

Cortex Uncariae: A Review on Pharmacology, Toxicology, Precautions, and Dosage

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Abstract: Cortex Uncariae is the stem of *Uncaria tomentosa* plant, which belongs to the family Rubiaceae. Cat's thorn and unha de gato are the famous names of Cortex Uncariae. *Uncaria tomentosa* plant is widely geographically distributed in Central and South American countries. The aim of this review was to focus on pharmacology, toxicology, precautions, and dosage of Cortex Uncariae. The indole alkaloids such as speciophylline, mitraphylline, pteropodine, uncarine F, and isomitraphylline, as well as tetracyclic alkaloids oxindoles such as isorhynchophylline and rhynchophylline are the major Cortex Uncariae chemical constituents. There are many medical applications of Cortex Uncariae, such as immunostimulant agents, increases the white blood cells and immunity, treatment of gastrointestinal ulcers, rheumatism, arthritis, viral infection, urinary tract infections, fever, asthma, abscesses, high blood pressure, high blood glucose, and high total cholesterol. Pharmacology of Cortex Uncariae includes experimental pharmacology and clinical pharmacology. Experimental pharmacology contains anti-inflammatory, antidepressant, neuroprotection, antitumor, immune-stimulating, and anti-obesity activities, while clinical pharmacology contains immune-stimulating activity. No acute or chronic toxicity was recorded after Cortex Uncariae water extract administration. Cortex Uncariae extract did not accompany loss of food intake, body or organ weight decrease, and no histopathological changes were recorded in the main body organs such as kidney, liver, spleen, and heart after Cortex Uncariae intake. Cortex Uncariae must store in a closely black container to avoid heat and light. In conclusion, Cortex Uncariae had anti-inflammatory, antidepressant and neuroprotection, antitumor, immune-stimulating, anti-inflammatory, and anti-obesity activities without acute or chronic toxicity.

Keywords: Cortex Uncariae; *Uncaria tomentosa*; Rubiaceae; pharmacology; toxicology; dose.

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1. Introduction

Cortex Uncariae refers to the stem of *Uncaria tomentosa* (Willd.) DC. (Family Rubiaceae). There are many famous names for Cortex Uncariae, such as cat's thorn, jipotatsa, kugukjaqui, paraguyayo, saventaro, tua juncara, una de gato de altura, and unha de gato [1-5]. *Uncaria tomentosa* plant widely occurs in South American countries, such as Colombia, Ecuador, Honduras, Peru, Venezuela, Brazil, Nicaragua, and Bolivia. This plant also spreads in Central America [1, 6, 7]. The plant is a shrub 20 to 30 m long and 25 cm in diameter. The plant leaves are opposite in shape, 1-1.5 cm in length. The plant leaves are oblong or ovate, 6 to 14.5 cm in length and 2.5 to 8.5 cm in width. The plant apex is acuminate or obtuse, with a margin complete at the top. The plant bottom is rounded in the newer plant but glabrous in the older one. The plant has 3 to 9 small flowers, 12 to 20 mm. The plant flowers are sessile with

0.5 to 0.8 mm in length. The plant's flowers have lobes 0.2 to 0.3 mm in length, and the flowers are arranged in a dense shape at the base. The flower corolla is arranged densely near the bottom and has a tube of 3.5 to 5 mm in length, 0.7 to 0.8 mm in width, and 1 mm wide at the top. The flower corolla has circular lobes 1 to 1.5 mm in length and 1 to 1.5 mm in width. The plant stamens are 5 in number with anthers 1 to 1.5 mm in length. These stamens are dense at the top and decreased at the bottom. The plant filaments are circular with 0.2 mm long. The plant ovary is 1.4 to 1.5 in length, and 0.9 to 1.3 mm wide. The ovary style is 6.5 to 9 mm in length. The ovary stigma is 1 mm in length. The plant seed capsules are 0.8 to 1.2 cm in length with 2 wings with 3.4 mm in length [6, 8-10]. *Uncaria tomentosa* plant is used as complementary and/or alternative medicine for COVID-19 treatment [11]. *Uncaria tomentosa* plant treats the human immunodeficiency virus [12]. *Uncaria tomentosa* plant has antiplatelet effects. Therefore the plant is considered a natural inhibitor of thrombin, which is needed to form the fibrin clot [13]. *Uncaria tomentosa* plant treats COVID-19 symptoms [14]. *Uncaria tomentosa* plant increases the viscosity of the red blood cells, protecting the red cells against the harmful effects of oxidative stress [15]. *Uncaria tomentosa* plant declines the cytotoxicity of the sealers. *Uncaria tomentosa* plant improves the sealer antibacterial activity. *Uncaria tomentosa* plants do not affect the physicochemical property of the sealers [16]. *Uncaria tomentosa* plays an important role in protecting and improving COVID-19-related syndromes [17]. *Uncaria tomentosa* extract has anti-resorptive and anabolic effects on the bone, which enables the extract to treat many osteolytic diseases such as periodontitis [18]. *Uncaria tomentosa* plant protects against Lyme disease (the most common disease in the United States and Europe) and this effect of the plant is due to its antimicrobial effect [19]. The water leaf extract of *Uncaria tomentosa* possesses an antioxidant effect [20]. The glucoindole alkaloid in *Uncaria tomentosa* root is involved in the protection and immunity of the plant [21].

Cortex Uncariae has several fibers (7 cm in length). Cortex Uncariae has 2 fibers (wood fibers = 1 cm in long and short fibers) [4]. Cortex Uncariae without any distinguished odor or taste [4]. Cortex Uncariae powder is a fine, clear, crystalline particle of the dry plant [4]. This powder should be passed through many investigations [1,4] to follow the ISO requirements for the World Health Organization (WHO) [4,22]. These investigations include microbiological, pesticide residues, heavy metals, radioactive residues, total ash, and drying tests. The chromatography methods, such as thin layer and high-performance liquid techniques, showed the presence of alkaloids such as oxindole alkaloids [4,23,24].

The aim of this review was to focus on pharmacology, toxicology, precautions, and dosage of Cortex Uncariae.

2. Chemical Constituents of Cortex Uncariae

Cortex Uncariae contains 0.02% of oxindole alkaloids detected by the chromatography technique [4, 23, 24]. *Uncaria tomentosa* extract is a rich source of tannin [25]. Proanthocyanidins from extracts of *Uncaria tomentosa* plants and these proanthocyanidins have antioxidant and antimicrobial effects and cytotoxicity on cancer cell lines. Proanthocyanidins include hydroxycinnamic acids, flavan-3-ol monomers, hydroxybenzoic, procyanidin dimers, procyanidin trimers, and propelargonidin dimers [26].

3. Major Chemical Constituents of Cortex Uncariae

Cortex Uncariae main ingredients are indole alkaloids (=0.15-4.60%). These indole alkaloids include; (1) pteropodine, (2) isopteropodine, (3) speciophylline, (4) uncarine F, (5) mitraphylline, and (6) isomitraphylline. The tetracyclic alkaloid oxindoles include; (1) isorhynchophylline and (2) rhynchophylline [1, 4, 5, 23, 27]. Mitraphylline (purity = 98%) was isolated by the *Uncaria tomentosa* plant by spectrophotometry method, representing the cheaper and faster quality method [28]. There were 2 new oxindole alkaloids (3b-7-methyl-isomitraphylline and 3c-6-fluoro-isomitraphylline) isolated and characterized from *Uncaria tomentosa* plant [29].

4. Medicinal uses of Cortex Uncariae

Cortex Uncariae is an immunostimulant that raises the white blood cells and immunity [30, 31]. Cortex Uncariae treats gastrointestinal ulcers, rheumatism, and arthritis [7, 10, 32]. Cortex Uncariae is used in treating viral infection, urinary tract infections, fever, asthma, and abscesses and is used as an emmenagogue [4, 5, 33]. Cortex Uncariae is similar to *Psidium guajava* in treating urinary infection [34]. *Uncaria Tomentosa* water-alcoholic extract is used to treat high blood pressure, high blood glucose, and high total cholesterol without any acute or subacute oral toxicity in humans [35]. *Uncaria tomentosa* extract is used as a spray to treat cutaneous pain and relief skin pathology [36]. *Uncaria guianensis* plant has been used for centuries throughout the whole world, and it is used in many cosmetic creams and spray due to its anti-inflammatory effect [37]. Strophanthidin and Isopteropodin ingredients in *Uncaria tomentosa* are used to treat brucellosis [38]. Oxindole ingredients of Cortex Uncariae show antioxidative, antileishmanial, antitubercular, antiviral, antimicrobial, α -glucosidase inhibitory, tyrosinase inhibitory, anti-rheumatoid arthritis, and intraocular pressure reducing effects [39]. *Uncaria tomentosa* plant is used to treat denture stomatitis [40]. *Uncaria tomentosa* plant is effective in the spray used to treat the syndromes related to cutaneous pain from inflammatory skin diseases [41]. *Uncaria tomentosa* plant stops the oxidative stress and liver damage induced by fipronil through the hanging-up of nuclear factor- κ B [42].

5. Pharmacology of Cortex Uncariae

5.1. Experimental pharmacology of Cortex Uncariae.

5.1.1. Anti-inflammatory activity.

In vitro study, 100 μ g/ml of Cortex Uncariae counteracts peroxynitrite-caused apoptosis in HT29 and RAW 264.7 cells. In this study, Cortex Uncariae extract stopped the higher nitrite formation, nitric oxide synthase gene expression, cell death, and nuclear transcription factor- κ B in RAW 264.7 cells caused by lipopolysaccharide. In another in-vivo study, oral intake of 5 mg/ml of Cortex Uncariae extract declined morphometric injury and liver metallothionein expression in rats [43]. In another study, 2 extracts of Cortex Uncariae (the 1st extract contains 5.61% alkaloids and the 2nd extract contains 0.26 alkaloids) were tested to inhibit rat paw edema. The 1st extract was more effective than the 2nd extract, which means that the higher alkaloids ingredient in Cortex Uncariae =higher edema inhibition. The 1st and 2nd extracts inhibited cyclooxygenase-1 and cyclooxygenase-2, as well as DNA-binding of NF- κ B [44]. In an *in-vitro* study, 10 μ g/ml of Cortex Uncariae extract inhibited ultraviolet radiation and

oxidative stress that caused cytotoxicity. Cortex Uncariae extract (1.2 to 28 ng/ml) stopped tumor necrosis factor- α by 85% [45]. Cortex Uncariae ingredient (Cinchonain Ib at 42.5 μ mol/ml) stopped the 5-lipoxygenase activity completely [46]. *Uncaria tomentosa* plant improves the inflammation process related to many chronic diseases [47]. *Uncaria tomentosa* plant is safe and effective as an anti-inflammatory factor in inhibiting inflammation cytokines [48]. *Uncaria tomentosa* extracts such as water plant extract and water leaf extract have anti-inflammatory activity in asthma. These 2 extracts inhibited the pro-inflammatory cytokines in vitro. In an *in-vivo* test, the water plant extract treats asthmatic soreness, while water leaf extract controls respiratory mechanisms. These 2 extracts represent good factors for treating allergic asthma [49]. The mitraphylline ingredient of *Uncaria tomentosa* plant inhibited the secretion of interleukins-1 α , interleukins-1 β , interleukins-17, and tumor necrosis factor- α by 50%. It also decreased the secretion of interleukin-4 by 40% [50].

5.1.2. Antidepressant and neuroprotection activities.

Isorhynchophylline (an oxindole alkaloid ingredient from *Uncaria rhynchophylla*) has an antidepressant effect by controlling neuroinflammation and neurotrophins [51]. Geissoschizine methyl ether (indole alkaloids in Uncaria hook) controls many serotonergic effects and functions by connecting to many serotonin receptors [52]. *Uncaria tomentosa* plant improves memory status, mending DNA injury, and modifies acetylcholinesterase activity; therefore, it has neuroprotection during aging [53]. *Uncaria rhynchophylla* amends amyloid beta peptide deposition and amyloid beta peptide-mediated neuropathology in the brain in experimental animals, and this refers to that *Uncaria rhynchophylla* is a protective and treatment factor for Alzheimer's disease [54]. *Uncaria tomentosa* plant plays an important role in the protection and treatment of Alzheimer's disease, and this plant is used in drug detection protocol for detecting safe and effective particles for Alzheimer's disease treatment [55]. *Uncaria tomentosa* plant and *Uncaria rhynchophylla* plant improve the learning and memory impairments where both plants inhibit the hyperphosphorylation of tau protein, decline the increase of pro-inflammatory cytokines (interleukin-1 β , interleukin-6 and tumor necrosis factor- α), increase the antioxidant enzymes and increase the protein expression consequently both plants treat Alzheimer's disease [56]. *Uncaria tomentosa* plant declined and stopped beta-amyloid protein fibrils and tau protein [57]. *Uncaria tomentosa* plant treats the Parkinson's disease, and the effect of this plant is due to its neuroprotective effect [58]. *Uncaria tomentosa* plant is a good natural agent in treating normal brain aging and Alzheimer's disease [59].

5.1.3. Antitumour activity.

In an *in-vitro* study, Cortex Uncariae water extract inhibited the cell growth of human leukemic cell lines (HL60) and human lymphoma cell line (Raji). The suppression effect of the extract was activated by cell apoptosis. The cell apoptosis was observed by DNA destruction and distinguished morphological injury. Cortex Uncariae water extract stopped the cell apoptosis following 2 days of extract application. Cortex Uncariae water extract jumped both DNA single and double strands after 1 day of extract treatment [60]. In an *in-vitro* study, alkaloid ingredients from *Uncaria tomentosa* plant root stopped the growth of Leukaemic HL60 and U-937 cells. The uncarine F alkaloid showed the most inhibition effect on Leukaemic HL60 and U-937 cells [24]. *Uncaria tomentosa* has a strong antitumor effect that stops the cancer cells *in vitro* and *in vivo* [61]. *Uncaria tomentosa* plant has an anti-cancer

effect that can be used in the treatment of prostate cancer [62]. Cortex Uncariae possesses antitumor activity in colon cancer [63]. *Uncaria tomentosa* plant is used in Spanish-speaking countries in South America to treat different types of tumors [64].

5.1.4. Immune stimulating activity.

1 $\mu\text{mol/l}$ of oxindole alkaloids of Cortex Uncariae increased the secretion of T and B lymphocytes. Simultaneously, these alkaloids stopped the human lymphoblastoid T cell line and the human lymphoblastoid B cell line Raji. On the contrary, the tetracyclic oxindole alkaloids of Cortex Uncariae declined the growth and expansion of lymphocytes inspired by oxindole alkaloids of Cortex Uncariae [65]. *Uncaria tomentosa* plant increases the immunity response in endometrial and vaginal cells, which is dependent on the anti-inflammatory and anti-proliferative effects of the plant [66]. Cortex Uncariae extract (0.025 to 0.1 mg/ml) initiated the secretion of interleukin-1 and interleukin-6 in the rat macrophages, and this effect was dose-dependent and indicated the immunity-stimulating effect of Cortex Uncariae [32]. Cortex Uncariae water extract (5 to 80 mg/kg/day for 8 weeks) initiated lymphocyte increase. The lymphocyte increase was accompanied by a lymphocyte increase in rat splenocytes. The dose was equal to 40 and 80 mg/kg. The lymphocytes were increased after treatment by 40, 80, and 160 mg/kg/day with regard to the control group. Cortex Uncariae improved the DNA single- and double-strand breakdowns during 3 hours of exposure [31]. Cortex Uncariae water extract (80 mg/kg/day for 16 days) recovered leukopenia in experimental animals, and the study showed lymphocytes increased; therefore, Cortex Uncariae repaired both immunity responses and DNA breakdowns [67]. The oxindole alkaloids ingredient of Cortex Uncariae increased the phagocytosis in mice, and the presence of catechin activated these alkaloids. The isopteropodine alkaloid ingredient of Cortex Uncariae exhibited the higher phagocytosis effect (55%) > pteropodine > isomitraphylline > isorhynchophylline [68].

5.1.5. Anti-obesity activity.

Uncaria tomentosa extract improved glucose homeostasis and reverted non-alcoholic fatty liver disease to a benign case. These effects were correlated with the anti-inflammatory effect of the plant to inhibit liver inflammation in obese mice [69]. The anti-obesity activity of Cortex Uncariae protects from cardiac disease and COVID-19 [70-72]. *Uncaria tomentosa* extract improved colitis, and this effect of the plant extract is due to the restoration of the gut integrity and the suppression of apoptosis and inflammation in mice fed a high-fat diet [73].

5.2. Clinical pharmacology of Cortex Uncariae.

5.2.1. Immune stimulating activity.

In a clinical study, oral administration with Cortex Uncariae water extract (350 mg/kg) to 4 normal persons daily for 6 weeks did not cause any harmful effects such as hemorrhage, body weight loss, diarrhea, constipation, nausea, headache, vomiting, edema, and pain was observed. There was an increase in lymphocytes following Cortex Uncariae treatment for 6 weeks [31]. The pharmacological and clinical applications of Cortex Uncariae are similar to that of *Anisi etheroleum* [74]. In another clinical study, oral intake with 350 mg/kg/day of Cortex Uncariae extracts to normal persons increased human immunity by increasing the lymphocyte/neutrophil ratio of the human blood and decreased the antibody response to

pneumococcal injection for 5 months [30]. *Uncaria tomentosa* extract amends fipronil-induced immunotoxicity by ameliorating the histology and biochemical parameters of the lymphoid organs [75].

6. Toxicity of Cortex Uncariae

No acute or chronic toxicity was recorded following Cortex Uncariae water extract (10 to 80 mg/kg for 8 weeks or 160 mg/kg for 4 weeks). The median lethal dose of Cortex Uncariae water extract was higher than 8 mg/kg in rats. Cortex Uncariae extract did not accompany the loss of food intake or body or organ weight decrease. No histopathological changes were recorded in the kidney, liver, spleen, and heart after the intake of Cortex Uncariae [31]. In an *in-vitro* study, Cortex Uncariae water extract did not contain any toxic substances, and the Cortex Uncariae extract was found safe without any toxic effect [76]. *Uncaria tomentosa* water extract did not alter the chemical components of hyphessobrycon eques; therefore, this extract has low toxicity to hyphessobrycon eques, and consequently, it can be used safely in this species [77].

7. Adverse Reactions of Cortex Uncariae

There were no publications regarding the adverse reactions of Cortex Uncariae.

8. Contraindications of Cortex Uncariae

Cortex Uncariae is used as an emmenagogue; therefore, it must be avoided for pregnant women.

9. Warnings of Cortex Uncariae

There were no publications regarding the warnings of the Cortex Uncariae application.

10. Precautions of Cortex Uncariae

10.1. Drug interactions.

Cortex Uncariae extract declined human cytochrome P450 activity. The median dose of Cortex Uncariae extracts responsible for this effect=1%. Consequently, Cortex Uncariae must administrate under medical precautions, especially in the case of drugs that are metabolized through cytochrome P450, such as estrogens and protease inhibitors [78].

10.2. Carcinogenesis, mutagenesis, impairment of fertility.

There were no publications regarding the carcinogenesis, mutagenesis, and impairment of fertility of Cortex Uncariae application. *Uncaria tomentosa* stops P2X7 receptor-mediated breast cancer, and consequently, *Uncaria tomentosa* is used clinically in breast cancer treatment [79]. *Uncaria tomentosa* water extract has anti-proliferative and pro-apoptotic activities in squamous carcinoma cells [80]. *Uncaria tomentosa* plant has antioxidant and anti-genotoxic effects that depend on the extract's phenolic ingredients, which increase protein synthesis [81,82]. *Uncaria tomentosa* extract has a role for cancer patients as a complementary therapy by reducing apoptosis [83].

10.3. Pregnancy: non-teratogenic effects.

Cortex Uncariae is used as an emmenagogue; therefore, it must be avoided for pregnant women. Cortex Uncariae has therapeutic effects on pregnancy hypertension due to enhancement of vascular endothelial function, as well as an antioxidative, sedative, anti-hypertensive, and anti-inflammatory effects of Cortex Uncariae [84]. *Uncaria tomentosa* plant controls blood pressure by controlling the balance between T cell and inflammatory cytokine secretion in non-pregnant and pregnant women [85].

10.4. Nursing mothers.

The use of Cortex Uncariae must be administrated under the supervision of a healthcare supplier.

10.5. Paediatric use.

The use of Cortex Uncariae must be administered in children at 12 years under the supervision of a healthcare supplier.

10.6. Other precautions

There was no general safety, drug safety, experimental test correlations, or teratogenicity properties in pregnancy for Cortex Uncariae.

11. Dosage of Cortex Uncariae

Cortex Uncariae occurs in many forms, such as (1) infusions, (2) decoctions, and (3) extracts. Cortex Uncariae also occurs in the form of capsules and tablets. Cortex Uncariae must store in a closely black container to avoid heat and light. The average daily dose of Cortex Uncariae is as follows: (1) Extracts = 20 to 350 mg [10, 31], (2) Capsules and tablets = 300 to 500 mg where Cortex Uncariae should be administrated as 1 capsule or tablet (2 to 3 times daily).

12. Conclusions

Cortex Uncariae is the stem of *Uncaria tomentosa* plant, where this plant has occurred in Central and South American countries. The plant is a shrub 20 to 30 m in length and 25 cm in diameter. The indole alkaloids and tetracyclic alkaloids oxindoles are the major Cortex Uncariae chemical constituents. Cortex Uncariae is used as an emmenagogue. It is used to treat arthritis, urinary tract infections, fever, asthma, high blood pressure, high blood glucose, and high total cholesterol. There was no general safety, drug safety, experimental test correlations, or teratogenicity for Cortex Uncariae. There were no adverse reactions, contraindications, or warnings for Cortex Uncariae. Cortex Uncariae has many forms, including infusions, decoctions, and extracts. The daily dose of Cortex Uncariae is equal to 1 capsule or tablet (2 to 3 times daily).

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Conflict of interest

The author declares no conflict of interest.

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