Uncaria tomentosa (Willd. ex Schult.): Focus on Nutraceutical Aspects

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Abstract: Medicinal plants have been globally exploiting as an alternative to chemical drugs in the treatment of several diseases due to low unwanted side effects, environmentally friendly nature, and low production costs. Therefore, it is important to analyze the therapeutic properties of various medicinal plants to understand their potential bioactivity. Uncaria tomentosa is one of these medicinal plants with many health-promoting effects. Although the geographical resources of cat's claw go back to the remote tropics of the Amazon, industrialized countries use the plant extensively in trade. Various parts of the plants such as flowers, leaves, stem, hooks, and seeds are mainly used medicinally to treat inflammation, asthma, allergies, skin impurities, microbial infections, neurodegenerative diseases, cancer, cirrhosis, gastrointestinal disorders, arthritis, heart disease, rheumatism, and fever. The endpoint of this review article is to prospectively scrutinize in vitro and in vivo the therapeutic potential of this plant, especially in terms of its nutritional applications and health-beneficial effects.

Keywords: Uncaria tomentosa (Willd. ex Schult.), biodiversity, bioactive compounds, nutraceuticals, biological properties, cirrhosis.

1. INTRODUCTION

Medicinal plants have been globally exploiting as an alternative to synthetic drugs in the treatment of several diseases due to lower unwanted side effects, environmentally friendly nature, great availability, and low production costs [1-2]. Uncaria tomentosa (Willd. ex Schult.), a plant belonging to Rubiaceae family, is one of these medicinal plants with many health-promoting effects, including neuroprotective, immunostimulant, anti-microbial, antioxidant, anti-cancer, anti-inflammatory, anti-diabetic potentials [3-4].

2. THE BOTANICAL, GEOGRAPHICAL ASPECTS OF UNCARIA TOMENTOSA WILDL EX SCHULT.

Uncaria tomentosa belongs to the family Rubiaceae, a medicinal plant with claw-shaped thorns with the ability to climb from tree trunks up to a height of 30 meters, and it is known for its cat claws that grow naturally in the rainy tropical forest in Central and South America, including Venezuela, Peru, Panama, Ecuador, Bolivia, Brazil, Costa Rica, and Colombia. The flowers are 1.5 to 2 cm long, sessil, shiny corolla in a bunch of capitulum. The fruit is bivalve capsules, completely oval with a length of 5-8 mm. The membranous leaves are rectangular, opaque yellowish-matte beams or just the lower nerve with 7-10 nerves. The stems have solid and woody thorns with a length of 2 cm inclined downwards. The geographical and botanical properties of Uncaria tomentosa are listed in Table 1.

3. THE HISTORY ASPECTS OF UNCARIA TOMENTOSA WILDL EX SCHULT.

The Ashaninka Indians, natives of the Amazon rainforest, have traditionally used, in a pure holistic based traditional approach, Uncaria tomentosa root/bark boiled extract for more than 2,000 years to treat inflammation, asthma, allergies, skin impurities, microbial infections, neurodegenerative diseases, cancer, cirrhosis, gastrointestinal disorders, arthritis, heart disease, rheumatism, and fever. There are also reports of indigenous Peruvian tribes based on the therapeutic applications of Uncaria tomentosa in the treatment of...
abscesses, bleeding, menstrual irregularities, female urinary tract cancer, as well as in the internal cleansing and body normalization. *Uncaria tomentosa* formulations on the market include tea, extract, capsules, decoctions, and tinctures [6]. These observations triggered the interest in the beneficial properties of this plant and stimulated interest in assessing the compounds responsible for the beneficial health effect and the mechanism of action.

Table 1. Summary of the *Uncaria tomentosa* Wild botanical characteristics.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Attributes</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Habit</td>
<td>Central and South America</td>
<td>[5]</td>
</tr>
<tr>
<td>Height</td>
<td>30m</td>
<td>[5]</td>
</tr>
<tr>
<td>Leaves</td>
<td>Oblong, oblong-ovate, elliptic with 5-12 cm in width and 7.5-17 cm in length</td>
<td>[6]</td>
</tr>
<tr>
<td>Flowers</td>
<td>Bisexual, actinomorphic and sessil</td>
<td>[6]</td>
</tr>
<tr>
<td>Fruits</td>
<td>Dry and dehiscent with 3-6 mm wide and 5-8 mm long</td>
<td>[6]</td>
</tr>
</tbody>
</table>

4. MAIN COMPONENTS AND NUTRACEUTICAL CHARACTER OF *UNCARIA TOMENTOSA* WILD EX SCHULT

The main chemical compounds which are present in *Uncaria tomentosa* extracts are flavonoids monomers, polyphenol (catechin-derived tannins, epicatechin, proanthocyanidins, quinovic, quinic, and chlorogenic acids), triterpenes (oleanolic glycosides and ursolic), pentacyclic oxindole alkaloids (uncarine F, speciophylline, isopteropodine, pteropodine, mi-traphylline), and tetracyclic oxindole alkaloids (rhynophylline and corynoxine); some are shown in Fig. (1). According to Pavei et al. [7], the UPLC/Q-TOF-MS and RP-HPLC-PDA techniques detected the presence of quinovic acid glycosides in bark extract of *Uncaria tomentosa*. The measurements results revealed that Limit of Detection (LOD), Relative Standard Deviation (RSD), and limit of quantification (LOQ) were calculated to be 13.87 μg/ml, <1.2% and 42.05 μg/ml, respectively [7]. A study reported that dichloromethane stem extract of *U. tomentosa* analyzed by MS and 1D, 2D NMR methods contained the compounds of scopoletin, isopteropodine, and ß-sitosterol [8]. Peñaloza et al. [9] prepared the extract of different parts of cat’s claw (common name for *Uncaria tomentosa*) from South-American rainforests, whose main chemical compositions were quinovic acid glycosides in stem bark, as well as polyphenol and alkaloid compounds in leaves, stem bark, and branches, which were identified by the HPLC-PDA method. Bertol et al. [10] identified oxindole alkaloids in *Uncaria tomentosa* extract exploiting the HPLC method, with the RSD value of <2.4%, the accuracy value of ≥ 96%, and the linearity value of r² ≥ 0.9996. In an in vitro investigation, the hydroethanolic extract of *Uncaria tomentosa* exerted antiviral activities through significant inhibitory impacts on the replication of herpes simplex virus type 1 (HSV-1) and virus attachment to the host cell, which were identified as its primary mechanism of action [11].

Yepes-Pérez et al. [12] reported that the chemical compositions of *Uncaria tomentosa* (including proanthocyanidin C1, QAG-2, 3-isodihydrocambine, uncaric acid, and uncarine F) exposed a well-predicted binding affinity for the RBD-ACE-2 interface relative to the sulfated heparin octasaccharide (HepOS), highlighting the effectiveness of cat’s claw to block SARS-CoV-2/ACE-2 junction and SARS-CoV-2 spike protein. In Table 2, the distribution of bioactive compounds in different parts of *Uncaria tomentosa* and in other *Uncaria* species for comparison is reported. A study applied *U. tomentosa* to inhibit 3CLpro as a key protease of SARS-CoV-2 through molecular modeling by structural bioinformatics techniques, the results of which confirmed the presence of three bioactive compounds, including proanthocyanidin B2, cadambine, and speciophylline [13]. These compounds were reported to have potent interaction with 3CLpro leading to therapeutic potentials.

5. IN VITRO AND IN VIVO THERAPEUTIC POTENTIALS OF *UNCARIA TOMENTOSA*: AN UPDATE SHOT

The first phase to recognize the health-promoting effects of the medicinal plants is to analyze their phytochemical compositions, structure and activities, and combined action [19-24]. The most effective oral dose for all of the mentioned agents is unknown. The oral dose has varied in recent reports generally from 100 to 1000 mg/d [25]. The findings on the therapeutic potentials of *Uncaria tomentosa* reported by in vitro and in vivo studies are summarized in Fig. (2).

5.1. Health-Promoting Activities of *Uncaria Tomentosa* Based on In Vitro Studies

Studies on *Uncaria tomentosa* extracts reported various in vitro health-promoting effects, the key findings of which can be seen in Table 3. Ribeiro et al. documented anticancer activity against prostate cancer cell lines (LNCaP and DU145) following the co-administration of poly-e-caprolactone (PCL) nanoparticles, poly-D,L-lactide-co-glycolide (PLGA), and *U. tomentosa* extract [26]. De-Oliveira et al. [27] exposed colorectal adenocarcinoma cell line (HT29) to *U. tomentosa* and oxalipatin extracts and found an increase in the induction of apoptosis through a decrease in the level of ERCC1 mRNA expression and an elevation in the level of caspases 1/3/8 activity [27]. In a recent study, *Uncaria tomentosa* leaf extracts protected HepG2 Cancer Cells Against Cisplatin (DDP) cytotoxicity by reducing activated NF-κB and increasing caspase-3/7 activity [28]. In a study by Dietrich et al., the quinovic acid glycosides extracted from *Uncaria tomentosa* extract prevented human T24 cancer cell growth via the translocation of NF-jB to the nucleus and the activation of the caspase-3-dependent apoptotic pathway [29]. The anti-tumoral effects of mitraphylline extracted from *Uncaria tomentosa* inner bark (5 to 40 mM concentrations) were reported on neuroblastoma SKN-BE and glioma GAMG cell lines with the IC₅₀ values of 12.3 mM (30 h) and 20 mM (48 h), respectively [30]. In another study, mitraphy-
Fig. (1). Chemical structures of the more common bioactive compounds identified in *Uncaria tomentosa*.

Table 2. Distribution of bioactive compounds in different part of *Uncaria tomentosa* and other *Uncaria* species.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Species</th>
<th>Part of the Plant</th>
<th>Analytical Approach</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procyanidin, propelar-gonidin, and flavaligands</td>
<td><em>U. tomentosa</em></td>
<td>Leaves</td>
<td>Ultra-Performance Liquid Chromatography coupled with Electrospray Ionization and Triple Quadrupole (TQD) Tandem Mass Spectrometry (UPLC/TQ-ESI-MS) and 13C-NMR</td>
<td>[14]</td>
</tr>
<tr>
<td>Mitraphylline</td>
<td><em>Uncaria tomentosa</em> (Willd. ex Schult.)</td>
<td>Barks</td>
<td>HPLC-UV/DAD (diode-array detector), mass spectrometry, UV-visible, infrared (IR) and 1H- and 13C-nuclear magnetic resonance (NMR) spectroscopy</td>
<td>[15]</td>
</tr>
<tr>
<td>Flavan-3-ols, and (±)-uncarins</td>
<td><em>Uncaria rhynchophylla</em></td>
<td>Leaves</td>
<td>NMR and HRESIMS approach</td>
<td>[16]</td>
</tr>
<tr>
<td>Isopteropdine</td>
<td><em>Uncaria tomentosa</em> (Willd. Ex Schult.)</td>
<td>-</td>
<td>Quantitatively analyzing multi-components with a single-marker (QAMS)</td>
<td>[17]</td>
</tr>
<tr>
<td>Isopteropodine Pteropodine Isopteropodic acid, and rutin</td>
<td><em>Uncaria lanosa</em> (Wall.)</td>
<td>Stem</td>
<td>Ultrahigh-performance liquid chromatography coupled with orbitrap mass spectrometry detectors (UHPLC-Orbitrap MS).</td>
<td>[18]</td>
</tr>
</tbody>
</table>

Table 3. Updated examples of *in vitro* studies related to *Uncaria tomentosa*.

<table>
<thead>
<tr>
<th>Biological Activity</th>
<th>Mechanism of Action</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticancer</td>
<td>The methanolic extract of <em>U. tomentosa</em> bark presented an anti-proliferative effect against HeLa and Caco2 cells with IC50 values of 763 and 881, respectively.</td>
<td>[34]</td>
</tr>
<tr>
<td>Anticancer</td>
<td>The pentacyclic oxindole as pretreatment for promyelocytic leukemia HL-60 cells with alkaloids enhanced proapoptotic properties by inhibiting the NF-kB activity.</td>
<td>[35]</td>
</tr>
<tr>
<td>Anticancer</td>
<td>The treatment inhibited the Wnt-signaling pathway and down-regulated beta-Catenin.</td>
<td>[36]</td>
</tr>
<tr>
<td>Anticancer</td>
<td>The uncarine F and pteropodine extract of <em>U. tomentosa</em> inhibited the proliferation of acute leukaemic lymphoblasts cells by inducing apoptosis.</td>
<td>[37]</td>
</tr>
<tr>
<td>Anticancer</td>
<td>The <em>U. tomentosa</em> extract had proapoptotic potential by activating caspase 3.</td>
<td>[38]</td>
</tr>
<tr>
<td>Antioxidant</td>
<td>The oxindole alkaloids and quinovic acid glycosides extracted from <em>U. tomentosa</em> extracts exhibited antiviral properties.</td>
<td>[39]</td>
</tr>
<tr>
<td>Antioxidant</td>
<td>The <em>U. tomentosa</em> aqueous extract presented antioxidant properties through SOD-like activity and DPPH radical scavenging.</td>
<td>[40]</td>
</tr>
<tr>
<td>Antiviral and immunomodulatory</td>
<td>Reduction in cell rates of Dengue Virus-infected human monocytes and IFN-α/ TNF-α level.</td>
<td>[41]</td>
</tr>
</tbody>
</table>
line (5μM to 40μM) was used to treat the human breast cancer MT-3 and Ewing’s sarcoma MHH-ES-1 cell lines, with IC50 ± SE values of 11.80 ± 1.03μM and 17.15 ± 0.82μM, respectively [31]. A study reported the inhibitory effect of four different Uncaria extracts against proteolytic and amylolytic potentials of thrombin, even at a dose of 5 μg/ml [32]. Among these, the ethanolic extracts of U. tomentosa bark and leaf had the greatest inhibitory effect. The findings of a study demonstrated that the main site of formation of compounds derived from different U. tomentosa extracts is the outer hydrophilic monolayer of the erythrocyte membrane, which means the protection of erythrocytes versus oxidative stress [33].

The proanthocyanidins extracted from Uncaria tomentosa were characterized by the quadrupole-time-of-flight analyser (ESI-QTOF MS); they were able to exert cytotoxicity against colon and gastric cancer cell lines and antimicrobial activity against P. aeruginosa, E. faecalis, and S. aureus, as well as antioxidant potential with TE/g values of 1.5 and 18.8 nmol for Oxygen Radical Absorbance Capacity [42]. In an in vitro study, the polyphenols extracted from U. tomentosa bark at the doses of 3.9 mg/L-15.62 mg/L exhibited the optimal anti-Candida activity [43]. Uncaria tomentosa leaf and bark aqueous and ethanolic extracts contained mainly 32 phenolic compounds, identified using HPLC-DAD/TQ-ESI-MS technique, and proanthocyanidins of leaf extract had the highest antioxidant activity [44]. A pentacycloxindolic alkaloid, like mitraphylline, from Uncaria tomentosa, reduced inflammatory response after 24h incubation in the presence of human primary monocytes, regulating monocytes/macrophages plasticity [45]. In a study by Shi et al. [46], Uncaria tomentosa aqueous extract showed neuroprotective activity in Caenorhabditis elegans by reducing α-synuclein accumulation, nitric oxide, intracellular reactive oxygen species, and lipid peroxidation levels, and increasing mitochondrial membrane potential and cell viability, respectively. Bors et al. [47] stated that the administration of 500 μg/ml of Uncaria tomentosa extracts protected human erythrocytes via the reduction of hemolysis and ROS level as well as the inhibition of lipid peroxidation and the extent of hemoglobin oxidation.

In a recent study, the alkaloidal fraction of U. tomentosa bark extract was administered to control the Dengue virus in human microvascular endothelial cell-1 (HMEC-1), and the findings demonstrated immunomodulatory and anti-viral properties via the reduction of paracellular permeability as well as the induction of permeability with IL-8 contribution [48]. The antibacterial activities were found for bioactive compounds present in Uncaria tomentosa against Bacillus subtilis, Klebsiella pneumonia, Staphylococcus aureus, and Escherchia coli. Artochamin C exhibited the maximum activity with various MIC values in the range from 4.1µg/mL to 6.7µg/mL [49]. Herrera et al. [50] observed that Uncaria tomentosa extract is capable of eliminating Candida albicans, Staphylococcus aureus, and Enterococcus faecalis as endodontic pathogens. According to their findings, the mean diameter of the zone of inhibition from 2% CHX+CC versus the studied microbial strains was 21.7-33.5 mm.
Uncaria tomentosa showed anti-inflammatory potential via the reduction of classical NF-κB and AP-1 activation and TNF-α expression [51]. Based on these results, Uncaria tomentosa exerts its effects significantly through regulation by activation of the NF-κB p52 subunit, as studies have reported, through activation of subunits and inhibitors as well as enhancement of IL-1β and inhibition of TNF-α level. It has also been observed that the exposure of THP-1 monocyte-like cells to Uncaria tomentosa resulted in altered cytokine expression as well as prevented phosphorylation of MEK1/2 and ERK1/2 and MAP kinase signaling pathways [52].

5.2. Health-Promoting Activities of U. Tomentosa Using in Animal Models

Numerous studies on animal models reported health-promoting effects of Uncaria tomentosa extracts; the results of some updated studies are shown in Table 4. In a recent study, the two-week treatment of rats with hydroalcoholic Uncaria tomentosa extract exhibited antioxidant and antineoplastic activities in tumor cells and hepatocytes due to an increase in catalase activity and a decrease in SOD and AST activity [53]. In a study by Zari et al., an anticancer activity was found for the aqueous, and ethanolic Uncaria tomentosa extracts show in a mouse model, with a decrease of 59% in B16-BL6 tumor weight, a decrease of 40% in tumor size, and a potent decrease in cell proliferation marker of Ki-67 protein [54]. Azevedo et al. [55] used an aqueous extract of Uncaria tomentosa leaf and observed increased oxidative stress resistance in C. elegans by decreasing hsp-16.2, gst-4, and sod-3 expression. In a study, 100 mg of Uncaria tomentosa extract administered to Wistar rats revealed renoprotective activity [56]. Moreover, the presence of urinary peroxides was the reason for the oxidative lesion in the model of ischemic acute kidney injury. The functional protection was enhanced following the pretreatment with Uncaria tomentosa in accordance with elevated creatinine clearance, decreased peroxidation, and urinary TBARs, probably due to the antioxidant potentials of phytotherapeutic compounds.

In a recent study, Uncaria tomentosa administered for six consecutive weeks protected the rats against fipronil-induced liver damage by reduction of cytokines production and inhibiting the NF-kB level [62]. The administration of Uncaria tomentosa at a dose of 5g/kg/day in rats for three months controlled fipronil-induced metabolic dysfunction [63].

In an in vitro test, the aqueous extracts of Uncaria tomentosa bark and leaf inhibited the activation of NF-kB and the production of IL-6 and TNF-α. As well, in an in-vivo test, the aqueous leaf extracts exhibited more effective potential when comparing with the aqueous bark extract in the control of respiratory mechanics, while the aqueous bark extract was more effective than the aqueous leaf extract in the treatment of asthmatic inflammation [64]. In a study by Rojas-Duran et al. [65], the administration of Mitraphylline (30 mg/kg/day) for three days in mice showed anti-inflammatory activity by inhibiting the production of TNF-α, IL-4, IL-17, IL-1α, and IL-1β. In a study, Uncaria tomentosa extract showed anti-arthritis potential in rats with adjuvant arthritis by inhibiting the E-NTPDase activity, as well as reducing MPO activity, paw thickness, and mechanical thresholds [66].

Domingues et al. [67] found an immunomodulatory activity for aqueous-ethanol extract of Uncaria tomentosa (10-400 mg/kg) in mice with immune-mediated diabetes induced by streptozotocin (40 mg/kg). After 21 days, the diabetes incidence and the glycemic levels were reduced in the treated animals. Additionally, higher doses of Uncaria tomentosa prevented destructive insulitis and intact islets higher number as well as caused the loss of insulin-secreting protection, Foxp3+ Treg cells enhancement, and Th1/2 modulation. In another study, the administration of Uncaria tomentosa for 4 days in mice treated with ifosfamide, reduced chemotherapy complications and neutropenia [68]. Furthermore, the results from the colony-forming cell (CFC) test confirmed the enlargement in the size of the granulocyte-macrophage colony-forming cells (CFU-GM) and CFU-GEMM at the extract concentrations of 100 and 200 μg/ml. 

5.3. Health-Promoting Activities Of Uncaria Tomentosa Using Clinical Trials

Some clinical trials investigated the therapeutic effects of Uncaria tomentosa extract. As Farias et al. [69] applied Uncaria tomentosa extract (300 mg) in a patient with colorectal cancer for 12 weeks to improve the antioxidant balance and reduce chemotherapy complications; their results demonstrated that Uncaria tomentosa extract was ineffective to control chemotherapy side effects. Sordi et al. [70]
prescribed *Uncaria tomentosa* (100 mg/day) three times a day for a month in patients with breast cancer and found ineffectiveness of this medicinal plant against Aromatase inhibitors-induced arthralgia when comparing with the placebo. In a study, the administration of *Uncaria tomentosa* (100 mg/day) three times a day for two months in patients showed anti-tumor activity, reduced fatigue, and promoted overall and social well-being [71]. The co-administration of *Paullinia cupana* extracts by patients with cancer controlled nausea and fatigue [72]. In another study, females with breast cancer received dried *Uncaria tomentosa* extract (300 mg/day), and the results showed the restoration of DNA damage and the reduction of neutropenia during the chemotherapy [73].

**CONCLUSION AND FUTURE REMARKS**

*Uncaria tomentosa* is a global medicinal plant which contains different naturally occurring biologically active compounds with therapeutic properties. However, a holistic approach should be substantiated by more *in vitro* and *in vivo* studies which are still needed to investigate the relationship between the chemical composition and molecular targets of this plant in the treatment of various diseases which have been reported, as well as to reach a final conclusion about the effects and consequences of long-term use of this plant and its extracts in a nutraceutical preventive or therapeutic approach. Studies in humans on a limited number of health conditions require the use of observational animal experiments to describe pharmacokinetics. Due to the health effects of this plant, novel nutraceuticals can be potentially extracted as a preventive profilaxis strategy before the start of conventional drug therapy, especially for patients who are not prone to conventional pharmacological approaches to diseases. New strategies are nowadays addressing the research approach towards nanopharmaceuticals and nanonutraceuticals that may lead to improved delivery, bioavailability, and use on human beings to better modulate the effect and control of the active compound delivery [74-76].

**AUTHORS’ CONTRIBUTIONS**

A.D., A.N., and A.S. were responsible for conceptualization. A.D., A.N., M.L., A.M.S., E.B.S. were responsible for data curation. A.D., A.N., M.L., A.M.S., E.B.S., and A.S. were responsible for writing and preparation. A.D., A.N., M.L., A.M.S., E.B.S. and A.S. were responsible for original draft preparation.

A.N., A.D., M.L., A.M.S., S.B.S., P.S., E.B.S., A.S. were responsible for writing, review, and editing. A.S. and A.D. were responsible for supervision.

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