SAMENTO MICROBIAL DEFENSE

Pentacyclic Chemotype *Uncaria tomentosa*

Selected Published Research

SAMENTO MICROBIAL DEFENSE

Awareness is growing that the rainforests are one of the world's greatest natural resources. Based on current knowledge, it is estimated that the rainforests contain 170,000 of the world's 250,000 known plant species, and more are still being discovered. Continuing scientific studies are revealing many to be greatly beneficial for a broad number of medicinal uses.

As you will find in the study abstracts that follow, one of the most unique in its diversity and potential in medicinal applications is SAMENTO, also known as TOA-Free Cat's Claw. SAMENTO is a rare chemotype of the medicinal plant commonly known as Cat's Claw, *Uncaria tomentosa*.

Samento was approved as a medicine in Ecuador in 2004. Government officials have allowed 3 drug claims to be used: *anti-inflammatory, antimicrobial and immune system modulator.* The Hungarian National Institute of Pharmacy (OGYI), the Hungarian equivalent of the FDA in the US, also approved SAMENTO in 2001 as paramedicament (OTC) pharmaceutical preparation as a "*sole or adjunct therapy for rheumatoid diseases, arthritis and locomotor conditions. It is also approved as a sole or adjunct therapy to enhance immune system function.*"

Unlike traditional Cat's Claw products, the SAMENTO chemotype does not contain Tetracyclic Oxindole Alkaloids (TOAs), a group of chemical antagonists that act upon the central nervous system and can greatly inhibit the positive effect of the Pentacyclic Oxindole Alkaloids (POAs). The POAs primarily affect the immune cells responsible for non-specific and cellular immunity, and demonstrate powerful immune system modulating properties. According to research conducted in Austria, traditional Cat's Claw products may contain as much as 80% TOAs, and as little as 1% TOAs can cause a 30% reduction in the immune system modulating properties that POAs provide.

As a result of these phytochemical differences between SAMENTO and Cat's Claw, SAMENTO can be safely used in a broader range of medical conditions. Cat's Claw acts as an immune system stimulant making it contraindicated in patients with autoimmune disorders, whereas SAMENTO is an immune system modulator. For this reason, SAMENTO can be used to treat all autoimmune disorders.

TOA-Free Cat's Claw (SAMENTO) and isolated POAs such as mitraphylline, isomytraphylline, isopteropodine, and pteropodine continue to show promising results as they have been studied. The studies below reveal exciting potential for the use of SAMENTO in various applications.

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SAMENTO – Microbial Defense

MEDICAL CONDITIONS TREATED BY SAMENTO

Alzheimer's disease

WASHINGTON--(BW HealthWire)--April 16, 1999—

Researchers Report That a Natural Plant Derivative From the Amazon Rain Forest in a Rodent Model Inhibits the Deposition of Beta-amyloid Deposits Associated With Alzheimer's Disease Plaques.

Researchers at the Experimental Biology 99 meeting today report PTI-00703(TM), a natural plant derivative from the Amazon rain forest woody vine Uncaria tomentosa (Cat's Claw), in rats inhibits the deposition of beta-amyloid protein deposits associated with Alzheimer's disease.

Further, researchers from the University of Washington, Seattle, WA, ProteoTech, Inc., a Redmond, WA-based biotechnology company, and Rexall Sundown, Boca Raton, FL, have completed in vitro studies that demonstrate PTI-00703(TM) alone, or in combination with certain other botanical ingredients, including Ginkgo biloba, rosemary, gotu kola, and bacopin, is a potent inhibitor of beta-amyloid protein fibril formation and growth. Researchers observed that PTI-00703(TM) and certain combination formulas:

-- Inhibit beta-amyloid protein fibril formation and growth.

-- Cause disruption and dissolution of pre-formed amyloid fibrils.

-- Inhibit interactions of beta-amyloid protein with glycosaminoglycans.

In comparison to PTI-00703(TM) alone, researchers observed a synergistic effect by the combination of PTI-00703(TM) with certain botanical ingredients causing:

-- Enhanced inhibition of amyloid fibril growth.

-- Enhanced disruption of preformed beta-amyloid protein fibrils.

In a related development, ProteoTech and Rexall Sundown, today announced plans to conduct a clinical trial testing PTI-00703(TM) in patients with mild-to-moderate Alzheimer's disease. Pending finalization of the contract, the principal investigator for the multi-center trial is anticipated to be Jeffrey Kaye, M.D., Professor of Neurology, Oregon Health Sciences University, and Director, Aging & Alzheimer's Disease Center, Portland, Oregon. Additional sites will be named later this month.

"Our initial in vitro data suggests that PTI-00703(TM) in combination with certain other botanical ingredients may be better than PTI-00703(TM) alone as a preventative in halting the growth of new amyloid fibrils and in causing a disruption of preformed amyloid fibrils," said Alan Snow, Ph.D., Research Associate Professor of Pathology at the University of Washington, and one of the co-founders of ProteoTech Inc. "This is an important finding

because many believe that the brain abnormalities observed in Alzheimer's disease may, in fact, be an inevitability of aging," he said.

ProteoTech is a drug discovery company focused on therapeutics and diagnostics for human disease utilizing proteoglycan technologies. The "amyloid diseases" all involve the accumulation of specific proteoglycans believed to augment the amyloid process and inhibit the body's natural ability to remove unwanted "amyloid deposits." Proteoglycans are synthesized by virtually all

cells of the body and play significant roles in the pathogenesis of a number of human diseases, including Alzheimer's, Down's syndrome, diabetes, cancer, arthritis, atherosclerosis, heart disease and AIDS. One of ProteoTech's human disease targets is Alzheimer's disease, one of a group of human diseases that are characterized by the deposition and persistence of an insoluble substance known as "amyloid.

Bladder Cancer

Food and Chemical Toxicology Volume 67, May 2014, Pages 222–229
doi:10.1016/j.fct.2014.02.037

Quinovic acid glycosides purified fraction from *Uncaria tomentosa* induces cell death by apoptosis in the T24 human bladder cancer cell line

Fabrícia Dietrich, Samuel Kaiser, Liliana Rockenbach, Fabrício Figueiró, Letícia Scussel Bergamin, Fernanda Monte da Cunha, Fernanda Bueno Morrone, George González Ortega, Ana Maria Oliveira Battastini

Bladder cancer is the second most prevalent malignancy in the genitourinary tract and remains a therapeutic challenge. In the search for new treatments, researchers have attempted to find compounds with low toxicity. With this goal in mind, *Uncaria tomentosa* is noteworthy because the bark and root of this species are widely used in traditional medicine and in adjuvant therapy for the treatment of numerous diseases. The objective of this study was to investigate the antitumor effect of one purified bioactive fraction of *U.tomentosa* bark on cell proliferation in two human bladder cancer cell lines, T24 and RT4. Quinovic acid glycosides purified fraction (QAPF) of *U.tomentosa* decreased the growth and viability of both T24 and RT4 cell lines. In T24 cells, QAPF induced apoptosis by activating caspase-3 and NF-κB. Further study showed that this fraction does not induce cell cycle arrest and does not alter PTEN and ERK levels. In conclusion, we demonstrated that QAPF of *U.tomentosa* has a potent inhibitory effect on the growth of human bladder cancer cell lines by inducing apoptosis through modulation of NF-κB, and we suggest that QAPF may become a potential therapeutic agent for the prevention and/or treatment of this cancer.

Brain Cancer

Phytomedicine. 2007 Apr;14(4):280-4. Epub 2007 Feb 12.

Antiproliferative effects of mitraphylline, a pentacyclic oxindole alkaloid of Uncaria tomentosa on human glioma and neuroblastoma cell lines.

García Prado E, García Gimenez MD, De la Puerta Vázquez R, Espartero Sánchez JL, Sáenz Rodríguez MT.

Uncaria tomentosa inner bark extract is a popular plant remedy used in folk medicine to treat tumor and inflammatory processes. In this study, the anti-tumoral effects of its pentacyclic alkaloid mitraphylline were investigated. Furthermore, its growth-inhibitory and cytotoxic effects on glioma GAMG and neuroblastoma SKN-BE(2) cell lines were studied using cyclophosphamide and vincristine as controls. A colter counter was used to determine viable cell numbers, followed by application of the tetrazolium compound [3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)2-(4-sulfophenyl)-2H-tetrazolium], inner salt, colorimetric method to evaluate cell viability in this cytotoxicity assay. Micromolar concentrations of mitraphylline (from 5 to 40 [micro]M) inhibited the growth of both cell lines. It inhibited the growth of the two cell lines studied in a dose-dependent manner. The [IC.sub.50] values were 12.3 [micro]M (30 h) for SKN-BE(2) and 20 [micro]M (48 h) for GAMG, respectively. This action suggests that mitraphylline is a new and promising agent in the treatment of human neuroblastoma and glioma.

PMID: 1729629

Breast Cancer

Anticancer Research [2001, 21(4A):2457-2461]

The antiproliferative effects of Uncaria tomentosa extracts and fractions on the growth of breast cancer cell line.

Riva L, Coradini D, Di Fronzo G, De Feo V, De Tommasi N, De Simone F, Pizza C

Oncologia Sperimentale C, Istituto Nazionale per lo Studio e la Cura dei Tumori, Milano, Italy.

Uncaria tomentosa, also known as "Uña de gato", is a Rubiaceae species widely used in South-American folk medicine for the treatment of cancer, arthritis, gastritis and epidemic diseases. Extracts of the plant have been shown to possess cytostatic and anti-inflammatory activity as well as mutagenic and antimutagenic properties. However, to date no studies have been carried out to verify the direct antitumor activity of the extracts. The present study investigates the effects of some extracts and their chromatographic fractions from the bark of U. tomentosa on the growth of a human breast cancer cell line (MCF7). Our data indicated that, in addition to the antimutagenic activity, U. tomentosa extracts and fractions exert a direct antiproliferative activity on MCF7. The bioassay-directed fractionation from barks and leaves resulted in the isolation of two active fractions, which displayed an IC50 of 10 mg/ml and 20 mg/ml, respectively and an antiproliferative effect, with about 90% of inhibition at a concentration of 100 mg/ml.

PMID: 11724307

Planta Med. 2010 Feb;76(2):133-6. doi: 10.1055/s-0029-1186048. Epub 2009 Sep 1.

Cytotoxic effect of the pentacyclic oxindole alkaloid mitraphylline isolated from Uncaria tomentosa bark on human Ewing's sarcoma and breast cancer cell lines.

García Giménez D[1], García Prado E, Sáenz Rodríguez T, Fernández Arche A, De la Puerta R.

Abstract

Preparations from Uncaria tomentosa, a South American Rubiaceae, have been used in the Peruvian traditional medicine for the treatment of infective, inflammatory and tumoral processes. In this study, the pentacyclic oxindole alkaloid mitraphylline was isolated from the dried inner bark of this plant species, and its structure elucidated by analysis of NMR spectroscopic data. Mitraphylline was differentially identified from its stereoisomeric pair isomitraphylline by (15)N-NMR. Its antiproliferative and cytotoxic effects have been tested on human Ewing's sarcoma MHH-ES-1 and breast cancer MT-3 cell lines, using cyclophosphamide and vincristine as reference controls. A Coulter counter was used to determine viable cell numbers, followed by the application of the tetrazolium compound MTS [3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxy phenyl)-2-(4-sulfophenyl)-2H-tetrazolium] an inner salt. A colorimetric method was employed to evaluate cell viability in this cytotoxic assay. Micromolar concentrations of mitraphylline (5 microM to 40 microM) inhibited the growth of both cell lines in a dose-dependent manner. The IC (50) +/- SE values were 17.15 +/- 0.82 microM for MHH-ES-1 and 11.80 +/- 1.03 microM for MT-3 for 30 hours, smaller than those obtained for the reference compounds. This action suggests that the pentacyclic oxindole alkaloid mitraphylline might be a new promising agent in the treatment of both human sarcoma and breast cancer.

Georg Thieme Verlag KG Stuttgart . New York.

PMID:19724995 DOI:10.1055/s-0029-1186048

Anticancer Agents Med Chem. 2017;17(6):770-783. doi: 10.2174/1871520616666160817111242.

The Immunomodulatory Potential of Selected Bioactive Plant-Based Compounds in Breast Cancer: A Review.

Baraya YS[1], Wong KK[2], Yaacob NS[3].

Author information

Abstract

Breast cancer has continued to cause high cancer death rates among women worldwide. The use of plants' natural products in breast cancer treatment has received more attention in recent years due to their potentially wider safety margin and the potential to complement conventional chemotherapeutic drugs. Plantbased products have demonstrated anticancer potential through different biological pathways including modulation of the immune system. Immunomodulatory properties of medicinal plants have been shown to mitigate breast cancer cell growth. Different immune cell types participate in this process especially cytotoxic T cells and natural killer cells, and cytokines including chemokines and tumor necrosis factor-α. Medicinal plants such as Glycyrrhiza glabra, Uncaria tomentosa, Camellia sinensis, Panax ginseng, Prunus armenaica (apricot), Allium sativum, Arctium lappa and Curcuma longa were reported to hold strong potential in breast cancer treatment in various parts of the world. Interestingly, research findings have shown that these plants possess bioactive immunomodulators as their main constituents producing the anticancer effects. These immunomodulatory compounds include ajoene, arctigenin, β-carotene, curcumin, epigallocatechin-3-gallate, ginsan, glabridin and quinic acid. In this review, we discussed the ability of these eight immunomodulators in regulating the immune system potentially applicable in breast cancer treatment via anti-inflammatory (curcumin, arctigenin, glabridin and ajoene) and lymphocytes activation (β-carotene, epigallocatechin-3-gallate, quinic acid and ginsan) properties, as well as future research direction in their use for breast cancer treatment.

Cystitis

PLOS, Published: July 8, 2015, http://dx.doi.org/10.1371/journal.pone.0131882

The Quinovic Acid Glycosides Purified Fraction from Uncaria tomentosa Protects against Hemorrhagic Cystitis Induced by Cyclophosphamide in Mice

Fabrícia Dietrich, Jerônimo Pietrobon Martins, Samuel Kaiser, Rodrigo Braccini Madeira Silva, Liliana Rockenbach, Maria Isabel Albano Edelweiss, George González Ortega, Fernanda Bueno Morrone, Maria Martha Campos, Ana Maria Oliveira Battastini

Uncaria tomentosa is widely used in folk medicine for the treatment of numerous diseases, such as urinary tract disease. Hemorrhagic cystitis (HE) is an inflammatory condition of the bladder associated with the use of anticancer drugs such as cyclophosphamide (CYP). Sodium 2-mercaptoethanesulfonate (Mesna) has been used to prevent the occurrence of HE, although this compound is not effective in established lesions. It has been demonstrated that the purinergic system is involved in several pathophysiological events. Among purinergic receptors, P2X7 deserves attention because it is involved in HE induced by CYP and, therefore, can be considered a therapeutic target. The objective of this study was to investigate the potential therapeutic effect of the quinovic acid glycosides purified fraction (QAPF) from *U*. *tomentosa* in the mouse model of CYP-induced HE. Pretreatment with QAPF not only had a protective effect on HE-induced urothelial damage (edema, hemorrhage and bladder wet weight) but was also able to control visceral pain, decrease IL-1β levels and down-regulates P2X7 receptors, most likely by inhibit the neutrophils migration to the bladder. This research clearly demonstrates the promising anti-inflammatory properties of QAPF, supporting its use as complementary therapy. QAPF represents a promising therapeutic option for this pathological condition.

Dengue Fever

Int Immunopharmacol. 2008 Mar;8(3):468-76. doi: 10.1016/j.intimp.2007.11.010. Epub 2007 Dec 26.

Immunomodulating and antiviral activities of Uncaria tomentosa on human monocytes infected with Dengue Virus-2.

Reis SR, Valente LM, Sampaio AL, Siani AC, Gandini M, Azeredo EL, D'Avila LA, Mazzei JL, Henriques Md, Kubelka CF.

Uncaria tomentosa (Willd.) DC., a large woody vine native to the Amazon and Central American rainforests has been used medicinally by indigenous peoples since ancient times and has scientifically proven immunomodulating, anti-inflammatory, cytotoxic and antioxidant activities. Several inflammatory mediators that are implicated in vascular permeability and shock are produced after Dengue Virus (DENV) infection by monocytes, the primary targets for virus replication. Here we assessed the immunoregulatory and antiviral activities from U. tomentosa-derived samples, which were tested in an in vitro DENV infection model. DENV-2 infected human monocytes were incubated with U. tomentosa hydro-alcoholic extract or either its pentacyclic oxindole alkaloid-enriched or non-alkaloid fractions. The antiviral activity was determined by viral antigen (DENV-Ag) detection in monocytes by flow cytometry. Our results demonstrated an in vitro inhibitory activity by both extract and alkaloidal fraction, reducing DENV-Ag+ cell rates in treated monocytes. A multiple microbead immunoassay was applied for cytokine determination (TNF-alpha, IFN-alpha, IL-6 and IL-10) in infected monocyte culture supernatants. The alkaloidal fraction induced a strong immunomodulation: TNF-alpha and IFN-alpha levels were significantly decreased and there was a tendency towards IL-10 modulation. We conclude that the alkaloidal fraction was the most effective in reducing monocyte infection rates and cytokine levels. The antiviral and immunomodulating in vitro effects from U. tomentosa pentacyclic oxindole alkaloids displayed novel properties regarding therapeutic procedures in Dengue Fever and might be further investigated as a promising candidate for clinical application.

PMID: 18279801

Denture Stomatitis

Journal of Prosthodontics Volume 24, Issue 7, pages 594–597, October 2015, Version of Record online: 9 FEB 2015, DOI: 10.1111/jopr.12248

Uncaria tomentosa Gel against Denture Stomatitis: Clinical Report

Lidia Y. Tay DDS, MSc, PhD, Fabio A. dos Santos DDS, MSc, PhD and Janaina H. Jorge DDS, MSc, PhD

The objective of this study is to report the clinical use of 2% *Uncaria tomentosa* gel against denture stomatitis (DS) as an alternative treatment. The patient was a 65-year-old, denture-wearing woman. At the clinical examination, her palate showed hyperplasic and erythematous mucosa indicating DS type II. DS is a chronic oral disease that affects denture wearers. It occurs as an inflammatory reaction in denture-wearing patients under maxillary prostheses. *Candida albicans* has been reported as the principal etiological agent. An alternative treatment, the topical application of a gel of 2% *U. tomentosa* three times a day for 1 week was given to the patient. After 1 week of this treatment, she had significantly reduced signs of the disease. Despite the existence of a great number of antifungal agents, treatment failure is observed frequently. Phytotherapy is becoming more popular worldwide. Currently, the most promising medicinal Amazonian herb is *U. tomentosa* (Willd.) DC., known as Cat's Claw. Studies of the chemical and pharmacological properties of this medicinal plant have allowed researchers to develop indications for its use. This report demonstrates the effectiveness of *U. tomentosa* against DS.

Endometriosis

Eur J Obstet Gynecol Reprod Biol. 2011 Feb;154(2):205-8. doi: 10.1016/j.ejogrb.2010.10.002. Epub 2010 Oct 27.

Experimental endometriosis reduction in rats treated with Uncaria tomentosa (cat's claw) extract.

Nogueira Neto J, Coelho TM, Aguiar GC, Carvalho LR, de Araújo AG, Girão MJ, Schor E.

The aim of this study was to analyze the macroscopic and histological changes that occur in experimental endometriosis after treatment with Uncaria tomentosa.

Experimental endometriosis was induced in twenty-five female Wistar rats. After three weeks, 24 animals developed grade III experimental endometriosis and were divided into two groups. Group "U" received U. tomentosa extract orally (32 mg/day), and group "C" (control group) received a 0.9% sodium chloride solution orally (1 ml/100g of body weight/day). Both groups were treated with gavage for 14 days. At the surgical intervention and after the animal was euthanized, the implant volume was calculated with the following formula: [4π (length/2)×(width/2)×(height/2)/3]. The autotransplants were removed, dyed with hematoxylin-eosin, and analyzed by light microscopy. The Mann-Whitney test was used for the independent samples, and the Wilcoxon test analyzed the related samples, with a significance level of 5%.

The difference between the initial average volumes of the autotransplants was not significant between the groups (p = 0.18). However, the final average volumes were significantly different between the groups (p = 0.001). There was a significant increase (p = 0.01) between the initial and final average volumes in the control group, and treatment with the U. tomentosa caused a marked reduction in the growth over time (p = 0.009). Histologically, in the experimental group (n = 10) six rats had a well-preserved epithelial layer, three had mildly preserved epithelium, and one had poorly preserved epithelium. The epithelial layer occasionally presented sporadic epithelial cells. The control group (n = 12) presented seven cases (58.3%) of well-preserved epithelial cells and five cases (41.7%) of mildly preserved epithelial cells.

Cat's claw extract appears to be a promising alternative for treating endometriosis.

Herpes

Food Chem Toxicol. 2014 Apr;66:30-5. doi: 10.1016/j.fct.2014.01.013. Epub 2014 Jan 18.

Antimutagenic and antiherpetic activities of different preparations from Uncaria tomentosa (cat's claw).

Caon T, Kaiser S, Feltrin C, de Carvalho A, Sincero TC, Ortega GG, Simões CM.

Uncaria tomentosa have been used to treat viral diseases such as herpes due to multiple pharmacological effects, but its therapeutic efficacy against this virus have not been reported yet. Thus, in vitro antiherpetic activity of hydroethanolic extract from barks, purified fractions of quinovic acid glycosides and oxindole alkaloids was evaluated by plaque reduction assay, including mechanistic studies (virucidal, attachment and penetration action). Once exposure to physical agents might lead to reactivation of the herpetic infection, antimutagenic effect (pre-, simultaneous and post-treatment protocols) was also evaluated by Comet assay. The antiherpetic activity from the samples under investigation seemed to be associated with the presence of polyphenols or their synergistic effect with oxindole alkaloids or quinovic acid glycosides, once both purified fractions did not present activity when evaluated alone. Inhibition of viral attachment in the host cells was the main mechanism of antiviral activity. Although both purified fractions displayed the lowest antimutagenic activity in pre and simultaneous treatment, they provided a similar effect to that of cat's claw hydroethanolic extract in post-treatment. Given that purified fractions may result in a reduced antiherpetic activity, the use of cat's claw hydroethanolic extract from barks should be prioritized in order to obtain a synergistic effect.

Immune – mediated diseases (diabetes)

J Ethnopharmacol. 2011 Sep 1;137(1):635-42. doi: 10.1016/j.jep.2011.06.021. Epub 2011 Jun 28.

Prevention of experimental diabetes by Uncaria tomentosa extract: Th2 polarization, regulatory T cell preservation or both?

Domingues A, Sartori A, Golim MA, Valente LM, da Rosa LC, Ishikawa LL, Siani AC, Viero RM.

Uncaria tomentosa (Willd.) DC (Rubiaceae) is a species native to the Amazon rainforest and surrounding tropical areas that is endowed with immunomodulatory properties and widely used around the world. In this study we investigated the immunomodulatory potential of Uncaria tomentosa (UT) aqueous-ethanol extract on the progression of immune-mediated diabetes.

C57BL/6 male mice were injected with MLDS (40 mg/kg) and orally treated with UT at 10-400mg/kg during 21 days. Control groups received MLDS alone or the respective dilution vehicle. Pancreatic mononuclear infiltrate and f3-cell insulin content were analyzed by HE and immunohistochemical staining, respectively, and measured by digital morphometry. Lymphocyte immunophenotyping and cytokine production were determined by flow cytometry analysis.

Treating the animals with 50-400mg/kg of UT caused a significant reduction in the glycemic levels, as well as in the incidence of diabetes. The morphometric analysis of insulitis revealed a clear protective effect. Animals treated with UT at 400mg/kg presented a higher number of intact islets and a significant inhibition of destructive insulitis. Furthermore, a significant protection against the loss of insulin-secreting presented f3-cells was achieved, as observed by a careful immunohistochemical evaluation. The phenotypic analysis indicated that the groups treated with higher doses (100-400mg/kg) presented CD4(+) and CD8(+) T-cell values similar to those observed in healthy animals. These same higher doses also increased the number of CD4(+)CD25(+)Foxp3(+) regulatory T-cells. Moreover, the extract modulated the production of Th1 and Th2, with increased levels of IL-4 and IL-5.

The extract was effective to prevent the progression of immune-mediated diabetes by distinct pathways.

Leukemia

Pharmacol Rep. 2007 Sep-Oct;59(5):565-72.

Antiproliferative activity of various Uncaria tomentosa preparations on HL-60 promyelocytic leukemia cells.

Pilarski R, Poczekaj-Kostrzewska M, Ciesiołka D, Szyfter K, Gulewicz K.

The woody Amazonian vine Uncaria tomentosa (cat's claw) has been recently more and more popular all over the world as an immunomodulatory, antiinflammatory and anti-cancer remedy. This study investigates anti-proliferative potency of several cat's claw preparations with different quantitative and qualitative alkaloid contents on HL-60 acute promyelocytic human cells by applying trypan blue exclusion and 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide reduction assay (MTT). By standardization and statistical comparison of the obtained results pteropodine and isomitraphylline are indicated to be most suitable for standardization of medical cat's claw preparations.

PMID: 18048957

Listeria

Int Immunopharmacol. 2005 Jul;5(7-8):1235-46. Epub 2005 Apr 1.
doi:10.1016/j.intimp.2005.03.001

Uncaria tomentosa extract increases the number of myeloid progenitor cells in the bone marrow of mice infected with *Listeria monocytogenes*

Samara Eberlin, Leonilda, M.B. dos Santos, Mary L.S. Queiroz'

In this study, we demonstrated that *Uncaria tomentosa* extract (UTE) protects mice from a lethal dose of *Listeria monocytogenes* when administered prophylactically at 50, 100, 150 and 200 mg/kg for 7 days, with survival rates up to 35%. These doses also prevented the myelosuppression and the splenomegaly caused by a sublethal infection with *L. monocytogenes*, due to increased numbers of granulocyte-macrophage progenitors (CFU-GM) in the bone marrow. Non-infected mice treated with 100 mg/kg UTE also presented higher numbers of CFU-GM in the bone marrow than the controls. Investigation of the production of colony-stimulating factors revealed increased colony-stimulating activity (CSA) in the serum of normal and infected mice pre-treated with UTE. Moreover, stimulation of myelopoiesis and CSA occurred in a dose-dependent manner, a plateaux being reached with the dose of 100 mg/kg. Further studies to investigate the levels of factors such as IL-1 and IL-6 were undertaken. We observed increases in the levels of IL-1 and IL-6 in mice infected with *L. monocytogenes* and treated with 100 mg/kg of UTE. White blood cells (WBC) and differential counting were also performed, and our results demonstrated no significant changes in these data, when infected mice were pre-treated with 100 mg/kg of UTE. All together, our results suggest that UTE indirectly modulates immune activity and probably disengages *Listeria*-induced supression of these responses by inducing a higher reserve of myeloid progenitors in the bone marrow in consequence of biologically active cytokine release (CSFs, IL-1 and IL-6).

Lyme disease

Townsend Letter – **The Examiner of Alternative Medicine, July 2010**

In Vitro Effectiveness of Samento and Banderol Herbal Extracts on the Different Morphological Forms of Borrelia Burgdorferi

Akshita Datar, Navroop Kaur, Seema Patel, David F. Luecke, and Eva Sapi, PhD
Lyme Disease Research Group

University of New Haven

A tick-borne, multisystemic disease, Lyme borreliosis caused by the spirochete Borrelia burgdorferi has grown into a major public health problem during the last 10 years. The primary treatment for chronic Lyme disease is administration of various antibiotics. However, relapse often occurs when antibiotic treatment is discontinued. One possible explanation for this is that B. burgdorferi become resistant to antibiotic treatment, by converting from their vegetative spirochete form into different round bodies and/or into biofilmlike colonies. There is an urgent need to find novel therapeutic agents that can eliminate all these different morphologies of B. burgdorferi. In this study, two herbal extracts, Samento and Banderol, as well as doxycycline (one of the primary antibiotics for Lyme disease treatment) were tested for their in vitro effectiveness on several of the different morphological forms of B. burgdorferi (spirochetes, round bodies, and biofilmlike colonies) using fluorescent, darkfield microscopic, and BacLight viability staining methods. Our results demonstrated that both herbal agents, but not doxycycline, had very significant effects on all forms of B. burgdorferi, especially when used in combination, suggesting that herbal agents could provide an effective therapeutic approach for Lyme disease patients.

Osteoarthritis

Inflamm Res. 2001 Sep;50(9):442-8.

Efficacy and safety of freeze-dried cat's claw in osteoarthritis of the knee: mechanisms of action of the species *Uncaria guianensis*

J. Piscoya, Z. Rodriguez, S.A. Bustamante, N.N. Okuhama, M.J.S. Miller, M. Sandoval

The purpose of this investigation was to evaluate the ability of cat's claw, an Amazonian medicinal plant, to treat osteoarthritis of the knee, collect safety and tolerance information and compare the antioxidant, and anti-inflammatory actions of *Uncaria guianensis* and *Uncaria tomentosa* in vitro.¶*Materials and methods:* Forty-five patients with osteoarthritis of the knee were recruited, 30 were treated with freeze-dried *U. guianensis*, and 15 with placebo. Hematological parameters were assessed on entry and exit of the four-week trial. Pain, medical and subject assessment scores and adverse effects were collected at weeks 1, 2 and 4. The antioxidant and anti-inflammatory activity of the cat's claw species was determined by the α,α-diphenyl-β-picrylhydrazyl (DPPH) free radical scavenging method. Inhibition of TNFα and prostaglandin E_2 (PGE_2) production was determined in RAW 264.7 cells by ELISA.¶*Results:* Cat's claw had no deleterious effects on blood or liver function or other significant side-effects compared to placebo. Pain associated with activity, medical and patient assessment scores were all significantly reduced, with benefits occurring within the first week of therapy. Knee pain at rest or at night, and knee circumference were not significantly reduced by cat's claw during this brief trial. In vitro tests indicated that *U. guianensis* and *U. tomentosa* were equivalent at quenching DPPH radicals (EC_{50}, 13.6-21.7 jig/ml) as well as inhibiting TNFα production. However, the latter action was registered at much lower concentrations (EC_{50}, 10.2-10.9 ng/ml). Cat's claw (10 jig/ml) had no effect on basal PGE_2 production, but reduced LPS-induced PGE_2 release ($P < 0.05$), but at higher concentrations than that required for TNFα inhibition.¶*Conclusion:* Cat's claw is an effective treatment for osteoarthritis. The species, *U. guianensis* and *U. tomentosa* are equiactive. They are effective antioxidants, but their anti-inflammatory properties may result from their ability to inhibit TNFα and to a lesser extent PGE_2 production.

Renal Ischemia

Rev Esc Enferm USP. 2011 Mar;45(1):194-8.

[Uncaria tomentosa and acute ischemic kidney injury in rats].

[Article in Portuguese]

de Fátima Fernandes Vattimo M, da Silva NO.

The objective of this study was to evaluate the renoprotective effects of Uncaria Tomentosa (cat's claw) on ischemic acute kidney injury induced by renal clamping in rats. The hypoxia and hypoperfusion increase the production of reactive species already present in the inflammatory process. Results showed that the renal function evaluated by creatinine clearance, the urinary excretion of peroxides and malondealdehyde indexes demonstrated that UT induced renoprotection, probably related to its antioxidant activities.

PMID: 21445508

Rheumatoid Arthritis

The Journal of Rheumatology 2002: 29:4

Randomized Double Blind Trial of an Extract from the Pentacyclic Alkaloid-Chemotype of Uncaria tomentosa for the Treatment of Rheumatoid Arthritis

ERICH MUR, FRANK HARTIG, GÜNTHER EIBL, and MICHAEL SCHIRMER

Objective. To evaluate safety and critical efficacy of a plant extract from the pentacyclic chemotype of Uncaria tomentosa (UT) in patients with active rheumatoid arthritis (RA). Methods. Forty patients undergoing sulfasalazine or hydroxychloroquine treatment were enrolled in a randomized 52 week, 2 phase study. During the first phase (24 weeks, double blind, placebo controlled), patients were treated with UT extract or placebo. In the second phase (28 weeks) all patients received the plant extract.

Results. Twenty-four weeks of treatment with the UT extract resulted in a reduction of the number of painful joints compared to placebo (by 53.2% vs. 24.1%; p=0.044). Patients receiving the UT extract only during the second phase experienced a reduction in the number of painful (p=0.003) and swollen joints (p=0.007) and the Ritchie Index (p=0.004) compared to the values after 24 weeks of placebo. Only minor effects were observed.

Conclusion. This small preliminary study demonstrates relative safety and modest benefit to the tender joint count of a highly purified extract from the pentacyclic chemotype of UT in patients with active RA taking sulfasalazine or hydroxychloroquine. (J Rheumatol 2002;29:678-81)

SKIN CANCER

J Ethnopharmacol. 2017 Sep 27. pii: S0378-8741(17)32266-3. doi: 10.1016/j.jep.2017.09.031. [Epub ahead of print]

Anti-proliferative and pro-apoptotic effects of Uncaria tomentosa aqueous extract in squamous carcinoma cells.

Ciani F1, Tafuri S2, Troiano A3, Cimmino A4, Saveria Fioretto B3, Maria Guarino A3, Pollice A3, Vivo M3, Evidente A4, Carotenuto D5, Calabrò V6.

Author information

Abstract

Uncaria tomentosa (Willd.) DC. (Rubiacee), also known as uña de gato, is a plant that grows wild in the upper Amazon region of Peru and has been widely used in folk medicine to treat several health conditions including cancer. We have produced an aqueous extract from Uncaria tomentosa (UT-ex) and analyzed its effects on squamous carcinoma cells and immortalized HaCaT keratinocytes. Squamous cell carcinoma (SCC) is an uncontrolled growth of abnormal cells arising in the skin's squamous layer of epidermis. When detected at an early stage, SCCs are almost curable, however, if left untreated, they can penetrate the underlying tissue and become disfiguring. We have evaluated cell proliferation, apoptosis and the level of reactive oxygen species following UT-ex treatment. UT-ex affected cell cycle progression and reduced cell viability in a dose and time-dependent manner. From a mechanistic point of view, this delay in cell growth coincided with the increase of reactive oxygen species (ROS). Furthermore, PARP1 cleavage was associated to the reduction of Y-box binding protein 1 (YB-1) 36kDa, a nuclear prosurvival factor involved in DNA damage repair. These data indicate that UT-ex-induced cell death can be ascribed, at least in part, to its ability both to induce oxidative DNA damage and antagonize the mechanism of DNA repair relying upon YB-1 activity. They also show that non metastatic SCCs are more susceptible to UT-ex treatment than untransformed keratinocytes supporting the use of UT-ex for the treatment of precancerous and early forms of squamous cell carcinomas. Preliminary chemical investigation of UT-ex revealed the presence of hydrophilic low-medium molecular weight metabolites with anticancer potential towards squamous carcinoma cells.

Thyroid cancer

Anticancer Res. 2009 Nov; 29(11):4519-28.

Antiproliferative and pro-apoptotic effects of Uncaria tomentosa in human medullary thyroid carcinoma cells.

Rinner B, Li ZX, Haas H, Siegl V, Sturm S, Stuppner H, Pfragner R.

Medullary thyroid carcinoma (MTC), a rare calcitonin-producing tumor, is derived from parafollicular C-cells of the thyroid and is characterized by constitutive Bcl-2 overexpression. The tumor is relatively insensitive to radiation therapy as well as conventional chemotherapy. To date, the only curative treatment is the early and complete surgical removal of all neoplastic tissue. In this study, the antiproliferative and pro-apoptotic effects of fractions obtained from Uncaria tomentosa (Willd.) DC, commonly known as uña de gato or cat's claw were investigated. Cell growth of MTC cells as well as enzymatic activity of mitochondrial dehydrogenase was markedly inhibited after treatment with different fractions of the plant. Furthermore, there was an increase in the expressions of caspase-3 and -7 and poly(ADP-ribose) polymerase (PARP) fraction, while bcl-2 overexpression remained constant. In particular, the alkaloids isopterpodine and pteropodine of U. tomentosa exhibited a significant pro-apoptotic effect on MTC cells, whereas the alkaloid-poor fraction inhibited cell proliferation but did not show any pro-apoptotic effects. These promising results indicate the growth-restraining and apoptotic potential of plant extracts against neuroendocrine tumors, which may add to existing therapies for cancer.

PMID: 2003240

Tumors

Journal of Ethnopharmacology Volume 130, Issue 1, 6 July 2010, Pages 127–133
doi:10.1016/j.jep.2010.04.029

Antitumoral and antioxidant effects of a hydroalcoholic extract of cat's claw (*Uncaria tomentosa*) (Willd. Ex Roem. & Schult) in an *in vivo* carcinosarcoma model

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The present work intended to study the antitumoral and antioxidant effects of *Uncaria tomentosa* (UT) hydroalcoholic extract in the Walker-256 cancer model.

Walker-256 cells were subcutaneously inoculated in the pelvic limb of male Wistar rats. Daily gavage with UT extract (10, 50 or 100 mg kg^{-1}, Groups *UT*) or saline solution (Control, Group *C*) was subsequently initiated, until 14 days afterwards. For some parameters, a group of healthy rats (Baseline, Group *B*) was added. At the end of treatment the following parameters were evaluated: (a) tumor volume and mass; (b) plasmatic concentration of urea, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT) and lactate dehydrogenase (LDH); (c) hepatic and tumoral activity of catalase (CAT) and superoxide dismutase (SOD), as well as the rate of lipid peroxidation (LPO) and gluthatione (GSH); and (d) hepatic glutathione-S-transferase (GST) activity. The reactivity of UT extract with the stable free radical 2,2-diphenyl-1-picrylhydrazyl (DPPH) was assessed in parallel.

UT hydroalcoholic extract successfully reduced the tumor growth. In addition, treatment with UT reduced the activity of AST, which had been increased as a result of tumor inoculation, thus attempting to return it to normal levels. UT did not reverse the increase of LDH and GGT plasma levels, although all doses were remarkably effective in reducing urea plasma levels. An important *in vitro* free radical-scavenging activity was detected at various concentrations of UT extract (1–300 μg mL^{-1}). Treatment also resulted in increased CAT activity in liver, while decreasing it in tumor tissue. SOD activity was reduced in liver as well as in tumor, compared to Group *C*. No statistical significance concerning ALT, GST, LPO or GSH were observed.

This data represent an *in vivo* demonstration of both antitumoral and antioxidant effects of UT hydroalcoholic extract. The antineoplastic activity may result, partially at least, from the ability of UT to regulate redox and metabolism homeostasis.

J Altern Complement Med. 2015 Jan;21(1):22-30. doi: 10.1089/acm.2014.0127. Epub 2014 Dec 11.

Uncaria tomentosa (cat's claw) improves quality of life in patients with advanced solid tumors.

de Paula LC, Fonseca F, Perazzo F, Cruz FM, Cubero D, Trufelli DC, Martins SP, Santi PX, da Silva EA, Del Giglio A.

Cat's claw (Uncaria tomentosa) is a native Amazon plant that exhibits anti-inflammatory and antitumor properties. We wanted to assess its activity for symptom management of terminal cancer patients.

This prospective phase II study assessed the effects of a 100-mg dose of a dry extract of U. tomentosa three times per day in patients with advanced solid tumors who had no further therapeutic options and a life expectancy of at least 2 months. The European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ C30) and Functional Assessment of Chronic Illness Therapy - Fatigue questionnaires were used to assess the participants' quality of life, the Hospital Anxiety and Depression Scale questionnaire was used to assess anxiety and depression, and the Pittsburgh Sleep Quality Index was used to assess sleep quality. In addition, several biochemical and inflammatory parameters were analyzed.

Fifty-one volunteers were recruited. Their median age was 64 (range, 33-85) years, and 47% of patients were female. More than 65% of patients had scores on the Karnofsky Performance Scale of 80% or less. Treatment improved the patients' overall quality of life (p=0.0411) and social functioning (p=0.0341), as assessed by the EORTC QLQ C-30, and reduced fatigue (p=0.0496) according to the Chalder Fatigue Questionnaire. None of the biochemical or inflammatory parameters assessed (interleukin-1 and -6, C-reactive protein, tumor necrosis factor-α, erythrocyte sedimentation rate, and α-1-acid glycoprotein) changed significantly. No tumor response was detected according to the Response Evaluation Criteria In Solid Tumors; however, the disease stabilized for more than 8 months in four participants. The medication was well tolerated by most patients.

Use of cat's claw might be beneficial in patients with advanced cancer by improving their quality of life and reducing fatigue. The mechanism of action does not seem to be related to the anti-inflammatory properties of this plant.

PMID: 254953

J Ethnopharmacol. 2016 Dec 24;194:108-116. doi: 10.1016/j.jep.2016.08.051. Epub 2016 Aug 31.

Uncaria tomentosa extract alters the catabolism of adenine nucleotides and expression of ecto-5'-nucleotidase/CD73 and P2X7 and A1 receptors in the MDA-MB-231 cell line.

Santos KF[1], Gutierres JM[2], Pillat MM[3], Rissi VB[4], Santos Araújo MD[5], Bertol G[6], Gonçalves PB[4], Schetinger MR[2], Morsch VM[7].

Author information

Abstract

ETHOPHARMACOLOGICAL RELEVANCE:

Uncaria tomentosa (Willd.) DC. (Rubiaceae) (Ut), also known as cat's claw, is a woody liana widely spread throughout the Amazon rainforest of Central and South America, containing many chemical constituents such as oxindole alkaloids, which are responsible for various biological activities. Since ancient times, the indigenous people of Peru have used it as a bark infusion for the treatment of a wide range of health problems gastric ulcers, arthritis and rheumatism. Recently, Ut is distributed worldwide and used as an immunomodulatory and anti-inflammatory herbal remedy. Additionally, U. tomentosa also has antitumural activity. However, little is known about the action of U. tomentosa on the purinergic system mechanisms, which is involved in tumor progression.

AIM OF THE STUDY:

Considering the pharmacological properties of U. tomentosa, we sought to evaluate the hydroalcoholic extract U tomentosa is able to influence the purinergic system in breast cancer cells, MDA-MB-231. Through the activity and expression of ectonucleotidases (NTPDase - CD39; Ecto-5'-nucleotidase - CD73) and purinergic repceptores (P2X7 and A1).

MATERIALS AND METHODS:

A hydroalcoholic extract was prepared in two concentrations, 250 and 500µg/mL. (Ut250; Ut500). The effect of these concentrations on the activity and expression of ectonucleotidases, as well as on the density of purinergic receptors were investigated in MDA-MB-231 breast cancer cells. Cells were treated with the hydroalcoholic extract of Uncaria tomentosa and/or doxorubicin (Doxo 1µM; Ut250+Doxo; Ut500+Doxo) for 24h.

RESULTS:

Although the results were not significant for the hydrolysis of the ATP, they presented an increase in the ADP hydrolysis in the Ut500+Doxo group when compared to the control group. Additionally, the activity of 5'-nucleotidase was inhibited in all groups when compared with the untreated group of cells. Inhibition of the enzyme was more evident in groups with U. tomentosa per se. The expression of CD39 was increased in the Ut250 and Ut250+Doxo groups when compared to the control group. No changes were found in the CD73 expression. Furthermore, a reduction in the density of the P2X7 receptor in all treated groups was detected. On the other hand, the density of the A1 receptor increased in all groups compared to the control group, with the exception of the Ut500+Doxo group.

CONCLUSION:

Therefore, we conclude that hydroalcoholic extract of U. tomentosa may be responsible for the reduction of adenosine levels in the extracellular medium, which accelerates tumor progression. Interestingly, the dysregulation of A1 and P2X7 receptors in the MDA-MB-231 cells exacerbate the proliferation of this cells and U. tomentosa treatment may be stimulate the antitumor activity of adenosine A1 receptor and control the P2X7 effects. Our study demonstrates the significant participation of purinergic pathway in the regulation of MDA-MB-231 progression; additionally, U. tomentosa treatment alone or combined with chemotherapy may favor the action of doxorubicin.

MEDICINAL PROPERTIES OF SAMENTO

Adjunctive to Chemotherapy

J Ethnopharmacol. 2011 Sep 1;137(1):856-63. doi: 10.1016/j.jep.2011.07.011. Epub 2011 Jul 8.

Uncaria tomentosa stimulates the proliferation of myeloid progenitor cells.

Farias I, do Carmo Araújo M, Zimmermann ES, Dalmora SL, Benedetti AL, Alvarez-Silva M, Asbahr AC, Bertol G, Farias J, Schetinger MR.

The Asháninkas, indigenous people of Peru, use cat's claw (Uncaria tomentosa) to restore health. Uncaria tomentosa has antioxidant activity and works as an agent to repair DNA damage. It causes different effects on cell proliferation depending on the cell type involved; specifically, it can stimulate the proliferation of myeloid progenitors and cause apoptosis of neoplastic cells. Neutropenia is the most common collateral effect of chemotherapy. For patients undergoing cancer treatment, the administration of a drug that stimulates the proliferation of healthy hematopoietic tissue cells is very desirable. It is important to assess the acute effects of Uncaria tomentosa on granulocyte-macrophage colony-forming cells (CFU-GM) and in the recovery of neutrophils after chemotherapy-induced neutropenia, by establishing the correlation with filgrastim (rhG-CSF) treatment to evaluate its possible use in clinical oncology.

The in vivo assay was performed in ifosfamide-treated mice receiving oral doses of 5 and 15 mg of Uncaria tomentosa and intraperitoneal doses of 3 and 9 jig of filgrastim, respectively, for four days. Colony-forming cell (CFC) assays were performed with human hematopoietic stem/precursor cells (hHSPCs) obtained from umbilical cord blood (UCB).

Bioassays showed that treatment with Uncaria tomentosa significantly increased the neutrophil count, and a potency of 85.2% was calculated in relation to filgrastim at the corresponding doses tested. An in vitro CFC assay showed an increase in CFU-GM size and mixed colonies (CFU-GEMM) size at the final concentrations of 100 and 200 jig extract/mL.

At the tested doses, Uncaria tomentosa had a positive effect on myeloid progenitor number and is promising for use with chemotherapy to minimize the adverse effects of this treatment. These results support the belief of the Asháninkas, who have classified Uncaria tomentosa as a 'powerful plant'.

PMID: 21771655

Pharmacognosy Res. 2017 Jul-Sep;9(3):221-229. doi: 10.4103/pr.pr_83_16.

Uncaria tomentosa (Willd. ex Schult.) DC (Rubiaceae) Sensitizes THP-1 Cells to Radiation-induced Cell Death.

Allen L1,2, Buckner A1,2, Buckner CA1,2, Cano P2, Lafrenie RM1,2,3,4.

Abstract

BACKGROUND:

Uncaria tomentosa (Willd. ex Schult.) DC (Rubiaceae), known as Cat's Claw or Uña de gato, is a traditionally used medicinal plant native to Peru. Some studies have shown that U. tomentosa can act as an antiapoptotic agent and enhance DNA repair in chemotherapy-treated cells although others have shown that U. tomentosa enhanced apoptosis.

OBJECTIVE:

To determine if treatment with U. tomentosa can significantly enhance cell death in THP-1 cells exposed to ionizing radiation.

MATERIALS AND METHODS:

THP-1 monocyte-like cells were treated with ethanolic extracts of U. tomentosa in the presence or absence of bacterial lipopolysaccharide and then exposed to ionizing radiation. Cell proliferation was assessed by MTT and clonogenic assays and the effects on cell cycle measured by flow cytometry and immunoblotting. Changes in cell signaling were determined by immunoblotting and cytokine ELISA and activation of apoptosis measured by caspase activation and DNA fragmentation analysis.

RESULTS:

Treatment of THP-1 cells with U. tomentosa had a small effect on cell proliferation. However, when the U. tomentosa-pretreated cells were also subjected to 5-9 Gy ionizing radiation, they showed a significant decrease in cell proliferation and increased cellular apoptosis as measured by DNA fragmentation and caspase activation. Treatment with U. tomentosa also decreased the expression of Cyclin E and Cyclin B, key regulators of normal cell cycle progression, and decreased the phosphorylation of various stress-activated, cell survival proteins including p38, ERK, and SAP/JNK kinase.

CONCLUSIONS:

These results suggest that U. tomentosa could be useful in enhancing cell death following anticancer therapies including ionizing radiation.

SUMMARY:

Treatment of THP-1 cells with Uncaria tomentosa increases their susceptibility to X-rays. The combination of Uncaria tomentosa and X-ray exposure strongly inhibits cell signaling and promotes apoptosis. Abbreviations Used: LPS: Lipopolysaccharide, TNF: Tumor necrosis factor: IL-1, Interleukin-1: SDS: Sodium dodecylsulphate, TBS: Tris-buffered saline.

Antibacterial

Central-European Journal of Immunology 34(3):162-165 · December 2008

The effect of the bark water extract Uncaria tomentosa on the Pseudomonas aeruginosa infection in mice

Julita Nowakowska, Janusz Bany, Danuta Zdanowska, and Ewa Skopinska-Rozewska

The influence of water extract of Uncaria tomentosa (Willd.) DC. bark on Pseudomonas aeruginosa infection was studied. The preparation was obtained by extraction of bark Uncaria tomentosa with water (37°C, 24 h) and further fractionation. Inbred C57BL/6 mice 7-9 weeks old, ca 20 g of body mass, females, were fed water extract for 7 days (10, 20 or 100 mg/kg), or water (controls). On the 8th day some mice were infected i.p. with P. aeruginosa strain ATCC. Livers were excised after four hours, homogenized and the numbers of viable bacteria were estimated by plating. After administration of Uncaria water extract a significantly decreased number of bacteria in P. aeruginosa infected mice livers, as compared with the control group, was demonstrated. The inhibitory effect of dose 10 and 20 mg/kg was highly statistically significant but highest dose of extract (100 mg/kg) has not evoked important changes in the number of bacteria.

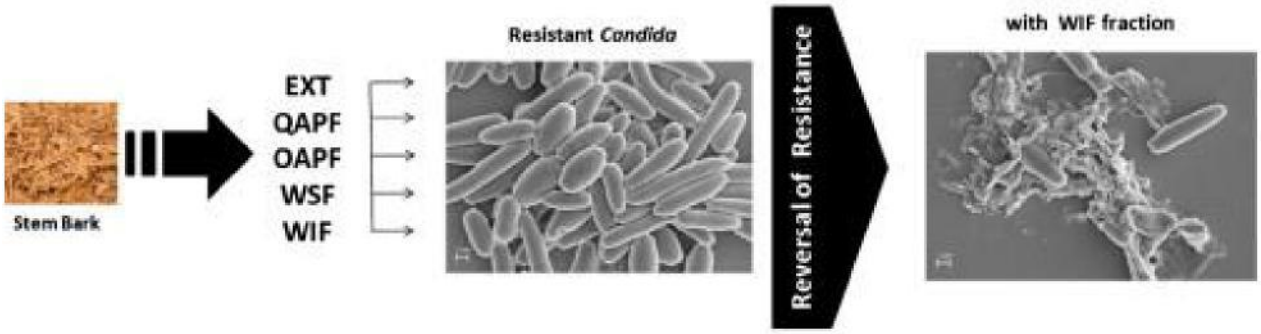
Antifungal

Industrial Crops and Products Volume 69, July 2015, Pages 7-14
doi:10.1016/j.indcrop.2015.01.033

Antifungal activity of *Uncaria tomentosa* (Willd.) D.C. against resistant non-*albicans Candida* isolates

Renata Cougo Moraes, Aline Jacobi Dalla Lana, Samuel Kaiser, Anderson Ramos Carvalho, Luis Flávio Souza de Oliveira, Alexandre Meneghello Fuentefria, George González Ortega,

This study investigated in vitro antifungal activity of the hydroethanolic extract (EXT), quinovic acid glycosides (QAPF), oxindole alkaloids (OAPF), water-soluble (WSF) and insoluble fractions of polyphenols (WIF) obtained from *Uncaria tomentosa* bark against non-*albicans Candida* resistant isolates. Cytotoxicity and genotoxicity of the major fractions were also assayed. Growth inhibition was assayed by the broth microdilution method according to the CLSI M27-A3 guideline. The most active fractions were evaluated regarding cell ultrastructure, sorbitol metabolism, and infrared (FT-IR) analysis of pseudomycelia of *C. krusei*, *C. glabrata* and *C. parapsilosis*. Fluconazole, terbinafine and anidulafungin were used as reference drugs. EXT and all fractions were able to inhibit non-*albicans C.* growth at concentrations ranging from 500 to 3.9 mg/L. Nonetheless, the WIF showed the best in vitro anti-*Candida* activity (3.9 mg/L– 15.62 mg/L). This fraction was composed mainly by high molecular mass polyphenols (70.8%) and, to a lesser extent, oxindole alkaloids (7.9%) and quinovic acid derivatives (7.8%). No significant cytotoxicity and genotoxicity was seen. As observed by scanning electron microscopy (SEM), yeasts treated with WIF presented morphological alterations and loss of integrity of the cell wall. The *U. tomentosa* water-insoluble fraction (WIF), composed mostly by high molecular mass polyphenols, showed significant antifungal activity in several non-*albicans* species, among them isolates resistant to terbinafine, fluconazole and anidulafungin. Noticeable microscopic and physicochemical changes in the cell wall indicated that it was the main target of this activity.



Pharm Biol. 2017 Dec;55(1):406-415.

In vitro synergism of a water insoluble fraction of Uncaria tomentosa combined with fluconazole and terbinafine against resistant non-Candida albicans isolates.

Moraes RC[1], Carvalho AR[1], Lana AJ[1], Kaiser S[1], Pippi B[2], Fuentefria AM[1,2], Ortega GG[1].

Abstract

CONTEXT:

Uncaria tomentosa D.C. (Rubiaceae) has several biological activities, including activity against resistant Candida strains. The synergistic interaction with terbinafine or fluconazole can be an important alternative to overcome this resistance.

OBJECTIVES:

The potential synergy between a water insoluble fraction (WIF) from Uncaria tomentosa bark and the antifungals terbinafine (TRB) and fluconazole (FLZ) against non-Candida albicans resistant strains was investigated.

MATERIALS AND METHODS:

TRB and FLZ, alone and combined with WIF, were tested by the checkerboard procedure using the micro-dilution technique against seven isolates of Candida glabrata and C. krusei. The molecular interactions occurring outside the cell wall were evaluated by scanning electron microscopy, Fourier transform infrared (FT-IR) and differential scanning calorimetry (DSC) analysis.

RESULTS:

The checkerboard inhibitory assay demonstrated synergy for WIF:TRB and WIF:FLZ combinations, respectively. The best synergistic cell damage was demonstrated unequivocally for the associations of WIF and TRB (1.95:4.0 µg/mL) and WIF and FLZ (1.95:8.0 µg/mL). The comparison of the FT-IR spectra of the antifungal alone, and in combination with WIF, allows recognizing clear differences in 3000, 1600, 1400, and 700-800 cm-1 bands. Additionally, modifications on TRB and FLZ thermograms were clearly noticed after their combination with WIF.

CONCLUSIONS:

DSC and infrared analysis demonstrated intermolecular interactions between WIF and either TRB or FLZ. Hence, quite likely the synergistic effect is related to interaction events occurring outside the cell wall between antifungal and cat's claw proanthocyanidins. A direct action on the cell wall is suggested, without connection with the ABC efflux pump mechanism.

Anti-inflammatory

Phytochemistry. 2005 Jan;66(1):89-98.

Antioxidant properties of proanthocyanidins of Uncaria tomentosa bark decoction: a mechanism for anti-inflammatory activity.

Gonçalves C, Dinis T, Batista MT.

Decoctions prepared from the bark of Uncaria tomentosa (cat's claw) are widely used in the traditional Peruvian medicine for the treatment of several diseases, in particular as a potent anti-inflammatory agent. Therefore, the main purpose of this study was to determine if the well-known anti-inflammatory activity of cat's claw decoction was related with its reactivity with the oxidant species generated in the inflammatory process and to establish a relationship between such antioxidant ability and its phenolic composition. We observed that the decoction prepared according to the traditional Peruvian medicine presented a potent radical scavenger activity, as suggested by its high capacity to reduce the free radical diphenylpicrylhydrazyl, and by its reaction with superoxide anion, peroxyl and hydroxyl radicals as well as with the oxidant species, hydrogen peroxide and hypochlorous acid. It also protected membrane lipids against peroxidation induced by the iron/ascorbate system, as evaluated by the formation of thiobarbituric acid-reactive substances (TBARs). The decoction phenolic profile was established by chromatographic analysis (HPLC/DAD and TLC) revealing essentially the presence of proanthocyanidins (oligomeric procyanidins) and phenolic acids, mainly caffeic acid. Thus, our results provide evidence for an antioxidant mechanism underlying the anti-inflammatory activity of cat's claw and support some of the biological effects of proanthocyanidins, more exactly its antioxidant and radical scavenging activities.

PMID: 15649515

Aliment Pharmacol Ther. 1998 Dec;12(12):1279-89.

Anti-inflammatory actions of cat's claw: the role of NF-kappaB.

Sandoval-Chacón M, Thompson JH, Zhang XJ, Liu X, Mannick EE, Sadowska-Krowicka H, Charbonnet RM, Clark DA, Miller MJ.

Uncaria tomentosa is a vine commonly known as cat's claw or 'uña de gato' (UG) and is used in traditional Peruvian medicine for the treatment of a wide range of health problems, particularly digestive complaints and arthritis.

The aim of this study was to determine the proposed anti-inflammatory properties of cat's claw. Specifically: (i) does a bark extract of cat's claw protect against oxidant-induced stress in vitro, and (ii) to determine if UG modifies transcriptionally regulated events.

Cell death was determined in two cell lines, RAW 264.7 and HT29 in response to peroxynitrite (PN, 300 microM). Gene expression of inducible nitric oxide synthase (iNOS) in HT29 cells, direct effects on nitric oxide and peroxynitrite levels, and activation of NF-kappaB in RAW 264.7 cells as influenced by UG were assessed. Chronic intestinal inflammation was induced in rats with indomethacin (7.5 mg/kg), with UG administered orally in the drinking water (5 mg/mL).

The administration of UG (100 microg/mL) attenuated ($P < 0.05$) peroxynitrite-induced apoptosis in HT29 (epithelial) and RAW 264.7 cells (macrophage). Cat's claw inhibited lipopolysaccharide-induced iNOS gene expression, nitrite formation, cell death and inhibited the activation of NF-kappaB. Cat's claw markedly attenuated indomethacin-enteritis as evident by reduced myeloperoxidase activity, morphometric damage and liver metallothionein expression.

Cat's claw protects cells against oxidative stress and negated the activation of NF-kappaB. These studies provide a mechanistic evidence for the widely held belief that cat's claw is an effective anti-inflammatory agent.

PMID: 9882039

J Ethnopharmacol. 2012 Oct 11;143(3):801-4. doi: 10.1016/j.jep.2012.07.015. Epub 2012 Jul 27.

Anti-inflammatory activity of Mitraphylline isolated from Uncaria tomentosa bark.

Rojas-Duran R[1], González-Aspajo G, Ruiz-Martel C, Bourdy G, Doroteo-Ortega VH, Alban-Castillo J, Robert G, Auberger P, Deharo E.

Abstract

ETHNOPHARMACOLOGICAL RELEVANCE: Uncaria tomentosa (Willd. ex Roem. & Schult.) DC. (Rubiaceae) is widely used by populations living in South America to treat many ailments associated with inflammatory disorders. Mitraphylline was shown to be the major pentacyclic oxindolic alkaloid present in the bark chloroformic extract of this plant. Its activity against cytokines involved in inflammation process was tested in a murine model in vivo.

MATERIALS AND METHODS: Mice received mitraphylline once a day for 3 days at 30 mg/kg/day by oral route. Then, they were subjected to bacterial lipopolysaccharide (LPS) endotoxin (15 mg/kg) and the LPS-induced production of 16 different cytokines was determined by Elisa multiplex. Control group received dexamethasone orally at 2mg/kg/day. Toxicity on K565 cells and murine peritoneal macrophages, in vitro, at doses up to 100 µM was monitored by XTT-colorimetric assay.

RESULTS AND CONCLUSIONS: For the first time mitraphylline was tested in vivo against a large range of cytokines that play a crucial role in inflammation. Mitraphylline inhibited around 50% of the release of interleukins 1α, 1β, 17, and TNF-α. This activity was similar to dexamethasone. It also reduced almost 40% of the production of interleukin 4 (IL-4) while the corticoid did not. Lastly it did not show any toxicity on K565 cells nor murine macrophages at doses up to 100 μM.

PMID: 22846434 DOI: 10.1016/j.jep.2012.07.015

Phytomedicine. 2016 Feb 15;23(2):141-8. doi: 10.1016/j.phymed.2015.12.015. Epub 2016 Jan 14.

Mitraphylline inhibits lipopolysaccharide-mediated activation of primary human neutrophils.

Montserrat-de la Paz S[1], Fernandez-Arche A[2], de la Puerta R[2], Quilez AM[2], Muriana FJ[3], Garcia-Gimenez MD[2], Bermudez B[4].

Abstract

BACKGROUND: Mitraphylline (MTP) is the major pentacyclic oxindolic alkaloid presented in Uncaria tomentosa. It has traditionally been used to treat disorders including arthritis, heart disease, cancer, and other inflammatory diseases. However, the specific role of MTP is still not clear, with more comprehensivestudies, our understanding of this ancient herbal medicine will continue growing.

HYPOTHESIS/PURPOSE: Some studies provided its ability to inhibit proinflamatory cytokines, such as TNF-α, through NF-κB-dependent mechanism. TNF-α primes neutrophils and modulates phagocytic and oxidative burst activities in inflammatory processes. Since, neutrophils represent the most abundant pool of leukocytes in human blood and play a crucial role in inflammation, we aimed to determine the ability of MTP to modulate neutrophil activation and differentially regulate inflammatory-related cytokines.

METHODS: To determine the mechanism of action of MTP, we investigated the effects on LPS-activated human primary neutrophils responses including activation surface markers by FACS and the expression of inflammatory cytokines, measured by real time PCR and ELISA.

RESULTS: Treatment with MTP reduced the LPS-dependent activation effects. Activated neutrophils (CD16(+)CD62L(-)) diminished after MTP administration. Moreover, proinflamatory cytokines (TNF-α, IL-6 or IL-8) expression and secretion were concomitantly reduced, similar to basal control conditions.

CONCLUSION: Taken together, our results demonstrate that MTP is able to elicit an anti-inflammatory response that modulates neutrophil activation contributing to the attenuation of inflammatory episodes. Further studies are need to characterize the mechanism by which MTP can affect this pathway that could provide a means to develop MTP as new candidate for inflammatory disease therapies.

Antigenotoxic and Antimutagenic

Basic Clin Pharmacol Toxicol. 2009 Mar;104(3):222-7. doi: 10.1111/j.1742-7843.2008.00366.x. Epub 2009 Jan 20.

Antigenotoxic, antioxidant and lymphocyte induction effects produced by pteropodine.

Paniagua-Pérez R, Madrigal-Bujaidar E, Molina-Jasso D, Reyes-Cadena S, Alvarez-González I, Sánchez-Chapul L, Pérez-Gallaga J.

Pteropodine is a heterohimbine-type oxindole alkaloid specifically isolated from 'Cat's claw' (Uncaria tomentosa), a plant that has shown cytostatic, anti-inflammatory and antimutagenic properties and is used in traditional medicine to cure a number of diseases. In this report, we studied the ability of pteropodine to decrease the rate of sister-chromatid exchanges and micronucleated polychromatic erythrocytes in mice administered doxorubicin. We also determined its capacity to induce lymphocyte production in mice as well as its free radical scavenging potential by applying the DPPH assay. We found pteropodine (100-600 mg/kg) to significantly decrease the frequency of sister-chromatid exchanges and micronucleated polychromatic erythrocytes in mice administered with 10 mg/kg of doxorubicin. Furthermore, we determined that pteropodine partially corrected bone marrow cytotoxicity induced by doxorubicin, as it showed an improvement in the rate of polychromatic erythrocytes. Besides, 600 mg/kg of pteropodine increased 25.8% of the production of lymphocytes over the control value along a 96-hr assay, and it exhibited a strong capacity to trap the DPPH-free radical (98.26% with 250 microg/ml). Our results establish that pteropodine is an effective antimutagen in the model used, and suggest that pteropodine deserves further research in the area of cell protective potential and its mechanism of action.

PMID: 19175366

Antimicrobial

Journal of Oral Science Vol. 52 (2010) No. 3 September P 473-476
http://doi.org/10.2334/josnusd.52.473

In vitro antimicrobial activity of phytotherapic *Uncaria tomentosa* against endodontic pathogens

Daniel R. Herrera, Lidia Y. Tay, Eluise C. Rezende, Vitoldo A. Kozlowski Jr, Elizabete B. dos Santos

Dentistry School, State University of Ponta Grossa (UEPG) Released 2010/09/24

The aim of this study was to evaluate the antimicrobial activity of *Uncaria tomentosa* (Willd.) DC (cat's claw) against *Enterococcus faecalis*, *Staphylococcus aureus*, and *Candida albicans*. Suspensions with 10^8 cells/ml of each microorganism were plated in triplicate on Mueller-Hinton agar. Wells in the agar were made and filled with 2% chlorhexidine (CHX) gel, 2% cat's claw (CC) gel, 2% CHX+CC, and 1% hydroxyethylcellulose (NAT) gel. Inhibition halos were measured after 24 h at 37°C and differences were analyzed using one-way ANOVA. The mean diameter of the microbial growth inhibition zones of 2% CHX+CC against the tested microbial strains ranged from 21.7 to 33.5 mm. This was the most effective substance against *E. faecalis* and *C. albicans*, followed by CHX and CC. Against *S. aureus*, CHX+CC, CHX, and CC showed similar antimicrobial activity ($P > 0.05$). The results indicate that all the investigated compounds had antimicrobial activity against microorganisms frequently found in infected root-filled teeth.

Antineoplastic

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Uncaria tomentosa Exerts Extensive Anti-Neoplastic Effects against the Walker-256 Tumour by Modulating Oxidative Stress and Not by Alkaloid Activity

Arturo Alejandro Dreifuss, Amanda Leite Bastos-Pereira, Isabella Aviles Fabossi, Francislaine Aparecida dos Reis Lívero, Aline Maria Stolf, Carlos Eduardo Alves de Souza, Liana de Oliveira Gomes, Rodrigo Polimeni Constantin, Aline Emmer Ferreira Furman, Regiane Lauriano Batista Strapasson, Simone Teixeira, Aleksander Roberto Zampronio, Marcelo Nicolás Muscará, Maria Elida Alves Stefanello, Alexandra Acco

This study aimed to compare the anti-neoplastic effects of an *Uncaria tomentosa* (UT) brute hydroethanolic (BHE) extract with those of two fractions derived from it. These fractions are choroformic ($CHCl_3$) and *n*-butanolic (BuOH), rich in pentacyclic oxindole alkaloids (POA) and antioxidant substances, respectively. The cancer model was the subcutaneous inoculation of Walker-256 tumour cells in the pelvic limb of male Wistar rat. Subsequently to the inoculation, gavage with BHE extract (50 $mg.kg^{-1}$) or its fractions (as per the yield of the fractioning process) or vehicle (Control) was performed during 14 days. Baseline values, corresponding to

individuals without tumour or treatment with UT, were also included. After treatment, tumour volume and mass, plasma biochemistry, oxidative stress in liver and tumour, TNF-α level in liver and tumour homogenates, and survival rates were analysed. Both the BHE extract and its BuOH fraction successfully reduced tumour weight and volume, and modulated anti-oxidant systems. The hepatic TNF-α level indicated a greater effect from the BHE extract as compared to its BuOH fraction. Importantly, both the BHE extract and its BuOH fraction increased the survival time of the tumour-bearing animals. Inversely, the $CHCl_3$ fraction was ineffective. These data represent an in vivo demonstration of the importance of the modulation of oxidative stress as part of the anti-neoplastic activity of UT, as well as constitute evidence of the lack of activity of isolated POAs in the primary tumour of this tumour lineage. These effects are possibly resulting from a synergic combination of substances, most of them with antioxidant properties.

Anticancer Res. 2009 Nov; 29(11):4519-28.

Antiproliferative and pro-apoptotic effects of Uncaria tomentosa in human medullary thyroid carcinoma cells.

Rinner B, Li ZX, Haas H, Siegl V, Sturm S, Stuppner H, Pfragner R.

Medullary thyroid carcinoma (MTC), a rare calcitonin-producing tumor, is derived from parafollicular C-cells of the thyroid and is characterized by constitutive Bcl-2 overexpression.

The tumor is relatively insensitive to radiation therapy as well as conventional chemotherapy. To date, the only curative treatment is the early and complete surgical removal of all neoplastic tissue. In this study, the antiproliferative and pro-apoptotic effects of fractions obtained from Uncaria tomentosa (Willd.) DC, commonly known as uña de gato or cat's claw were investigated. Cell growth of MTC cells as well as enzymatic activity of mitochondrial dehydrogenase was markedly inhibited after treatment with different fractions of the plant. Furthermore, there was an increase in the expressions of caspase-3 and -7 and poly(ADP-ribose) polymerase (PARP) fraction, while bcl-2 overexpression remained constant. In particular, the alkaloids isopterpodine and pteropodine of U. tomentosa exhibited a significant pro-apoptotic effect on MTC cells, whereas the alkaloid-poor fraction inhibited cell proliferation but did not show any pro-apoptotic effects. These promising results indicate the growth-restraining and apoptotic potential of plant extracts against neuroendocrine tumors, which may add to existing therapies for cancer.

PMID: 2003240

Antioxidant

Biotechnology and Bioengineering Volume 98, Issue 1, 1 September 2007 Pages 230–238
DOI: 10.1002/bit.21384

Hydrodynamic stress induces monoterpenoid oxindole alkaloid accumulation by *Uncaria tomentosa* (Willd) D. C. cell suspension cultures via oxidative burst

Trejo-Tapia, G., et al.

Uncaria tomentosa cell suspension cultures were grown in a 2-L stirred tank bioreactor operating at a shear rate γavg -86s^{-1}. The cultures showed an early monophasic oxidative burst measured as H_2O_2 production (2.15 µmol H_2O_2 g_{-1} dw). This response was followed by a transient production of monoterpenoid oxindole alkaloids (178 ± 40 µg L^{-1} at 24 h). At the stationary phase (144 h), the increase of the shear rate γavg up to 150 s^{-1} and/or oxygen tension up to 85% generated H_2O_2, restoring oxindole alkaloid production. *U. tomentosa* cells cultured in Erlenmeyer flasks also exhibited the monophasic oxidative burst but the H_2O_2 production was 16-fold lower and the alkaloids were not detected. These cells exposed to H_2O_2 generated in situ produced oxindole alkaloids reaching a maximum of 234 ± 40 µg L^{-1}. A positive correlation was observed between the oxindole alkaloid production and the endogenous H_2O_2 level. On the other hand, addition of 1 µM diphenyleneiodonium (NAD(P)H oxidase inhibitor) or 10 µM sodium azide (peroxidases inhibitor) reduced both H_2O_2 production and oxindole alkaloids build up, suggesting that these enzymes might play a role in the oxidative burst induced by the hydrodynamic stress.

Bioorganic & Medicinal Chemistry Volume 17, Issue 5, 1 March 2009, Pages 1876–1883
doi:10.1016/j.bmc.2009.01.045

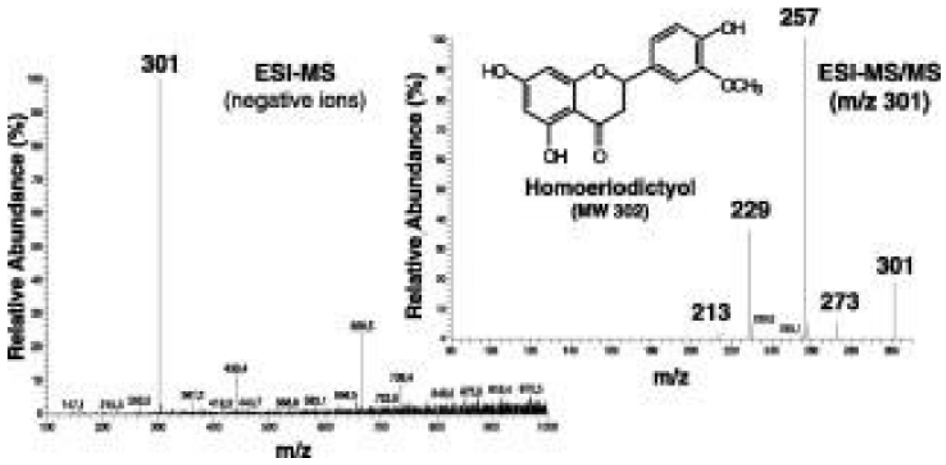
Plant extracts with anti-inflammatory properties—A new approach for characterization of their bioactive compounds and establishment of structure–antioxidant activity relationships

Sónia Amaral, Lurdes Mira, J.M.F. Nogueira, Alda Pereira da Silva, M. Helena Florêncio′

Geranium robertianum L. (Geraniacea) and *Uncaria tomentosa* (Willd.) DC. (Rubiaceae) plant extracts, frequently used in traditional medicine for treatment of inflammatory and cancer diseases, were studied to identify potential bioactive compounds that may justify their therapeutic use and their underlying mechanisms of action. Since some of the pharmacological

properties of these plant extracts may be linked to their antioxidant potential, the antioxidant activity, in relation to free radical scavenging, was measured by the ABTS/HRP and DPPH assays, presenting *U. tomentosa* the higher activity. The antioxidant activity was also evaluated by scavenging of HOCl, the major strong oxidant produced by neutrophils and a potent pro-inflammatory agent. *U. tomentosa* was found to be a better protector against HOCl, which may justify its effectiveness against inflammatory diseases. SPE/LC-DAD was used for separation/purification purposes and ESI-MS/MS for identification/characterization of the major non-volatile components, mainly flavonoids and phenolic acids. The ESI-MS/MS methodology proposed can be used as a model procedure for identification/characterization of unknowns without the prerequisite for standard compounds analysis. The ESI-MS/MS data obtained were consistent with the antioxidant activity results and structure–activity relationships for the compounds identified were discussed.

The ESI-MS/MS methodology proposed can be used as a model procedure for identification and characterization of unknowns without the prerequisite for standard compounds analysis.



Journal of Ethnopharmacology Volume 96, Issue 3, 15 January 2005, Pages 355–364
doi:10.1016/j.jep.2004.06.039

An *Uncaria tomentosa* (cat's claw) extract protects mice against ozone-induced lung inflammation

Francisco J. Cisneros, Manuel Jayo, Linda Niedzielac

Ozone (O_3) inhalation has been associated with respiratory tract inflammation and lung functional alterations. To characterize the O_3-induced lung inflammation in mice, the effective dose and exposure time were determined. Total protein levels of bronchoalveolar lavage fluid

(BALF), cytological smears, and lung histopathology and morphometry were used to assess and measure the degree of pulmonary inflammation in the mouse model. Ozone inhalation caused acute pneumonitis that was characterized by a high number of infiltrating neutrophils (PMNs) immediately after exposure and increased levels of protein in BALF in mice killed 8 h after O_3 exposure. The anti-inflammatory properties of *Uncaria tomentosa* (UT) have been documented previously. To evaluate the anti-inflammatory effects of UT, male mice were given an UT extract for 8 days, exposed to O_3, and killed 0 or 8 h after O_3 exposure. When compared to untreated controls, UT-treated mice had significantly ($p < 0.05$) lower levels of protein in BALF, lower degree of epithelial necrosis, higher number of intact epithelial cell nuclei in bronchial wall, and decreased number of PMNs in the bronchiolar lumen. Therefore, UT extract appeared to prevent O_3-induced respiratory inflammation in male mice.

Food Chem Toxicol. 2012 Jun;50(6):2123-7. doi: 10.1016/j.fct.2012.02.099. Epub 2012 Mar 9.

Uncaria tomentosa extracts protect human erythrocyte catalase against damage induced by 2,4-D-Na and its metabolites.

Bukowska B, Bors M, Gulewicz K, Koter-Michalak M.

The effect of ethanolic and aqueous extracts from leaves and bark of Uncaria tomentosa was studied, with particular attention to catalase activity (CAT - EC. 1.11.1.6). We observed that all tested extracts, at a concentration of 250 µg/mL were not toxic to erythrocyte catalase because they did not decreased its activity. Additionally, we investigated the protective effect of extracts on changes in CAT activity in the erythrocytes incubated with sodium salt of 2,4-dichlorophenoxyacetic acid (2,4-D-Na) and its metabolites i.e., 2,4-dichlorophenol (2,4-DCP) and catechol. Previous investigations showed that these chemicals decreased activity of erythrocyte catalase (Bukowska et al., 2000; Bukowska and Kowalska, 2004). The erythrocytes were divided into two portions. The first portion was incubated for 1 and 5h at 37°C with 2,4-D-Na, 2,4-DCP and catechol, and second portion was preincubated with extracts for 10 min and then incubated with xenobiotics for 1 and 5h. CAT activity was measured in the first and second portion of the erythrocytes. We found a protective effect of the extracts from U. tomentosa on the activity of catalase incubated with xenobiotics studied. Probably, phenolic compounds contained in U. tomentosa scavenged free radicals, and therefore protected active center (containing -SH groups) of catalase.

PMID: 22426

Central Nervous System (CNS) Support

European Journal of Pharmacology Volume 444, Issues 1–2, 24 May 2002, Pages 39–45

Pteropodine and isopteropodine positively modulate the function of rat muscarinic M_1 and 5-HT_2 receptors expressed in *Xenopus* oocyte

Tai-Hyun Kang, Kinzo Matsumoto, Michihisa Tohda, Yukihisa Murakami, Hiromitsu Takayama, Mariko Kitajima, Norio Aimi, Hiroshi Watanabe

Pteropodine and isopteropodine are heteroyohimbine-type oxindole alkaloid components of *Uncaria tomentosa* (Willd.) DC, a Peruvian medicinal plant known as cat's claw. In this study, the effects of these alkaloids on the function of Ca^{2+}-activated Cl^- currents evoked by stimulation of G protein-coupled muscarinic M_1 acetylcholine and 5-HT_2 receptors were studied in *Xenopus* oocytes in which rat cortex total RNA was translated. Pteropodine and isopteropodine (1–30 μM) failed to induce membrane current by themselves. However, these alkaloids markedly enhanced the current responses evoked by both acetylcholine and 5-hydroxyhyptamine (5-HT) in a concentration-dependent and reversible manner with the maximal effects at 30 μM. Pteropodine and isopteropodine produced 2.7- and 3.3-fold increases in the acetylcholine response with EC_{50} values of 9.52 and 9.92 μM, respectively, and 2.4- and 2.5-fold increases in the 5-HT response with EC_{50} values of 13.5 and 14.5 μM, respectively. In contrast, in oocytes injected with total RNA from the rat cerebellum or spinal cord, neither alkaloid had an effect on the metabotropic current responses mediated by glutamate receptor$_{1 \text{ and } 5}$ ($mGlu_{1/5}$) receptors or ionotropic responses mediated by *N*-methyl-d-aspartate, kainic acid or glycine. Pteropodine and isopteropodine (10 μM) significantly reduced the EC_{50} values of acetylcholine and 5-HT that elicited current responses, but had no effect on the maximal current responses elicited by acetylcholine and 5-HT. On the other hand, mitraphylline, a stereoisomer of pteropodine, failed to modulate acetylcholine- and 5-HT-induced responses. These results suggest that pteropodine and isopteropodine act as positive modulators of muscarinic M_1 and 5-HT_2 receptors.

Cytoprotective

Free Radical Biology and Medicine Volume 29, Issue 1, 1 July 2000, Pages 71–78
doi:10.1016/S0891-5849(00)00327-0

Cat's claw inhibits TNFα production and scavenges free radicals: role in cytoprotection

Manuel Sandoval, Randi M Charbonnet, Nataly N Okuhama, Jarod Roberts, Zdenka Krenova, Ann Marie Trentacosti, Mark J.S Miller

Cat's claw (*Uncaria tomentosa*) is a medicinal plant from the Amazon River basin that is widely used for inflammatory disorders and was previously described as an inhibitor of NF-κB. Cat's claw was prepared as a decoction (water extraction) of micropulverized bark with and without concentration by freeze-drying. Murine macrophages (RAW 264.7 cells) were used in cytotoxicity assays (trypan blue exclusion) in response to the free radical 1,1-diphenyl-2-picrilhydrazyl (DPPH, 0.3 jiM) and ultraviolet light (UV) light. TNFα production was induced by lipopolysaccharide (LPS 0.5 jig/ml). Cat's claw was an effective scavenger of DPPH; the EC_{50} value for freeze-dried concentrates was significantly less than micropulverized (18 vs. 150 jig/ml, $p < .05$). Cat's claw (10 jig/ml freeze-dried) was fully protective against DPPH and UV irradiation-induced cytotoxicity. LPS increased TNFα media levels from 3 to 97 ng/ml. Cat's claw suppressed TNFα production by approximately 65–85% ($p < .01$) but at concentrations considerably lower than its antioxidant activity: freeze-dried EC_{50} = 1.2 ng/ml, micropulverized EC_{50} = 28 ng/ml. In conclusion, cat's claw is an effective antioxidant, but perhaps more importantly a remarkably potent inhibitor of TNFα production. The primary mechanism for cat's claw anti-inflammatory actions appears to be immunomodulation via suppression of TNFα synthesis.

Immunomodulating

Phytother Res. 2011 Aug;25(8):1229-35. doi: 10.1002/ptr.3549. Epub 2011 Jun 8.

Uncaria tomentosa aqueous-ethanol extract triggers an immunomodulation toward a Th2 cytokine profile.

Domingues A, Sartori A, Valente LM, Golim MA, Siani AC, Viero RM.

Uncaria tomentosa (Willd.) DC (Rubiaceae) is a large woody vine that is native to the Amazon and Central American rainforests and is used widely in traditional medicine for its immunomodulatory and anti-inflammatory activities. The present work used in vivo immunotoxic and in vitro immunomodulatory experiments to investigate the effects of a pentacyclic oxindole alkaloid extract from U. tomentosa bark on lymphocyte phenotype, Th1/Th2 cytokine production, cellular proliferation and cytotoxicity. For the in vivo immunotoxicity testing, BALB/c male mice were treated once a day with 125, 500 or 1250 mg/kg of U. tomentosa extract for 28 days. For the in vitro protocol, lymphocytes were cultured with 10-500 μg/mg of the extract for 48 h. The extract increased the cellularity of splenic white pulp and the thymic medulla and increased the number of T helper lymphocytes and B lymphocytes. Also, a large stimulatory effect on lymphocyte viability was observed. However, mitogen-induced T lymphocyte proliferation was significantly inhibited at higher concentrations of U. tomentosa extract. Furthermore, an immunological polarization toward a Th2 cytokine profile was observed. These results suggest that the U. tomentosa aqueous-ethanol extract was not immunotoxic to mice and was able to modulate distinct patterns of the immune system in a dose-dependent manner.

PMID: 21656603

Rev Peru Med Exp Salud Publica. 2015 Oct;32(4):633-42.

[Lymphocyte subsets, dendritic cells and cytokine profiles in mice with melanoma treated with Uncaria tomentosa].

Lozada-Requena I[1], Núñez C[1], Alvárez Y[1], Kahn L[1], Aguilar J[1].

Abstract

OBJECTIVES: To evaluate the immunomodulatory effect on lymphocyte subsets, dendritic cells (DC), Th1 / Th2 / Th17 and inflammatory cytokines on systemic level and/or in the tumor microenvironment of mice with or without melanoma.

MATERIALS AND METHODS: Peripheral blood and/or primary tumors samples were obtained of mice with B16 melanoma treated or not with a hydroalcoholic extract of Uncaria tomentosa (UT)

with 5.03% of pentacyclic oxindole alkaloids (UT-POA) obtained from the bark of the plant. All cell assays and cytokine measurements were performed by flow cytometry.

RESULTS: UT-POA systemically increased CD4/CD8a relation while cell activation was inversely proportional; increased the proportion of DCm; induced a pro-inflammatory Th1 profile and reduced Th17 response. TNF-α and IL-17A positively and negatively correlated with CD4/CD8a relation.

CONCLUSIONS: The increase of Th1 (TNF-α) may result in the increase of CD4 or M1 macrophage activation. Although UT-POA shows increased DCm, is not dose-dependent. Th17(IL-17A) decreased can support the function of CD8a lymphocytes. UT-POA shows better systemic immunomodulatory effects than intratumoral.

Rev Peru Med Exp Salud Publica. 2015 Oct;32(4):643-51.

[Immunomodulation of Uncaria tomentosa over dendritic cells, il-12 and profile TH1/TH2/TH17 in breast cancer].

Núñez C[1], Lozada-Requena I[1], Ysmodes T[1], Zegarra D[1], Saldaña F[1], Aguilar J[1].

Abstract

Objectives. This study aimed to research the in vitro immunomodulatory effects of an Uncaria tomentosa hydroalcoholic extract standardized (5.03%, pentacyclic oxindole alkaloids) (UT-POA) on the immunophenotype of dendritic cells (DC) subsets, Th1, Th2, Th17 and IL-12 cytokines from patients with stage II breast cancer (BCII) and healthy women (H).

MATERIALS AND METHODS: Blood of 11 H and 7 BCII was obtained, PBMC were isolated and cultured for 2h with/without various concentrations of UT-POA and stimulated or not with LPS for 24h. PBMC were labeled with specific antibodies for DC and in the supernatant we measured Th1/Th2/Th17 cytokines, both by flow cytometry. Furthermore IL-12 was measured by ELISA.

RESULTS: UT-POA did not alter DC or accessory molecules expression in BCII. However, H exhibited a decrease in the percentage of mDC (myeloid DC) and an increase in HLA-DR and CD86 expression at 1000 µg/mL. IL-12 secretion was modified only in the H group, increasing p70 subunit and decreasing p40 subunit. UT-POA increased Th1 (IFN-γ and IL-2), Th2 (IL-4) and Th17 (IL-17) secretion in both groups.

CONCLUSIONS: UT-POA increased the production of cytokines related with anti-tumoral response at concentrations of 500-1000 µg/mL. This positive effect should be evaluated not only

systemically but also in the tumor microenvironment in further studies. UT-POA may be a useful phytochemical in chemoprevention and in the alternative use in cancer therapies.

J Ethnopharmacol. 2015 Jul 21;170:128-35. doi: 10.1016/j.jep.2015.05.002. Epub 2015 May 11.

Pharmacological effects of mitraphylline from Uncaria tomentosa in primary human monocytes: Skew toward M2 macrophages.

Montserrat-de la Paz S[1], de la Puerta R[2], Fernandez-Arche A[2], Quilez AM[2], Muriana FJ[3], Garcia-Gimenez MD[2], Bermudez B[4].

Abstract

ETHNOPHARMACOLOGICAL RELEVANCE: Uncaria tomentosa (Willdenow ex Roemer & Schultes) DC. (Rubiaceae) is a Peruvian thorny liana, commonly known as "cat's claw", and traditionally used in folk medicine to deal with several inflammatory diseases. Mitraphylline (MTP) is the most abundant pentacyclic oxindolic alkaloid (POA) from U. Tomentosa and has been reported to modify the inflammatory response. Herein, we have sought to identify the mechanisms underlying this modulatory effect of MTP on primary human monocytes and its ability to regulate differentiation processes on human primary monocyte and monocyte-derived macrophages.

MATERIAL AND METHODS: In vitro studies with human primary monocytes and monocyte-derived macrophages were performed. Monocytes and M0 macrophages were exposed to MTP (25μM) and LPS (100ng/mL). M0 macrophages were polarized to M1 and M2 phenotypes in the absence or presence of MTP. The activation state of monocytes/macrophages was assessed by flow cytometry, gene expression and protein analysis of different specific markers.

RESULTS: In human primary monocytes, the incubation of MTP for 24h reduced the number of classical (CD14(++)CD16(-)) and intermediate (CD14(++)CD16(+)) subsets when compared to untreated or LPS-treated cells. MTP also reduced the chemotactic capacity of human primary monocytes. In addition, MTP promoted the polarization of M0 macrophages toward an anti-inflammatory M2 phenotype, the abrogation of the release of pro-inflammatory cytokines such as TNFα, IL-6 or IL-1β, as well as the restoration of markers for M2 macrophages in LPS-treated M1 macrophages.

CONCLUSIONS: Our results suggest that MTP may be a key modulator for regulating the plasticity of monocytes/macrophages and the attenuation of the inflammatory response.

Int Immunopharmacol. 2008 Mar;8(3):468-76. doi: 10.1016/j.intimp.2007.11.010. Epub 2007 Dec 26.

Immunomodulating and antiviral activities of Uncaria tomentosa on human monocytes infected with Dengue Virus-2.

Reis SR[1], Valente LM, Sampaio AL, Siani AC, Gandini M, Azeredo EL, D'Avila LA, Mazzei JL, Henriques Md, Kubelka CF.

Abstract

Uncaria tomentosa (Willd.) DC., a large woody vine native to the Amazon and Central American rainforests has been used medicinally by indigenous peoples since ancient times and has scientifically proven immunomodulating, anti-inflammatory, cytotoxic and antioxidant activities. Several inflammatory mediators that are implicated in vascular permeability and shock are produced after Dengue Virus (DENV) infection by monocytes, the primary targets for virus replication. Here we assessed the immunoregulatory and antiviral activities from U. tomentosa-derived samples, which were tested in an in vitro DENV infection model. DENV-2 infected human monocytes were incubated with U. tomentosa hydro-alcoholic extract or either its pentacyclic oxindole alkaloid-enriched or non-alkaloid fractions. The antiviral activity was determined by viral antigen (DENV-Ag) detection in monocytes by flow cytometry. Our results demonstrated an in vitro inhibitory activity by both extract and alkaloidal fraction, reducing DENV-Ag+ cell rates in treated monocytes. A multiple microbead immunoassay was applied for cytokine determination (TNF-alpha, IFN-alpha, IL-6 and IL-10) in infected monocyte culture supernatants. The alkaloidal fraction induced a strong immunomodulation: TNF-alpha and IFN-alpha levels were significantly decreased and there was a tendency towards IL-10 modulation. We conclude that the alkaloidal fraction was the most effective in reducing monocyte infection rates and cytokine levels. The antiviral and immunomodulating in vitro effects from U. tomentosa pentacyclic oxindole alkaloids displayed novel properties regarding therapeutic procedures in Dengue Fever and might be further investigated as a promising candidate for clinical application.

Eur J Pharmacol. 2002 May 24;444(1-2):39-45.

Pteropodine and isopteropodine positively modulate the function of rat muscarinic M(1) and 5-HT(2) receptors expressed in Xenopus oocyte.

Kang TH[1], Matsumoto K, Tohda M, Murakami Y, Takayama H, Kitajima M, Aimi N, Watanabe H.

Abstract

Pteropodine and isopteropodine are heteroyohimbine-type oxindole alkaloid components of Uncaria tomentosa (Willd.) DC, a Peruvian medicinal plant known as cat's claw. In this study, the effects of these alkaloids on the function of Ca(2+)-activated Cl(-) currents evoked by stimulation of G protein-coupled muscarinic M(1) acetylcholine and 5-HT(2) receptors were studied in Xenopus oocytes in which rat cortex total RNA was translated. Pteropodine and isopteropodine (1-30 microM) failed to induce membrane current by themselves. However, these alkaloids markedly enhanced the current responses evoked by both acetylcholine and 5-hydroxyhyptamine (5-HT) in a concentration-dependent and reversible manner with the maximal effects at 30 microM. Pteropodine and isopteropodine produced 2.7- and 3.3-fold increases in the acetylcholine response with EC(50) values of 9.52 and 9.92 microM, respectively, and 2.4- and 2.5-fold increases in the 5-HT response with EC(50) values of 13.5 and 14.5 microM, respectively. In contrast, in oocytes injected with total RNA from the rat cerebellum or spinal cord, neither alkaloid had an effect on the metabotropic current responses mediated by glutamate receptor(1 and 5) (mGlu(1/5)) receptors or ionotropic responses mediated by N-methyl-D-aspartate, kainic acid or glycine. Pteropodine and isopteropodine (10 microM) significantly reduced the EC(50) values of acetylcholine and 5-HT that elicited current responses, but had no effect on the maximal current responses elicited by acetylcholine and 5-HT. On the other hand, mitraphylline, a stereoisomer of pteropodine, failed to modulate acetylcholine- and 5-HT-induced responses. These results suggest that pteropodine and isopteropodine act as positive modulators of muscarinic M(1) and 5-HT(2) receptors.