

PHYTOPHARMACOLOGY OF UNCARIA TOMENTOSA: A REVIEW

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Summary

Uncaria tomentosa, commonly known as “Cats Claw” belonging to the family *Rubiaceae* is a woody long vine that grows in highlands of the Amazonian rain forest. *Uncaria tomentosa* inner bark extract is a popular plant remedy used in folk medicine to treat tumor and anti-inflammatory process. The aqueous and hydroalcoholic extracts from the bark are also used in the treatment of other different health problems like rheumatism, arthritis, gastrointestinal disorders, weakness, viral infections (including AIDS), skin impurities and as contraceptives. The ethnomedicinal uses are as an antioxidant, has antiapoptotic properties and can enhance DNA repair. The efficacy of cat's claw originally believed to be due to presence of oxindole alkaloids. In majority of the latest studies high biological activity of cat's claw is attributed to unique tetracyclic and pentacyclic oxindole alkaloids.

Keywords: *Uncaria tomentosa*, Cats Claw , phytochemistry, pharmacology; standardization, review.

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Introduction

In the past, almost all the medicines were from the plants, the plant being man's only chemist for ages. Herbs are staging a comeback, herbal 'renaissance' is happening all over the globe and more and more people are taking note of herbal therapies to treat various kinds of ailments in place of mainstream medicine^[1]. A significant proportion of people in developing countries depend on folk medicine for the treatment of their health disorders. It is well known that the central feature of inflammatory activity^[2] is the activation of phagocytic cells that synthesize and release large amounts of reactive species causing cell and tissue injury, either directly by oxidative degradation of essential cellular components or indirectly by altering the normal protease / antiprotease balance^[3]. Some 0.5 – 1% of the global population suffers from Rheumatoid Arthritis with women being affected around 3 times more often than men. The onset of the disease is usually between 35 – 45 years of age or above 60 years of age.

A standardised extract from the root of the South American medicinal plant *Uncaria tomentosa* (Willd) DC offers a new adjunctive therapy option for rheumatoid arthritis. A preparation produced from this standardized extract is approved as a prescription drug in Austria. As a homeopathic treatment, Cat's Claw is used to treat intestinal ailments such as Crohn's disease, gastric ulcers and tumors, parasites, colitis, gastritis, diverticulitis and leaky bowel syndrome, while manufacturers claim that *Uncaria tomentosa* can also be used in the treatment of AIDS in combination with AZT, the treatment and prevention of arthritis and rheumatism, diabetes, PMS, chronic fatigue syndrome, prostate conditions, immune modulation, Lyme disease, and systemic lupus erythematosus. Cat's Claw indicates there is supporting evidence toward its use in treating cancer, inflammation, viral infection and vascular conditions, and for its use as an immunostimulant, antioxidant, antibacterial and CNS-related agent.^[4]

Vernacular names

Uncaria surinamensis, *Nauclea aculeata*, *N. tomentosa*, *Ourouparia tomentosa*.^[5]

Uncaria tomentosa popularly known in

English : Cat's Claw

Spanish : *Uña de Gato*,

Indian : Vilcacora

Bejuco de agua, cat's thorn, garabato amarillo, micho-mentis, rangaya, tua juncara, unha De gato, unganangi, deixa, garabato, garabato Colorado, garra gavilan, hank's clay, jipotatsa, Katzenkralle, kug kukjaqui, paotati-mosha, paraguayayo, saventaro, toron, tsachik, uncucha, unha de gato.^[6, 7, 8, 9, 10, 11]

Taxonomy^[12]

Kingdom : *Plantae*

Division : *Magnoliophyta*

Class : *Magnoliopsida*

Order : *Gentianales*

Family : *Rubiaceae*

Genus : *Uncaria*

Species : *tomentosa*

Binomial name : *Uncaria tomentosa* (Willd.ex Schult) DC

Morphology ^[12, 13]

Uncaria tomentosa (Willd.) DC.(Rubiaceae) (Figure 1), Uña de Gato or Cat's Claw, is a woody liana widely spread in the Amazonic forest of Central and South America which derives its name from its claw-shaped thorns. The external bark has superficial longitudinal fissures, and the internal bark is fibrous. The terminal branchlets are quadrangular and yellow-green in color. The leaves are simple, opposite and distinct; oblong, oblong-ovate, elliptic; 7.5–17 cm in length and 5–12 cm in width. The leaf margins are entire; apex is acute, or rarely acumate; base is round and/or cordate. The stipules are deltoid, 6–12 mm long and 4–8 mm wide. The spines are woody, occur in pairs, are slightly curved but straight, and pointy; 8–10 mm in length and 3–6 mm in width. The inflorescences occur in racemes or globular cymes, are axillary and/or terminal, 7–18 cm in length, 1.5–2.5 cm in diameter. Flowers are bisexual, actinomorphic and sessil. The calyx is gamosepalous, tubular, 1–1.5 mm in length and 0.8–1 mm in diameter. The corolla is gamopetalous, 7–13 mm in length, 3–5 mm in diameter, with 5 round lobes; yellow. Stamens are sessil; 5-fused to the throat. The anthers are oblong with prolonged and divergent bases; 1–1.2 mm in length and 0.3–0.4 mm in width. The stigma is ellipsoid, 0.5 mm in length, with linear 4 mm long styles; inferior ovary. The fruits are dry and dehiscent; elliptic capsules; 5–8 mm long and 3–6 mm wide. *Uncaria tomentosa* can grow up to 30m tall, climbing by means of its thorns.

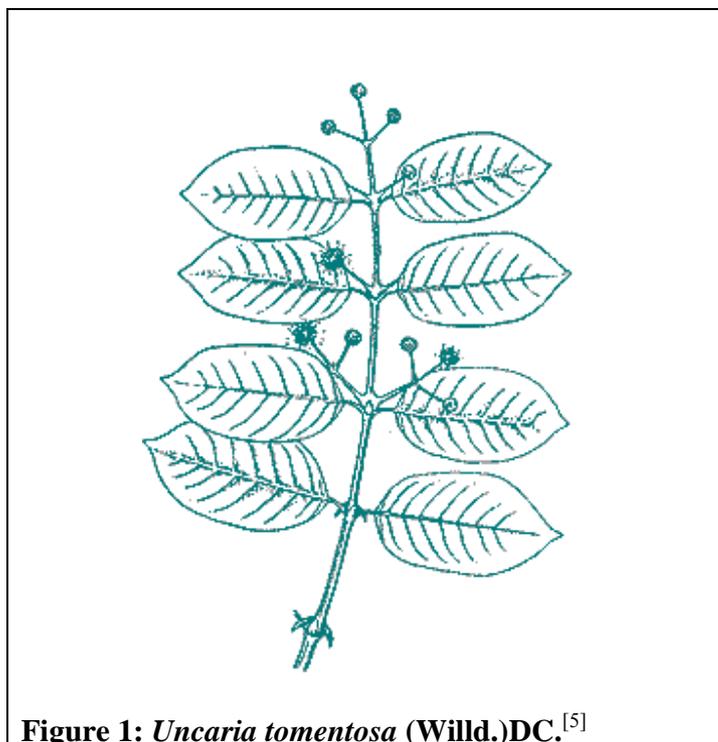


Figure 1: *Uncaria tomentosa* (Willd.)DC.^[5]

Geographical Source

Cat's claw has been reported growing in the Western countries of the Central and South American continent as far North as Belize, and South into Paraguay. Marañao, Brazil, is the most Eastern area cat's claw has been reported to grow naturally^[17].

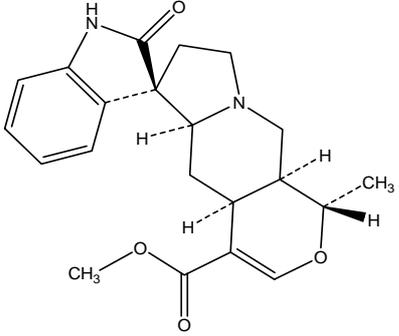
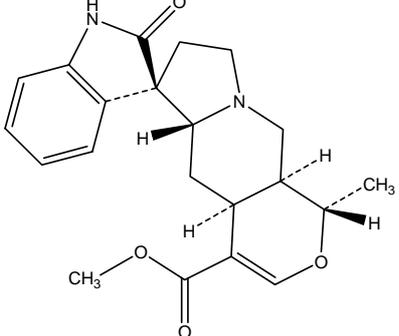
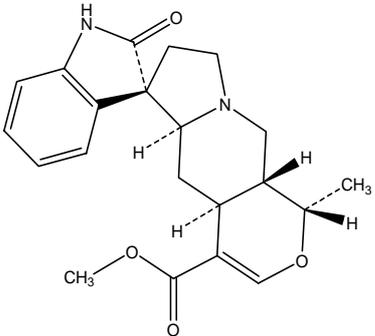
Phytochemistry ^[18]

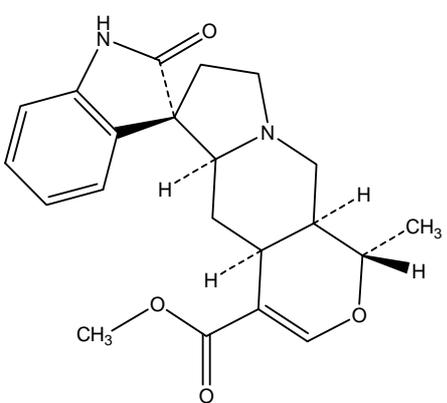
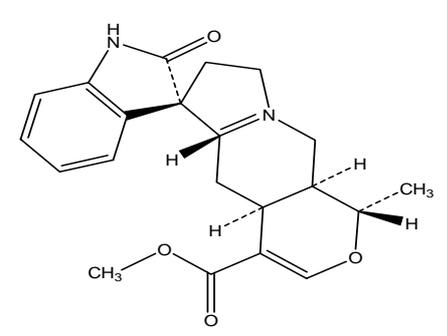
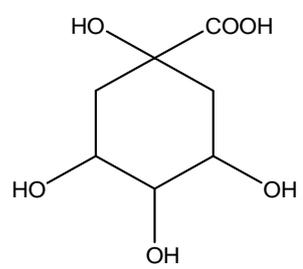
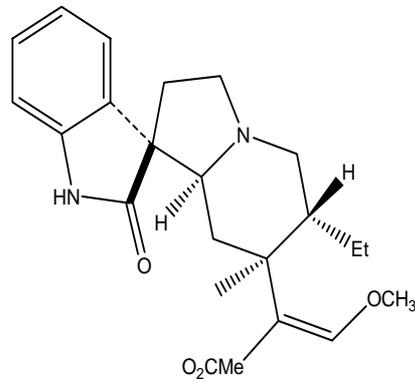
Phytochemical studies have shown the presence in the plant of tetracyclic and pentacyclic oxindole alkaloids as well as quinovic acid glycosides.^[2,19] Polyhydroxylated triterpenes, flavonoids, procyanidines^[2,19] and sterols^[20] have also been isolated from the plant. In the first report on its constituents, the leaves and stems of *U. tomentosa* were found to contain rhynchophylline and isorhynchophylline as the major alkaloids, mitraphylline, isomitraphylline, dihydrocorynantheine, hirsutine and hirsuteine, together with their N-oxides. In addition, rotundifoline and isorotundifoline were found as minor alkaloids in one herbarium sample^[21, 22]. The presence of the stereoisomeric alkaloids pteropodine, isopteropodine, speciophylline, *Uncarine F* and isomitraphylline in the bark of 'unã de gato' (either *U. tomentosa* or *U. guianensis*) was reported^[23]. (Table 1)

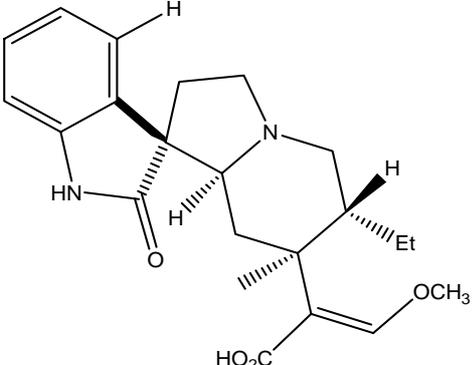
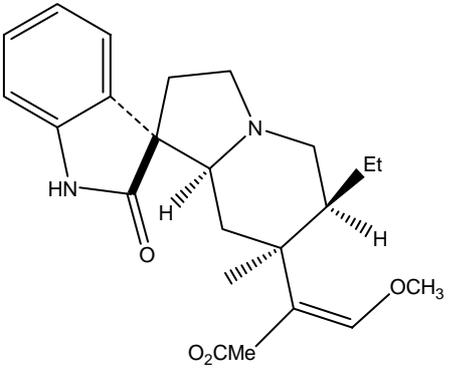
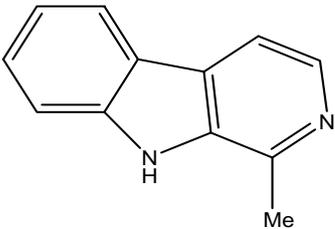
Phenolic constituents, such as flavonoids, phenolic acids, diterpenes and tannins are especially worthy of notice due to their high antioxidative activity^[24, 25, 26]. Many investigations indicate that these compounds are of great value in preventing the onset or progression of many human diseases^[24, 27-30]. Therefore, over the past few years, a number of medicinal plants have been extensively investigated for the presence and activity of polyphenols and other antioxidants^[31-34]. Cat's claw contains ajmalicine, akuammigine, campesterol, catechin, carboxyl alkyl esters, chlorogenic acid, cinchonain, corynantheine, corynoxine, daucosterol, epicatechin, harman, hirsuteine, hirsutine, iso-pteropodine, loganic acid, lyaloside, mitraphylline, oleanolic acid, palmitoleic acid, procyanidins, pteropodine quinovic acid glycosides, rhynchophylline, rutin, sitosterols, speciophylline, stigmasterol, strictosidines, uncarine A thru F, and vaccenic acid. (Table 1)

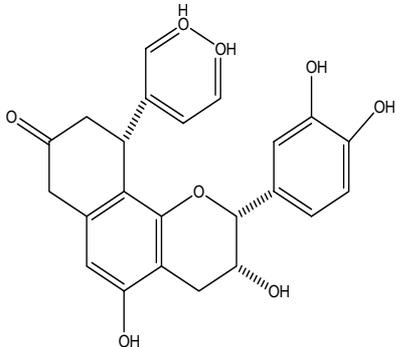
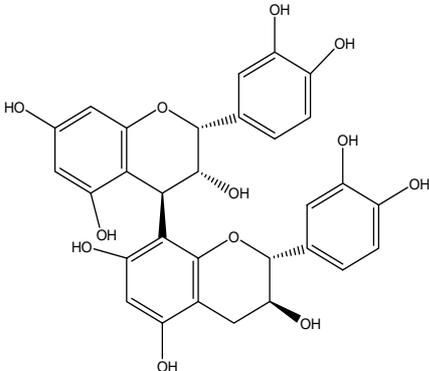
Table 1

Sr.No.	Name	Structures	Reference no.
1.	Mitraphylline		[6]

2.	Pteropodine	 <p>The chemical structure of Pteropodine is a complex polycyclic alkaloid. It features a piperidine ring fused to a piperazine ring, which is further fused to a dihydropyridine ring. A benzamide group is attached to the piperidine ring. The dihydropyridine ring has a methoxy group and a methyl group attached to it. The stereochemistry is indicated with wedges and dashes.</p>	[6]
3.	Uncarine F	 <p>The chemical structure of Uncarine F is very similar to Pteropodine, but with a different stereochemistry at the chiral centers. It features the same polycyclic core and substituents as Pteropodine.</p>	[6]
4.	Isometraphylline	 <p>The chemical structure of Isometraphylline is another stereoisomer of the pteropodine alkaloid family, sharing the same polycyclic core and substituents as the other three compounds.</p>	[6]
5.	Isopteropodine		[6]

			
6.	Speciophylline		[6]
7.	Quinic Acid		[71]
8.	Rhynchophylline		[72, 73,74,75,76,77,78]

9.	Isorhynchophylline	 <p>The structure of Isorhynchophylline is a complex pentacyclic alkaloid. It features a benzene ring fused to a five-membered ring containing an NH group. This is further fused to a six-membered ring containing a nitrogen atom. A side chain is attached to the six-membered ring, containing a chiral center with an ethyl group (Et) and a hydrogen atom (H). The side chain ends in a vinyl group substituted with a methoxy group (OCH₃) and a carboxylic acid group (HO₂C).</p>	[72,73,74,75,76,77,78]
11.	Corynoxine	 <p>The structure of Corynoxine is similar to Isorhynchophylline but lacks the carboxylic acid group. It features a benzene ring fused to a five-membered ring containing an NH group. This is further fused to a six-membered ring containing a nitrogen atom. A side chain is attached to the six-membered ring, containing a chiral center with an ethyl group (Et) and a hydrogen atom (H). The side chain ends in a vinyl group substituted with a methoxy group (OCH₃) and a methyl ester group (O₂CMe).</p>	[72,73,79]
12.	Harmaline	 <p>The structure of Harmaline is a tricyclic alkaloid consisting of a benzene ring fused to an imidazole ring, which is further fused to a pyridine ring. A methyl group (Me) is attached to the pyridine ring.</p>	[72,80]

13.	Cinchonain		[75,76]
14.	Procyanidin		[75]

Medicinal use

There are two species of Cat's Claw, *Uncaria tomentosa* and *Uncaria guianensis* each having different properties and uses. The two are frequently confused but *Uncaria tomentosa* is the most heavily researched for medicinal use ^[13,14] and immune modulation while *Uncaria guianensis* may be more useful for osteoarthritis ^[13,15]. Water extracts of the root bark are used in traditional Peruvian medicine for the treatment of cancer, arthritis, gastritis and some epidemic diseases as well as a contraceptive. ^[13,16] Cat's claw can aid in DNA cellular repair and prevent cells from mutating; it also can help prevent the loss of white blood cells and immune cell damage caused by many chemotherapy drugs (a common side effect called leukopenia). ^[5,35,36,37]

Main Uses: ^[5]

As an immune stimulant and an adjunctive therapy for cancer (to reduce side effects of chemotherapy and protect cells). As a bowel cleanser and anti-inflammatory for Crohn's, colitis, diverticulitis, irritable bowel syndrome (IBS), and other bowel problems. As an anti-inflammatory for arthritis (all kinds) and muscle pains/strains/injuries. As a general daily tonic (to tone, balance, and strengthen all body functions). For stomach ulcers and ulcerative colitis and as an ulcer preventative/ stomach and bowel protector.

Uses supported by clinical data ^[6]

Cortex Uncariae may be an immunostimulant and increase the number of white blood cells ^[36, 38].

Uses described in pharmacopeias and well established documents:

Symptomatic treatment of arthritis, rheumatism and gastric ulcers ^[39, 40, 41].

Uses described in traditional medicine:

Treatment of abscesses, asthma, fevers, urinary tract infections, viral infections and wounds ^[10, 11, 42]. The Asháninka use cat's claw to treat asthma, inflammations of the urinary tract, arthritis, rheumatism, and bone pain; to recover from childbirth; as a kidney cleanser; to cure deep wounds; to control inflammation and gastric ulcers; and for cancer. Indigenous tribes in Piura use cat's claw to treat tumors, inflammations, rheumatism, and gastric ulcers. Other Peruvian indigenous tribes use cat's claw to treat diabetes, urinary tract cancer in women, hemorrhages, menstrual irregularity, cirrhosis, fevers, abscesses, gastritis, rheumatism, tumors, and inflammations as well as for internal cleansing and to "normalize the body." Cat's claw has also been used as a contraceptive by several different tribes of Peru (but only in very large dosages). ^[10]

Documented properties and Actions ^[5]

The main actions performed by *uncaria tomentosa* are firstly it stimulates immune system, reduces inflammation, protect cells, fights free radicals, cleanses bowels, cleans cancer cells, kills leukaemia cells and tones balances. Some other actions performed are it relieves pain, Kills viruses, Detoxifies, Cleanses blood, Increases urination, Lowers blood pressure, Reduces cholestrol, Decreases depression

Pharmacological Activity

Cat's claw is an effective antioxidant. It is an antioxidant as well as a remarkably potent inhibitor of tumor necrosis factor (TNF) alpha production. TNF represents a model for tumor growth driven by an inflammatory cytokine chemical. The anti-inflammatory actions of cat's claw are not attributable to immunostimulating alkaloids but rather to another group of chemicals called carboxyl alkyl esters ^[43]. In addition to the immunostimulant alkaloids, cat's claw contains the alkaloids rhynchophylline, hirsutine, and mitraphylline, which have demonstrated hypotensive and vasodilating properties. ^[44,45]

Rhynchophylline has shown to prevent blood clots in blood vessels, dilate peripheral blood vessels, lower the heart rate, and lower blood levels of cholesterol. ^[45,46] Some of the newer research indicates that cat's claw might be helpful to people with Alzheimer's disease; this could be attributable to the antioxidant effects already confirmed or, possibly, to the dilation of peripheral blood vessels in the brain by alkaloids such as rhynchophylline. ^[47,48] Cat's claw's immune-stimulating alkaloids pteropodine and isopteropodine might have other properties and applications. These two chemicals have shown to have a positive modulating effect on brain neurotransmitters called 5-HT (2) receptors. These receptor sites are targets for drugs used in treating a variety of conditions, including depression, anxiety, eating disorders, chronic pain conditions, and obesity. ^[5]

Experimental pharmacology: ^[6]

Enhancement of phagocytosis: Extracts and pure alkaloids were tested using a granulocyte-smear test, a chemoluminescence model and an in vivo carbon-clearance test to evaluate the stimulating effect on the phagocytic activity of granulocytes. Phagocytosis was enhanced by pteropodine, isomitraphylline and isorhynchophylline. The strongest stimulation was observed with isopteropodine whereas mitraphylline and rhynchophylline had no effect. In the in vivo carbon-clearance test, activity was observed only after the admixture of catechin to the otherwise inactive alkaloids ^[49, 50, 51].

Antiviral activity: Antiviral activity of six quinovic acid glycosides from *U. tomentosa* was tested against two RNA virus infections (vesicular stomatitis virus and rhinovirus 1B) in CER and HeLa cells, respectively. An inhibitory effect against VSV infection was observed for all six glycosides at MIC₅₀ values of 20–60 mg/l. In contrast, only one compound, quinovic acid-β-D-glucopyranosyl-(28.1)-β-D-glucopyranosyl ester with an undefined position of the glycosidic linkage, reduced the cytopathic effect of rhinovirus 1B by 50% at 30 mg/l ^[52].

Anti-inflammatory activity: Several extracts of *U. tomentosa* root bark and fractions thereof were tested for anti-inflammatory activity using the carrageenan-induced rat paw oedema. A new quinovic acid glycoside was isolated as one of the active principles. Quinovic acid-3-β-O-(β-D-quinovopyranosyl)-(27.1)-β-D-glucopyranosyl ester reduced the inflammatory response by 33% at 20 mg/kg p.o. It could not be ruled out that the strong anti-inflammatory effect of the extracts could be due to a combination of compounds ^[53]. 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) 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 the nuclear transcription factor-κβ in RAW 264.7 cells. Oral administration of the extract in drinking-water, 5mg/ml, attenuated indometacin-enteritis in rodents as evidenced by reduced myeloperoxidase activity, morphometric damage and liver metallothionein expression ^[54].

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 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-κβ was observed ^[53]. 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 invitro. The decoction prevented oxidative- and ultraviolet irradiation-induced cytotoxicity. It also suppressed TNF-α production by approximately 65-85% (P<0.01) at concentration of 1.2-28.0 ng/ml ^[55]. 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 ^[56].

Antitumour activity : Growth inhibitory activities of an aqueous extract of the stem bark were examined *invitro* 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 inhibition of apoptosis, which was shown by characteristic morphological changes, internucleosomal 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^[57]. Leukaemic HL60 and U-937 cells were incubated with pure alkaloids from *Uncaria tomentosa* root. The pentacyclic oxindole alkaloids inhibited the growth, median inhibitory concentration 10^{-5} - 10^{-4} mol/l; the most pronounced effect was found for *Uncarine F*^[58].

Mutagenic and antimutagenic activity: The Ames test (*Salmonella*: mammalian microsome test) with and without metabolic activation was used to evaluate the mutagenic potential of extracts of *U. tomentosa*. Antimutagenic activity was studied on photomutagenesis induced by 8-methoxypsoralen and UV-A irradiation in *Salmonella typhimurium*. Extracts and fractions of *U. tomentosa* bark showed no mutagenic effect in several strains of *S. typhimurium* but rather a protective antimutagenic activity in vitro against photomutagenesis. A decoction of *U. tomentosa* ingested daily for 15 days by a smoker decreased the mutagenicity of the subject's urine^[59].

Antileukaemic activity: Leukaemic HL60 and U-937 cells were incubated with different concentrations of alkaloids for 7 days. The antiproliferative effect was measured by colorimetric and clonogenic assays. The pentacyclic oxindole alkaloids of *U. tomentosa* inhibited the growth of HL60 and U-937 leukaemic cells. IC50 values were in the range 10^{-5} to 10^{-4} mol/l. The most pronounced effect was found for *Uncarine F*. Selectivity between leukaemic and normal cells was observed^[60].

Immune stimulating activity : Addition of $1\mu\text{mol/l}$ of pentacyclic oxindole alkaloids(POA) endothelial cells to release some as yet to be determined factors into the supernatant, which enhanced the proliferation of normal human resting or weakly activated B and T lymphocytes. In contrast, proliferation of normal 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^[61].

Two commercial extracts of the stem bark, containing approximately 6mg/gm 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^[42].

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 also significantly improved ($P<0.05$) in rats treated with the stem bark^[38].

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 first treated with doxorubicin (DXR), three intraperitoneal injections of 2 mg/kg BW given at 24-hours intervals, to induce leukopenia. Beginning 24 hours after the last DXR treatment, the rats received 80mg/kg BW of the aqueous extract per day the 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 ^[62].

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 ^[63]. *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 ^[63].

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 the 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 ^[38].

Oral administration of two doses of 350 mg of an extract of the stem bark containing 0.05% oxindole 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 blood and a reduced decay in 12 serotype antibody titre responses to pneumococcal vaccination at 5 months ^[37].

Posology ^[5, 6]

Standard Dosage: Vine bark

Decoction : 1 cup twice daily.

Capsule : 1-2g two-three times daily.

Tablets : 300.0-500.0 mg two or three times. ^[19, 38]

Fluid extract : 2-4 ml twice, daily.

Tinctures : 2-4 ml twice, daily.

Contraindications ^[5]

Cat's claw has been clinically documented with immunostimulant effects and is contraindicated before or following any organ or bone marrow transplant or skin graft. Cat's claw has been documented with antifertility properties and is contraindicated in persons seeking to get pregnant. However, this effect has not been proven to be sufficient for the product to be used as a contraceptive, and it should not be relied on for such. Cat's claw has chemicals that can reduce platelet aggregation and thin the blood. Check with your doctor first if you are taking

coumadin or other blood-thinning drugs and discontinue use one week to ten days prior to any major surgical procedure. Cat's claw vine bark requires sufficient stomach acid to help break down the tannins and alkaloids during digestion and to aid in absorption. Avoid taking bark capsules or tablets at the same time as antacids. Avoid taking high tannin (dark-colored) liquid extracts and tinctures directly by mouth and dilute first in water or acidic juice (such as orange juice). Large dosages of cat's claw (3-4 gram dosages at a time) have been reported to cause some abdominal pain or gastrointestinal problems, including diarrhea (due to the tannin content of the vine bark) in some people. The diarrhea or loose stools tend to be mild and go away with continued use. Discontinue use or reduce dosage if diarrhea persists longer than three or four days.

Drug Interactions ^[5]

Due to its immunostimulant effects, cat's claw should not be used with medications intended to suppress the immune system, such as cyclosporin or other medications prescribed following an organ transplant. Based upon in vivo rat studies, cat's claw may protect against gastrointestinal damage associated with nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen. Cat's claw may potentiate coumadin and blood-thinning drugs. May potentiate action of antihypertensive drugs.

Toxicity Studies

The median lethal and toxic dose of a single oral dose of an aqueous extract of the stem bark in rats was >8.0 gm/kg bw. Although the rats were treated 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 ^[38]. Aqueous extracts of 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 ^[64].

Standardization

Standardization of commercial formulations of cat's claw (*U. tomentosa*) is based on their alkaloid content. The most current available medical and scientific literature indicates that this dietary supplement should be standardized to 3% alkaloids and 15% total phenols per dose. An extract of Cat's claw from Europe containing only pentacyclic oxindole alkaloids (mainly isomitraphylline isolated from the root) may be more beneficial as an immune enhancing product than the standard mixture of pentacyclic and tetracyclic alkaloids. When the two chemotypes are mixed, immune enhancement may be decreased. This product should be standardized to not less than 1.3% pentacyclic oxindole alkaloids and not more than 0.06% tetracyclic oxindole alkaloids per dose ^[65, 66]

HPLC analysis: To 100 mg of the bark, 15mL of 2% sulphuric acid solution was added and sonified for 15 min in an ultrasonic bath (Bandelin Sonorex RK 103H). The mixture was then centrifuged 3000 rpm for 10 min and extracted three times with 10mL of ethylacetate. The aqueous phase was separated and adjusted to pH 10 with 10% NH₄OH and then extracted three times with 10mL of ethylacetate each. The organic extracts were combined, evaporated to dryness and the residue dissolved in 1mL of methanol. The qualitative and quantitative content of alkaloids was determined by the HPLC fingerprint analysis ^[24, 67, 68]. *Uncaria tomentosa* extracts were filtered with a 0.2 µm filter prior to HPLC analysis. Separation was achieved using a

125mm×4.6mm×18.5µm Superspher column with a 4mm guard. The oven temperature was set at 45 °C with a flow rate of 1ml/min. The solvents used were; A: 5 nM Na₂HPO₄, 5nM KH₂PO₄, pH 6.6, and B: 1:1 MeOH: MeCN. The solvent program was 40–70% B in 30 min, 70–80% B in 2 min, hold at 80% B for 10 min, 80–40% B in 3 min and equilibrate 15 min. The detection wavelength was 245 nm^[69].

Trypan blue analysis^[69]: Samples were stained with 0.1% of the vital dye trypan blue, and then examined on a hemocytometer. Dead cells were identified by lack of exclusion of stain.

Conclusion and perspectives

In the present review we have made an attempt to congregate the botanical, phytochemical, ethnopharmacological and pharmacological information on *Uncaria tomentosa*.

All products have risk when combined with other products, even those that when used traditionally may be considered safe. Now a days literature report of adverse drug events and clinical studies with herbal products are increasing. All products have risk, with risk generally increasing in patients who have confounding health, genetic, and environmental factors, including polypharmacy. Health care professionals should inform their patients on risk which may be associated with combined use of drug and herbal products containing active constituents of *Uncaria tomentosa*.^[70] A critical survey of the literatures also pin points the fact that although the number of diseases for which *Uncaria tomentosa* finds use as a medicine is fairly large, yet its therapeutic efficacy has been assessed only in few cases. In view of the wide range of medicinal uses of *Uncaria tomentosa* as mentioned in ethnobotanical surveys, Ayurveda system and otherwise, it is imperative that more clinical and pharmacological studies should be conducted to investigate unexploited potential of this plant. This review will definitely help for the researcher as well as practitioners, dealing with this plant, to know its nature proper usage.

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