**Cortex Uncariae**

**Deﬁ nition**

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 suri-

namensis Miq., U. tomentosa DC, Uruparia tomentosa (Willd.) O. Kun-

tze (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, Hon-

duras, 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 diam-

eter. 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 hir-

tellous; 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 subcor-

date; margin entire or occasionally crenulate in the upper half, glabrous or

subglabrous above except strigillose on veins, area between veins densely

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puberulent to subglabrous beneath; lateral veins six to ten pairs, level

above, prominent beneath, tertiary veins distinct. Spines strongly re-

curved, tomentose in younger branches, glabrous in older ones. Inﬂ ores-

cences thyrsic with three to nine nodes, lateral units with one to eight

pseudo-heads, the bracts reduced; heads small, 12–20 mm in diameter; pe-

duncles 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 villosu-

lous outside, densely sericeous inside at the base; corolla densely retrorse-

ly 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 suborbicu-

lar, rounded, 1–1.5 mm long, 1–1.5 mm wide. Stamens ﬁ ve, some sterile;

anthers 1.0–1.5 mm long, obtuse at the apex, prolonged and attenuated at

the base; ﬁ laments 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 biﬁ d, 3.4 mm long (6, 8–10).

Plant material of interest: dried stem bark

General appearance

Shavings or chopped stem bark contain numerous bast ﬁ bres up to 7 cm

long, ﬁ bre bundles and ﬁ ne-crumbling rind/bark breaking into pieces. The

sawdust-like chopped stem bark consists of wood ﬁ bres up to 1 cm long

with a small fraction of short bast ﬁ bres 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 ﬁ bres show net-like or reticulate structure; with illumination from

above, they glimmer with a brownish shimmer. Powdered stem bark con-

sists of ﬁ nely 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 chromato-

graphy (4, 11), and high-performance liquid chromatography for the

presence of characteristic oxindole alkaloids (4, 12, 13).

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Purity tests

Microbiological

Tests for speciﬁ c microorganisms and microbial contamination limits are

as described in the WHO guidelines on quality control methods for me-

dicinal 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, mitra-

phylline and isomitraphylline. Tetracyclic oxindoles present include

isorhynchophylline and rhynchophylline (1, 4, 5, 12, 17). The struc-

tures of the major pentacyclic oxindole alkaloids are presented

below.

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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 in-

fections and wounds. As an emmenagogue (4, 5, 21).

Pharmacology

Experimental pharmacology

Anti-inﬂ ammatory activity

Addition of an undeﬁ ned extract of the stem bark to the cell medium at a

concentration of 100 μg/ml signiﬁ cantly attenuated (P < 0.05) peroxy-

nitrite-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-

isomitraphylline

N

The anti-inﬂ ammatory 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 contain-

ing 0.26% alkaloids (extract B) were assessed in the carrageenan-induced

rat paw oedema test. Extract A was signiﬁ cantly 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 cy-

clooxygenase-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 lipo-

polysaccharide-stimulated murine macrophages (RAW 264.7 cells) was as-

sessed in vitro. The decoction prevented oxidative- and ultraviolet irradia-

tion-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 activ-

ity of 5-lipoxygenase, ≥ 100% at 42.5 μmol/ml, indicating an anti-inﬂ am-

matory 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 apop-

tosis, which was shown by characteristic morphological changes, internu-

cleosomal DNA fragmentation after agarose gel electrophoresis and DNA

fragmentation quantiﬁ cation. 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 ox-

indole alkaloids inhibited the growth, median inhibitory concentration

(IC50

) 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

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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 inhib-

ited, 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 pro-

duction of interleukin-1 (IL-1) and interleukin-6 (IL-6) in alveolar mac-

rophages. A phosphate-buffered saline solution of the extracts stimulated

IL-1 and IL-6 production by rat macrophages in a dose-dependent man-

ner 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 stimu-

lating effect (20).

The immune effects of an aqueous stem bark extract were assessed af-

ter intragastric administration of the extract, 5.0–80.0 mg/kg body weight

(bw) per day for 8 consecutive weeks. Phytohaemagglutinin (PHA)-stim-

ulated lymphocyte proliferation was signiﬁ cantly (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 signiﬁ cantly 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 signiﬁ cantly 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 ﬁ rst 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 intragas-

tric administration for 16 days. Animals treated with the extract recov-

ered signiﬁ cantly 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).

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Intraperitoneal administration of 10.0 mg/kg bw of an oxindole alka-

loid-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 tan-

nin fraction of the root (29). In vitro, alkaloids from the stem bark were

tested in two chemoluminescence models (granulocyte activation, phago-

cytosis) for their ability to enhance phagocytotic activity. Isopteropodine

showed the strongest activity (55%), followed by pteropodine, isomitra-

phylline and isorhynchophylline (29).

Toxicity

The median lethal and toxic dose of a single oral dose of an aqueous ex-

tract 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 patho-

logical 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 (Pho-

tobacterium 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 ad-

ministered 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 haema-

tology, body weight changes, diarrhoea, constipation, headache, nausea,

vomiting, rash, oedema or pain. A signiﬁ cant 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 pneumo-

coccal vaccination at 5 months (18).

Adverse reactions

No information available.

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Contraindications

Owing to its traditional use as an emmenagogue, Cortex Uncariae is con-

traindicated during pregnancy.

Warnings

No information available.

Precautions

Drug interactions

Commercial extracts of the stem bark inhibited the activity of human cy-

tochrome P450, IC50

< 1%. Cortex Uncariae should only be taken in con-

junction with prescription drugs metabolized via cytochrome P450, such

as protease inhibitors, warfarin, estrogens and theophylline under the su-

pervision 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 nurs-

ing 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 supervi-

sion of a health-care provider.

Other precautions

No information available on general precautions or precautions concern-

ing drug and laboratory test interactions; and teratogenic effects in preg-

nancy.

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.

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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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