cases of temporary constipation or a slightly looser stool. Sometimes, HIV patients with previous acne symptoms have shown an increased occurrence due to the

therapy. In rare cases, uric acid values rose due to the increased activity of the cellular immune system. The application of extracts of the pentacyclic chemotype of *Uncaria tomentosa* must be avoided when there is a chance of organ transplant rejection due to upregulated immunological functions. This also holds true for bone marrow transplants. Pregnant and nursing mothers and children under the age of 3 years are advised to avoid the intake of *Uncaria Tomentosa* due to a lack of experience to date regarding the effect on the immature immune system (Immodal Pharmaka, 1996).

## FORMS OF ADMINISTRATION

In traditional Asháninka medicine, 20g of cut drug of *Radix Uncariae tomentosae* of the pentacyclic chemotype are placed in 1 L of cold water, heated up to 80°C and then maintained at this temperature for 50 minutes. Subsequently, one filters the liquid and the filtrate is topped up with clear water to 1 L again. For daily use, one mixes approximately 1/16th liter (62.5 mL) of the decoction with an equal amount of water and drinks it before the first meal of the day. However, this form of administration will not suffice in modern healthcare unless the alkaloid content of the drug is standardized.

Preparations containing either the pulverized raw drug or diverse extracts are predominantly offered in Peru, a country rich in *Uncaria tomentosa*. These are found in the form of tea, capsules, pressed tablets, alcoholic tinctures, and aqueous extracts. However, there are reasons to assume that these preparations contain adulterations, especially those of *Uncaria tomentosa* of the tetracyclic chemotype, and considerable microbiological contamination by aerobes and fungal spores. In Austria, the pentacyclic oxindole chemotype of *Radix Uncariae tomentosae* is prepared according to a patent-protected process into a standardized dry extract through aqueous-acidic percolation and is then processed into capsules and drops under the trade name Krallendom®. (claw thorn)(Immodal Pharmaka GmbH, Volders, Austria).

## CONCLUSION

The fact that many thorny plants in the tropical Americas are called uña de gato is a confusing situation for the consumer made even worse by the existence of 2 chemotypes of the traditional plant *Uncaria tomentosa*, which shares the common name. In light of the antagonistic immunological effect of the 2 types of alkaloids, a strictly controlled harvest is required in order to obtain an herbal drug that conforms to traditional Asháninka use. Today, we know that the pentacyclic oxindole alkaloids directly increase the phagocytic performance of granulocytes, increase the proliferation of lymphocytes via endothelial cells, and inhibit the proliferation of lymphoblasts. The extent of this regulation depends on the condition of the immunologic system and does not seem to be connected with any immunogenic route of action. This indicates an exceptional and, for medicinal research, highly interesting mechanism of action. From an ethnopharmacological

**point of view, *Uncaria tomentosa* is of special interest. This finding proves that only through an earnest approach to traditional knowledge, which has been gathered over centuries, new scientific understanding can be gained in the service of humanity. Although there are still questions today surrounding *Uncaria tomentosa* and the possibilities of its medicinal application, the application of the pentacyclic alkaloid-chemotype, described as *savéntaro* in the traditional medicine of the Asháninka healer-priest of Perú, has a scientifically sound, factual background.**

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