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Review Article

Cat's Claw Nutrients for Medical Treatments

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Abstract:

Uncaria tomentosa (Willd. ex Schult.) DC is commonly known as cat's claw that is derived from the Spanish word Uña de Gato that identifies the small, curved-back thorns on the stem at the leaf junction. It is a tropical medicinal vine of the Rubiaceae family that is widely distributed in the Amazon rainforest and other areas of South and Central America. Cat's claw, which is scientifically known as Uncaria tomentosa, has been historically used to treat and prevent inflammatory disorders, particularly osteoarthritis. Traditionally, it has been used to treat chronic viral infections, bacterial infections, numerous inflammatory and immunological disorders, asthma, dysentery, cancers, arthritis, and as a birth control agent. Nutraceuticals, including food or products containing cat's claw, can be used to prevent and modify symptoms in osteoarthritis patients. So, cat's claw is possibly effective in reducing the pain in patient's joints.

U. tomentosa is a potent complimentary herb for treating most parasites. Various chemical constituents are reported from the extracts of U. tomentosa along with their biological activities. It is worth noting that more than 50 phytochemical molecules have been identified and isolated from U. tomentosa, some of them are considered new to that species. It also was used for the treatment of various ailments including abscesses, urinary tract infections, contraception, rheumatism, and weakness. Additionally, it was used as a treatment option for mental disorders (anxiety). The preclinical assessment revealed that the cat's claw defends towards various oxidative stresses, involving peroxynitrite that has been included in arthritis and other chronic inflammatory diseases along with inhibiting acute or chronic gastritis caused by high doses of nonsteroidal anti-inflammatory drugs (NSAIDs). U. tomentosa aqueous extract was used to protect against oxidative stress in human erythrocytes and relieve chronic intestinal inflammation.

Cat's claw has antitumor and immunostimulatory effects because of its oxindole alkaloids content. Anti proliferative effect of U. tomentosa against several cancer cell lines, namely cervical carcinoma, osteosarcoma, and breast cancer were documented. U. tomentosa hot water extract prevents inflammatory responses as well as tumor cell proliferation by inhibiting the transcriptional regulator nuclear factor kappa beta (NF-B) activation without interfering with interleukin-2 (IL-2) production or IL-2 receptor signaling. Medical technologists documented the ant proliferative effect of cat's claw extracts against several cell lines, including glioma, premyelocytic leukemia, MCF7 breast cancer, acute lymphoblastic leukaemia, and neuroblastoma.

Key words: cervical carcinoma; osteosarcoma; peroxynitrite; nutraceutical and neuroblastoma

Introduction

Severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) is a part of corona virus (CoV) family and was initially identified in Wuhan, China, at the end of December, 2019. COVID-19 is highly contagious and is most frequently transmitted from human to human, spreading the virus easily to other countries in a very short time (Singhal, 2020). According to the last report of the World Health Organization (WHO), the severe acute respiratory syndrome (corona virus disease (COVID-19)) caused by SARS-CoV-2 is considered a pandemic, affecting Asia and Europe with the highest death rate followed by America and other regions, causing serious public health problems and considerable economic losses worldwide (Chen et al., 2020). Respiratory viral infections are the frequent causes of morbidity and millions of hospital admissions in developing countries every year (Wang et al., 2020). For this reason, the pharmacotherapy based on natural products may be a proper alternative for treating viral diseases. On the other hand, traditional medicine is practiced by native South American inhabitants who know the medicinal properties of many plants from the rainforest (Williamson et al., 2015). Therefore, many of them are collected by ethnobotanists who investigate

their resources as antimicrobial (Bussmann et al., 2010) and antitumor agents and being the main source for target selection during scientific investigation on compounds with antiviral activity (Ben-Shabat et al., 2020). The biodiversity of South America countries (Herrera-Calderon et al., 20207) offers a series of medicinal plants which could combat the symptoms of infections such as corona virus disease COVID-19.

Uncaria tomentosa (Willd. ex Schult.) DC. named Cat's claw ("uña de gato" in Spanish) is a woody vine indigenousto the Peruvian Amazon and other tropical areas of South and Central America and belongs to Rubiaceae family (Heitzman et al., 2005). Currently, the raw material of U. tomentosa is dispensed in Public Hospitals of the Social Health Insurance (EsSalud-Peru) as Complementary Medicine Service (CMS) (Gonzales et al., 2010).Traditionally, extracts prepared by root and bark decoction are used against several diseases, such as allergies, arthritis, inflammations, rheumatism infections, and cancer (Ko´smider et al., 2017). However, its popular use has been widely known worldwide, and analytical tests can be found in the United States Pharmacopeia and dosage forms have been authorized only as dietary supplements. Currently, there are about 34 species of Uncaria, with Uncaria tomentosa being the most common species (Zhu et al., 2017).

Bioactive constituents of U. tomentosaextracts include proanthocyanidins (proanthocyanidin B2 or epicatechin-(4β⟶8)-epicatechin, the main component; proantho-cyanidin B4, proanthocyanidin C1, an epicatechin trimer, epiafzelechin-4β⟶8-epicatechin, and an epicatechin tet-ramer) (Snow et al., 2019), oxindole alkaloids (isopteropodine, pteropodine, rhynchophylline, mytraphylline, speciophylline, uncarine F, and uncarine E) , indole alkaloidal gluco-sides (cadambine, 3-dihydrocadambine, and 3-iso-dihydrocadambine) (Vera-Reyes et al., 2015; Montoro et al., 2004), quinovic acid glycosides, tannins, polyphenols, catechins, beta-sitosterol, and proteins which individually or synergistically contribute to their therapeutic properties (Heitzman et al., 2005; Hoyos et al., 2015; Yunis Aguinaga et al., 2015).In regard to the antiviral properties of U. tomentosa, the alkaloid fraction has been demonstrated to be the most effective on human monocytes infected with dengue virus-2 (DENV) in vitro (Peñaloza et al., 2015). Another study revealed that only the alkaloidal fraction has inhibitory activity on dengue virus, and the negative effect was observed with the nonalkaloidal fraction. In another study, the anti-herpetic activity of U. tomentosaseems to be associated with polyphenols or their synergistic effect with penta-cyclic oxindole alkaloids or quinovic acid glycosides (Caon et al., 2004).

Furthermore, other investigations mentioned immunomodulating activity which includes stimulation of phagocytosis, en-hancement of B- and T-lymphocytes, suppression of NF-kappa B, and enhancement of IL-1 and IL-6 (Allen-Hall et al., 2010; Williams et al., 2004). In a Peruvian study on rats, the investigators found that phagocytosis was increased and might act as the potent inhibitor of TNF-α (Sandoval et al., 2000). In 2008, a study evidenced a possible drug-drug interaction between Cat's claw andprotease inhibitors such as saquinavir, atazanavir, and ritonavir, increasing level of these drugs in plasma (L´opez Galera et al., 2008). Individuals supplemented with a novel water-soluble ex-tract of Uncaria tomentosa(C-Med-100®) showed in-creased effectiveness of pneumococcal vaccination as aresult of an increase the lymphocyte/neutrophil ratios of peripheral blood and a reduced decay in the 12 serotypeantibody titer responses to pneumococcal vaccination (Akesson et al., 2003).

Particularly in developing countries, in which the accessibility to these plants is easier and more economically viable, adding these medicinal herbs to the general medical kit may be beneficial. In addition, traditional knowledge of these remedies may reduce possible side effects, allowing them to be implemented with fewer medical risks (Chen et al., 2016).On the basis of the aforementioned background of Uncaria tormentors (Cat's claw), this work aims at computationally identifying potential bioactive compounds againstCOVID-19. It focuses on possible interactions and inhibition of the 3CLproprotease (also called Mpro). 3CLpro is responsible for 100% of the proteolytic mechanism of the virus and is involved in virulence, infectivity, transcription, and replication cycle of the virus (Prajapat et al., 2020; Wu et al., 2020). It has been identified as the main druggable target of SARS-CoV-2 for new antiviral discovery. Moreover, its X-ray structure has been recently released, hence allowing possible computational analysis. In fact, several computational studies have already been undertaken on this system including a long20μs Peele molecular dynamics (MD) study and virtual screening of several databases (Elmezayen et al., 2020; Peele et al., 2020).

Uncaria tomentosa (Willd. ex Schult.) DC is commonly known as cat's claw that is derived from the Spanish word Uña de Gato that identifies the small, curved-back thorns on the stem at the leaf junction. It is a tropical medicinal vine of the Rubiaceae family that is widely distributed in the Amazon rainforest and other areas of South and Central America (Heitzman et al., 2005). It is also reported to be effective as an immune system rejuvenator, antioxidant, antimicrobial, and anti-inflammatory. U. tomentosa is a potent complimentary herb for treating most parasites (Santos et al., 2016). Various chemical constituents are reported from the extracts of U. tomentosa along with their biological activities. It is worth noting that more than 50 phytochemical molecules have been identified and isolated from U. tomentosa, some of them are considered new to that species (Navarro Hoyos et al., 2015).

A recent study about the chemical variation of a wild population of cat's claw from Peru reported the existence of three specific chemotypes that producing dierent alkaloidal constituents (Peñaloza et al., 2015). Chemotype I ismainly composedof thePOAwith the intersectionofD/E ring, chemotype II consists primarilyof POA with trans D/E ring junction, while chemotype III consists primarily of TOAderivative. Uncarine C and uncarine E are two POA stereoisomers, while mitraphylline, rhynchophylline, and isorhynchophylline are TOAs found in cat's claw. On the basis of these results, theU.S. Pharmacopeia revealed that dried raw material of cat's claw included 0.05% (w/w) of the TOA concerning the POA amount, whereas cat's claw powdered dried extract, tablets, and capsules contained up to 25% (w/w). Cat's claw contains several active compositions including ajmalicine, campesterol, carboxyl alkyl esters, akuammigine, sitosterols, rutin, chlorogenic acid, speciophylline, catechin, cinchonain (Gable,2007), corynoxeine, harman, daucosterol, epicatechin, hirsuteine, corynantheine, hirsutine, loganic acid, mitraphylline, iso-pteropodine, oleanolic acid, ursolic acid, lyaloside (Sheng et al., 2005), rhynchophylline, palmitoleic acid, pteropodine quinovic acid glycosides, procyanidins (Heitzman et al., 2005), stigmasterol, 3,4-dehydro-5-carboxystrictosidine, vaccenic acid, uncarine A thru F, and strictosidines (Heitzman et al., 2005; Lee et al., 2000). Moreover, other reports revealed that various compounds other than oxindole alkaloids such as rotundifoline and isorotundifolune, coumarins, flavonoids, quinovic acid glycosides, and triterpenes may be responsible for the cat's claw medicinal effects (Sheng et al., 2000; Dreifuss et al., 2013).

It was documented to be used for blood purifications, after child delivery as a wash for wounds to allow skin healing, cleansing the kidneys, asthma, inhibition of several diseases, menstrual irregularity and hemorrhages, fevers, and possess a normalizing activity on body systems (Laus,2004). It also was used for the treatment of various ailments including abscesses, urinary tract infections, contraception, rheumatism, and weakness. Additionally, it was used as a treatment option for mental disorders (e.g., anxiety). Some indigenous people in America used the water stored in the stem to quench thirst, and as a restorative drink (Azevedo et al., 2018).The preclinical assessment revealed that the cat's claw defends toward various oxidative stresses, involving peroxynitrite that has been included in arthritis and other chronic inflammatory diseases along with inhibiting acute or chronic gastritis caused by high doses of nonsteroidal anti-inflammatory drugs (NSAIDs) (Sandoval et al., 2000; Piscoya et al.,

2020). U. tomentosa aqueous extract was found to protect against oxidative stress in human erythrocytes and relieve chronic intestinal inflammation in rats caused by indomethacin (Bors et al., 2011). Another study documented that hydroxybenzoic acids, proanthocyanidins acids hydroxycinnamic were responsible for potent radical scavenging and anti-inflammatory activities of the cat's claw (Navarro et al., 2019; Navarro-Hoyos et al., 2017).

Cat's clawwas supposed to have antitumor and immunostimulatory effects because of its oxindole alkaloids content (Heitzman et al., 2005; Piscoya et al., 2020; Zhang et al., 2015). U. tomentosa extracts were found to have anti proliferative efficacy againstSW620 colon adenocarcinoma, MCF7 breast cancer, and AGS gastric cells (Sheng et al., 2000). Interestingly, several studies suggested the anti proliferative effect of U. tomentosa against several cancer cell lines, namely cervical carcinoma, osteosarcoma, and breast cancer. For instance, an in vitro study reported that U. tomentosa hot water extract prevents inflammatory responses as well as tumor cell proliferation by inhibiting the transcriptional regulator nuclear factor kappa beta (NF-B) activation without interfering with interleukin-2 (IL-2) production or IL-2 receptor signaling (Akesson et al., 2003). Cheng et al. (2007) documented the antiproliferative effect of cat's claw extracts against several cell lines, including glioma, premyelocytic leukemia, MCF7 breast cancer, acute lymphoblastic leukaemia, and neuroblastoma.

Recently, POA isolated from U. tomentosa extract has been documented to enhance the lymphocyte proliferation-regulating factor released from human endothelial cells; however, TOA was found to reduce POA activity on these cells in a dose-related manner (Sandoval et al., 2000; Erowele et al., 2009). Additionally, U. tomentosa stem bark extracts have been revealed to stimulate the in vitro production of IL-6 and IL-1 in rat alveolar and lipopolysaccharide-stimulated macrophages in a dose-related manner and its suppressive activities on cancer cell multiplication appear to be due to apoptosis induction (Lee et al., 2000; Rinner et al., 2009). Xiang et al. (2018) documented the ability of rhynchophylline to suppress rabbit and rat platelet accumulation ex vivo.

Additionally, the anti-inflammatory activity of the standardized aqueous extract of U. tomentosa (AC11 of U. tomentosa extract) was attributed to NF-B inhibition (Allen-Hall et al., 2010). Recently, several studies reported the antioxidant, anti-neoplastic and immunomodulant activities of the alkaloids isolated from the cat'sclaw (Paniagua-Pérez et al., 2009; Bacher et al., 2006 and Garcia Prado et al., 2007). For instance, Lopes et al. (2017) revealed that U. tomentosa extract encourages the myeloid precursor's proliferation by increasing serum colony-stimulating growth factors (CSFs). Moreover, in vivo studies demonstrated the effectiveness of aqueous U. tomentosa extract on leukocyte counts in healthy animals and doxorubicin-induced neutropenia (Piscoya et al., 2020; Sheng et al., 2000 and Farias et al., 2012). Interestingly, Cisneros et al. (2005) reported that lung inflammation was reduced in all mice treated with U. tomentosa bark extract.The previous study documented the antimicrobial effect of U. tomentosa bark extracts against several morphological forms of Borrelia burgdorferi and respiratory pathogens namely Enterococcus faecalis, Pseudomonas aeruginosa and Staphylococcus aureus and this activitywere attributed to the presence of proanthocyanidins, including dimers and oligomers up to undecamers (Ccahuana-Vasquez et al., 2020). U. tomentosa showed remarkable antifungal efficacy against various anidulafungin, terbinafine and fluconazole-resistant non-albicans species (Moraes et al., 2015). The antiprotozoal activity has been recently documented by Batiha et al. (2018) against Babesia and Theileria parasites and this efficacy was attributed to its ability to digest harmful microorganisms. Caon et al. (2014) assessed the in vitro antiherpetic activity of hydroethanolic U. tomentosa extract, as well as the purified fractions of oxindole alkaloids and quinovic acid glycosides against herpes simplex virus (HSV) infections as well as the protective activity of these preparations on UV-induced DNA damage.

Smith et al. (2003) reported that the POA isolated from U. tomentosa extracts improved the cellular immune system, while the TOA suppressed this immunostimulating effect of this POA in vitro. Another in vitro study showed the effect of different cat's claw extracts and mixtures of alkaloids in modulating the immune biochemical pathways enhanced by interferon-gamma (Ko´smider et al., 2017). Notably, in vivo experiments revealed that U. tomentosa extracts exhibited immunomodulatory activity indirectly and promoted a higher provider of myeloid progenitors in the bone marrow as a result of the release of biologically active cytokines (e.g., CSFs, IL-6, and IL-1) (Eberlin et al., 2005). Moreover, Allen-Hall et al. (2007) documented that U. tomentosa extracts prevented the mitogen-activated protein kinases (MAPK) signaling pathway and change cytokine expression in the human acute monocytic leukemia cell line THP-1. Hirsutine isolated from U. rhynchophylla extract was found to decrease intracellular calcium concentrations in rat aortas by inhibiting the calcium channels and effecting calcium stores (Zhu et al., 2015). Moreover, it showed a vasodilated, negative chronotropic, and antiarrhythmic effect. TOA namely corynoxeine, isocorynoxiene, rhynchophylline, and isorhynchophylline exhibited a Ca2+ channel blocking effect, which resulted in low blood pressure and may affect the central nervous system (Leenen et al., 2001).

Proanthocyanid in B2 (epicatechin-4 A-8-epicatechin) is one major cat's claw-identified specific polyphenol that markedly diminished the brain plaque load and enhanced short-term memory in younger and older AB precursor protein (APP) transgenic mice "plaque-producing". Moreover, proanthocyanidin B2 has been shown to be a strong inhibitor of the brain inflammation as evidenced by a decrease in astrocytosis and gliosis in TASD-41 transgenic mice (Snow et al., 2019).Previous reports noted several adverse effects after administration of high doses of cat's claw including nausea, acute renal failure, slow heart rate, stomach discomfort, hormonal effects, diarrhea, hepatotoxicity, decrease progesterone and estrogen levels, neuropathy (Cosentino et al., 2008; Navarro et al., 2014), and increased risk of bleeding when administered with blood thinner agents such as warfarin, therefore, patients may be recommended to stop cat's claw administration before surgeries (Ernst, 2003; Vogel et al., 2020). Signs of allergic reactions including swelling of face, lips, tongue, or throat, difficulty breathing, and hives have been observed (Standard, 2016). Additionally, acute renal failure was noticed in systemic lupus erythematosus patients after the daily administration of four capsules of the cat's claw (Gabardi et al., 2007).Cat's claw prevents the microsomal CYP 3A4 activity, and thus, increased the serum levels of drugs that are metabolized by CYP 3A4 such like nonnucleoside reverse-transcriptase inhibitors, cyclosporine, and some benzodiazepines and increased the serious adverse effects of these drugs (Budzinski et al., 2000). Moreover, the cat's claw may interact with allergic drugs like fexofenadine, anti-cancer agents as paclitaxel, antifungals like ketoconazole, antiviral drugs, and oral contraceptives (Scott and Elmer, 2002).A standardized extract attributed to specific chemotype of this species consisting of less than 0.5% oxindole alkaloids and 8% to 10% carboxy alkyl esters has been used in doses of 250 to 300 mg in several clinical studies (Sheng et al., 2010). In rats, it was determined that the average lethal dose for a single dose of water extract from U. tomentosa is higher than 8 g/kg. In humans, no toxic symptoms were noticed with frequent administration of 350 mg/day for 6 successive weeks (Valerio and Gonzales, 2005 and Williams, 2001).

Cat's claw, which is scientifically known as Uncaria tomentosa, has been historically used to treat and prevent inflammatory disorders, particularly osteoarthritis (Khanna et al., 2007). Traditionally, it has been used to treat chronic viral infections, bacterial infections, numerous inflammatory and immunological disorders, asthma, dysentery, cancers, arthritis, and as a birth control agent (Heitzman et al., 2005). Nutraceuticals, including food or products containing cat's claw, can be used to prevent and modify symptoms in osteoarthritis patients. So, cat's claw is possibly effective in reducing the pain in patient's joints (Hardin, 2007).

Most investigators attribute the biological effects of this plant to the POAs, an assumption that has been corroborated by studies of several such alkaloids that indicated their antioxidant, immunomodulatory, and anti-neoplastic properties.4 initially, the POAs were associated with increases in phagocytosis (Dreifuss et al., 2013). Later studies described its effective inhibition of growth in leukemia, (Bacher et al., 2006; Pilarski et al., 2007), glioma, neuroblastoma, (Garcia Prado et al., 2007) and medullary thyroid carcinoma cells, (Rinner et al.,2009) partly because of apoptosis induction. Alternatively, the anti-inflammatory and antineoplastic effects of U. tomentosa could be due to its reduction of the expression of transcription factor nuclear factor j light-chain enhancer of activated B cells (NF-jB) (Akesson et al., 2003), an effect that, in turn, regulates the expression of tumor necrosis factor-a(TNF-a). By reducing the expression of NF-jB, U. tomentosa also reduces the TNF-a level and intensifies its anti-inflammatory action Allen-Hall et al., 2010). Furthermore, some extracts and fractions of U. tomentosa exhibit a substantial antimutagenic protective action, which is associated with its antioxidant potential (Sandoval et al., 2000).

References

1. Akesson C, Lindgren H, Pero RW, Leanderson T, Ivars F. An extract of Uncaria tomentosa inhibiting cell division and NF-kappa B activity without inducing cell death. Int Immunopharmacol. 2003;3:1889–1900.
2. Allen-Hall L., J. T. Arnason, P. Cano, and R. M. Lafrenie, “Uncaria tomentosaacts as a potent TNF-αinhibitor through NF-κB,” Journal of Ethnopharmacology, vol. 127, no. 3, pp. 685–693, 2010.
3. Allen-Hall, L.; Cano, P.; Arnason, J.T.; Rojas, R.; Lock, O.; Lafrenie, R.M. Treatment of THP-1 cells withUncaria tomentosa extracts diferentially regulates the expression if IL-1beta and TNF-alpha. J. Ethnopharmacol.2007, 109, 312–317. [CrossRef]
4. Azevedo, B.C.; Morel, L.J.F.; Carmona, F.; Cunha, T.M.; Contini, S.H.T.; Delprete, P.G.; Ramalho, F.S.; Crevelin, E.; Bertoni, B.W.; França, S.C.; et al. Aqueous extracts from Uncaria tomentosa (Willd. ex Schult.) DC. reduce bronchial hyper responsiveness and inflammation in a murine model of asthma. J. Ethnopharmacol. 2018, 218, 76–89. [CrossRef]
5. Bacher N, Tiefenthaler M, Sturm S, et al. Oxindole alka-loids from Uncaria tomentosa induce apoptosis in prolif-erating, G0/G1-arrested and bcl-2-expressing acute lymphoblastic leukaemia cells. Br J Haematol. 2006; 132:615–622.
6. Batiha, G.E.S.; Beshbishy, A.A.; Tayebwa, D.S.; Shaheen, M.H.; Yokoyama, N.; Igarashi, I. Inhibitory effects of Uncaria tomentosa bark, Myrtus communis roots, Origanum vulgare leaves and Cuminum cyminum seedsextracts against the growth of Babesia and Theileria in vitro. Jpn. J. Vet. Parasitol. 2018, 17, 1–13.
7. Ben-Shabat S., L. Yarmolinsky, D. Porat, and A. Dahan, “Antiviral effect of phytochemicals from medicinal plants: applications and drug delivery strategies, ”Drug Delivery and Translational Research, vol. 10, no. 2, pp. 354–367, 2020.
8. Bors, M.; Bukowska, B.; Pilarski, R.; Gulewicz, K.; Oszmia´nski, J.; Michałowicz, J.; Koter-Michalak, M. Protective activity of the Uncaria tomentosa extracts on human erythrocytes in oxidative stress induced by 2,4-dichlorophenol (2,4-DCP) and catechol. Food Chem. Toxicol. 2011, 49, 2202–2211. [CrossRef]
9. Budzinski, J.W.; Foster, B.C.; Vandenhoek, S.; Arnason, J.T. An in vitro evaluation of human cytochromeP450 3A4 inhibition by selected commercial herbal extracts and tinctures. Phytomedicine 2000, 7, 273–282.[Cross Ref]
10. Bussmann R. W., G. Malca-Garc´ıa, A. Glenn et al., “Minimum inhibitory concentrations of medicinal plants used in Northern Peru as antibacterial remedies,”Journal of Ethno-pharmacology, vol. 132, no. 1, pp. 101–108, 2010.
11. Caon T., S. Kaiser, C. Feltrin et al., “Antimutagenic and antiherpetic activities of different preparations fromUncaria tomentosa (cat’s claw),” Food and Chemical Toxicology, vol. 66, pp. 30–35, 2014.
12. Ccahuana-Vasquez, R.A.; Santos, S.S.; Koga-Ito, C.Y.; Jorge, A.O. Antimicrobial activity of Uncaria tomentosa against oral human pathogens. Braz. Oral Res. 2007, 21, 46–50. [CrossRef] Appl. Sci. 2020, 10, 2668 11 of 12
13. Chen S. L., H. Yu, H. M. Luo et al., “Conservation and sustainable use of medicinal plants: problems, progress, and prospects, ”Chinese Medicine (United Kingdom), vol.11, no.1,2016.
14. Chen Y. W., C. P. B. Yiu, and K. Y. Wong, “Prediction of the SARS-CoV-2 (2019-nCoV) 3C-like protease (3CLpro) structure: virtual screening reveals velpatasvir, ledipasvir, and other drug repurposing candidates,”F1000 Research, vol. 9, p. 129, 2020.
15. Cheng, A.C.; Jian, C.B.; Huang, Y.T.; Lai, C.S.; Hsu, P.C.; Pan, M.H. Induction of apoptosis by Uncaria tomentosa through reactive oxygen species production, cytochrome c release, and caspases activation in human leukemia cells. Food Chem. Toxicol. 2007, 45, 2206–2218. [CrossRef]
16. Cisneros, F.J.; Jayo, M.; Niedziela, L. An Uncaria tomentosa (cat’s claw) extract protects mice against ozone-induced lung inflammation. J. Ethnopharmacol. 2005, 96, 355–364. [CrossRef]
17. Cosentino, C.; Torres, L. Reversible worsening of Parkinson’s disease motor symptoms after oral intake of Uncaria tomentosa (cat’s claw). Clin. Neuropharmacol. 2008, 31, 293–294. [CrossRef]
18. Dreifuss AA, Bastos-Pereira AL, Fabossi IA, et al. Uncaria tomentosa exerts extensive anti-neoplastic effects against the Walker-256 tumour by modulating oxidative stress and not by alkaloid activity. PLoS One. 2013;8:-54618.
19. Eberlin, S.; dos Santos, L.M.; Queiroz, M.L. Uncaria tomentosa extract increases the number of myeloid progenitor cells in the bone marrow of mice infected with Listeria monocytogenes. Int. Immunopharmacol. 2005,5, 1235–1246. [CrossRef] [PubMed]
20. Elmezayen A. D., A. Al-Obaidi, A. T. S¸ahin, and K. Yelekçi, “Drug repurposing for corona virus (COVID-19): in silico screening of known drugs against corona virus 3CL hydrolase and protease enzymes,”Journal of Biomolecular Structure and Dynamics, vol. 1-13, 2020.
21. Ernst, E. Cardiovascular adverse effects of herbal medicines: A systematic review of the recent literature.Can. J. Cardiol. 2003, 19, 818–827.
22. Erowele, G.I.; Kalejaiye, A.O. Pharmacology and therapeutic uses of cat’s claw. Am. J. Health Syst. Pharm. 2009, 66, 992–995. [CrossRef]
23. Farias, I.L.G.; Araújo,M.C.S.; Farias, J.G.; Rossato, L.V.; Elsenbach, L.I.; Dalmora, S.L.; Flores,N.M.; Durigon,M.; Cruz, I.B.; Morsch, V.M.; et al. Uncaria tomentosa for reducing side effects caused by chemotherapy in CRC Patients: Clinical trial. Evid. Based Complement. Alternat. Med. 2012, 2012, 892182. [CrossRef]
24. Gabardi, S.; Munz, K.; Ulbricht, C. A review of dietary supplement–induced renal dysfunction. Clin. J. Amer.Soc. Nephr. 2007, 2, 757–765. [CrossRef] [PubMed]
25. Gable, R.S. Risk assessment of ritual use of oral dimethyltryptamine (DMT) and harmala alkaloids. Addiction2007, 102, 24–34. [CrossRef]

26. Garcia Prado, E.; Garcia Gimenez, M.D.; De la Puerta Vazquez, R.; Espartero Sánchez, J.L.; Sáenz Rodríguez, M.T. Antiproliferative effects of mitraphylline, a pentacyclic oxindole alkaloid of Uncaria tomentosa on human glioma and neuroblastoma cell lines. Phytomedicine 2007, 14, 280–284. [CrossRef]
27. Gonzales G. F., J. Aguilar, and M. Villar, "1e world summit of harmonization on traditional, alternative and complementary medicine (TACM) in Lima, Peru,"Evidence-based Complementary and Alternative Medicine, vol. 7, no. 2, pp. 271–275, 2010.
28. Hardin, S. R. (2007). Cat's claw: An amazonian vine decrases inflammation in osteoarthritis. Complementry Therapies in Clinical Practice, 13, 25-28.
29. Heitzman, M. E., Neto, C. C., Winiarz, E., Vaisberg, A. J., & Hammond, G. B. (2005). Ethnobotany, phytochemistry and pharmacology of Uncaria (Rubiaceae). Phytochemistry, 66(1), 5-29.
30. Herrera-Calderon O., J. L. Arroyo-Acevedo, J. Rojas-Armas et al., "Phytochemical screening, total phenolic content, antioxidant and cytotoxic activity of chromolaena laevigata on human tumor cell lines,"Annual Research & Review in Biology, vol. 21, no. 1, pp. 1–9, 2017.
31. Hoyos M. N., F. S´anchez-Pat´an, R. M. Masis et al., "Phenolic assessment of Uncaria tomentosa L. (cat's claw): leaves, stem, bark and wood extracts," Molecules, vol. 20, no. 12, pp. 22703–22717, 2015.
32. Khanna, D., Sethi, G., Ahn, K. S., Pandey, M. K., Kunnumakkara, A. B., Sung, B., … Aggarwal, B. B. (2007). Natural products as a gold mine for arthritis treatment. Current Opinion in Pharmacology, 7(3), 344-351.
33. Kitajima M., K. I. Hashimoto, M. Yokoya, H. Takayama, and N. Aimi, "Two new 19-hydroxyursolic acid-type triterpenes from Peruvian 'Una de Gato' (Uncaria tomentosa)," Tetrahedron, vol. 56, no. 4, pp. 547–552, 2000.
34. Ko´smider A., E. Czepielewska, M. Kura´s et al., "Uncaria tomentosa leaves decoction modulates differently ROS production in cancer and normal cells, and effects cisplatin cytotoxicity," Molecules, vol. 22, no. 4, p. 620, 2017.
35. L´opez Galera R. M., E. Ribera Pascuet, J. I. Esteban Mur, J. B. Montoro Ronsano, and J. C. Ju´arez Gim´enez, "Interaction between cat's claw and protease inhibitors atazanavir, rito-navir and saquinavir,"European Journal of Clinical Phar-macology, vol. 64, no. 12, pp. 1235-1236, 2008.
36. Laus, G. Advances in chemistry and bioactivity of the genus Uncaria. Phytother. Res. 2004, 18, 259–274.
37. Lee, J.S.; Kim, J.; Kim, B.Y.; Lee, H.S.; Ahn, J.S.; Chang, Y.S. Inhibition of phospholipase cgamma1 and cancer cell proliferation by triterpene esters from Uncaria rhynchophylla. J. Nat. Prod. 2000, 63, 753–756.
38. Leenen, F.H.; Ruzicka, M.; Huang, B.S. Central sympathoinhibitory effects of calcium channel blockers. Curr. Hypertens. Rep. 2001, 3, 314–321.
39. Lima-Junior R. S., C. Da Silva Mello, C. F. Kubelka, A. C. Siani, and L. M. M. Valente, "Uncaria tomentosa al-kaloidal fraction reduces paracellular permeability, IL-8 and NS1 production on human microvascular endothelial cells infected with dengue virus," Natural Product Communica-tions, vol. 8, no. 11, Article ID 1934578X1300801, 2013.
40. Lopes, C.M.; Dourado, A.; Oliveira, R. Phytotherapy and nutritional supplements on breast cancer. Biomed. Res. Int. 2017, 2017, 42.
41. Montoro P., V. Carbone, J. de Dioz Zuniga Quiroz, F. De Simone, and C. Pizza, "Identification and quantification of components in extracts of Uncaria tomentosa by HPLC-ES/MS,"Phytochemical Analysis, vol. 15, no. 1, pp. 55–64, 2004.
42. Moraes, R.C.; Dalla Lana, A.J.; Kaiser, S.; Carvalho, A.R.; de Oliveira, L.F.S.; Fuentefria, A.M.; Ortega, G.G. Antifungal activity of Uncaria tomentosa (Willd.) DCagainst resistant non-albicans Candida isolates. Ind. Crops Prod. 2015, 69, 7–14. [CrossRef]
43. Navarro Hoyos, M.; Sánchez-Patán, F.; Murillo Masis, R.; Martín-Álvarez, P.J.; Zamora Ramirez, W.;Monagas, M.J.; Bartolomé, B. Phenolic assessment of Uncaria tomentosa L. (cat's claw): Leaves, stem, barkand wood extracts. Molecules 2015, 20, 22703–22717. [CrossRef] [PubMed]
44. Navarro, M.; Arnaez, E.; Moreira, I.; Hurtado, A.; Monge, D.; Monagas, M. Polyphenolic composition and antioxidant activity of Uncaria tomentosa commercial bark products. Antioxidants 2019, 8, 339.
45. Navarro, V.J.; Barnhart, H.; Bonkovsky, H.L.; Davern, T.; Fontana, R.J.; Grant, L.; Reddy, K.R.; See , L.B.; Serrano, J.; Sherker, A.H.; et al. Liver injury from herbals and dietary supplements in the U.S. Drug-Induced Liver Injury Network. Hepatology 2014, 60, 1399–1408. [CrossRef] [PubMed]
46. Navarro-Hoyos,M.; Lebrón-Aguilar, R.; Quintanilla-López, J.E.; Cueva, C.; Hevia, D.; Quesada, S.; Azofeifa, G.; Moreno-Arribas, M.V.; Monagas, M.; Bartolomé, B. Proanthocyanidin characterization and bioactivity of extracts from different parts of Uncaria tomentosa L. (Cat's Claw). Antioxidants 2017, 6, 12. [CrossRef]
47. Paniagua-Pérez, R.; Madrigal-Bujaidar, E.; Molina-Jasso, D.; Reyes-Cadena, S.; Alvarez-González, I.;Sánchez-Chapul, L.; Pérez-Gallaga, J. Antigenotoxic, antioxidant and lymphocyte induction effects produced by pteropodine. Basic Clin. Pharmacol. Toxicol. 2009, 104, 222–227. [CrossRef]
48. Peele K. A., C. Potla Durthi, T. Srihansa et al., "Molecular docking and dynamic simulations for antiviral compounds against SARS-CoV-2: a computational study,"Informatics in Medicine Unlocked, vol. 19, Article ID 100345, 2020.
49. Peñaloza E. M. C., S. Kaiser, P. E. De Resende et al., "Chemical composition variability in the Uncaria tomentosa (cat's claw) wild population,"Qu´ımica Nova, vol. 38, no. 3, 2015 , 378–386.
50. Pilarski R, Poczekaj-Kostrzewska M, Ciesiolka D, Szyfter K, Gulewicz K. Antiproliferative activity of various Un-caria tomentosa preparations on HL-60 promyelocytic leukemia cells. Pharmacol Rep. 2007; 59:565–572.
51. Piscoya, J.; Rodriguez, Z.; Bustamante, S.A.; Okuhama, N.N.; Miller, M.J.; Sandoval, M. Efficacy and safety of freeze-dried cat's claw in osteoarthritis of the knee: Mechanisms of action of the species Uncaria guianensis. Inflamm. Res. 2001, 50, 442–448.
52. Prajapat M., P. Sarma, N. Shekhar et al., "Drug targets for corona virus: a systematic review," Scholars International Journal of Biochemistry, vol. 3, no. 6, pp. 143–153, 2020.
53. Reis S. R. I. N., L. M. M. Valente, A. L. Sampaio et al., "Immunomodulating and antiviral activities of Uncaria tomentosa on human monocytes infected with dengue virus-2," International Immunopharmacology, vol. 8, no. 3, pp. 468–476, 2008.
54. Rinner, B.; Li, Z.X.; Haas, H.; Siegl, V.; Sturm, S.; Stuppner, H.; Pfragner, R. Antiproliferative andpro-apoptotic effects of Uncaria tomentosa in human medullary thyroid carcinoma cells. Anticancer Res. 2009, 29, 4519–4528. [PubMed]
55. Sandoval M., R. M. Charbonnet, N. N. Okuhama et al., "Cat's claw inhibits TNFαproduction and scavenges free radicals: role in cytoprotection," Free Radical Biology and Medicine, vol. 29, no. 1, pp. 71–78, 2000.

56. Santos, K.F.; Gutierres, J.M.; Pillat, M.M.; Rissi, V.B.; dos Santos Araújo, M.D.C.; Bertol, G.; Gonçalves, P.B.D.;Schetinger, M.R.C.; Morsch, V.M. Uncaria tomentosa extract alters the catabolism of adenine nucleotides and expression of ecto 50-nucleotidase/CD73 and P2X7 and A1 receptors in the MDA-MB-231 cell line.J. Ethnopharmacol. 2016, 194, 108–116.
57. Scott, G.N.; Elmer, G.W. Update on natural product—Drug interactions. Am. J. Health Syst. Pharm. 2002, 59,339–347.
58. Sheng, Y.; Akesson, C.; Holmgren, K.; Bryngelsson, C.; Giamapa, V.; Pero, R.W. An active ingredient of cat'sclaw water extracts identification and efficacy of quinic acid. J. Ethnopharmacol. 2005, 96, 577–584. [CrossRef]
59. Sheng, Y.; Bryngelsson, C.; Pero, R.W. Enhanced DNA repair, immune function and reduced toxicity of C-MED-100, a novel aqueous extract from Uncaria tomentosa. J. Ethnopharmacol. 2000, 69, 115–126. [CrossRef]
60. Sheng, Y.; Li, L.; Holmgren, K.; Pero, R.W. DNA repair enhancement of aqueous extracts of Uncaria tomentosa in a human volunteer study. Phytomedicine 2010, 8, 275–282. [CrossRef]
61. Sheng, Y.; Pero, R.W.; Wagner, H. Treatment of chemotherapy-induced leukopenia in a rat model with aqueous extract from Uncaria tomentosa. Phytomedicine 2000, 7, 137–143. [CrossRef]
62. Singhal T., "A review of coronavirus disease-2019 (COVID-19),"Indian Journal of Pediatrics, 87(4); 281–286, 2020.
63. Smith, V.J.; Brown, J.H.; Hauton, C. Immunostimulation in crustaceans: Does it really protect against infection? Fish Shellfish Immunol. 2003, 15, 71–90.
64. Snow A. D., G. M. Castillo, B. P. Nguyen et al., "1e Amazon rain forest plant Uncaria tomentosa (cat's claw) and its specific proanthocyanidin constituents are potent inhibitors and reducers of both brain plaques and tangles, "Scientific Reports, vol. 9, no. 1, 2019, 561.
65. Standard, N. Natural Standard Herb & Supplement Guide-E-Book: An Evidence-Based Reference; Elsevier Health Sciences: Amsterdam, The Netherlands, 2016.
66. Valerio, L.G., Jr.; Gonzales,G.F. Toxicological aspects of theSouthAmericanherbs cat's claw(Uncaria tomentosa) and Maca (Lepidium meyenii): A critical synopsis. Toxicol. Rev. 2005, 24, 11–35. [CrossRef]
67. Vera-Reyes I., A. A. Huerta-Heredia, T. Ponce-Noyola et al., "Monoterpenoid indole alkaloids and phenols are required antioxidants in glutathione depleted Uncaria tomentosa root cultures,"Frontiers in Environmental Science, vol. 3, 2015.
68. Vogel, J.H.; Bolling, S.F.; Costello, R.B.; Guarneri, E.M.; Kruco, M.W.; Longhurst, J.C.; Olshansky, B.;Pelletier, K.R.; Tracy, C.M.; Vogel, R.A.; et al. Integrating complementary medicine into cardiovascular medicine: A report of the American college of cardiology foundation task force on clinical expert consensus documents (writing committee to develop an expert consensus document on complementary and integrative medicine). J. Am. Coll. Cardiol. 2005, 46, 184–221.Appl. Sci. 2020, 10, 2668 12 of 12
69. Wang C., P. W. Horby, F. G. Hayden, and G. F. Gao, "A novel coronavirus outbreak of global health concern, "Ge Lancet, vol. 395, no. 10223, pp. 470–473, 2020.
70. Williams, J.E. Review of antiviral and immunomodulating properties of plants of the Peruvian rainforest with a particular emphasis on Una de Gato and Sangre de Grado. Altern. Med. Rev. 2001, 6, 567–579
71. Williamson J., R. Ramirez, and T. Wingfield, "Health, healthcare access, and use of traditional versus modern medicine in remote Peruvian Amazon communities: a descriptive study of knowledge, attitudes, and practices," Ge American Journal of Tropical Medicine and Hygiene, vol. 92, no. 4, pp. 857–864, 2015.
72. Wu C., Y. Liu, Y. Yang et al., "Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods,"Acta pharmaceutica Sinica. B.vol. 10, no. 5, pp. 766–788, 2020.
73. Xiang, L.; Li, Y.; Deng, X.; Kosanovic, D.; Schermuly, R.T.; Li, X. Natural plant products in treatment of pulmonary arterial hypertension. Pulm. Circ. 2018, 8. [CrossRef] [PubMed]
74. Yunis Aguinaga J., G. S. Claudiano, P. F. Marcusso et al.,"Acute toxicity and determination of the active constituents ofaqueous extract ofUncaria tomentosabark in Hyphessobrycon eques," Journal of Toxicology, vol. 2014, Article ID 412437, 5 pages, 2014.
75. Zhang, Q.; Zhao, J.J.; Xu, J.; Feng, F.; Qu, W. Medicinal uses, phytochemistry and pharmacology of the genus Uncaria. J. Ethnopharmacol. 2015, 173, 48–80.
76. Zhu S., Q. Li, S. Chen et al., "Phylogenetic analysis of Uncaria]species based on internal transcribed spacer (ITS) region andITS2 secondary structure," Pharmaceutical Biology, vol. 56,no. 1, pp. 548–558, 2018.
77. Zhu, K.; Yang, S.N.; Ma, F.F.; Gu, X.F.; Zhu, Y.C.; Zhu, Y.Z. The novel analogue of hirsutine as an anti-hypertension and vasodilatary agent both in vitro and in vivo. PLoS ONE 2015, 10, e0119477.

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