

## *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* WILLD 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 tro-

pical 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, sessile, 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* WILLD 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

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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* Willd botanical characteristics.**

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

#### 4. MAIN COMPONENTS AND NUTRACEUTICAL CHARACTER OF *UNCARIA TOMENTOSA* WILD EXSCHULT

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 (rhynchophylline 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 *Uncaria tomentosa* analyzed by MS and 1D, 2D NMR methods contained the compounds of scopoletin, isopteropodine, and β-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  $r^2 \geq 0.9996$ . 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].

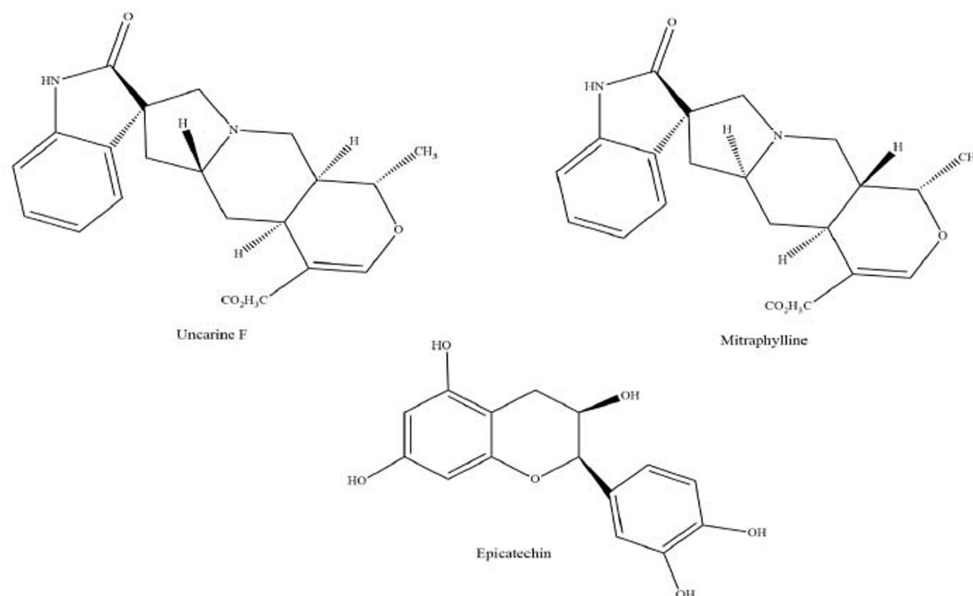
Yepes-Pérez *et al.* [12] reported that the chemical compositions of *Uncaria tomentosa* (including proanthocyanidin C1, QAG-2, 3-isodihydrocadambine, uncaric acid, and uncarine F) exposed a well-predicted binding affinity for the RB-D-ACE-2 interface relative to the sulfated heparin octasaccharide (HepOS), 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 3CL<sup>pro</sup> 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 3CL<sup>pro</sup> 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-ε-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 oxaliplatin 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 (CDDP) 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-κB 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 IC<sub>50</sub> values of 12.3 mM (30 h) and 20 mM (48 h), respectively [30]. In another study, mitraphy-



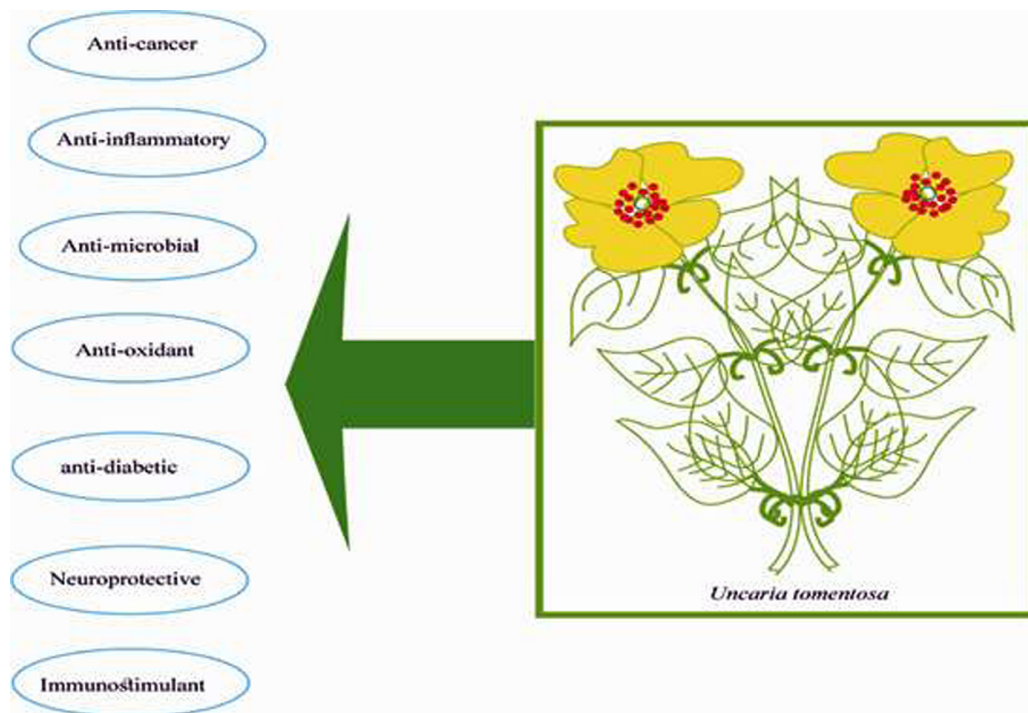
**Fig. (1).** Chemical structures of the more common bioactive compounds identified in *Uncaria tomentosa*.

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

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

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

Biological Activity	Mechanism of Action	References
Anticancer	The methanolic extract of <i>U. tomentosa</i> bark presented an anti-proliferative effect against HeLa and Caco2 cells with IC <sub>50</sub> values of 763 and 881, respectively.	[34]
Anticancer	The pentacyclic oxindole as pretreatment for promyelocytic leukemia HL-60 cells with alkaloids enhanced proapoptotic properties by inhibiting the NF-κB activity.	[35]
Anticancer	The treatment inhibited the Wnt-signaling pathway and down-regulated beta-Catenin.	[36]
Anticancer	The uncarine F and pteropidine extract of <i>U. tomentosa</i> inhibited the proliferation of acute leukaemic lymphoblasts cells by inducing apoptosis.	[37]
Anticancer	The <i>U. tomentosa</i> extract had proapoptotic potential by activating caspase 3.	[38]
Antioxidant	The oxindole alkaloids and quinovic acid glycosides extracted from <i>U. tomentosa</i> extracts exhibited antihyperlipidemic potentials.	[39]
Antioxidant	The <i>U. tomentosa</i> aqueous extract presented antioxidant properties through SOD-like activity and DPPH radical scavenging.	[40]
Antiviral and immunomodulatory	Reduction in cell rates of Dengue Virus-infected human monocytes and IFN-α/ TNF-α level.	[41]



**Fig. (2).** A picture of the main beneficial known properties of *Uncaria tomentosa*. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

line (5  $\mu$ M to 40  $\mu$ M) was used to treat the human breast cancer MT-3 and Ewing's sarcoma MHH-ES-1 cell lines, with  $IC_{50} \pm SE$  values of  $11.80 \pm 1.03 \mu$ M and  $17.15 \pm 0.82 \mu$ M, respectively [31]. A study reported the inhibitory effect of four different *Uncaria* extracts against proteolytic and amidolytic potentials of thrombin, even at a dose of 5  $\mu$ g/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 mmol 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 pentacyclicoxindolic 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  $\alpha$ -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  $\mu$ g/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 *Escherichia coli*. Artochamin C exhibited the maximum activity with various MIC values in the range from 4.1  $\mu$ g/mL to 6.7  $\mu$ g/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.

Table 4. Examples of updated studies in animal models.

Biological Activity	Mechanism of Action	References
Anti-inflammatory effect	The administration of <i>U. tomentosa</i> extract (50 mg/kg) reduced liver inflammation and steatosis after five days in obese models of mice.	[57]
Anti-diabetic effect	The administration of <i>U. tomentosa</i> extracts (32mg/ml) exhibited contraceptive function in rats with endometriosis after two weeks.	[58]
Anticancer	The administration of <i>U. tomentosa</i> (5 and 0.5mg/day) inhibited tumor growth in mice with Lewis lung carcinoma after 21 days.	[59]
Neuroprotective effect	The administration of <i>U. tomentosa</i> extract (30 mg/kg) for a year in middle-aged rats improved learning, memory, and cognition	[60]
Anti-resorptive and anabolic effects	The treatment of ligature-induced rats with compounds extracted from <i>U. tomentosa</i> caused a reduction in the periodontal attachment loss and alveolar bone resorption	[61]

*Uncaria tomentosa* showed anti-inflammatory potential via the reduction of classical NF- $\kappa$ B and AP-1 activation and TNF- $\alpha$  expression [51]. Based on these results, *Uncaria tomentosa* exerts its effects significantly through regulation by activation of the NF- $\kappa$ B p52 subunit, as studies have reported, through activation of subunits and inhibitors as well as enhancement of IL-1 $\beta$  and inhibition of TNF- $\alpha$  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 *U. 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]. Azevado *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- $\kappa$ B 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- $\kappa$ B and the production of IL-6 and TNF- $\alpha$ . 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 Mitrephylline (30 mg/kg/day) for three days in mice showed anti-inflammatory activity by inhibiting the production of TNF- $\alpha$ , IL-4, IL-17, IL-1 $\alpha$ , and IL-1 $\beta$ . 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 insulinitis 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  $\mu$ g/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* with *Uncaria tomentosa* 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.

## CONSENT FOR PUBLICATION

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## CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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