Cortex Uncariae

Definition

Cortex Uncariae consists of the dried stem bark of *Uncaria tomentosa* (Willd.) DC. (Rubiaceae).

Synonyms

Nauclea aculeata auct. Non Willd., *N. cinchoneae* DC, N. polycephala A. Rich., *N. tomentosa* Willd., *Ourouparia polycephala* Baill., *Uncaria surinamensis* Miq., *U. tomentosa* DC, *Uruparia tomentosa* (Willd.) O. Kuntze (*1*, *2*).

Selected vernacular names

Bejuco de agua, cat's claw, cat's thorn, deixa, garabato, garabato amarillo, garabato colorado, garra gavilán, hank's clay, jipotatsa, Katzenkralle, kug kukjaqui, micho-mentis, paotati-mosha, paraguyayo, rangaya, saventaro, toroñ, tsachik, tua juncara, uña de gato, uña de gato de altura, uncucha, unganangi, unganangi, unha de gato (*1–5*).

Geographical distribution

Indigenous to Central America and northern South America including Belize, Bolivia, Brazil, Colombia, Costa Rica, Ecuador, Guatemala, Honduras, Nicaragua, Peru, Suriname, Trinidad and Tobago, and Venezuela, with Peru being the main source (*1*, *6*, *7*).

Description

A scrambling liana, up to 20–30 m long, main stem up to 25 cm in diameter. Branches obtusely quadrangular, generally puberulous. Stipules widely ovate-triangular, minutely and densely puberulous outside. Leaves opposite, petiolate; petioles 1.0–1.5 cm long, minutely puberulous or hirtellous; leaf blades ovate to ovate-oblong, 6.0–14.5 cm long, 2.5–8.5 cm wide; apex obtuse to acuminate; base rounded or subtruncate or subcordate; margin entire or occasionally crenulate in the upper half, glabrous or subglabrous above except strigillose on veins, area between veins densely

puberulent to subglabrous beneath; lateral veins six to ten pairs, level above, prominent beneath, tertiary veins distinct. Spines strongly recurved, tomentose in younger branches, glabrous in older ones. Inflorescences thyrsic with three to nine nodes, lateral units with one to eight pseudo-heads, the bracts reduced; heads small, 12–20 mm in diameter; peduncles densely hirtellous, 1.5–4 cm long. Flowers sessile; calyx tubular, 0.5–0.8 mm long with the obtuse lobes 0.2–0.3 mm long, densely villosulous outside, densely sericeous inside at the base; corolla densely retrorsely adpressed, puberulous outside, glabrous inside, tubes 3.5–5.0 mm long, 0.7–0.8 mm wide at the base, 1.0 mm wide at the mouth, lobes suborbicular, rounded, 1–1.5 mm long, 1–1.5 mm wide. Stamens five, some sterile; anthers 1.0–1.5 mm long, obtuse at the apex, prolonged and attenuated at the base; filaments around 0.2 mm long. Ovary 1.4–1.6 long, 0.9–1.3 mm wide, densely villosulous, style 6.5–9 mm long, glabrous; stigma 1.0 mm long, clavate. Capsules 0.8–1.2 cm long, pubescent outside; seeds with two long narrow wings, one bifid, 3.4 mm long (*6, 8–10*).

Plant material of interest: dried stem bark

General appearance

Shavings or chopped stem bark contain numerous bast fibres up to 7 cm long, fibre bundles and fine-crumbling rind/bark breaking into pieces. The sawdust-like chopped stem bark consists of wood fibres up to 1 cm long with a small fraction of short bast fibres and traces of powdered bark (*4*).

Organoleptic properties

No characteristic odour or taste (*4*).

Microscopic characteristics

Rings dark, partly elevated, but hardly structured. Under illumination, bast fibres show net-like or reticulate structure; with illumination from above, they glimmer with a brownish shimmer. Powdered stem bark consists of finely broken pieces of wood, bast and bark, and clear, crystalline particles of dried sap (*4*).

Powdered plant material

To be established in accordance with national requirements.

General identity tests

Macroscopic and microscopic examinations (*1, 4*), thin-layer chromatography (*4, 11*), and high-performance liquid chromatography for the presence of characteristic oxindole alkaloids (*4, 12, 13*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*14*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*15*). For other pesticides, see the European pharmacopoeia (*15*) and the WHO guidelines on quality control methods for medicinal plants (*14*) and pesticide residues (*16*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*14*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*14*) for the analysis of radioactive isotopes.

Other purity tests

Chemical, foreign organic matter, total ash, acid-insoluble ash, sulfated ash, water-soluble extractive, alcohol-soluble extractive and loss on drying tests to be established in accordance with national requirements.

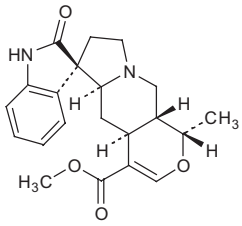
Chemical assays

Not more than 0.02% total tetracyclic oxindole alkaloids determined by high-performance liquid chromatography (*4, 12, 13*).

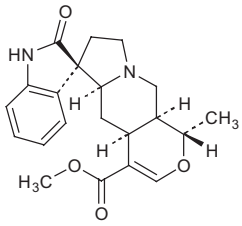
Major chemical constituents

The major constituents are indole alkaloids (0.15–4.60%), primarily pentacyclic oxindoles. The principal pentacyclic oxindole alkaloids are pteropodine, isopteropodine, speciophylline, uncarine F, mitraphylline and isomitraphylline. Tetracyclic oxindoles present include isorhynchophylline and rhynchophylline (*1, 4, 5, 12, 17*). The structures of the major pentacyclic oxindole alkaloids are presented below.

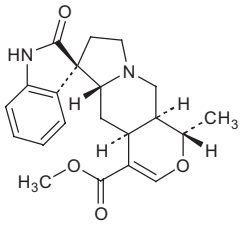
mitraphylline



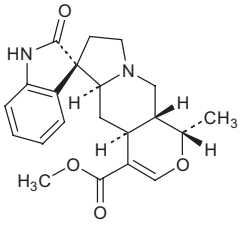
pteropodine



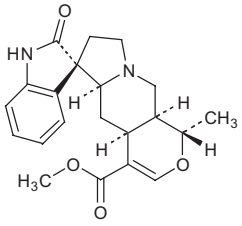
uncarine F



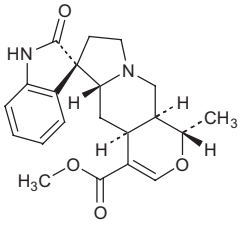
isomitraphylline



isopteropodine



speciophylline



Medicinal uses

Uses supported by clinical data

None. Although two clinical studies have suggested that Cortex Uncariae may be an immunostimulant and increase the number of white blood cells (*18, 19*), data from controlled clinical trials are lacking.

Uses described in pharmacopoeias and well established documents

Symptomatic treatment of arthritis, rheumatism and gastric ulcers (*7, 10, 20*).

Uses described in traditional medicine

Treatment of abscesses, asthma, fevers, urinary tract infections, viral infections and wounds. As an emmenagogue (*4, 5, 21*).

Pharmacology

Experimental pharmacology

Anti-inflammatory activity

Addition of an undefined extract of the stem bark to the cell medium at a concentration of 100 µg/ml significantly attenuated ($P < 0.05$) peroxynitrite-induced apoptosis in HT29 (epithelial cells) and RAW 264.7 cells (macrophages). The extract further inhibited lipopolysaccharide-induced nitric oxide synthase gene expression (iNOS), nitrite formation, cell death, and the activation of nuclear transcription factor-κβ in RAW 264.7 cells. Oral administration of the extract in drinking-water, 5 mg/ml, attenuated indometacin-enteritis in rodents as evidenced by reduced myeloperoxi-

dase activity, morphometric damage and liver metallothionein expression (*22*).

The anti-inflammatory activities of two types of extracts from the stem bark: a hydroalcoholic extract containing 5.61% alkaloids (mainly of the pentacyclic type, extract A) and an aqueous freeze-dried extract containing 0.26% alkaloids (extract B) were assessed in the carrageenan-induced rat paw oedema test. Extract A was significantly more active than extract B, suggesting that the effect could be due to the presence of pentacyclic oxindole alkaloids. Both extracts showed little inhibitory activity on cyclooxygenase-1 and -2. Only a slight inhibitory activity on DNA-binding of NF-κB was observed (*23*).

The effects of a decoction of the stem bark, 10.0 µg/ml freeze-dried, on tumour necrosis factor-α (TNF-α) production and cytotoxicity in lipopolysaccharide-stimulated murine macrophages (RAW 264.7 cells) was assessed in vitro. The decoction prevented oxidative- and ultraviolet irradiation-induced cytotoxicity. It also suppressed TNF-α production by approximately 65–85% ($P < 0.01$) at concentrations of 1.2–28.0 ng/ml (*24*).

Cinchonain Ib, a procyanidin from the stem bark, inhibited the activity of 5-lipoxygenase, ≥ 100% at 42.5 µmol/ml, indicating an anti-inflammatory effect (*25*).

Antitumour activity

Growth inhibitory activities of an aqueous extract of the stem bark were examined in vitro using two human leukaemic cell lines (K562 and HL60) and one human Epstein–Barr virus-transformed B lymphoma cell line (Raji). Cell proliferation of HL60 and Raji cells was strongly suppressed in the presence of the aqueous extract, while K562 was more resistant to the inhibition. The suppressive effect was mediated through induction of apoptosis, which was shown by characteristic morphological changes, internucleosomal DNA fragmentation after agarose gel electrophoresis and DNA fragmentation quantification. The extract also induced a delayed type of apoptosis becoming most dose-dependently prominent after 48 hours of exposure. Both DNA single- and double-strand breaks were increased 24 hours following treatment (*26*). Leukaemic HL60 and U-937 cells were incubated with pure alkaloids from *U. tomentosa* root. The pentacyclic oxindole alkaloids inhibited the growth, median inhibitory concentration (IC_{50}) 10^{-5}–10^{-4} mol/l; the most pronounced effect was found for uncarine F. Selectivity between leukaemic and normal cells was observed (*13*).

Immune stimulating activity

Addition of 1 µmol/l of pentacyclic oxindole alkaloids (POA) induced endothelial cells to release some as yet to be determined factor(s) into the

supernatant, which enhanced the proliferation of normal human resting or weakly activated B and T lymphocytes. In contrast, proliferation of normal human lymphoblasts and of both the human lymphoblastoid B cell line Raji and the human lymphoblastoid T cell line Jurkat was inhibited, while cell viability was not affected. However, it was shown that the tetracyclic oxindole alkaloids had antagonistic effects to the POA, and dose-dependently reduced the proliferation of lymphocytes stimulated by POA (*27*).

Two commercial extracts of the stem bark, containing approximately 6 mg/g total oxindoles were assessed for the ability to stimulate the production of interleukin-1 (IL-1) and interleukin-6 (IL-6) in alveolar macrophages. A phosphate-buffered saline solution of the extracts stimulated IL-1 and IL-6 production by rat macrophages in a dose-dependent manner in the concentration range 0.025–0.1 mg/ml. In lipopolysaccharide (LPS)-stimulated macrophages, the extracts potentiated the stimulating effects of LPS on IL-1 and IL-6 production indicating an immune stimulating effect (*20*).

The immune effects of an aqueous stem bark extract were assessed after intragastric administration of the extract, 5.0–80.0 mg/kg body weight (bw) per day for 8 consecutive weeks. Phytohaemagglutinin (PHA)-stimulated lymphocyte proliferation was significantly ($P < 0.05$) increased in splenocytes of rats treated at doses of 40.0 mg/kg bw and 80.0 mg/kg bw. White blood cells from the groups treated with 40.0 mg/kg bw and 80.0 mg/kg bw per day for 8 weeks or 160.0 mg/kg bw per day for 4 weeks were significantly elevated ($P < 0.05$) as compared with controls. Repair of DNA single- and double-strand breaks 3 hours after 12 whole body irradiations were also significantly improved ($P < 0.05$) in rats treated with the stem bark (*19*).

Aqueous extracts of the stem bark, depleted of indole alkaloids (< 0.05%, w/w), were assessed for the treatment of chemically-induced leukopenia in rats. The animals were treated first with doxorubicin (DXR), three intraperitoneal injections of 2 mg/kg bw given at 24-hour intervals, to induce leukopenia. Beginning 24 hours after the last DXR treatment, the rats received 80 mg/kg bw of the aqueous extract per day by intragastric administration for 16 days. Animals treated with the extract recovered significantly sooner ($P < 0.05$) than those receiving DXR alone, and all fractions of white blood cells were proportionally increased. The mechanism of action on white blood cells is not known; however, data showing enhanced effects on DNA repair and immune cell proliferative response support a general immune enhancement (*28*).

Intraperitoneal administration of 10.0 mg/kg bw of an oxindole alkaloid-enriched extract of the stem bark enhanced phagocytosis in mice as assessed by the clearance of colloidal carbon. However, the pure alkaloids were not active without the presence of catechins such as the catechin tannin fraction of the root (*29*). In vitro, alkaloids from the stem bark were tested in two chemoluminescence models (granulocyte activation, phagocytosis) for their ability to enhance phagocytotic activity. Isopteropodine showed the strongest activity (55%), followed by pteropodine, isomitraphylline and isorhynchophylline (*29*).

Toxicity

The median lethal and toxic dose of a single oral dose of an aqueous extract of the stem bark in rats was > 8.0 g/kg bw. Although the rats were treated daily with aqueous extracts at doses of 10–80 mg/kg bw for 8 weeks or 160 mg/kg bw for 4 weeks, no symptoms of acute or chronic toxicity were observed. In addition, no changes in body weight, food consumption and organ weight, or kidney, liver, spleen and heart pathological changes were found to be associated with treatment (*19*).

Aqueous extracts of the stem bark were analysed for the presence of toxic compounds in Chinese hamster ovary cells and bacterial cells (*Photobacterium phosphoreum*) in vitro. At concentrations of 10.0–20.0 mg/ml, the extracts were not cytotoxic (*30*).

Clinical pharmacology

Immune stimulating activity

In a human volunteer study, an aqueous extract of the stem bark was administered to four healthy volunteers daily at a dose of 350.0 mg/day for 6 consecutive weeks. No side-effects were reported as judged by haematology, body weight changes, diarrhoea, constipation, headache, nausea, vomiting, rash, oedema or pain. A significant increase ($P < 0.05$) in the number of white blood cells was observed after 6 weeks of treatment (*19*).

Oral administration of two doses of 350 mg of an extract of the stem bark containing 0.05% oxindol alkaloids and 8–10% carboxy alkyl esters per day to human volunteers stimulated the immune system, as evidenced by an elevation in the lymphocyte/neutrophil ratios of peripheral blood and a reduced decay in 12 serotype antibody titre responses to pneumococcal vaccination at 5 months (*18*).

Adverse reactions

No information available.

Contraindications

Owing to its traditional use as an emmenagogue, Cortex Uncariae is contraindicated during pregnancy.

Warnings

No information available.

Precautions

Drug interactions

Commercial extracts of the stem bark inhibited the activity of human cytochrome P450, $IC_{50} < 1\%$. Cortex Uncariae should only be taken in conjunction with prescription drugs metabolized via cytochrome P450, such as protease inhibitors, warfarin, estrogens and theophylline under the supervision of a health-care provider (*31*).

Carcinogenesis, mutagenesis, impairment of fertility

No information available.

Pregnancy: non-teratogenic effects

See Contraindications.

Nursing mothers

Owing to the lack of safety data, the use of Cortex Uncariae during nursing is not recommended, unless under the supervision of a health-care provider.

Paediatric use

Owing to the lack of safety data, the use of Cortex Uncariae in children under the age of 12 years is not recommended, unless under the supervision of a health-care provider.

Other precautions

No information available on general precautions or precautions concerning drug and laboratory test interactions; and teratogenic effects in pregnancy.

Dosage forms

Dried stem bark for infusions and decoctions, and extracts. Capsules and tablets. Store in a tightly sealed container away from heat and light.

Posology

(Unless otherwise indicated)
Average daily dose: extracts, 20.0–350.0 mg (*10, 19*). Capsules and tablets: 300.0–500.0 mg, one capsule or tablet two to three times.

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