Uncaria

Uncaria tomentosa

Nome botanico

Uncaria tomentosa (Willd. ex Schult.) DC. *(Rubiaceae)*

Parti usate

Corteccia.

Componenti principali

Alcaloidi ossindolici pentaciclici. Glicosidi dell'acido quinovico. Triterpeni poliidrossilati. Steroli.

Attività farmacologica

Azione immunostimolante. Azione antireumatica.

Impiego clinico

Prevenzione e terapia delle malattie infettive. Artrite reumatoide e altre malattie reumatiche articolari.

Controindicazioni

Non assumere la droga in gravidanza e durante l'allattamento.

Avvertenze e speciali precauzioni d'uso

Nessuna nota.

Interazioni

Nessuna nota.

Effetti indesiderati

Nessuno degno di nota.

Note Bibliografiche

Composizione

I composti più interessanti presenti nella corteccia di *Uncaria tomentosa*[1] sono alcuni alcaloidi ossindolici pentaciclici: pteropodina, isopteropodina, unacarina F, speciofillina, rincofillina, isorincofillina, mitrafillina, isomitrafillina, irsutina, diidrocorinanteina. Inoltre composti polifenolici (epitechina e 4 procianidine dimeriche)[2]; glicosidi dell'acido quinovico (sono stati isolati almeno 5 derivati diversi dell'acido quinovico con il sito di attacco della porzione glicosidica su carboni diversi della molecola pentaciclica)[3,4]; triterpeni poliidrossilati[5]; flavonoidi; steroli (beta-sitosterolo, stigmasterolo e campesterolo); tannini; mucillagini[6].

Attività biologiche ed impieghi clinici descritti in letteratura

Le attività biologiche e gli impieghi clinici descritti per il fitocomplesso di *Uncaria tomentosa* sono:

Medicina popolare. La scoperta e lo studio delle attività biologiche della *Uncaria tomentosa* risalgono alla prima metà degli anni '80, per opera di un gruppo di ricercatori Italiani[7]. Tradizionalmente l'Uncaria viene utilizzata dalle popolazioni amazzoniche, in quanto sembra possedere proprietà antinfiammatorie, immunostimolanti, cardioprotettive, antivirale e recentemente la ricerca si è indirizzata verso lo studio delle sue possibili attività antineoplastiche[8].

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1 *Montoro P, Carbone V, Quiroz Jde D, De Simone F, Pizza C. Identification and quantification of components in extracts of Uncaria tomentosa by HPLC-ES/MS. Phytochem Anal. 2004 Jan-Feb;15(1):55-64*

2 *Wirth C, Wagner H. Pharmacologically active procyanidines from the bark of Uncaria tomentosa. Phytomedicine 1997; 4: 265-266.*

3 "Bioassay-directed fractionation of the anti-inflammatory extracts of Uncaria tomentosa, using the carrageenan induced edema in rat paw, has led to the isolation of a new quinovic acid glycoside 7 as one of the active principles. Furthermore, a new triterpene 8 was isolated as its methyl ester. The structures were elucidated by spectral and chemical studies." *(Aquino R, De Feo V, De Simone F, Pizza C, Cirino G. Plant metabolites. New compounds and anti-inflammatory activity of Uncaria tomentosa. J Nat Prod 1991; 54: 453-9).*

4 "From the bark of Uncaria guianensis, two new quinovic acid glycosides, quinovic acid 3 β-O-β-D quinovopyranoside and quinovic acid 3 β-O-β-D-fucopyranosyl-(27-1)-β-D-glucopyranosylester, have been isolated, in addition to known quinovic acid 3 β-O-[β-D-glucopyranosyl-(1-3)-β-D-fucopyranosyl]-(27-1)- β-D glucopyranosylester and quinovic acid 3 β-O-β-D-fucopyranoside. Their structures were elucidated by spectral and chemical studies." *(Yepez AM, de Ugaz OL, Alvarez CM, De Feo V, Aquino R, De Simone F, Pizza C. Quinovic acid glycosides from Uncaria guianensis. Phytochemistry 1991; 30: 1635-7).*

5 *Aquino R, De Simone F, Vincieri FF, Pizza C, Gacs-Baitz E. New polyhydroxylated triterpenes from Uncaria tomentosa. J Nat Prod 1990; 53: 559-64.*

6 *Tirillini B. Fingerprints of Uncaria Tomentosa leaf, stem and root bark decoction. Phytotherapy Res 1996; 10:567-568.*

7 *Bianchi A. Uncaria tomentosa: profilo botanico, fitochimico e farmacologico. Erboristeria Domani, Marzo 1996, pag. 105 e seguenti.*

8 *Castleman M. 2007. Le erbe curative Guida completa alle proprietà terapeutiche dei farmaci naturali – seconda edizione – Tecniche Nuove ed. italiana.*

Attività immunostimolante. La più importante attività per l'Uncaria è quella di stimolare le difese immunitarie: nel corso degli anni le ricerche nel campo farmacologico hanno dimostrato che gli alcaloidi isolati dalla *Uncaria tomentosa* sono in grado di stimolare la fagocitosi e la reattività delle cellule immunitarie nei confronti di differenti antigeni, come virus e batteri. Questa attività nell'uomo è stata verificata in una sperimentazione clinica in doppio cieco in 20 volontari sani, trattati per 8 settimane con placebo o con un estratto di *Uncaria tomentosa*, alla posologia equivalente di 2.7 mg/die di alcaloidi ossindolici. I risultati hanno evidenziato nei soggetti trattati con il fitocomplesso, una marcata stimolazione delle difese immunitarie ed un incremento statisticamente significativo rispetto al placebo, di tutti i parametri utilizzati per valutare la reattività delle cellule immunocompetenti. Inoltre, il trattamento con *Uncaria tomentosa*, ma non quello con placebo, era in grado di incrementare la blastogenesi indotta da tre mitogeni, quali la Concanavalina A (ConA), il PWM (pokeweed mitogen) ed i lipopolisaccaridi (LPS). L'azione della *Uncaria tomentosa* risultava statisticamente diversa da quella del placebo, a partire dalla quarta settimana di trattamento[9]. Un altro studio clinico americano sulle proprietà immunostimolanti di un particolare estratto commerciale di Uncaria è stato somministrato per os per due mesi, risultando estremamente utile nel favorire la risposta immunitaria ad un vaccino pneumococcico polivalente. La risposta immunitaria è risultata incrementata sia nel titolo linfocitario che di quello anticorpale. Considerando che l'efficacia del vaccino pneumocicco è di circa il 70%, il risultato una volta che sarà confermato in una corte più ampia potrebbe essere estremamente interessante[10]. L'attività immunostimolante si esplica anche attraverso: soppressione di una proteina complessa come NF-kappa B (fattore di trascrizione nucleare B), coinvolta in numerosi processi biologici; incremento di linfociti B e T; stimolazione della fagocitosi e innalzamento di IL-1 e IL-6[11]. Inoltre è stata riscontrata una stimolazione dose dipendente della produzione di Interleuchine da parte dei macrofagi. L'attività immunomodulante è collegata con la capacità di inibire la sintesi di TNF-alpha, attività collegata con l'azione antinfiammatoria. In un modello sperimentale in vivo condotto con un estratto acquoso di Uncaria si evidenzia una maggior sopravvivenza di cellule del sistema immunitario (Linfociti B e T), Natural Killer (NK) e granulociti. Gli AA. ipotizzano che tale attività possa essere data da un innalzamento della protezione contro stress ossidativi, contrasta l'attivazione di

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9 *Firenzuoli F. Attività del Servizio Ospedaliero presso l'Ospedale S. Giuseppe di Empoli. Acta Phytotherapeutica Vol. I, N° 1.*

10 "A human intervention study was carried out using male volunteers attending a General Practice Clinic in New York City involving comparison of individuals supplemented with 350 mg x 2 C-Med-100 daily dose for two months with untreated controls for their abilities to respond to a 23 valent pneumococcal vaccine. C-Med-100 is a novel nutraceutical extract from the South American plant Uncaria tomentosa or Cat's Claw which is known to possess immune enhancing and antiinflammatory properties in animals. There were no toxic side effects observed as judged by medical examination, clinical chemistry and blood cell analysis. However, statistically significant immune enhancement for the individuals on C-Med-100 supplement was observed by (i) an elevation in the lymphocyte/neutrophil ratios of peripheral blood and (ii) a reduced decay in the 12 serotype antibody titer responses to pneumococcal vaccination at 5 months." *(Lamm S, Sheng Y, Pero RW. Persistent response to pneumococcal vaccine in individuals supplemented with a novel water soluble extract of Uncaria tomentosa, C-Med-100. Phytomedicine. 2001 Jul; 8(4):267-74.)*

11 *Spelman K, Burns J, Nichols D, Winters N, Ottersberg S, Tenborg M. Modulation of cytokine expression by traditional medicines: a review of herbal immunomodulators. Altern Med Rev. 2006 Jun; 11(2):128-50.*

NF-kappa B, l'apoptosi cellulare[12] e inoltre sembra favorire i meccanismi di riparazione del DNA[13,14].

Attività antinfiammatoria e antireumatica. I glicosidi dell'acido quinovico sono in parte responsabili delle proprietà antinfiammatorie assieme agli steroli ai polifenoli e alle proantocianidine[15]. Sia l'*Uncaria tomentosa* sia la *Uncaria guianensis*, sono state tradizionalmente impiegate per il trattamento di stati infiammatori. Alcuni studi realizzati in passato individuavano come potenziali responsabili di tale effetto, gli alcaloidi pentaciclici e ossindolici. Tuttavia ricerche successive hanno messo in discussione questi risultati, e a oggi la questione rimane ancora controversa. Piscoya et al. hanno condotto uno studio clinico su 45 soggetti affetti da osteoartrite del ginocchio, a cui sono stati somministrati un estratto acquoso di *Uncaria guianensis* e *Uncaria tomentosa* (100mg/die) per un

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12 "The Uncaria genus is an important source of medicinal natural products, particularly alkaloids and triterpenes. The collected information is an attempt to cover the more recent developments in the ethnobotany, pharmacology and phytochemistry of this genus. During the past 20 years, alkaloids, terpenes, quinovic acid glycosides, flavonoids and coumarins have been isolated from Uncaria. Fifty-three novel structures are reported in this review. The species in which the largest number of compounds has been identified is the Peruvian Uncaria tomentosa or 'cat's claw.' Pharmacological studies are described according to cytotoxicity, anti-inflammatory, antiviral, immunostimulation, antioxidant, CNS-related response, vascular, hypotensive, mutagenicity and antibacterial properties. The potential for development of leads from Uncaria continues to grow, particularly in the area of immunomodulatory, anti-inflammatory and vascular-related conditions." *(Heitzman ME, Neto CC, Winiarz E, Vaisberg AJ, Hammond GB. Ethnobotany, phytochemistry and pharmacology of Uncaria (Rubiaceae). Phytochemistry. 2005 Jan; 66(1):5-29.)*

13 "The Uncaria tomentosa water extracts (C-Med-100) have been shown to enhance DNA repair, mitogenic response and leukocyte recovery after chemotherapy-induced DNA damage in vivo. In this study, the effect of C-Med-100 supplement was evaluated in a human volunteer study. Twelve apparently healthy adults working in the same environment were randomly assigned into 3 groups with age and gender matched. One group was daily supplemented with a 250 mg tablet containing an aqueous extract of Uncaria tomentosa of C-Med-100, and another group with a 350 mg tablet, for 8 consecutive weeks. DNA repair after induction of DNA damage by a standard dose of hydrogen peroxide was measured 3 times before supplement and 3 times after the supplement for the last 3 weeks of the 8 week-supplement period. There were no drug-related toxic responses to C-Med-100 supplement when judged in terms of clinical symptoms, serum clinical chemistry, whole blood analysis and leukocyte differential counts. There was a statistically significant decrease of DNA damage and a concomitant increase of DNA repair in the supplement groups (250 and 350 mg/day) when compared with non-supplemented controls ($p < 0.05$). There was also an increased tendency of PHA induced lymphocyte proliferation in the treatment groups. Taken together, this trial has confirmed the earlier results obtained in the rat model when estimating DNA repair enhancement by C-Med-100." *(Sheng Y, Li L, Holmgren K, Pero RW.DNA repair enhancement of aqueous extracts of Uncaria tomentosa in a human volunteer study. Phytomedicine. 2001 Jul; 8(4):275-82.)*

14 *Emanuel P, Scheinfeld N. A review of DNA repair and possible DNA-repair adjuvants and selected natural anti-oxidants. Dermatol Online J. 2007 Jul 13; 13(3):10.*

15 "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, the 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." *(Gonçalves C, Dinis T, Batista MT. Antioxidant properties of proanthocyanidins of Uncaria tomentosa bark decoction: a mechanism for anti-inflammatory activity. Phytochemistry. 2005 Jan; 66(1):89-98.).*

periodo totale di circa 10 settimane, mediante un modello di cross-over in cui il gruppo A veniva trattato con la sostanza attiva per 4 settimane e il gruppo B con placebo. Dopodiché a seguito di un periodo di riposo di due settimane al gruppo A veniva somministrato il placebo e al gruppo B la sostanza attiva. Il risultato ha evidenziato un miglioramento sintomatologico relativo al dolore nei soggetti trattati con la sostanza attiva. Gli stessi autori hanno testato l'attività antinfiammatoria sia dell'*Uncaria guianensis* che *tomentosa* concludendo che la prima risultava essere la più attiva come conseguenza di una maggiore azione antiossidante[16]. In un altro studio è stato dimostrato che somministrando per un periodo di 52 settimane, a 40 soggetti affetti da artrite reumatoide un estratto di *Uncaria tomentosa* (standardizzato in alcaloidi ossindolici pentaciclici pari a 14.7mg/die) si otteneva un netto miglioramento nel gruppo trattato[17]. L'ipotesi più probabile è che data l'efficacia mostrata sia dall'estratto standardizzato in alcaloidi che da quello privo, l'attività sia indipendente dalla presenza della frazione alcaloidea. Probabilmente molti AA. ipotizzano che esista una frazione non alcaloidea, presente in entrambe le specie, responsabile di questa attività[18]. Recentemente anche i glicosidi dell'acido quinico, identificati nell'estratto di *Uncaria tomentosa* mostrano in modelli *in vitro* un'attività antinfiammatoria, che coinvolge l'inibizione del fattore di

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16 "Forty-five patients with osteoarthritis of the knee were recruited, 30 were treated with freeze-dried U guianensis, and 15 with placebo. 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 (EC50, 13.6-21.7 microg/ml) as well as inhibiting TNFalpha production. However, the latter action was registered at much lower concentrations (EC50, 10.2-10.9 ng/ml). Cat's claw (10 microg/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 TNFalpha inhibition. 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 TNFalpha and to a lesser extent PGE_2 production." *(Piscoya J, Rodriguez Z, Bustamante SA, Okuhama NN, Miller MJ, Sandoval M. Efficacy and safety of freeze-dried cat's claw in osteoarthritis of the knee: mechanisms of action of the species Uncaria guianensis. Inflamm Res. 2001 Sep; 50(9):442-8.)*

17 "To evaluate safety and clinical efficacy of a plant extract from the pentacyclic chemotype of Uncaria tomentosa (UT) in patients with active rheumatoid arthritis (RA). 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 side effects were observed.: 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." *(Mur E, Hartig F, Eibl G, Schirmer M. Randomized double blind trial of an extract from the pentacyclic alkaloid-chemotype of uncaria tomentosa for the treatment of rheumatoid arthritis. J Rheumatol. 2002 Apr; 29(4):678-81.)*

18 "More recently water-soluble Cat's Claw extracts were shown not to contain significant amounts of alkaloids (<0.05%), and yet still were shown to be very efficacious. Here we characterize the active ingredients of a water-soluble Cat's Claw extract called C-Med-100 as inhibiting cell growth without cell death thus providing enhanced opportunities for DNA repair, and the consequences thereof, such as immune stimulation, anti-inflammation and cancer prevention. The active ingredients were chemically defined as quinic acid esters and could also be shown to be bioactive in vivo as quinic acid." *(Sheng Y, Akesson C, Holmgren K, Bryngelsson C, Giamapa V, Pero RW. An active ingredient of Cat's Claw water extracts identification and efficacy of quinic acid. J Ethnopharmacol. 2005 Jan 15; 96 (3):577-84.)*

trascrizione nucleare (NF-kB) pro-infiammatorio[19]. Inoltre in virtù della presenza di steroli soprattutto, di β-sitosterolo (60% della frazione sterolica totale) presenti nell'*Uncaria tomentosa*, potrebbero contribuire all'attività antinfiammatoria[20,21]. È noto, infatti, che molti steroli presenti in diversi fitocomplessi hanno attività antiinfiammatoria in vari modelli sperimentali di infiammazione, con un meccanismo di azione che è, con molta probabilità riferibile alla loro struttura steroidea[22].

Attività antivirale e antimicrobica. Nella corteccia di *Uncaria tomentosa* sono stati isolati una serie di glicosidi dell'acido quinovico che possiedono attività antivirale[23]. Questi principi isolati sono in grado di inibire l'attività della DNA-polimerasi e della transcriptasi inversa, due degli enzimi chiave coinvolti nella replicazione dei virus a DNA e dei retrovirus.
In uno studio in vitro un estratto idroalcolico di *Uncaria tomentosa* dimostra di essere efficace anche nei confronti del virus *Dengue* (agente eziologico di una malattia febbrile acuta associata spesso a delle complicanze piuttosto gravi), riducendo significativamente i livelli delle citochine TNF-alpha e INF-alpha[24]. Un estratto di *Uncaria tomentosa* micropolverizzato ha mostrato *in vitro* di un'attività

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19 "Quinic acid (QA) esters found in hot water extracts of Uncaria tomentosa (a.k.a. cat's claw) exert anti-inflammatory activity through mechanisms involving inhibition of the pro-inflammatory transcription factor nuclear factor kappa B (NF-kappaB). Mechanistic studies and pre-clinical efficacy studies in various inflammatory animal models are on-going. " (*Zeng K, Thompson KE, Yates CR, Miller DD. Synthesis and biological evaluation of quinic acid derivatives as anti-inflammatory agents. Bioorg Med Chem Lett. 2009 Sep 15; 19(18):5458-60.)*

20 "The investigation on steroidic fraction of Uncaria tomentosa, commonly called Una de gato, showed the presence of β-sitosterol (60%), stigmasterol, and campesterol. The percentage of sterols have been carried out by GLC. The spectroscopic data 1H-NMR and MS of the three compounds are also reported, with the β-sitosterol as the main sterol. Preliminary pharmacological investigations prove a moderate antiinflammatory activity." *(Senatore A, Cataldo A, Iaccarino FP, Elberti MG. Phytochemical and biological study of Uncaria tomentosa. Boll Soc Ital Biol Sper 1989; 65: 517-20).*

21 *Sandoval M, Mannick EE, Mishra J, Sadowska-Krowicka H. Cat's claw (Uncaria tomentosa) protects against oxidative stress and indomethacin-induced intestinal inflammation. Gastroenterology 1997; 112: A1081.*

22 "The oxygenated stigmastane-type sterols stigmastane-3β, 6α-diol, stigmastane-3β, 6β-diol, 7α-hydroxysitosterol and its diacetyl derivative, 7β-hydroxysitosterol and its diacetyl derivative, 7-oxositosterol, 4β-hydroxysitosterol, and stigmast-4-ene-3β, 6β-diol were evaluated with respect to their anti-inflammatory activity against 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced inflammation in mice. All of the sterols, with the exception of 7α-hydroxysitosterol and its diacetyl derivative, were found to possess marked inhibitory activity. The 50% inhibitory dose of these compounds for TPA-inflammation (1 μg) was 0.5-1.0 mg/ear)." *(Kimura Y, Yasukawa K, Takido M, Akihisa T, Tamura T. Inhibitory effect of some oxygenated stigmastane-type sterols on 12-O-tetradecanoylphorbol-13-acetate-induced inflammation in mice. Biol Pharm Bull 1995; 18: 1617-9).*

23 "A reinvestigation of the bark of Uncaria tomentosa afforded, in addition to the major quinovic acid glycosides 1-3, three further glycosides 4-6. The structures were elucidated by spectral and chemical studies. Furthermore, a series of antiviral tests were performed on all these glycosides and on the related glycosides 7-9, previously isolated from Guettarda platypoda" *(Aquino R, De Simone F, Pizza C, Conti C, Stein ML. Plant metabolites. Structure and in vitro antiviral activity of quinovic acid glycosides from Uncaria tomentosa and Guettarda platypoda. J Nat Prod 1989; 52:679-85).*

24 "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

antimicrobica nei confronti di patogeni comuni delle affezioni del cavo orale, in particolare si è rivelata attiva nell'inibire la crescita di Enterobacteriacee, *Stroptococcus mutans* e *Staphylococcus* spp[25]. Le proprietà antinfiammatorie e antivirali giustificano quindi l'impiego della specie nelle malattie infettive. L'*Uncaria tomentosa* ha mostrato possedere una forte attività antiossidante *in vitro*, che potrebbe ulteriormente giustificare la sua efficacia nei confronti di patologie infiammatorie[26]**.**

Attività antimutagena, antiproliferativa e proapoptotica. L'attività antimutagena è stata confermata in vivo[27]. Preparati a base di Uncaria, somministrati contemporaneamente a terapie antineoplastiche (chemioterapia e irradiazioni), hanno consentito una maggiore tollerabilità, un minor numero di pancitopenie e un accorciamento della fase di recupero[28]. Recenti pubblicazioni indicano che estratti della radice di Uncaria tomentosa esplicano un effetto citostatico in alcune linee cellulari tumorali. Questo effetto sembra essere mediato attraverso un possibile meccanismo

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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**." *(Reis SR, Valente LM, Sampaio AL, Siani AC, Gandini M, Azeredo EL, D'Avila LA, Mazzei JL, Henriques MG, Kubelka CF. Immunomodulating and antiviral activities of Uncaria tomentosa on human monocytes infected with Dengue Virus-2. Int Immunopharmacol. 2008 Mar; 8(3):468-76.)*

25 "The aim of the present study was to evaluate the antimicrobial activity of different concentrations of Uncaria tomentosa on different strains of microorganisms isolated from the human oral cavity. Micropulverized Uncaria tomentosa was tested in vitro to determine the minimum inhibitory concentration (MIC) on selected microbial strains. The tested strains were oral clinical isolates of Streptococcus mutans, Staphylococcus spp., Candida albicans, Enterobacteriaceae and Pseudomonas aeruginosa. The tested concentrations of Uncaria tomentosa ranged from 0.25-5% in Müeller-Hinton agar. Three percent **Uncaria tomentosa inhibited 8% of Enterobacteriaceae isolates, 52% of S. mutans and 96% of Staphylococcus spp**. The tested concentrations did not present inhibitory effect on P. aeruginosa and C. albicans. It could be concluded that **micropulverized Uncaria tomentosa presented antimicrobial activity on Enterobacteriaceae, S. mutans and Staphylococcus spp. isolates**." (Ccahuana-Vasquez RA, Santos SS, Koga-Ito CY, Jorge AO. Antimicrobial activity of Uncaria tomentosa against oral human pathogens. Braz Oral Res. 2007 Jan-Mar;21(1):46-50.)

26 "….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." *(Amaral S, Mira L, Nogueira JM, da Silva AP, Helena Florêncio M. Plant extracts with anti-inflammatory properties--a new approach for characterization of their bioactive compounds and establishment of structure-antioxidant activity relationships. Bioorg Med Chem. 2009 Mar 1;17(5):1876-83.)*

27 "Mutagenic and antimutagenic activities of extracts and chromatographic fractions of Uncaria tomentosa bark are reported. The plant extracts and fractions show no mutagenic effect in different strains of Salmonella typhimurium with and without metabolic activation. However, the plant extracts and fractions show a protective antimutagenic effect in vitro against photomutagenesis induced by 8-methoxy-psoralen (8-MOP) plus UVA in S. typhimurium TA 102. A decoction of U. tomentosa ingested daily for 15 days by a smoker decreased the mutagenicity induced in S. typhimurium TA98 and TA100 by the subject's urine." *(Rizzi R, Re F, Bianchi A, De Feo V, de Simone F, Bianchi L, Stivala LA. Mutagenic and antimutagenic activities of Uncaria tomentosaand its extracts. J Ethnopharmacol 1993; 38: 63-77).*

28 *Tirillini B. Il tesoro della foresta peruviana. L'Erborista 1995; 2: 36-39.*

proapoptotico attivando la Caspasi-3 (una proteasi effettrice)[29]. In particolare di questa attività sembrano essere responsabili gli alcaloidi ossindolici[30], come l'isopterpodina e la pteropodina[31].

Tollerabilità. L'Uncaria risulta essere una droga caratterizzata da una elevata tollerabilità. Tuttavia possono raramente insorgere lievi disturbi gastrointestinali[32]. Non sono noti studi clinici controllati in donne in gravidanza e durante l'allattamento, tuttavia è consigliabile non assumere la droga durante la gravidanza e nell'allattamento.

[29] " Recent literature reports cytostatic, antiproliferative, anti-inflammatory, mutagenic and anti-mutagenic properties of extracts of the plant. The present study investigates the possible proapoptotic mechanism via the activation of caspase3, in cytostatic effects of root bark extracts of Uncaria tomentosa on three different tumoral cell lines." (*De Martino L, Martinot JL, Franceschelli S, Leone A, Pizza C, De Feo V. Proapoptotic effect of Uncaria tomentosa extracts. J Ethnopharmacol. 2006 Aug 11;107(1):91-4.)*

[30] "…we investigated for the first time the antiproliferative and apoptotic effects of highly purified oxindole alkaloids, namely isopteropodine (A1), pteropodine (A2), isomitraphylline (A3), uncarine F (A4) and mitraphylline (A5) obtained from Uncaria tomentosa, a South American Rubiaceae, on human lymphoblastic leukaemia T cells (CCRF-CEM-C7H2). Four of the five tested alkaloids inhibited proliferation of acute lymphoblastic leukaemia cells. Furthermore, the antiproliferative effect of the most potent alkaloids pteropodine (A2) and uncarine F (A4) correlated with induction of apoptosis. After 48 h, 100 micromol/l A2 or A4 increased apoptotic cells by 57%. CEM-C7H2 sublines with tetracycline-regulated expression of bcl-2, p16ink4A or constitutively expressing the cowpox virus protein crm-A were used for further studies of the apoptosis-inducing properties of these alkaloids. Neither overexpression of bcl-2 or crm-A nor cell-cycle arrest in G0/G1 phase by tetracycline-regulated expression of p16INK4A could prevent alkaloid-induced apoptosis. Our results show the strong apoptotic effects of pteropodine and uncarine F on acute leukaemic lymphoblasts and recommend the alkaloids for further studies in xenograft models." (*Bacher N, Tiefenthaler M, Sturm S, Stuppner H, Ausserlechner MJ, Kofler R, Konwalinka G. Oxindole alkaloids from Uncaria tomentosa induce apoptosis in proliferating, G0/G1-arrested and bcl-2-expressing acute lymphoblastic leukaemia cells. Br J Haematol. 2006 Mar; 132(5):615-22.*)

[31] "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**." *(Rinner B, Li ZX, Haas H, Siegl V, Sturm S, Stuppner H, Pfragner R. Antiproliferative and pro-apoptotic effects of Uncaria tomentosa in human medullary thyroid carcinoma cells. Anticancer Res. 2009 Nov; 29(11):4519-28.)*

[32] *Mills S & Bone K. The essential guide to herbal safety. Ed. Elsevier.2005*