

Cat's Claw

Uncaria tomentosa (Willd.) DC.; *Uncaria guianensis* (Aubl.) Gmel.

[Fam. Rubiaceae]

OVERVIEW

Cat's claw (*uña de gato* in Spanish) is the common name for at least 20 plants (from 12 families) with sharp, curved thorns. Among them are the two climbing, woody vine discussed in this clinical overview: *Uncaria tomentosa* and *U. guianensis*, both native to the South and Central American tropical rain forests. [EDITORS' NOTE: In this clinical overview, *U. tomentosa* will be abbreviated as "UT" and *U. guianensis* as "UG".] Both UT and UG are said to have a long history of use by indigenous people to treat health problems including rheumatism, arthritis, and other chronic inflammatory disorders, gastric ulcers and gastrointestinal disorders, tumors, and as a contraceptive.

UT plants occur naturally as two chemotypes that appear botanically identical, but are chemically different. One chemotype contains predominantly pentacyclic oxindole alkaloids (POAs) with little or no tetracyclic oxindole alkaloids (TOAs), and the other contains TOAs with either no POAs or up to a considerable amount of POAs. TOAs are reported to act antagonistically to some POA activity. While early studies focused on POAs as the primary active components, more recent studies report that activity is well spread over a range of polar constituents.

Cat's claw has gained recent popularity in the U.S. herb market, but not yet in mainstream retail markets, being sold primarily in health food stores, mail order, and ethnic markets. The cat's claw market is defined by the following five types of products offered mainly by three manufacturers: (1) an aqueous-acid or hydroalcoholic extract of UT root standardized to POAs with no TOAs [herein referred to as UT-POA], (2) an aqueous UT extract standardized to carboxy alkyl esters (CAEs) [herein referred to as UT-CAE], (3) and an aqueous UG extract [herein referred to as UG]. Two additional types of cat's claw products are relatively generic and usually labeled as UT: extracts not standardized to any particular constituent [herein referred to as UT-unspecified] and raw root bark products powdered in capsules or tablets, or finely cut for teas (decoction, the traditional form of use). Little scientific research has been performed on this fifth class of crude products. Because there are numerous plants in Central and South America commonly referred to "uña de gato," there have been reports of inappropriately labeled products in ethnic markets. [Editor's NOTE: Because the information on each species and preparation type may be specific to that particular species or preparation type, the actions and uses of 1 may not apply to another.]

PRIMARY USES

Anti-Inflammatory

- Osteoarthritis (of the knee); reduces pain (UG)
- Rheumatoid arthritis, adjunct therapy to conventional treatment: reduces number of painful and swollen joints (UT-POA)

OTHER POTENTIAL USES

- UT-CAE: enhanced DNA repair; extends immunity from pneumonia vaccine
- UT-POA: ulcers and gastritis; in cancer patients as an adjunctive to chemotherapy and radiation increases vitality and reduces side effects; in HIV patients as an adjunctive to antiretroviral therapy stabilizes and/or reduces CD4-cell count, increases vitality and mobility, and reduces HIV-related symptoms; externally, active against *Herpes simplex* and *Varicella-zoster*
- UT-UNSPECIFIED: decreased mutagenicity of one smoker's urine

PHARMACOLOGICAL ACTIONS

UG: Anti-inflammatory. In *in vitro* studies: antioxidant.

UT-UNSPECIFIED: Antimutagenic. In animal studies: anti-inflammatory. In *in vitro* studies: antioxidant.

UT-CAE: Immunomodulation/immune support; antimutagenic.

UT-POA: Anti-inflammatory; immunomodulation/immune support.

DOSAGE AND ADMINISTRATION

At this time, there is little scientific information on how long cat's claw can be consumed safely. Published clinical trials have been conducted from 4 weeks to 1 year of continuous internal use, while unpublished treatment observations report continuous (uncontrolled) use for up to 10 years. There are no known reports of adverse effects associated with use of cat's claw preparations for extended periods.

Crude Preparations

UG

- CAPSULES: aqueous extract of bark powder, freeze-dried: 100 mg 1–3x/day.

UT-unspecified

- CAPSULES: 350–500 mg, 1–2x/day.
- DECOCTION: 1 g root bark boiled for 15 min. in 250 ml water, 1–3x/day.
- TINCTURE: 1–2 ml, 2–3x/day.

Standardized Preparations

UT-CAE

- TABLETS: 350 mg/day.

UT-POA

- CAPSULES: One, 3x/day for the 1st 10 days, and 1/day thereafter.

CONTRAINDICATIONS

None reported for UG, UT-unspecified, and UT-CAE.

UT-POA: Based on the belief that cat's claw is an immunostimulant, the herb has been contraindicated for leukemia patients awaiting bone marrow or organ transplant and persons with iatrogenically-induced immunosuppression (e.g., organ transplants), autoimmune disease, multiple sclerosis, or tuberculosis. However, some researchers disagree with this view and suggest that cat's claw may be helpful for transplant patients. Elevated production of TNF α is characteristic of numerous autoimmune disorders, including those in which cat's claw offers benefits (arthritis, gut inflammation); and lowering TNF α levels, as has been documented with cat's claw, may be desirable rather than contraindicated for these patients. HIV/AIDS patients should proceed with caution when introducing any new therapeutic agent. Cat's claw is not for use in children under 3 years due to lack of data regarding its effects on the immature immune system.

PREGNANCY AND LACTATION: Not recommended due to lack of data regarding the effects of cat's claw during pregnancy and on the immature immune system.

ADVERSE EFFECTS

Recent human trials conclude that various cat's claw preparations tested are safe, with no adverse effects reported in hepatic, renal, central nervous system, or hematological functions. Cat's claw teas or crude extracts may cause mild nausea, due to bitter taste; however, this appears speculative as nausea is not a frequently reported effect.

UG: One study reports infrequent headache, dizziness, and vomiting, but the incidence and frequency were the same as with placebo.

UT-CAE: None reported.

UT-POA: In AIDS patients and patients receiving large doses of chemotherapy, individual cases of a mild erythrocytosis have been reported. During the first 1–2 weeks of cat's claw tea use, temporary constipation or mild diarrhea was sometimes observed. Increased occurrence of acne symptoms has been reported in HIV patients with prior symptoms. In rare cases, elevated uric acid values were observed in HIV and cancer patients; extensive cell die-off in tumor patients may cause lytic fever lasting 1–2 weeks.

DRUG INTERACTIONS

UG: None reported.

UT-UNSPECIFIED: May potentially reduce the metabolism rate, increasing serum levels of drugs taken orally as observed in an *in vitro* assay where the CYP3A4 isozyme production was inhibited.

UT-CAE: None reported.

UT-POA: According to a communication to physicians and pharmacists from the leading Austrian research and manufacturing company on cat's claw, the following advice should be given to patients, based on the product's proposed immunomodulatory effects:

Take between chemotherapy treatments and after completion, but not with chemotherapy treatments; Do not take in conjunction with passive animal vaccines, intravenous hyperimmunoglobulin therapy; intravenous thymic extracts, drugs using animal protein or peptide hormones (e.g., bovine or porcine insulin), cryoprecipitates, or fresh blood plasma.

CLINICAL REVIEW

Fourteen clinical trials on various cat's claw preparations are summarized in the monograph. In general, the studies are small, most are uncontrolled (U), and some unpublished (UP). One prospective, randomized, double-blind, placebo-controlled, parallel group, multi-center (P, R, DB, PC, PG, MC) trial was conducted on UG for osteoarthritis of the knee. The study reports a significant improvement in pain associated with activity and in medical and patient assessment scores, but no significant improvement in knee circumference or pain at rest or at night. There were no significant adverse side effects in UG and placebo groups.

The UT-CAE preparation was tested in 3 trials. One small R, PC trial resulted in no loss of immunity after 5 months in patients given a pneumonia vaccine after 2 months of treatment with the UT-CAE extract compared to loss with placebo. Another small trial reported an increase in DNA repair with no adverse effects. One U trial on healthy volunteers resulted in an increase in white blood cells.

UT-POA extract was tested for anti-inflammatory effects in 3 trials. One 52-week trial tested cat's claw for rheumatoid arthritis (RA). The first phase was R, DB, PC; in the second phase all patients received the treatment. There was a significant decrease in pain and a shorter period of morning stiffness for the treatment group compared to placebo after the first phase and a further reduction after the second phase. The placebo-cat's claw treatment group experienced some reduction of symptoms in the second phase. Two small uncontrolled, unpublished trials tested the UT-POA extract on patients with RA, and on ulcers and gastritis.

The UT-POA extract was tested for immune function effects in 5 trials. All 5 trials are U, UP, thereby raising questions as to the significance of the results. Two trials tested the UT-POAs extract as an adjuvant therapy for cancer patients undergoing chemotherapy, radiation, and/or surgery with generally favorable results, 3 trials testing UT-POA extract as an adjuvant therapy for HIV-positive patients reported stabilized or increased CD-4 cell counts, increased vitality and no adverse effects.

Two U, UP trials using the UT-POA extract in topical preparations for *Herpes simplex* and *Varicella zoster* lesions, showed improvement and no adverse effects.



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Uncaria tomentosa (Willd.) DC.; *Uncaria guianensis* (Aubl.) Gmel.
[Fam. Rubiaceae]

OVERVIEW

Cat's claw (*uña de gato* in Spanish), refers to at least 20 plants with sharp, curved thorns, two of which are discussed in this sheet: *Uncaria tomentosa* (UT) and *U. guianensis* (UG), both native to the South and Central American tropical rain forests. UT and UG have a long history of use by indigenous people of these areas to treat health problems including rheumatism, arthritis, other chronic inflammatory disorders, gastric ulcers, gastrointestinal disorders, tumors, and as a contraceptive.

There are five types of products offered mainly by three manufacturers: (1) an aqueous-acid or hydroalcoholic extract of UT root standardized to pentacyclic oxindole acids (POAs) with no tetracyclic oxindole acids (TOAs) [herein referred to as UT-POA]; (2) an aqueous UT extract standardized to carboxy alkyl esters (CAEs) [UT-CAEs]; (3) and an aqueous UG extract [UG]. Two additional types of cat's claw products are relatively generic and usually labeled as UT: extracts not standardized to any particular constituent [UT-unspecified] and raw root bark products powdered in capsules or tablets, or finely cut for teas (the traditional form of use). [EDITORS' NOTE: Because each cat's claw species and preparation-type has a different chemical profile, the biological actions and uses for one may not apply to another.]

PRIMARY USES

Osteoarthritis (of the knee); rheumatoid arthritis along with conventional treatment. Other potential uses: anti-inflammatory; immune system modulator.

DOSAGE

Crude Preparations

UG CAPSULES: 100 mg 1–3x/day.

UT-unspecified:

CAPSULES: 350–500 mg, 1–2x/day.

TEA: 1 g root bark boiled for 15 min. in 250 ml water, 1–3x/day.

TINCTURE: 1–2 ml, 2–3x/day.

Standardized Preparations

UT-CAE TABLETS: 350 mg/day.

Comments

When using a dietary supplement, purchase it from a reliable source. For best results, use the same brand of product throughout the period of use. As with all medications and dietary supplements, please inform your healthcare provider of all herbs and medications you are taking. Interactions may occur between medications and herbs or even among different herbs when taken at the same time. Treat your herbal supplement with care by taking it as directed, storing it as advised on the label, and keeping it out of the reach of children and pets. Consult your healthcare provider with any questions.

UT-POA CAPSULES: One capsule 3x/day for the 1st 10 days, and one capsule/day thereafter.

CONTRAINDICATIONS

None reported for UG, UT-unspecified, and UT-CAE.

UT-POA: Based on the belief that cat's claw is an immunostimulant, it is not advised for patients awaiting bone marrow or organ transplant, persons with medically-induced immunosuppression (e.g., patients with organ transplants), autoimmune disease, multiple sclerosis, or tuberculosis. HIV/AIDS patients should proceed with caution when introducing any new therapeutic agent. Cat's claw is not for use in children under 3 years.

PREGNANCY AND LACTATION: Not recommended due to lack of data.

ADVERSE EFFECTS

Recent human trials conclude that various cat's claw preparations are safe, with no adverse effects reported in liver, kidney, central nervous system, cardiovascular or blood functions. Cat's claw teas or crude extracts may cause mild nausea, due to bitter taste; however, this appears speculative as nausea is not frequently reported.

UT-POA: In AIDS patients and patients receiving large doses of chemotherapy, individual mild cases of red blood cell elevation were reported. During the first 1–2 weeks of cat's claw tea use constipation or mild diarrhea was sometimes observed. Increased occurrence of acne symptoms was reported in HIV patients with prior acne symptoms. In rare cases, elevated uric acid values were observed in HIV and cancer patients; extensive cell die-off in cancer patients may cause a fever lasting 1–2 weeks.

DRUG INTERACTIONS

None reported for UG, UT-unspecified, and UT-CAE.

UT-POA: The leading Austrian cat's claw manufacturer advises: Take between and after chemotherapy treatment, but not during; do not take with passive animal vaccines, intravenous hyperimmunoglobulin therapy; intravenous thymic extracts, drugs using animal protein or peptide hormones (e.g., bovine or porcine insulin), or precipitate from frozen or fresh blood plasma.



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Cat's Claw

Uncaria tomentosa (Willd.) DC.; *Uncaria guianensis* (Aubl.) Gmel.

[Fam. Rubiaceae]

OVERVIEW

Cat's claw, also known by its Spanish name, *uña de gato*, is an herb that has gained recent popularity in the U.S. herb market. *Uña de gato* is the common name for at least 20 plants (from 12 different families) with sharp, curved thorns (Obregon, 1995; Cabieses, 1994). Among them are two climbing, woody vines: *Uncaria tomentosa* and *U. guianensis*, the two species of *Uncaria* (there are approximately 60 species) (Obregon, 1995; Cabieses, 1994) native to the South and Central American tropical rain forests that are the subject of this monograph. According to U.S. herb industry policy, the standardized common name "cat's claw" refers to only *U. tomentosa* (McGuffin *et al.*, 2000), presumably because products containing *U. guianensis* were not generally available in the U.S. market during most of the 1990s, having been introduced in the past several years. [EDITORS' NOTE: For the purposes of this monograph, *U. tomentosa* will be abbreviated as "UT" and *U. guianensis* will be abbreviated as "UG." Because the information on each species and preparation type may be specific to that particular species or preparation type, it may have been preferable to write two or three separate monographs instead of one. However, the editors chose to include all the relevant information on "cat's claw" in this single monograph, with subheadings designating species and preparation type, where applicable. In doing so, the editors acknowledge that actions and uses based on one species or preparation type may not be transferable to another.]



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Both UT and UG are said to have a long history of use by indigenous people to treat a diverse set of health problems, particularly rheumatism, arthritis, and other chronic inflammatory disorders, gastric ulcers and gastrointestinal disorders, tumors, and as a contraceptive (Cabieses, 1994; Jones, 1995; Obregon, 1995; Anon., 1996; Miller, 2001a). Although no written records are available describing their traditional use (Cabieses, 1994), a

study of the medicinal system of the Ashaninka (also spelled Asháninka) tribe in Peru has been published. To the priests of this tribe, cat's claw (UT) is a sacred plant used to eliminate disturbance in the communication between body and spirit (Keplinger *et al.*, 1999). One account of the Asháninka Indians states that the priests differentiate between the two UT chemotypes and use only the pentacyclic oxindole alkaloid (POA) chemotype (Keplinger *et al.*, 1999), but how the priests can distinguish between chemotypes without the scientific tools of chemical analysis is not described. Despite some recent interest in this herb's potential immunomodulating activity, ethnomedical evidence of such use is lacking.

Several types of cat's claw preparations have grown in popularity in the U.S. with the market defined by the following five types of products offered mainly by three manufacturers, each with their own distinct focus: (1) an aqueous-acid or hydroalcoholic extract of UT root standardized to pentacyclic oxindole alkaloids (POAs) with no tetracyclic oxindole alkaloids (TOAs) [herein referred to as UT-POA], (2) an aqueous UT extract standardized to carboxy alkyl esters (CAEs) [herein referred to as UT-CAE], (3) and an aqueous UG extract [herein referred to as UG]. Two additional types of cat's claw products are relatively generic and usually labeled as UT: extracts not standardized to any particular constituent [herein referred to as UT-unspecified] and raw root bark products powdered in capsules or tablets, or finely cut for teas (decoctions, the traditional form of use). Little scientific research has been performed on this fifth class of crude products. Occasionally, products labeled as "cat's claw" in ethnic markets have been shown to be mislabeled due to the vast number of plants known by the common name cat's claw, and the lack of adequate quality control with some small importers and distributors.

Fourteen clinical trials on various preparations are summarized herein. One controlled clinical trial with UG suggests efficacy in the treatment of osteoarthritis of the knee (Piscoya *et al.*, 2001). While cat's claw's popularity is partly due to European reports of its clinical effectiveness in combination with AZT (zidovudine) for AIDS treatment, these findings lack confirmation by well-controlled clinical studies. Other current studies report on cat's claw's anti-inflammatory and antioxidant properties, and its ability to affect gene expression and thereby modulate the immune system.

Cat's claw is not yet popular in mainstream retail markets, being sold primarily in health food stores where it ranked 25th in total herb sales in 2000 (Richman and Witkowski, 2001), mail order, and in the ethnic Hispanic market.

DESCRIPTION

Cat's claw preparations are made from extracts of the dried stalk, stalk bark (commonly called "root" bark), or actual root of *U. tomentosa* (Willd.) DC. or *U. guianensis* (Aubl.) Gmel. [Fam. Rubiaceae]. Products standardized to POAs will often use the

root rather than the root (stalk) bark, as it contains a higher concentration of POAs. However, this practice destroys the plant, whereas use of the stalk or root bark allows the vine to regenerate. Given that a considerable portion of cat's claw is still wild harvested, from an environmental/sustainability perspective it may be more prudent long-term to utilize the stalk and root bark rather than the actual root, or cultivate the plants if the actual root is desired. *Uncaria tomentosa* and *U. guianensis* are distinguished by flower color, thorn shape, and leaf characteristics (Jones, 1995; Cabrieses, 1994). In addition, *U. guianensis* contains lower levels of alkaloids (35 times less) and flavanols than *U. tomentosa* (Sandoval *et al.*, 2002, 2000; Miller *et al.*, 2001). The *U. tomentosa* plants occur naturally as two chemotypes that appear botanically identical, but are chemically different in their alkaloid content (Laus *et al.*, 1997). One chemotype contains predominantly POAs with little or no TOAs, and the other contains TOAs with either no POAs or up to a considerable amount. TOAs are reported to act antagonistically to some POA activity (Wurm *et al.*, 1998). While early studies focused on POAs as the active components, more recent studies report that activity is well spread over a range of polar materials. Several commercial preparations of *U. tomentosa* are available: aqueous-acid and hydroalcoholic extracts standardized to POAs (containing no TOAs); a nonstandardized mixture of both chemotypes; and an aqueous extract, ultrafiltrated, containing a negligible level of oxindole alkaloids, and standardized to CAEs. One *U. guianensis* preparation is composed of a freeze-dried aqueous extract. No monographs on any cat's claw preparation have been published to date in any official pharmacopeias.

PRIMARY USES

Anti-inflammatory

- **Osteoarthritis (of the knee)**
UG: reduces pain (Piscoya *et al.*, 2001)
- **Rheumatoid arthritis—adjunct therapy to conventional treatment**
UT-POA: reduces number of painful and swollen joints (Mur *et al.*, 2002; Immodal, 1995, 2002)

OTHER POTENTIAL USES

[EDITORS' NOTE: the following potential uses are based on clinical trials unless otherwise noted.]

- **Anti-inflammatory/Gastrointestinal**
UG: protects gastric epithelial cells against NSAID-induced gastritis and apoptosis in *in vitro* tests (Sandoval *et al.*, 2002)
UT-UNSPECIFIED: protects gastric epithelial cells against NSAID-induced gastritis and apoptosis in animal and *in vitro* tests (Sandoval *et al.*, 2002; Sandoval-Chacón *et al.*, 1998)
UT-POA: ulcers and gastritis (Immodal 1995, 1999a)
- **Antioxidant**
UG: effectively scavenges DPPH (α , α -diphenyl- β -picrylhydrazyl), protects against deoxyribose degradation, and inhibits ABTS (2,2'-azino bis [3-ethyl-benzthiazoline-6-sulfonic acid]) radicals in *in vitro* tests (Sandoval *et al.*, 2002); limits gastric epithelial cell death in response to oxidative stress *in vitro* (Miller *et al.*, 2001)
UT-UNSPECIFIED: effectively scavenges DPPH, protects against deoxyribose degradation, and inhibits ABTS radicals in *in vitro* tests (Sandoval *et al.*, 2002); cytoprotective

against oxidative stress *in vitro* (Sandoval-Chacón *et al.*, 1998)

- **Cancer—adjunctive to chemotherapy & radiation**
UT-POA: increases vitality and reduces side effects (Immodal, 1995, 1999a, 2002)
- **DNA-Repair/Antimutagenic**
UT-UNSPECIFIED: decreased mutagenicity of one smoker's urine (Rizzi *et al.*, 1993)
UT-CAE: enhanced DNA repair (Sheng *et al.*, 2001)
- **External Use**
UT-POA: *Herpes simplex* and *Varicella-zoster* (Immodal 1995, 1999a, 2002)
- **HIV—adjunctive to antiretroviral therapy**
UT-POA: stabilizes and/or reduces CD4-cell count, increases vitality and mobility, reduced HIV-related symptoms (Immodal, 1995, 1999a, 2002)
- **Immune system support**
UT-CAE: extends immunity from pneumonia vaccine (Lamm *et al.*, 2001); increases white blood cells (Sheng *et al.*, 2001, 2000a) in animal study (Sheng *et al.*, 2000b)
- **Protection against UV radiation**
UT-UNSPECIFIED: cytoprotective against UV radiation *in vitro* (Sandoval *et al.*, 2000; Rizzi *et al.*, 1993)

DOSAGES

Crude Preparations

[EDITOR'S NOTE: There is little scientific or clinical documentation supporting the use of crude cat's claw products. Most clinical research has been conducted on special standardized preparations of various types.]

- ***Uncaria guianensis***
CAPSULES: aqueous extract of bark powder, freeze-dried: 100 mg 1–3 times daily (Piscoya *et al.*, 2001; Miller, 2001a).
- ***Uncaria tomentosa*—chemotype and active component unspecified**
CAPSULES: 350–500 mg, 1–2 times daily (CAMR, 1999).
DECOCTION: 1 g root bark boiled for 15 minutes in 250 ml water, 1–3 times daily (Access, 2000; CAMR, 1999).
TINCTURE: 1–2 ml, 2–3 times daily (CAMR, 1999).

Standardized Preparations

- ***Uncaria tomentosa*—standardized to CAEs**
TABLETS: 350 mg daily (Lamm *et al.*, 2001; Sheng *et al.*, 2001, 2000a).
- ***Uncaria tomentosa*—standardized to POAs**
CAPSULES: 20 mg (0.26 mg POAs), 3 times daily for the first 10 days, and one capsule daily thereafter (Enzymatic Therapy, 2002).
CAPSULES: 1–3 capsules/day (in acute cases, triple dose for 1st wk) (Immodal, 1995).
DROPS (d): Adults: 3x20 d/day; 3–6 yrs: 3x7 d/day; 7–9 yrs: 3x10 d/day; 10–12 yrs: 3x15 d/day; 12+ yrs: 3x20 d/day (Immodal, 1995).
TEA: 20 g ground root bark in 1 L water, boiled 45 min, cooled 10 min, filtered water added to make 1 L. Adults: 60 ml decoction in 60 ml hot water before breakfast; Children: decoction in hot water before breakfast according to the following amounts: 3–6 yrs: 20 ml in 20 ml;

7–9 yrs: 30 ml in 30 ml; 10–12 yrs: 50 ml in 50 ml; 12+ yrs: same as adult (Immodal, 1995).

OINTMENT: applied externally several times daily (Immodal, 1995).

SPRAY: applied externally several times daily (Immodal, 1995).

DURATION OF ADMINISTRATION

At this time, there is little scientific information other than ethnobotanical observations and 14 clinical trials (including case reports and treatment observations) on how long cat's claw can be consumed. Published clinical trials have been conducted from as short as 4 weeks to 1 year of continuous internal use, while unpublished treatment observations using Krallendorn® (Immodal Pharmaka GmbH) products report on continuous (uncontrolled) use for up to 10 years. There are no known reports of adverse effects associated with the use of cat's claw preparations for extended periods.

CHEMISTRY

Although chemical research on cat's claw began with UG in 1952 (Cabieses, 1994), most of the chemical research since then has focussed on UT and its alkaloids, particularly the oxindole alkaloids. However, these alkaloids are a small component of cat's claw (approximately 0.9% in UT and 0.03% in UG [Sandoval *et al.*, 2002]), which is rich in flavonoids, quinovic glycosides, polyhydroxylated triterpenes, and tannins. While earlier studies reported alkaloids as the active components of cat's claw (Aguilar *et al.*, 2000; Laus *et al.*, 1998; Stuppner *et al.*, 1993; Kreuzkamp, 1984; Wagner *et al.*, 1985a, 1985b), more recent studies report that bioactivity is spread over a wide range of components (Aguilar *et al.*, 2002; Sandoval *et al.*, 2002; Kitajima *et al.*, 2000; Lee *et al.*, 1999; Sheng *et al.*, 1998; Wirth and Wagner, 1997; Aquino *et al.*, 1991, 1989; Cerri *et al.*, 1988), and one study suggests that the anti-inflammatory and antioxidant activities of cat's claw are not affected by the presence or relative level of alkaloids (Sandoval *et al.*, 2002).

Uncaria guianensis

The little chemical research performed on UG has been limited to its alkaloid, quinovic acid glycoside, and flavanol content. UG contains very low levels of alkaloids—35 times less than UT (Sandoval *et al.*, 2002; Miller *et al.*, 2001)—including specio-phylline, mitraphylline, isomitraphylline, uncarine E, and uncarine C (Sandoval *et al.*, 2002; Miller *et al.*, 2001; Lee *et al.*, 1999). UG also contains quinovic acid glycosides (Yépez *et al.*, 1991), flavanols (catechin, epigallocatechin, epicatechin, and epigallocatechin) (Sandoval *et al.*, 2002; Miller *et al.*, 2001), and polyphenols (Miller *et al.*, 2001). UG has lower concentrations of the flavanols (except for epigallocatechin) than does UT (Sandoval *et al.*, 2002).

Uncaria tomentosa

UT has two chemotypes: the pentacyclic alkaloid type and tetracyclic alkaloid type. The first contains POAs, which some consider to be the main active component of cat's claw (Immodal 1995, 1999a, 1999b), with little or no TOAs. The second chemotype contains predominantly TOAs with either no POAs or up to a considerable amount of POAs (Laus *et al.*, 1997). TOAs are considered antagonistic to the purported beneficial effects of the POAs (Wurm *et al.*, 1998) and thus, the significance in distinguishing between the two chemotypes. As in any determination of the source of bioactivity in an unknown natural product any

proposed active constituent must mimic the actions of the extract from which it was derived, and exert these actions at a concentration that reflects its relative amount within that botanical or botanical extract. Studies demonstrating that purified POAs or TOAs share the same bioactivity of cat's claw preparations but enhanced for the relative concentrations in these extracts are lacking. Therefore, these chemical constituents may be more useful as marker compounds rather than mediating the bioactivity of the botanical.

POAs in UT include pteropodine (uncarine C), isopteropodine (uncarine E), speciophylline (uncarine D), uncarine F, mitraphylline, and isomitraphylline (Muhammad *et al.*, 2001a; Laus *et al.*, 1997; Stuppner *et al.*, 1992; Wagner *et al.*, 1985b). The TOAs present in UT include rhynchophylline, isorhynchophylline, corynoxine, isocorynoxine (Keplinger *et al.*, 1999; Laus *et al.*, 1997; Wagner *et al.*, 1985b). Other alkaloids in UT include pentacyclic indol alkaloids (akuammigine, tetrahydroalstonine, isoajmalicin) (Laus *et al.*, 1997), tetracyclic indol alkaloids (hirsutine, dihydrocorynantheine, hirsuteine, corynantheine) (Keplinger *et al.*, 1999; Laus *et al.*, 1997), and precursor alkaloids (5 α -carboxystrictosidine, lyaloside) (Aquino *et al.*, 1991).

In addition to alkaloids, UT contains triterpenes (ursolic acid derivatives, quinovic acid glycosides, oleanolic acid derivatives) (Laus *et al.*, 1997; Aquino *et al.*, 1991, 1990, 1989; Cerri *et al.*, 1988), polyhydroxylated triterpenes (Aquino *et al.*, 1991, 1990, 1989; Cerri *et al.*, 1988), procyanidins ([-]-epicatechin, cinchonain 1a, cinchonain 1b) (Wirth and Wagner, 1997), sterols (β -sitosterol, stigmasterol, campesterol) (Senatore *et al.*, 1989), flavanols (catechin, epigallocatechin, epicatechin and epigallocatechin) (Sandoval *et al.*, 2002), tannins (Wagner *et al.*, 1985b) and CAEs (Sheng *et al.*, 2001).

PHARMACOLOGICAL ACTIONS

Human

• *Uncaria guianensis*

ANTI-INFLAMMATORY: significantly reduced pain associated with activity in patients with osteoarthritis of the knee (Piscoya *et al.*, 2001).

• *Uncaria tomentosa*—unspecified preparations

ANTIMUTAGENIC: ingestion for 15 days decreased mutagenicity of one smoker's urine (Rizzi *et al.*, 1993).

• *Uncaria tomentosa*—standardized to CAEs

IMMUNOMODULATION/IMMUNE SUPPORT: enhanced response to pneumococcal vaccine by reducing decay of antibody titers and elevating lymphocyte/neutrophil (Lamm *et al.*, 2001); decreased DNA damage (measured as single strand breaks in DNA) from single dose of hydrogen peroxide and increased DNA repair (Sheng *et al.*, 2001); increased white blood cell levels in healthy males (Sheng *et al.*, 2000a).

ANTIMUTAGENIC: decreased DNA damage (measured as single strand breaks in DNA) from single dose of hydrogen peroxide and increased DNA repair (Sheng *et al.*, 2001); enhances DNA repair (Sheng *et al.*, 2000a).

• *Uncaria tomentosa*—POA chemotype

ANTI-INFLAMMATORY: reduced number of painful and tender joints and decreased duration of morning stiffness in rheumatoid arthritis patients (Mur *et al.*, 2002; Immodal, 1995, 2002); eliminated symptoms and need for antacids in ulcer and gastritis patients (Immodal 1995, 1999a).

IMMUNOMODULATION/IMMUNE SUPPORT: increased vitality and reduced side effects in cancer patients undergoing chemotherapy, radiation, or surgery (Immodal 1995, 1999a, 2002); reduced HIV-related symptoms and increased vitality of HIV patients receiving antiretroviral treatment, increased lymphocyte numbers in HIV patients although total leukocyte numbers remained unchanged, stabilized or increased CD4 cell count in HIV patients (Immodal 1995, 1999a, 2002).

Animal

• *Uncaria tomentosa*–unspecified preparations

ANTI-INFLAMMATORY: significantly reduced paw volume in carrageen-induced rat paw edema (Aguilar *et al.*, 2002, 2000; Aquino *et al.*, 1991); protected against NSAID-induced gastritis by reducing lesions and apoptosis of the mucosal epithelial cells (Sandoval *et al.*, 2002); prevention of NSAID-induced enteropathy in rats (Sandoval-Chacón *et al.*, 1998).

• *Uncaria tomentosa*–standardized to CAEs

IMMUNOMODULATION/IMMUNE SUPPORT: increased DNA repair of single and double strand breaks from whole body irradiation in rats (Sheng *et al.*, 2000a); increased white blood cell count sooner, and all fractions proportionally, compared with control in rat model of chemotherapy-induced leukopenia (Sheng *et al.*, 2000b); prolonged leukocyte survival in rats at daily doses of 125–500 mg/kg body weight (Åkesson *et al.*, 2003).

• *Uncaria tomentosa*–POA chemotype

ANTI-INFLAMMATORY: significantly reduced paw volume in carrageen-induced rat paw edema (Aguilar *et al.*, 2002, 2000).

• Isolated components of *Uncaria* species

[EDITORS' NOTE: The studies referenced in this subsection were performed with compounds isolated from *U. rhynchophylla* or *U. sinensis*. While these compounds are also found in *U. guianensis* and/or *U. tomentosa*, no studies have been performed on extracts or fractions derived from UG or UT to verify that these actions apply to them as well; thus their clinical significance is undetermined. These studies have been included because some proponents of the UT products standardized to POAs and no TOAs, cite them in support of the need for removal of TOAs from cat's claw products.]

Isorhynchophylline reduced blood pressure and heart rate in rats and dogs (Shi *et al.*, 1989); rhynchophylline and isorhynchophylline reduced blood pressure and heart rate in dogs, with isorhynchophylline demonstrating a stronger effect (Shi *et al.*, 1992).

In vitro

• *Uncaria guianensis*

ANTI-INFLAMMATORY: reduces excessive production of cytokines and inflammatory mediators at the genetic level (Sandoval *et al.*, 2002; Piscocoy *et al.*, 2001) with UG being more potent than UT (Sandoval *et al.*, 2002), and at extract concentrations far lower than required for antioxidant activity (Piscocoy *et al.*, 2001); prevents and eliminates gastrointestinal injury and inflammation in NSAID-induced gastritis (Sandoval *et al.*, 2002).

ANTIOXIDANT: scavenges DPPH (UG more potent than UT despite lower concentrations of alkaloids and flavanols), protects against deoxyribose degradation in a dose-dependent

manner, and inhibits ABTS-radicals (Sandoval *et al.*, 2002); effectively scavenges free radicals and inhibits lipid peroxidation (Piscocoy *et al.*, 2001); protects human gastric epithelial cells from apoptosis induced by DPPH, peroxynitrite and H₂O₂ (Miller *et al.*, 2001).

• *Uncaria tomentosa*–unspecified preparations

ANTI-INFLAMMATORY: reduces excessive production of cytokines and inflammatory mediators at the genetic level with UG being more potent than UT, and at extract concentrations far lower than required for antioxidant activity (Sandoval *et al.*, 2002; Piscocoy *et al.*, 2001); suppressed tumor necrosis factor alpha (TNF α) production by 65–85% (Sandoval *et al.*, 2000); prevents and eliminates gastrointestinal injury and inflammation in NSAID-induced gastritis (Piscocoy *et al.*, 2001; Sandoval *et al.*, 2000; Sandoval-Chacón *et al.*, 1998); reduces cyclo-oxygenase-2 (COX-2) expression (Piscocoy *et al.*, 2001).

ANTIOXIDANT: scavenges DPPH (UG more potent than UT reflected as lower IC50 value despite lower concentrations of alkaloids and flavanols), protects against deoxyribose degradation in a dose-dependent manner, and inhibits ABTS-radicals (Sandoval *et al.*, 2002, 2000); effectively scavenges free radicals and inhibits lipid peroxidation (Piscocoy *et al.*, 2001); protects human gastric epithelial cells from apoptosis induced by DPPH, peroxynitrite and hydrogen peroxide (Miller *et al.*, 2001); reduces peroxynitrite-induced apoptosis in human gastric epithelial cells and in macrophages (Sandoval-Chacón *et al.*, 1998); protective against UV irradiation-induced cytotoxicity (Sandoval *et al.*, 2000).

IMMUNOMODULATION/IMMUNE SUPPORT: Increased cytokine (IL-1 and IL-6) production in alveolar macrophages (Lemaire *et al.*, 1999) although high concentrations were used that might reflect a toxicologic response and may be incompatible with *in vivo* efficacy (Sandoval *et al.*, 2002).

ANTIMUTAGENIC: protective against photomutagenesis, (Rizzi *et al.*, 1993).

• *Uncaria tomentosa*–standardized to CAEs

IMMUNOMODULATION/IMMUNE SUPPORT: CAE: significantly increased PHA (phytohemagglutinin)-stimulated lymphocyte proliferation in splenocytes and significantly elevated white blood cell (WBC) count (Sheng *et al.*, 2000a).

ANTIPROLIFERATIVE: inhibited proliferation and induced apoptosis in some tumor cell lines (Sheng *et al.*, 1998) at high concentrations that might reflect a toxicologic response (Sandoval *et al.*, 2000).

• *Uncaria tomentosa*–POA chemotype

ANTI-INFLAMMATORY: moderate to weak activity against cyclo-oxygenase-1 and -2 (COX-1 and COX-2) (Aguilar *et al.*, 2002).

ANTIPROLIFERATIVE: Inhibited proliferation of some human tumor cell lines (Immodal, 1999b).

• Isolated Chemical Components from Cat's Claw

[EDITORS' NOTE: As in any determination of the source of bioactivity in an unknown natural product, any proposed active constituent must mimic the actions of the extract from which it was derived, and exert these actions at a concentration that reflects its relative amount within that botanical or botanical extract. Studies demonstrating that purified POAs or TOAs

share the same bioactivity of cat's claw preparations but enhanced for the relative concentrations in these extracts are lacking. Therefore, these chemical constituents may be more useful as marker compounds rather than mediating the bioactivity of the botanical.]

IMMUNOMODULATION/IMMUNE SUPPORT: Phagocytosis was enhanced *in vitro* by pteropodine, isomitraphylline, and isorhynchophylline (two POAs and one TOA, isolated from UT), but phagocytosis was enhanced *in vivo* only after addition of catechin to POAs (Wagner *et al.*, 1985a, 1985b; Kreutzkamp, 1984); POAs isolated from UT induced endothelial cells to release a factor that inhibited proliferation of normal human lymphoblasts and stimulated proliferation of normal human resting lymphocytes, while TOAs dose-dependently reduced these effects (Wurm *et al.*, 1998); POAs isolated from UT inhibited growth of HL60 and U-937 leukemic cells, with uncarine F demonstrating the strongest effect; (Stuppner *et al.*, 1993 cited in Keplinger *et al.*, 1999); isopteropodine (POA isolated from UT) increases the phagocytosis of granulocytes and reticuloendothelial system (RES) cells (Kreutzkamp, 1984; Wagner *et al.*, 1985a, 1985b).

ANTI-INFLAMMATORY: 17 non-alkaloid HPLC fractions from UT reduced TNF α and nitrite production induced by lipopolysaccharide (LPS) in RAW 264.7 cells (Sandoval *et al.*, 2002); one quinovic acid glycoside isolated from UT demonstrated anti-inflammatory effects, but it appears that the strong anti-inflammatory effects of cat's claw extracts and fractions may be the result of the synergistic activity of a combination of compounds (Aquino *et al.*, 1991); moderate anti-inflammatory activity has been demonstrated for β -sitosterol, stigmasterol and campesterol isolated from UT (Senatore *et al.*, 1989); one procyanidine (cinchonin 1b) isolated from UT inhibited 5-lipoxygenase, demonstrating anti-inflammatory activity (Wirth and Wagner, 1997).

ANTIVIRAL: 9 quinovic acid glycosides isolated from UT showed moderate antiviral activity against vesicular stomatitis virus, but at concentrations approaching cellular toxicity (Aquino *et al.*, 1989); two quinovic acid glycosides isolated from UT (those with free carboxyl groups) reduced by 50% the viral cytopathic effect of rhinovirus type 1b infection (Aquino *et al.*, 1989).

ANTI-PROLIFERATIVE: Uncarine D showed weak cytotoxic activity against SK-MEL, KB, BT-549 and SK-OV-3 cell lines with IC₅₀ values between 30 and 40 μ g/ml, while uncarine C exhibited weak cytotoxicity only against ovarian carcinoma (IC₅₀ at 37 μ g/ml) (Muhammad *et al.*, 2001b). However, given the concentration of uncarine C in cat's claw, the amount of cat's claw that would have to be consumed to achieve these concentrations *in vivo* may be unrealistic. In addition to the antimutagenic activity, UT extracts and fractions exert a direct antiproliferative activity on the MCF7 human breast cancer cell line. The bioassay-directed fraction from barks and leaves resulted in the isolation of 2 active fractions, displaying an IC₅₀ of 10 mg/ml and 20 mg/ml, respectively and an antiproliferative effect, with about 90% of inhibition at a concentration of 100 mg/ml (Riva *et al.*, 2001). As noted above, for the alkaloids uncarine D and C, these fractions would require an unrealistic consumption of kilogram quantities of cat's claw to achieve these actions.

• Isolated Chemical Components from other *Uncaria* species

[EDITORS' NOTE: The studies referenced in this subsection were performed with compounds isolated from *U. rhynchophylla* or *U. sinensis*. While these compounds are also found in *U. guianensis* and/or *U. tomentosa*, no studies have been performed on extracts or fractions derived from UG or UT to verify that these actions apply to them as well; thus their clinical significance is undetermined. These studies have been included because some proponents of the UT products standardized to POAs and no TOAs, cite them in support of the need for removal of TOAs from cat's claw products.]

Rhynchophylline and isorhynchophylline produced negative chronotropic and inotropic effects (Zhu and Guozing, 1993); rhynchophylline inhibits platelet aggregation (Chen *et al.*, 1992; Jin *et al.*, 1991); rhynchophylline may be a calcium antagonist (Sun *et al.*, 1988; Zhang *et al.*, 1987); rhynchophylline, corynoxine, isorhynchophylline, isocorynoxine, and indole alkaloids such as hirsuteine and hirsutine inhibit Ca²⁺ influx which protects against glutamate-induced neuronal death (Shimada *et al.*, 1999; Yano *et al.*, 1991); corynantheine and dihydrocorynantheine have sedative action which in toxic dosages may lead to respiratory paralysis and ataxia (Kanatani, 1985); corynantheine and dihydrocorynantheine reduced specific [³H]5-HT binding and were found to be partial agonists for 5-HT receptors (Kanatani, 1985).

MECHANISMS OF ACTION

Uncaria guianensis

ANTI-INFLAMMATORY

- Modifies gene expression by inhibiting redox-sensitive transcription factors (Piscoya *et al.*, 2001; Sandoval *et al.*, 2002).
- Inhibits transcription factor NF- κ B thereby modifying expression of genes involved in the inflammatory process including TNF α , inducible nitric oxide synthase (iNOS), and COX-2 (Sandoval *et al.*, 2002; Piscoya *et al.*, 2001).
- Inhibits production of TNF α (Sandoval *et al.*, 2002; Piscoya *et al.*, 2001) with UG being more potent than UT (Sandoval *et al.*, 2002).
- Decreases production of lipopolysaccharide-induced prostaglandin E-2 (Piscoya *et al.*, 2001).

ANTIOXIDANT

- Scavenges DPPH (UG more potent than UT despite lower concentrations of alkaloids and flavanols), protects against deoxyribose degradation in a dose-dependent manner, and inhibits ABTS-radicals (Sandoval *et al.*, 2002).
- Effectively scavenges free radicals and inhibits lipid peroxidation (Piscoya *et al.*, 2001; Miller *et al.*, 2001).
- Protects human gastric epithelial cells from apoptosis induced by DPPH, peroxyxynitrite and hydrogen peroxide (Miller *et al.*, 2001).
- More effective in limiting the cellular response to oxidants than degrading the oxidant itself (Miller *et al.*, 2001; Piscoya *et al.*, 2001).

Uncaria tomentosa—unspecified

ANTI-INFLAMMATORY

- Modifies gene expression by inhibiting redox-sensitive transcription factors (Piscoya *et al.*, 2001; Sandoval *et al.*, 2000; Sandoval-Chacón *et al.*, 1998).
- Inhibits transcription factor NF- κ B thereby modifying expression of more than 28 genes involved in the inflammatory process including TNF α , iNOS, and COX-2 (Aguilar *et al.*, 2002; Sandoval *et al.*, 2002; Piscoya *et al.*, 2001; Sandoval-Chacón *et al.*, 1998).
- Inhibits lipopolysaccharide-induced iNOS gene expression, nitrite formation, and cell death (Sandoval-Chacón *et al.*, 1998).
- Inhibits production of TNF α , iNOS, and COX-2 (Sandoval *et al.*, 2002; Piscoya *et al.*, 2001; Sandoval-Chacón *et al.*, 1998).
- Moderate to weak activity against COX-1 and COX-2 (Aguilar *et al.*, 2002).
- Decreased production of lipopolysaccharide-induced prostaglandin E-2 (Piscoya *et al.*, 2001).
- Suppressed TNF α production (Sandoval *et al.*, 2002; Piscoya *et al.*, 2001; Sandoval-Chacón *et al.*, 1998) by 65–85% (Sandoval *et al.*, 2000).

ANTIOXIDANT

- Scavenges DPPH (UG more potent than UT despite lower concentrations of alkaloids and flavanols), protects against deoxyribose degradation in a dose-dependent manner, and inhibits ABTS-radicals (Sandoval *et al.*, 2002; 2000).
- Effectively scavenges free radicals and inhibits lipid peroxidation (Piscoya *et al.*, 2001).
- Protects human gastric epithelial cells from apoptosis induced by DPPH, peroxynitrite and H₂O₂ (Miller *et al.*, 2001).
- Reduces peroxynitrite-induced apoptosis in human gastric epithelial cells and in macrophages (Sandoval-Chacón *et al.*, 1998).
- Cytoprotective against UV irradiation (Sandoval *et al.*, 2000).

IMMUNOMODULATION/IMMUNE SUPPORT

- Increased cytokine (IL-1 and IL-6) production in alveolar macrophages (Lemaire *et al.*, 1999) although high concentrations were used suggesting that this action could only be observed *in vivo* with ingestion of kilogram quantities; a dosing regimen that might reflect a toxicologic response (Sandoval *et al.*, 2002).
- Stimulates interleukin-1 (IL-1) and interleukin-6 (IL-6) production at a rate of 10.0x and 7.5x control levels, respectively. The effect is dose-dependent and diminishes when the dose exceeds the range of 0.025–0.1 mg/ml (Lemaire *et al.*, 1999).

Uncaria tomentosa—standardized to CAEs

ANTIMUTAGENIC

- Stimulation of DNA repair mechanisms (Sheng *et al.*, 2000a, 2001).

IMMUNOMODULATION/IMMUNE SUPPORT

- Stimulates lymphocyte proliferation and elevates white blood cells (Sheng *et al.*, 2000a, 2000b; Lamm *et al.*, 2001).

ANTI-TUMOR

- Suppresses tumor growth through selective induction of apoptosis in two human leukemic cell lines (K562 and HL60) and one human EBV-transformed B-lymphoma cell line (Raji) (Sheng *et al.*, 1998); however, some authors have reported apoptosis in these same cell lines due to inhibition of NF- κ B (Sandoval *et al.*, 2002; Mannick *et al.*, 1997; Beg and Baltimore, 1996).

Uncaria tomentosa—POA chemotype

ANTI-INFLAMMATORY

- Moderate to weak activity against COX-1 and COX-2 (Aguilar *et al.*, 2002).
- Inhibits synthesis of NF- κ B (Aguilar *et al.*, 2002; 2000).

IMMUNOMODULATION/IMMUNE SUPPORT

- POAs induce the release of a lymphocyte-growth factor from endothelial cells that regulates lymphocyte proliferation (Wurm *et al.*, 1998), but does not change total leukocyte numbers (Keplinger *et al.*, 1999). TOAs act antagonistically to this effect of POAs (Wurm *et al.*, 1998; Keplinger *et al.*, 1999).

CONTRAINDICATIONS

Cat's claw has been contraindicated for leukemia patients awaiting bone marrow transplant, any patient awaiting organ transplant, persons with iatrogenically-induced immunosuppression (e.g., organ transplants), autoimmune disease, multiple sclerosis, or tuberculosis (CAMR, 1999). These contraindications are based on the belief that cat's claw is an immunostimulant. However, some researchers disagree with this view (Miller, 2001b; Sandoval-Chacón *et al.*, 1998; Sandoval *et al.*, 2000, 2002) and suggest that cat's claw may be helpful for transplant patients (Miller, 2001a). The elevated production of TNF α is a characteristic of numerous autoimmune disorders, including those in which cat's claw offers benefits (arthritis, gut inflammation) and lowering TNF α levels, as with cat's claw, may be desirable rather than contraindicated for these patients. HIV/AIDS patients should proceed with caution when introducing any new therapeutic agent (Miller, 2001b). Cat's claw is not for use in children under 3 years due to lack of data regarding its effects on the immature immune system (Immodal, 1995).

PREGNANCY AND LACTATION: Not recommended (Jones, 1995) due to lack of data regarding the effects of cat's claw on the immature immune system (Immodal, 1995).

ADVERSE EFFECTS

Recent human trials have concluded that the various cat's claw preparations tested are safe, with no adverse effects reported in liver, renal, central nervous system, or hematological function (Piscoya *et al.*, 2001; Sheng *et al.*, 2001, 2000a; Lamm *et al.*, 2001). Cat's claw teas or crude extracts may cause mild nausea, due to the bitter taste (Williams, 2001); however, this appears speculative as nausea is not a frequently reported effect. In one case report, a patient with systemic lupus erythematosus (SLE) experienced acute renal failure, which the authors attributed to an idiosyncratic adverse reaction to the purported cat's claw preparation which was not adequately documented (Hilepo *et al.*, 1997).

Uncaria guianensis

In one study infrequent reports of headache, dizziness, and vomiting were reported but the incidence and frequency were the same as with placebo (Piscoya *et al.*, 2001).

Uncaria tomentosa—standardized to CAEs

None reported.

Uncaria tomentosa—POA chemotype

In AIDS patients and patients receiving large doses of chemotherapy, individual cases of a mild erythrocytosis have been reported. During the first 1–2 weeks of ingesting cat's claw tea (Krallendorn®) temporary constipation or mild diarrhea was sometimes observed. Increased occurrence of acne symptoms has been reported in HIV patients with prior symptoms. In rare cases, elevated uric acid values were observed in HIV and cancer patients; extensive cell die-off in tumor patients may cause lytic fever lasting 1–2 weeks (Immodal, 1999a, 1995).

Components from Other Species of *Uncaria*

Cat's claw products containing larger amounts of TOAs could possibly result in sedative effects and circulatory complaints (e.g., reduced blood pressure, coronary blood flow, and heart rate; inhibited platelet aggregation) (Reinhard, 1999), due to the reported effects of TOAs in *Uncaria* species other than UT or UG (Shi *et al.*, 1992, 1989; Jin *et al.*, 1991). However, no such effects have been reported in studies using products made with UT or UG.

DRUG INTERACTIONS

Uncaria guianensis

None reported.

Uncaria tomentosa—unspecified preparations

UT may potentially reduce the rate of metabolism and thus increase serum levels of drugs taken orally as observed in an *in vitro* assay on an unspecified UT tincture where the CYP3A4 isozyme production was inhibited (Budzinski *et al.*, 2000).

Some authors warn that some unspecified forms of cat's claw may increase the effects of anticoagulants and antihypertensives (Fetrow and Avila, 2000; CAMR, 1999; Spaulding-Albright, 1997; INPR, 1999). However, this is based on research on TOA components isolated from *Uncaria* species other than UG or UT. While it is possible that cat's claw products rich in TOAs may interact with these classes of drugs, there are no reliable data to support this conclusion. Further, there is little evidence to support this interaction with cat's claw products that contain little or no TOAs such as UG products or the UT product Krallendorn®, or C-Med-100® (AF Nutraceutical Group).

Uncaria tomentosa—standardized to CAEs

None reported.

Uncaria tomentosa—POA chemotype

According to a communication to physicians and pharmacists from the leading Austrian research and manufacturing company of cat's claw, the following advice should be given to patients, based on the products proposed immunomodulatory effects:

Take between chemotherapy treatments and after completion, but not with chemotherapy treatments; do not take in conjunction with passive animal vaccines, intravenous hyperimmunoglobulin therapy; intravenous thymic extracts, drugs using animal protein or peptide hormones (e.g., bovine or porcine insulin), cryoprecipitates, or fresh blood plasma (Immodal, 1995).

AMERICAN HERBAL PRODUCTS ASSOCIATION (AHPA) SAFETY RATING

CLASS 4: Insufficient data available for classification (McGuffin *et al.*, 1997).

[EDITORS' NOTE: Cat's claw was not widely marketed during the time that the literature upon which this book is based was published, mainly 1980s and early to mid-1990s. Of potential relevance is the fact that numerous studies show cat's claw to be safe. Human, animal, and *in vitro* studies demonstrate the antimutagenic activity of cat's claw (Sheng *et al.*, 2001, 2000a, 1998; Immodal, 1999b; Leon *et al.*, 1996; Rizzi *et al.*, 1993). One human trial found no toxic effects at a dose of 350 mg/day of C-Med-100® for 6 consecutive weeks (Sheng *et al.*, 2000a). One animal study reports an LD50 of greater than 16 g/kg of body weight using a freeze-dried aqueous extract of POA type UT (Kynoch and Lloyd, 1975), while a second reports an LD50 of greater than 8 g/kg for C-Med-100. Another study found daily oral administration of an aqueous-acid extract of UT at 1,000 mg/kg body weight for 28 days to be atoxic in rats (Svendson and Skydsgaard, 1986). In an additional test, an aqueous extract of UT was atoxic up to the maximum dosage of 5 g/kg body weight administered orally, and up to a concentration of 2 g/kg body weight administered intraperitoneally (Kreutzkamp, 1984). The alkaloid fraction of UT was found to be atoxic up to the maximum dosage of 2 g/kg body weight orally, and 1 g/kg body weight intraperitoneally (Kreutzkamp, 1984).]

REGULATORY STATUS

AUSTRIA: Prescription drug Krallendorn® (pentacyclic chemotype).

CANADA: Status undetermined. No products containing cat's claw are listed in the Health Canada Drugs Product Database (Health Canada, 2001).

GERMANY: No German Commission E monograph (Blumenthal *et al.*, 1998). No monograph in the *German Pharmacopoeia* (DAB, 1999).

SWEDEN: No products containing cat's claw are listed in the Medical Products Agency (MPA) "Authorised Natural Remedies" (MPA, 2001).

SWITZERLAND: No products containing cat's claw are listed in the *Swiss Drug Compendium* (Morant and Ruppner, 2001). No monograph in the *Swiss Pharmacopoeia*.

U.K.: Not listed in the *General Sale List* (GSL, 1994). No monograph in the *British Pharmacopoeia*.

U.S.: Dietary supplement (USC, 1994). No monograph in the USP-NF.

CLINICAL REVIEW

There are 14 clinical trials on various preparations made from the two species of *Uncaria* summarized in the clinical studies Tables in this monograph. In general, the studies are relatively small, most are uncontrolled, and some have not been published. One prospective (P), randomized (R), double-blind (DB), placebo-controlled (PC), parallel group (PG), multi-center (MC) trial was conducted on 45 men who consumed 100 mg of a freeze-dried aqueous extract of UG for 4 weeks for osteoarthritis of the knee (Piscoya *et al.*, 2001). The study reports a significant improvement in pain associated with activity, and medical and patient assessment scores, but no significant improvement in pain at rest or at night, or knee circumference. There were no significant side effects in the UG and placebo groups.

Three trials tested the UT-CAE preparation (C-Med-100®) on immunomodulatory parameters. One small R, PC trial (n=23) resulted in no loss of immunity after 5 months in patients given a pneumonia vaccine after 2 months of treatment with 700 mg per day of the UT-CAE extract when compared to loss in the placebo group (Lamm *et al.*, 2001). Another small trial (n=12) reported an increase in DNA repair with no adverse effects (Sheng *et al.*, 2001). An uncontrolled trial on healthy volunteers resulted in an increase in white blood cells (Sheng *et al.*, 2000a).

Three trials tested a proprietary extract of UT standardized to POAs (Krallendorn®) for anti-inflammatory effects. One 52-week trial on 40 people with rheumatoid arthritis (RA) used 60 mg per day of the extract in capsules (Mur *et al.*, 2002). The first phase (24 weeks) was R, DB, PC; the second phase (28 weeks) was not blinded—all patients received the treatment. There was a significant decrease in pain and a shorter period of morning stiffness for the treatment group compared to placebo after the first phase and a further reduction after the second phase. The placebo-cat's claw treatment group experienced some reduction of symptoms in the second phase. Two small uncontrolled, unpublished trials test the UT-POA extract on patients with RA (Immodal, 1995, 2002) and on ulcers and gastritis (Immodal, 1995, 1999a).

Five trials tested the UT-POA extract for its effects on immune function. All five trials were uncontrolled and unpublished, thereby raising questions as to the significance of the results. Two trials tested the UT-POA extract as an adjuvant therapy for cancer patients undergoing chemotherapy, radiation, and/or surgery (Immodal 1995, 1999a, 2002) with generally favorable results, including patients' reports of a greater sense of vitality and fewer side effects; three additional trials tested UT-POA extract as an adjuvant therapy for HIV-positive patients (Immodal 1995, 1999a, 2002) and reported stabilized or increased CD-4 cell counts, increased vitality, and no adverse effects.

Two uncontrolled, unpublished trials were performed on the UT-POA extract in topical preparations for use on lesions caused by *Herpes simplex* (Immodal, 1995, 1999a, 2002) and *Varicella zoster* (Immodal, 1995, 1999a, 2002), showing improvement and no adverse effects.

BRANDED PRODUCTS

C-MED-100®: Campamed, LLC / 437 Madison Avenue / New York, NY 10022 / U.S.A. / Tel: 212-616-6814 / Fax: 212-838-8918. Patented extract of *Uncaria tomentosa*, standardized to 8% by carboxy alkyl esters. Ultrafiltrated, 100% water soluble extract spray-dried and compressed into 350 mg tablets.

Krallendorn® Capsules: Immodal Pharmaka GmbH / Bundesstrasse 44 / 6111 Volders / Austria / Tel: +43-05-22-45-7678 / Fax: +43-05-22-45-7646. Cat's claw root (pentacyclic chemotype) aqueous-acid extract standardized to contain 1.3% POAs, and undetectable TOAs.

Krallendorn® Drops: Immodal Pharmaka GmbH. Cat's claw root (pentacyclic chemotype) aqueous-acid extract standardized to contain 1.3% POAs, and undetectable TOAs; each 100 g of drop solution contains 600 mg cat's claw extract, water, ethanol (95% by volume).

Krallendorn® Ointment: Immodal Pharmaka GmbH. Cat's claw root (pentacyclic chemotype) aqueous-acid extract standardized to contain 1.3% POAs, and undetectable TOAs; each 75 g of ointment contains 300 mg cat's claw extract.

Krallendorn® Spray: Immodal Pharmaka GmbH. Cat's claw root (pentacyclic chemotype) aqueous-acid extract standardized to contain 1.3% POAs, and undetectable TOAs; each 100 g of spray solution contains 600 mg cat's claw extract.

Krallendorn® Tea: Immodal Pharmaka GmbH. Cat's claw root (pentacyclic chemotype), ground.

*American equivalents, if any, are found in the Product Table beginning on page 398.

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Clinical Studies on Cat's Claw (*Uncaria guianensis* [Aubl.] Gmel.)

| Anti-inflammatory | | | | | | |
|----------------------|---|---|---|-------------------------|--|---|
| Author/Year | Subject | Design | Duration | Dosage | Preparation | Results/Conclusion |
| Piscoya et al., 2001 | Safety and efficacy for osteoarthritis (knee) | P, R, DB, PC, PG, MC n=45 men (30=cat's claw; 15=placebo); with symptomatic osteoarthritis (OA) of knee, experiencing pain for most of prior month and requiring NSAID therapy for 3 months prior to study, with knee pain on movement (45–75 years) | 4 weeks 7-day washout for NSAIDs; 12 hours for analgesics | One, 100 mg capsule/day | Freeze-dried cat's claw water extract; material made for study | UG group had significant improvement in pain associated with activity and patient assessment scores determined after 1 week of trial (p<0.05). Further, UG group showed highly significant improvement of these indices and medical assessment scores at weeks 2 and 4 (p<0.001). There was significant improvement in all 3 indices with treatment at week 4, compared to baseline and week 1 (p<0.05). However, pain at rest or at night, and knee circumference, were not significantly altered in either placebo or UG group, and there was no significant difference in side effects in either group and no adverse effects in blood or liver function were observed. Authors conclude based on human trial and in vitro component of study that UG and UT are safe and effective antioxidants, and UG and UT are equally bioactive for treatment of OA. |

Clinical Studies on Cat's Claw (*Uncaria tomentosa* [Willd.] DC.)—focusing on preparations standardized to carboxy alkyl esters (CAEs)

| Immunomodulation | | | | | | |
|---------------------|---|--|--|---------------------------------------|--|--|
| Author/Year | Subject | Design | Duration | Dosage | Preparation | Results/Conclusion |
| Lamm et al., 2001 | Immune system response to pneumonia vaccine | R, PC n=23 healthy caucasian males (40–60 years old) | 2 months of treatment; evaluation at days 1, 30, 60, 180 | 700 mg/day (350 mg 2x/day) or placebo | C-Med-100® tablets (water soluble UT extract standardized to 8–10% CAEs) | UT group had elevated lymphocyte/neutrophil ratio at 2 months (p<0.05) and at 5 months showed no loss of immunity based on decay of 12 serotype pneumococcal antibody titers (p<0.01). Placebo group showed highly significant loss of immunity at 5 months. No toxic side effects were reported. |
| Sheng et al., 2001 | DNA repair, immune enhancement, and safety | R, PC n=12 healthy volunteers (mean age 44 years) | Baseline period of 3 weeks, then 8-week treatment | 250 mg/day, or 350 mg/day, or placebo | C-Med-100® tablets | In both UT groups, there was 12–15% enhanced DNA repair (from 72–74% before treatment to 81–85% after treatment), as measured by alkaline elution, after 8 weeks of treatment (p<0.05). There was a tendency towards increased proliferation of phytohemagglutinin-induced lymphocyte proliferation, but results were not significant. No toxic responses were observed. |
| Sheng et al., 2000a | Safety and immune enhancement | Volunteer supplement study n=4 apparently healthy adult males (32–58 years) | 9 weeks Baseline then 6 weeks treatment | 350 mg/day | C-Med-100® tablets | Subjects showed a significantly (p<0.05) increased level of white blood cells. No signs or symptoms of toxicity were observed. |

KEY: C – controlled, CAEs – carboxy alkyl esters, CC – case-control, CH – cohort, CI – confidence interval, Cm – comparison, CO – crossover, CS – cross-sectional, DB – double-blind, E – epidemiological, LC – longitudinal cohort, MA – meta-analysis, MC – multi-center, n – number of patients, O – open, OB – observational, OL – open label, OR – odds ratio, P – prospective, PB – patient-blind, PC – placebo-controlled, PG – parallel group, POAs – pentacyclic oxindole alkaloids, PS – pilot study, R – randomized, RC – reference-controlled, RCS – retrospective cross-sectional, RS – retrospective, S – surveillance, SB – single-blind, SC – single-center, TOAs – tetracyclic oxindole alkaloids, U – uncontrolled, UG – *Uncaria guianensis*, UP – unpublished, UT – *Uncaria tomentosa*, VC – vehicle-controlled.

Clinical Studies on Cat's Claw (*Uncaria tomentosa* [Willd.] DC.)—focusing on preparations standardized to pentacyclic oxindole alkaloids (POAs) with no tetracyclic oxindole alkaloids (TOAs)

Anti-inflammatory

| Author/Year | Subject | Design | Duration | Dosage | Preparation | Results/Conclusion |
|--------------------------|---|---|--|---|---|---|
| Mur <i>et al.</i> , 2002 | Safety and efficacy in active rheumatoid arthritis (RA) | Phase 1: R, DB, PC Phase 2: all participants received cat's claw extract n=40 patients with active RA (Steinbrocker functional class II or III) (> or = 20 years of age) | 52 weeks total with assessment at weeks 4, 8, 16, 24, 36, 52: Phase 1: 24 weeks Phase 2: 28 weeks | One capsule 3x/day (total 60 mg/day) | Krallendorn® capsules (20 mg cat's claw extract per capsule, containing 14.7 mg/g POAs and no TOAs) | At 24 weeks UT group compared to placebo showed reduced number of painful joints (by 53.2% vs. 24.1%; p=0.044). UT group experienced fewer tender joints (p=0.001) decrease in Ritchie Index (p=0.002) and shorter period of morning stiffness (p=0.002), whereas placebo group experienced no significant change. At 52 weeks UT-UT group showed further reduction in number of tender joints and in Ritchie Index, while placebo-UT group had a decrease in the number of painful and swollen joints (p=0.003; p=0.007) and decrease in Ritchie Index (p=0.004) compared to values at end of Phase I (placebo). |
| Immodal, 1995, 2002 | Rheumatoid arthritis (RA), adjuvant to conventional treatment | C, UP n=6 patients (2 in Steinbrocker class I/II, 4 in Steinbrocker class II/III) | 24 months of cat's claw treatment with assessment at months 3, 6, 12, 18, 24, and 8 years after completion of cat's claw treatment | Months 1–24: 60 mL tea/day (3 mg alkaloids/day) 4 patients continued treatment on their own after 2 years controlled phase: 1–3 capsules daily | Krallendorn® tea and capsules | At 3 months 3 patients had an increase in pain, while the other 3 had reduced pain. At 6 months all patients experienced reduced pain and joint stiffness. At 12 months 3 were largely pain-free, 3 had reduced pain with some pain-free periods, and dosages of conventional medications were reduced. At 18 months all patients were pain free. The 2 patients in class I/II remained symptom-free for 5–7 years after cat's claw treatment, while class II/III patients remained symptom-free for 1–2 years after cat's claw treatment. No adverse effects were reported. |
| Immodal, 1995, 1999a | Ulcers and gastritis | C, OB, UP Case reports n=7 patients with stomach or duodenal ulcers (n=5) or gastritis (n=2) | 4 months. Months 1–3: cat's claw treatment Month 4 observation only | Decoction of 1.5 g in 120 ml water taken on empty stomach in morning | Krallendorn® tea | All 5 ulcer patients were asymptomatic after an average of 10 days and discontinued antacid treatment. Both patients with recurrent gastritis were asymptomatic after an average of 3 days and also stopped antacid treatment. All patients remained asymptomatic 1 month after discontinuation of cat's claw. |

Immunomodulation

| Author/Year | Subject | Design | Duration | Dosage | Preparation | Results/Conclusion |
|----------------------------|--|--|-----------------------|---|--|--|
| Immodal, 1999a, 2002 | Adjuvant to chemotherapy, radiation, and brain tumor resection | O, U, UP n=60 | Varied: 12–31 months | 60 mg/day | Krallendorn® drops | All patients reported greater vitality and fewer side effects from chemotherapy and radiation. Survival rates were not measurable since there were no controls. |
| Immodal, 1995, 2002 | Adjuvant to chemotherapy, radiation, and surgery | U, UP n=22 patients with tumor diseases | 12 months to 10 years | Tea: 60 ml/day Capsules: one capsule 1–3 x/day (20–60 mg/day) | Krallendorn® tea or Krallendorn® capsules | All patients showed increased vitality and fewer side effects. Partial remission in 5 patients, full remission in 13 patients, and prolonged survival time (>4 years in 7 patients). However, survival rates were not measurable, since there were no controls. |
| Immodal, 1995, 1999a, 2002 | Adjuvant therapy for HIV patients | MC, O, U, UP n=44 patients in stages CDC A (n=16), CDC B (n=13), and CDC C (n=15) | 12–60 months | 1–6 capsules/day or equivalent amounts of drops or tea (20–120 mg/day capsules) | Krallendorn® capsules (n=41) or Drops (n=2) or Tea (n=1) | Cat's claw stabilized CD4-cell count in stage A patients and stabilized or increased it in stage B & C patients. A direct correlation was observed between CD4 cell count and total leukocyte and CD8 cell count. Symptoms decreased in stage B patients and disease progression was reduced in stage C patients. All patients experienced increased vitality and mobility. No adverse effects or drug interactions were observed. |

KEY: C – controlled, CAEs – carboxy alkyl esters, CC – case-control, CH – cohort, CI – confidence interval, Cm – comparison, CO – crossover, CS – cross-sectional, DB – double-blind, E – epidemiological, LC – longitudinal cohort, MA – meta-analysis, MC – multi-center, n – number of patients, O – open, OB – observational, OL – open label, OR – odds ratio, P – prospective, PB – patient-blind, PC – placebo-controlled, PG – parallel group, POAs – pentacyclic oxindole alkaloids, PS – pilot study, R – randomized, RC – reference-controlled, RCS – retrospective cross-sectional, RS – retrospective, S – surveillance, SB – single-blind, SC – single-center, TOAs – tetracyclic oxindole alkaloids, U – uncontrolled, UG – *Uncaria guianensis*, UP – unpublished, UT – *Uncaria tomentosa*, VC – vehicle-controlled.

Clinical Studies on Cat's Claw (*Uncaria tomentosa* [Willd.] DC.)—focusing on preparations standardized to pentacyclic oxindole alkaloids (POAs) with no tetracyclic oxindole alkaloids (TOAs) (cont.)

Immunomodulation (cont.)

| Author/Year | Subject | Design | Duration | Dosage | Preparation | Results/Conclusion |
|----------------------|-----------------------------------|--|--|----------------------------------|-----------------------|---|
| Immodal, 1999a | Adjuvant therapy for HIV patients | O, U, UP n=14 patients with HIV or AIDS and a T4-cell count of 200–500 cells/mcL (6 also received AZT, 1 also received DDI) | 1 year with assessments at months 0, 3, 6, 9, 12 | 2–3 capsules/day (40–60 mg/day) | Krallendorn® capsules | HIV-related symptoms were reduced. Slight increases were observed in heart beat, lymphocytes, uric acid, and in percent of T8 cells, as well as a decrease in granulocytes and a slight decrease in percent of T4 cells. Patients reported increased vitality. |
| Immodal, 1999a, 2002 | Adjuvant therapy for HIV patients | RS, O, U, UP n=16 patients with HIV or AIDS | 1–5.8 years | 1–6 capsules/day (20–120 mg/day) | Krallendorn® capsules | Patients receiving antiretroviral therapy and cat's claw remained clinically stable and showed stable or increased CD4-cell counts. In those patients receiving cat's claw only, most remained clinically stable with stable CD4-cell counts. All patients reported increased vitality and mobility. No adverse effects or drug interactions were observed. |

External Use

| Author/Year | Subject | Design | Duration | Dosage | Preparation | Results/Conclusion |
|----------------------------|-------------------------|----------------------|----------|---|---|--|
| Immodal, 1995, 1999a, 2002 | <i>Herpes simplex</i> | O, MC, U, UP n=17 | 17 days | Once daily | Krallendorn® topical preparations of root extract: spray, ointment, cream, or gel containing 8 mcg POA/mg | Pain was eliminated in 14 patients by day 3 and in all 17 patients by day 7. Lesions had healed completely in 9 patients by day 7 and in all 17 patients by day 17. No adverse effects were observed. |
| Immodal, 1995, 1999a, 2002 | <i>Varicella zoster</i> | O, U, UP n=20 | 13 days | Low dose group (n=16): once daily; High dose group (n=4): every 2 hours during waking hours | Krallendorn® topical preparations of root extract: spray, ointment, or cream containing 8 mcg POA/mg | Low dose group: 15 of 16 were symptom free by day 7 and lesions had healed for 15 of 16 by day 13. High dose group: all had greatly reduced pain on day 2 and all were pain-free by day 4. Scabs had disappeared by day 5. No adverse effects were observed. |

KEY: C – controlled, CAEs – carboxy alkyl esters, CC – case-control, CH – cohort, CI – confidence interval, Cm – comparison, CO – crossover, CS – cross-sectional, DB – double-blind, E – epidemiological, LC – longitudinal cohort, MA – meta-analysis, MC – multi-center, n – number of patients, O – open, OB – observational, OL – open label, OR – odds ratio, P – prospective, PB – patient-blind, PC – placebo-controlled, PG – parallel group, POAs – pentacyclic oxindole alkaloids, PS – pilot study, R – randomized, RC – reference-controlled, RCS – retrospective cross-sectional, RS – retrospective, S – surveillance, SB – single-blind, SC – single-center, TOAs – tetracyclic oxindole alkaloids, U – uncontrolled, UG – *Uncaria guianensis*, UP – unpublished, UT – *Uncaria tomentosa*, VC – vehicle-controlled.