Echinacea

Echinacea pallida

Nome botanico

Echinacea pallida Nutt. *(Compositae)*

Parti usate

Radici.

Componenti principali

Alcammidi e chetoalcheni(ini), coniugati caffeici (acido cicorico, echinacoside), polisaccaridi a struttura arabino- e ramnogalattosidica.

Attività farmacologica

Attività immunomodulante. Azione antinfiammatoria e cicatrizzante.

Impiego clinico

Terapia coadiuvante e di profilassi nelle infezioni ricorrenti del tratto respiratorio superiore (raffreddore comune) e di altre patologie su base infettiva, p.e. sindrome influenzale. Stati di debilitazione in corso di convalescenza da malattia cronica.

Controindicazioni

Ipersensibilità nota a piante della famiglia delle *Compositae*. L'assunzione di Echinacea è sconsigliata nei pazienti in terapia immunosoppressiva e nei soggetti affetti da disturbi sistemici progressivi o patologie autoimmuni come AIDS/HIV, lupus, malattia tubercolare, sclerosi multipla, leucocitosi, patologie del tessuti connettivo, collagenosi.

Avvertenze e speciali precauzioni d'uso

La durata del trattamento con preparati a base di Echinacea non dovrebbe superare le 8 settimane. Usare con molta cautela in pazienti con insufficienza epatica manifesta. Non sono noti studi clinici controllati in donne in gravidanza e durante allattamento: in conformità con la prassi medica generale, il prodotto non deve essere impiegato senza prima avere sentito il parere del medico.

Interazioni

Potrebbe potenziare l'effetto negativo sul fegato di farmaci epatotossici come paracetamolo, steroidi anabolizzanti, amiodarone, metotressato e chetoconazolo.

Effetti indesiderati

Possono verificarsi reazioni da ipersensibilità in pazienti con intolleranza alle *Asteraceae,* quali reazioni cutanee.

Note Bibliografiche

Composizione

Tra le specie appartenenti al genere Echinacea, tre sono quelle riconosciute officinali: *Echinacea pallida* Nutt., *Echinacea angustifolia* DC., *Echinacea purpurea* (L.) Moench[1,2].

Anche se indubbiamente vi sono delle differenze, le tre echinacee sono abbastanza simili dal punto di vista della composizione chimica e quindi delle proprietà farmacologiche. Di conseguenza vengono spesso considerate equivalenti anche per quanto riguarda gli impieghi clinici[3]. Nel fitocomplesso di *Echinacea pallida* si distinguono: una frazione polifenolica costituita da caffeoil derivati, principalmente echinacoside (0,5-1,0%), acido clorogenico, acido cicorico, verbascoside; una frazione lipofila, costituita da un olio essenziale ricco di composti poliacetilenici (pentadeca-1,8Z-diene, 1,8pentadecene, pentadecenoni, echinolone)[4] e di numerose N-isobutilamidi a struttura lineare (p.e. echinaceina); una frazione polare contenente polisaccaridi ad elevato peso molecolare a struttura arabino- e ramnogalattosidica (eteroxilani, arabinogalattani, fruttani, xiloglucani)[5,6].

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1 *Wu L, Dixon PM, Nikolau BJ, Kraus GA, Widrlechner MP, Wurtele ES. Metabolic profiling of echinacea genotypes and a test of alternative taxonomic treatments. Planta Med. 2009 Feb;75(2):178-83.*

2 *Frédérich M, Jansen C, de Tullio P, Tits M, Demoulin V, Angenot L. Metabolomic analysis of Echinacea spp. by 1H nuclear magnetic resonance spectrometry and multivariate data analysis technique. Phytochem Anal. 2010 Jan;21(1):61-5.*

3 "The rising interest in medicinal plants has brought several species of the genus Echinacea to the attention of many scientists. Echinacea angustifolia, E. pallida, and E. purpurea are the most important for their immunological properties, well known and widely used by the native Americans. **The three species are easily distinguishable on the basis of their morphological characteristics, but it would be difficult, if not impossible, to distinguish them in commercial preparations of ground, dry plant parts of E. purpurea (the most valuable species for chemotherapeutic properties) mixed with the other two species. Species-specific molecular markers could be useful to address this issue. In the present work, using fresh material collected from cultivated Echinacea spp., AFLP analysis was used to discriminate the three species and to detect species-specific DNA fragments.** By using 14 primer combinations it was possible to detect a total of 994 fragments, of which 565 were polymorphic. Overall, 89 fragments were unique to E. purpurea, 32 to E. angustifolia, and 26 to E. pallida. E+CAC/M+AAT or E+CAC/M+AGC alone provided 13, 9, and 4 or 7, 5, and 5 specific fragments for E. purpurea, E. angustifolia, and E. pallida, respectively. A validation trial to confirm the results was carried out on bulked samples of 23 accessions covering most of the genetic diversity of the three species. The results are discussed in terms of practical applications in the field of popular medicine, detecting frauds, and implications for the genus Echinacea." *(Russi L, Moretti C, Raggi L, Albertini E, Falistocco E.. Identifying commercially relevant Echinacea species by AFLP molecular markers. Genome. 2009 Nov;52(11):912-8).*

4 *Pellati F, Calò S, Benvenuti S. High-performance liquid chromatography analysis of polyacetylenes and polyenes in Echinacea pallida by using a monolithic reversed-phase silica column. J Chromatogr A. 2007 May 11;1149(1):56-65.*

5 *Pale Coneflower Root - Echinaceae pallidae radix. Pharmeuropa 2002;14:137-8.*

6 *Laasonen M, Wennberg T, Harmia-Pulkkinen T, Vuorela H. Simultaneous analysis of alkamides and caffeic acid derivatives for the identification of Echinacea purpurea, Echinacea angustifolia, Echinacea pallida and Parthenium integrifolium roots. Planta Med. 2002 Jun;68(6):572-4.*

Attività biologiche ed impieghi clinici descritti in letteratura

Le attività biologiche e gli impieghi clinici descritti per il fitocomplesso della radice di *Echinacea pallida* sono:

Medicina popolare. L'uso medicinale dell'Echinacea è originario degli indiani del Nord-America, dove sappiamo che era nota presso diverse tribù (Cheyenne, Dakota, Sioux, Omaha, Pawnee, Comancee, ecc.)[7]. La droga veniva utilizzata con un ampio spettro di indicazioni: dal trattamento esterno di piaghe e ferite, ustioni, punture di insetti, ghiandole linfatiche ingrossate, a quello interno delle malattie febbrili, della tosse, del raffreddore, del mal di testa, del mal di denti e dei crampi allo stomaco. Contro il cimurro dei cavalli se ne impiegava il fumo. Era inoltre ritenuta un buon antidoto ai morsi di serpente, in particolare del serpente a sonagli, e in numerosi altri casi di avvelenamento[8]. Venivano usate soprattutto le radici di *E. angustifolia* ed *E. pallida*, botanicamente molto simili tra loro (quindi facilmente confondibili). Ed è dai nativi americani che i coloni bianchi appresero l'uso medicinale dell'Echinacea, documentato fin dal 1700 e giunto alla sua massima diffusione alla fine del XIX secolo, tanto che, divenuta di gran lunga una delle droghe più diffuse negli Stati Uniti, nel 1916 l'Echinacea venne ammessa nel National Formulary of the United States ed impiegata addirittura per curare il tifo, la difterite e la setticemia. In Europa l'Echinacea è nota dagli inizi del XX secolo.

Attività immunomodulante. Le immunodeficienze sono un gruppo eterogeneo di condizioni caratterizzate da una compromissione del sistema immunitario e della sua funzionalità. Mentre le immunodeficienze primarie sono rare e generalmente associate a difetti congeniti, le immunodeficienze secondarie sono alterazioni delle funzioni immunitarie conseguenti a processi morbosi che coinvolgono in maniera primitiva organi e sistemi immunitari.

L'interessamento del sistema immunitario può essere direttamente causato dalla patologia in atto (p.e., l'infezione acuta da virus del morbillo) o essere conseguenza di interventi iatrogeni (trattamenti farmacologici, ecc). In queste condizioni può risultare utile l'utilizzo di composti ad attività genericamente stimolante la reattività delle cellule immunitarie (macrofagi, citochine, linfociti T, ecc.). L'attività immunomodulante è comune a tre specie del genere Echinacea: *Echinacea angustifolia* (radice), *Echinacea purpurea* (herba) ed *Echinacea pallida* (radice). Per queste proprietà le Echinacee sono utilizzate, ad uso interno, come terapia di supporto nel raffreddore e nelle infezioni acute e croniche delle vie aeree superiori. L'uso è particolarmente indicato laddove si manifesta la tendenza alla cronicizzazione e alle recidive, e in individui che presentano un sistema immunitario poco efficiente. I trattamenti a base di queste piante riducono la durata della malattia e i sintomi

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7 *Bauer R, Wagner. Echinacea, Wissenschftliche Verlagsgesellschft mbH Stuttgart, 1990.*

8 *Moerman DE. Medicinal Plants of Native America, Res. Rep. Ethnobotany, University of Michigan Museum of Anthropology, Technical Reports N.19, 1986.*

delle infezioni, attraverso la modulazione delle difese immunitarie dell'organismo[9,10].

L'azione immunomodulante dell'Echinacea si manifesta con una stimolazione aspecifica delle reazioni difensive, che si concretizza in un globale aumento della resistenza dell'organismo all'aggressione degli agenti patogeni. In particolare si osserva un incremento della fagocitosi, con aumento del numero di neutrofili, della produzione di linfociti T e della loro attività citotossica, nonché del rilascio di citochine, linfochine e interferoni coinvolti nelle prime fasi della risposta immunitaria[11]. Prove sperimentali condotte *in vitro* con estratti della droga confermano che l'Echinacea induce aumento della fagocitosi (con incremento del numero dei leucociti totali e dei neutrofili in particolare), della differenziazione dei granulociti immaturi in granulociti maturi, delle cellule linfocitarie, della citotossicità delle cellule NK nonché della produzione di interferone, di interleuchine e di TNF-α da parte dei macrofagi. Le interleuchine maggiormente sensibili all'azione dell'Echinacea sono l'interleuchina-1 (IL-1), l'interleuchina-6 (IL-6) e l'interleuchina-10 (IL-10)[12]. Particolarmente

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9 "This paper reviews the chemistry, pharmacology and clinical properties of Echinacea species used medicinally. The Echinacea species Echinacea angustifolia, Echinacea pallida and Echinacea purpurea have a long history of medicinal use for a variety of conditions, particularly infections, and today echinacea products are among the best-selling herbal preparations in several developed countries. **Modern interest in echinacea is focused on its immunomodulatory effects, particularly in the prevention and treatment of upper respiratory tract infections. The chemistry of Echinacea species is well documented, and several groups of constituents, including alkamides and caffeic acid derivatives, are considered important for activity**. There are, however, differences in the constituent profile of the three species. Commercial echinacea samples and marketed echinacea products may contain one or more of the three species, and analysis of samples of raw material and products has shown that some do not meet recognized standards for pharmaceutical quality. **Evidence from preclinical studies supports some of the traditional and modern uses for echinacea, particularly the reputed immunostimulant (or immunomodulatory) properties. Several, but not all, clinical trials of echinacea preparations have reported effects superior to those of placebo in the prevention and treatment of upper respiratory tract infections**. However, evidence of efficacy is not definitive as studies have included different patient groups and tested various different preparations and dosage regimens of echinacea. On the basis of the available limited safety data, echinacea appears to be well tolerated. However, further investigation and surveillance are required to establish the safety profiles of different echinacea preparations. Safety issues include the possibility of allergic reactions, the use of echinacea by patients with autoimmune diseases and the potential for echinacea preparations to interact with conventional medicines." *(Barnes J, Anderson LA, Gibbons S, Phillipson JD. Echinacea species (Echinacea angustifolia (DC.) Hell., Echinacea pallida (Nutt.) Nutt., Echinacea purpurea (L.) Moench): a review of their chemistry, pharmacology and clinical properties. J Pharm Pharmacol. 2005 Aug;57(8):929-54).*

10 *Bauer R. Echinacea drugs: effects and active ingredients. Z Arztl Fortbild (Jena) 1996; 90: 111-5.*

11 *Schwarz E, Parlesak A, Henneickevon Zepelin HH, Bode JC, Bode C. Effect of oral administration of freshly pressed juice of Echinacea purpurea on the number of various subpopulations of B- and T-lymphocytes in healthy volunteers: Results of a double-blind, placebo-controlled cross-over study. Phytomedicine 2005; (12):25–631.*

12 "Echinacea preparations are commonly used as nonspecific immunomodulatory agents. Alcohol extracts from three widely used Echinacea species, Echinacea angustifolia, Echinacea pallida, and Echinacea purpurea, were investigated for immunomodulating properties. The three Echinacea species demonstrated a broad difference in concentrations of individual lipophilic amides and hydrophilic caffeic acid derivatives. Mice were gavaged once a day (for 7 days) with one of the Echinacea extracts (130 mg/kg) or vehicle and immunized with sheep red blood cells (sRBC) 4 days prior to collection of immune cells for multiple immunological assays. **The three herb extracts induced similar, but differential, changes in the percentage of immune cell populations and their biological functions, including increased percentages of CD49+ and CD19+ lymphocytes in spleen and natural killer cell cytotoxicity**. **Antibody response to sRBC was significantly increased equally by extracts of all three Echinacea species**. Concanavalin A-stimulated splenocytes from E. angustifolia- and E. pallida-treated mice demonstrated **significantly higher T cell proliferation**. In addition, the Echinacea treatment significantly altered the cytokine production by mitogen-stimulated splenic cells. The three herbal extracts significantly increased interferon-alpha

importante l'aumento della produzione di interleuchina-10, la quale svolge un ruolo primario nella stimolazione dei linfociti sia di tipo T sia di tipo B e nella regolazione degli antigeni di classe II del maggiore complesso di istocompatibilità. Le ricerche farmacologiche sull'Echinacea hanno dimostrato in vitro un aumento di oltre il 50% dell'attività fagocitaria dei macrofagi e linfociti umani[13], mentre in altri studi l'aumento della fagocitosi indotto dalla droga viene quantificato tra il 20 e il 30% rispetto al controllo. L'attività immunomodulante è accompagnata da una aumentata liberazione di TNF (tumour necrosis factor) e sembra indicativa di una attivazione non-specifica dei linfociti T. *In vivo*, la somministrazione nel topo di un estratto etanolico di Echinacea determina una stimolazione dell'attività fagocitaria, metabolica e battericida dei macrofagi peritoneali[14]. Estratti etanolici di *Echinacea purpurea*, *Echinacea pallida* e *Echinacea angustifolia* sono stati studiati nel test *in vivo* di clearance del carbonio nel topo: somministrato per via orale, l'estratto ha fortemente stimolato la fagocitosi confermando quanto già osservato in vitro. Secondo tali AA. il principio attivo responsabile dell'attività immunomodulante sembra risiedere nella frazione lipofila[15], mentre secondo altri AA. sono attivi anche i polisaccaridi ad alto peso molecolare della frazione polare[16]. Sono stati analizzati gli effetti di due estratti di Echinacea, uno prevalentemente

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production, but inhibited the release of tumor necrosis factor-gamma and interleukin (IL)-1beta. Only E. angustifolia- and E. pallida-treated mice demonstrated **significantly higher production of IL-4 and increased IL-10 production**. Taken together, these findings demonstrated that Echinacea is a wide-spectrum immunomodulator that modulates both innate and adaptive immune responses. In particular, **E. angustifolia or E. pallida may have more anti-inflammatory potential**." *(Zhai Z, Liu Y, Wu L, Senchina DS, Wurtele ES, Murphy PA, Kohut ML, Cunnick JE. Enhancement of innate and adaptive immune functions by multiple Echinacea species. J Med Food. 2007 Sep;10(3):423-34).*

13 "The activity of phagocytosis was tested in the in vitro granulocyte test and the in vivo carbon-clearance-test in the mouse for an extract combination consisting of four plant extracts (*Echinacea angustifolia, Eupatoriumperfoliatum, Baptisia tinctoria and Arnica montana)*. In both immune models, **a step by step stimulation of the activity of phagocytosis by the addition of the four plant extracts was shown with an increase in effectiveness of partially over 50% in comparison to the pure Echinacea angustifolia mono-extract.** The extract combination showed also in both test models a higher efficiency than two other differently composed combination preparations and two Echinacea mono-preparation." *(Wagner H, Jurcic K. Immunologic studies of plantcombination preparations. In-vitro and in-vivo studies on the stimulation of phagocytosis. Arzneimittelforschung 1991; 41: 1072-6.*

14 *Bukovsky M, Kostalova D, Magnusova R, Vaverkova S. Katedra biochemie a mikrobiologie a katedra farmakognozie a botaniky Farmaceutickej fakulty Univerzity Komenskeho, Bratislava, SR. Testing for immunomodulating effects of ethanol-water extracts of the above-ground parts of the plants Echinaceae (Moench) and Rudbeckia L. Cesk Farm 1993; 42: 228-31.*

15 "Immunological *in vivo* and *in vitro* examinations of *Echinacea* extracts. Ethanolic extracts of *Echinacea purpurea*, *Echinacea pallida* and *Echinacea angustifolia* roots were examined for immunological activity in the carbon clearance test with mice and in the granulocyte test. In the in vivo experiment all extracts, administered orally, were found to enhance phagocytosis significantly. These results correlate with the stimulation of phagocytosis in the in vitro granulocyte test. The lipophilic fractions of the extracts appeared to be more active than the polar fractions. All extracts were analyzed by HPLV in order to correlate the chemical constituents with the immunological activitirs." *(Bauer R, Jurcic K, Puhlmann J, Wagner W. Immunologische in vivo und in vitro undersuchungen mit Echinacea-extracten. Arzeim Forsch Drug Res 1988; 38: 276-278).*

16 "The immunomodulating effects of two Echinacea species, E. purpurea and E. angustifolia and larch arabinogalactan extracted from Larix occidentalis were examined in a randomized, double-blind, placebo-controlled, prospective four-week clinical trial at a naturopathic medical school research center. Forty-eight healthy female volunteers (22-51 y) were randomly assigned to one of six groups: standardized extract of E. purpurea (EP); ultra-refined E. purpurea/E. angustifolia (urEPA); E. purpurea/E. angustifolia (EPA); E. purpurea/E. angustifolia plus larch arabinogalactan (EPALA); larch arabinogalactan (LA); or placebo. Immunological

ricco di polisaccaridi e l'altro di alchilamidi[17] e derivati dell'acido caffeico sull'espressione genica in una linea di cellule epiteliali bronchiali umane, con o senza infezione da Rhinovirus. Entrambi gli estratti hanno modulato l'espressione di numerosi geni connessi con la risposta immunitaria, in particolare quelli codificanti per una serie di citochine e chemochine. In aggiunta, gli estratti di Echinacea tendevano a neutralizzare gli effetti del virus sulle cellule[18]. Anche un altro studio *in vitro* conferma che un estratto idroalcolico di Echinacea (purpurea) inibisce la produzione di citochine flogogene (soprattutto IL-6 e IL-8) indotta dal Rhinovirus in cellule epiteliali bronchiali umane, sia che l'estratto venga aggiunto alla coltura prima del rinovirus o dopo di esso[19]. Questi ed altri studi condotti sulla droga confermano l'uso dell'Echinacea come immunomodulante, e ne

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tests with enumerative measurements, stool cultures for Lactobacillus acidophilus and yeast, and health-related quality of life (HRQoL) using the Medical Outcomes Study derived SF-36 self-administered questionnaire were assessed at baseline and at four weeks. Results: Complement properdin increased by 21 percent in the EPA group ($p<0.05$) and by 18 percent in the EPALA group ($p<0.05$), compared to the placebo group ($p>0.05$). SF-36 showed improvements in overall physical health, vitality, and emotional health in the same two groups (EPA and EPALA). Discussion: Volunteers in the EPA and EPALA groups had increased production of complement properdin after four weeks of intervention. **The increased complement properdin may be an indication of one aspect of immune system stimulation in patients treated with either E. purpurea/E. angustifolia or E. purpurea/E. angustifolia plus larch arabinogalactan**." *(Kim LS, Waters RF, Burkholder PM. Immunological activity of larch arabinogalactan and Echinacea: a preliminary, randomized, double-blind, placebo-controlled trial. Altern Med Rev. 2002 Apr;7(2):138-49).*

[17] *Pellati F, Calò S, Benvenuti S. High-performance liquid chromatography analysis of polyacetylenes and polyenes in Echinacea pallida by using a monolithic reversed-phase silica column. J Chromatogr A. 2007 May 11;1149(1):56-65.*

[18] "Echinacea extracts have traditionally been used in the treatment of many infectious and other diseases (such as rhinovirus colds), and research has revealed the presence of various bioactivities in these extracts, particularly those connected with immune responses. **We examined the effects of Echinacea by using gene expression analysis in a line of human bronchial epithelial cells, with or without rhinovirus infection**. **More than 13 000 human genes were evaluated. From these analyses we focused primarily on immune response genes and found that both Echinacea extracts, one predominantly rich in polysaccharides and the other rich in alkylamides and caffeic acid derivatives, stimulated the expression of numerous genes. These included a number of cytokines and chemokines, although the pattern of stimulation was different. In addition, Echinacea extracts tended to neutralize the effects of the rhinovirus**. When the immune response gene pathways were analyzed with the Ingenuity Pathway program, it became apparent that many of them were interconnected through a major node, the transcription factor C/EBPbeta (CAAT/enhancer-binding protein beta) and its related C/EBP proteins. This suggests that **Echinacea can bring about important biological responses in cells by virtue of interactions between components of the extract and a small number of intracellular factors involved in multiple signaling pathways**." *(Altamirano-Dimas M, Hudson JB, Cochrane D, Nelson C, Arnason JT. Modulation of immune response gene expression by echinacea extracts: results of a gene array analysis. Can J Physiol Pharmacol. 2007 Nov;85(11):1091-8).*

[19] "Numerous Echinacea preparations are available on the market for the prevention and treatment of cold and flu symptoms and inflammatory conditions associated with infections. Most of these preparations are consumed orally in the form of aqueous or ethanol extracts and tinctures. Since the recommended consumption normally involves a brief local exposure to the diluted preparation at an unspecified time in relation to the actual infection, then it is important that experimental models for the evaluation of Echinacea reflect these limitations. **A line of human bronchial epithelial cells, in which rhinoviruses stimulate the production of pro-inflammatory cytokines, was used to evaluate several relevant parameters**. **The chemically characterized Echinacea preparation (Echinaforce) was capable of inhibiting completely the rhinovirus induced secretion of IL-6 (interleukin-6) and IL-8 (chemokine CXCL-8) in these cells, regardless of whether the Echinacea was added before or after virus infection, and in response to a range of virus doses**. This inhibitory effect was also manifest under conditions resembling normal consumption with respect to the duration of exposure to Echinacea and the Echinacea dilution. **It is concluded that under real life conditions of Echinacea consumption, the virus-induced stimulation of pro-inflammatory cytokines can be effectively reversed or alleviated**." *(Sharma M, Schoop R, Hudson JB. Echinacea as an antiinflammatory agent: the influence of physiologically relevant parameters. Phytother Res. 2009 Jun;23(6):863-7).*

suggeriscono l'impiego nella prevenzione e nella terapia di quelle patologie che riconoscono in una immunodepressione un fattore determinante o aggravante, e che potrebbero trarre beneficio da una stimolazione delle difese immunitarie. Uno studio nel ratto ha valutato se la somministrazione cronica di estratto di Echinacea, dalla giovinezza fino alla senescenza, fosse capace di aumentare la longevità e il benessere delle cellule del sistema immunitario, dal momento che è noto che l'attività di queste cellule è fondamentale per la sopravvivenza e la longevità. Gli animali venivano nutriti con 2 mg/die di estratto di Echinacea o con un placebo per tutta la loro vita ed erano tenuti e dieta libera. Dopo 10 mesi si valutava la sopravvivenza degli animali, che era del 79% nel gruppo placebo e del 100% nel gruppo verum. Dopo 13 mesi i risultati di sopravvivenza erano del 46% nel gruppo placebo e del 74% in quello verum. Agli stessi tempi si valutavano le cellule immunocompetenti e quelle ematopoietiche: in particolare si è notato che le cellule NK erano più numerose e vitali sia nel midollo sia nella milza sia nel sangue periferico dei ratti del gruppo trattato con Echinacea, mentre i leucociti non differivano in modo significativo tra i due gruppi. Lo studio indica che la somministrazione prolungata della droga per la maggior parte della vita del ratto aumenta la sopravvivenza degli animali, probabilmente per un effetto trofico sulle cellule NK[20]. Uno studio in vitro che ha esaminato l'effetto dell'Echinacea e dell'infezione da Rhinovirus sull'attivazione di una serie di fattori trascrizionali che giocano un ruolo chiave nella regolazione della risposta immunitaria alle infezioni, come NF-KappaB, AP-1, AP-2 e STAT(1-6), indica che l'estratto della droga esercita un notevole effetto inibitorio sull'espressione dei fattori trascrizionali indotta nelle cellule infettate con il virus e sulla conseguente produzione di citochine e chemochine[21]. Risultati positivi sono

[20] "…We sought to find out if mice, receiving dietary Echinacea daily, throughout life, from youth until late middle-age, demonstrated any longevity/survival differences, and/or any differences in their various populations of immune/ hemopoietic cells. Sustained and/or high levels of these cells are crucial for longevity. Some mice were maintained on a regular chow diet to which was added Echinacea purpurea daily (2 mg/mouse), from puberty (7 week) until just beyond 13 months of age (late middle-age in mice). Control mice, identically housed and maintained, received identical chow without the herb. Mice consuming untreated diet had a 79% survival by 10 months of age, while those consuming Echinacea daily in the diet were still 100% alive by 10 months. **At approximately 13 months of age, mice consuming untreated diet had a 46% survival rate while those consuming Echinacea, were 74% alive at this time. Moreover, the key immune cells, acting as the first line of defense against developing neoplasms in mice and humans, i.e., natural killer (NK) cells, were significantly elevated in absolute number both in their bone marrow production site, as well as in the major organ to which they traffic and function, i.e., the spleen**. The cells of the myeloid/granulocyte lineages remained steadfastly at control levels in both the bone marrow and spleen in Echinacea-consuming mice. Thus, **it appears that regular intake of Echinacea may indeed be beneficial/ prophylactic, if only for the reason that it maintains in an elevated state, NK cells, prime elements in immunosurveillance against spontaneous-developing tumors**, a phenomenon which increases in frequency with progressive aging." *(Brousseau M, Miller SC. Enhancement of natural killer cells and increased survival of aging mice fed daily Echinacea root extract from youth. Biogerontology. 2005;6(3):157-63).*

[21] "Extracts of Echinacea are widely used for the prevention and treatment of common colds, coughs, bronchitis and other upper respiratory infections, many of which are caused by rhinoviruses (RVs). Recent reports have indicated that rhinoviruses can stimulate the release of various pro-inflammatory cytokines and chemokines from cultured nasal and bronchial human epithelial cells, and several transcription factors (TFs) have been implicated in this process. **The effects of Echinacea treatment and rhinovirus infection on the activation of a range of transcription factors were evaluated by means of a protein/ DNA array analysis.** The BEAS-2B cell line was used as the model, and nuclear extracts of uninfected cells and rhinovirus-14 infected cells were examined with and without treatment with one of two chemically different Echinacea extracts. **It was found that both Echinacea extracts increased the nuclear content of more than 30 transcription factors, including the 12**

stato ottenuti anche con la contemporanea somministrazione di estratti di Echinacea insieme ad altri fitocomplessi ad azione sinergica, quali p.e. la propoli[22].

Profilassi e trattamento delle malattie da raffreddamento. L'Echinacea è stata soprattutto studiata per la prevenzione ed il trattamento delle infezioni non complicate del tratto respiratorio superiore. I risultati dei numerosi studi clinici controllati condotti allo scopo di valutare l'efficacia dei preparati di Echinacea sembrano avvalorare l'uso del fitocomplesso nel trattamento coadiuvante delle malattie infettive di origine sia batterica sia virale, nonché nella prevenzione di condizioni caratterizzate da depressione delle difese immunitarie[23,24,25]. L'uso più frequente e più diffuso dell'Echinacea è rappresentato dalla profilassi e dal trattamento delle malattie da raffreddamento, quali raffreddore e influenza.

Il raffreddore in particolare è un'infezione virale delle vie aeree superiori causata da un ceppo di Rhinovirus, mentre l'influenza è provocata da mixovirus e trasmessa per mezzo di goccioline aeree. Sebbene esistano tre ceppi principali di virus influenzali (noti come A, B e C), periodicamente, ad intervalli regolari, emergono nuovi ceppi virali che vengono denominati in funzione della regione geografica di origine. L'influenza si può presentare in casi isolati ma anche sotto forma di epidemie o pandemie ed è caratterizzata dai sintomi tipici del raffreddore (congestione nasale, mal di gola, tosse, laringite, congestione bronchiale, mal di testa) con l'aggiunta di febbre, dolori muscolari e articolari e disturbi gastrointestinali. Nell'eziopatogenesi dell'influenza e delle malattie da raffreddamento risultano infatti fondamentali la reattività immunologica del soggetto colpito e la rapidità di produzione di anticorpi, sia contro l'emoagglutinina, impedendo l'adsorbimento del virus da parte delle cellule, sia contro la neuraminidasi, inibendo la trasmissione del virus. Inoltre, il mantenimento di concentrazioni plasmatiche adeguate di anticorpi impedisce la recidiva di sindromi

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pro-inflammatory factors examined, such as NFkB, AP-1, AP-2 and STATs 1-6. Virus infection resulted in a more dramatic increase in these same TFs. **However, when RV-infected cells were treated with either of the two Echinacea extracts, TF levels were reduced to low levels, although the pattern of the reductions was different for the two extracts. These results indicate that rhinovirus infection of epithelial cells, and treatment with Echinacea extracts, led to profound effects on numerous transcription factors, which could explain the previously observed modulation of secreted cytokines and chemokines, as well as other signaling pathways**. In addition, the results could help to explain the beneficial effects of Echinacea consumption." *(Sharma M, Arnason JT, Hudson JB. Echinacea extracts modulate the production of multiple transcription factors in uninfected cells and rhinovirus-infected cells. Phytother Res. 2006 Dec;20(12):1074-9).*

22 *Cohen HA, Varsano I, Kahan E, Sarrell EM, Uziel Y. Effectiveness of an herbal preparation containing echinacea, propolis, and vitamin C in preventing respiratory tract infections in children: a randomized, double-blind, placebo-controlled, multicenter study. Arch Pediatr Adolesc Med. 2004 Mar;158(3):217-21.*

23 *Dorsch W. Clinical application of extracts of Echinacea purpurea or Echinacea pallida. Critical evaluation of controlled clinical studies. Z ArztlFortbild (Jena) 1996; 90: 117-22.*

24 *Taylor J.A. et al. Efficacy and safety of echinacea in treating upper respiratory tract infections in children: a randomized controlled trial. JAMA. 290(21):2824- 30, 2003.*

25 *Woelkart K, Linde K, Bauer R. Echinacea for preventing and treating the common cold. Planta Med. 2008 May;74(6):633-7. Epub 2008 Jan 10.*

influenzali e di altre malattie da raffreddamento (sinusiti, faringotracheiti, bronchiti, ecc). Generalmente, il trattamento del raffreddore e dell'influenza è sintomatico e prevede la somministrazione di farmaci antireumatici ed antinfiammatori, mentre nei soggetti ad elevato rischio si può prevedere l'utilizzo preventivo di farmaci antivirali[26].

Gli studi clinici pubblicati entro il 2004 che hanno valutato l'effetto dell'Echinacea nella prevenzione e nel trattamento delle malattie infettive delle prime vie aeree sono stati complessivamente 322, di cui solo 9 soddisfano tutti i requisiti qualitativi richiesti dalla letteratura internazionale. Di questi 6 hanno fornito risultati migliori del placebo mentre 3 non sono risultati a favore della droga[27].

Una metanalisi condotta nel gennaio 2006 ha valutato se l'Echinacea fosse migliore del placebo oppure simile ad altri trattamenti nelle prevenzione e/o nel trattamento delle malattie infettive delle prime vie aeree. Sono stati inclusi nella metanalisi solo gli studi clinici controllati che utilizzavano l'Echinacea in monocomponente sia verso placebo sia verso altri trattamenti nella prevenzione e/o nel trattamento delle malattie infettive delle prime vie aeree. Sono stati valutati 22 studi per un totale di oltre 3.300 pazienti, di cui 19 versus placebo, 2 versus nessun trattamento e 1 versus un'altra droga vegetale, tutti di qualità accettabile o buona. Di questi studi 19 valutavano l'azione curativa e 3 quella preventiva dell'Echinacea. I 3 studi che hanno indagato l'effetto preventivo hanno fornito risultati al limite della significatività statistica versus placebo, mentre per quanto attiene l'effetto curativo 9 studi indicano una superiorità significativa rispetto al placebo, 1 una superiorità al limite della significatività e 6 studi non superiorità rispetto al placebo. La metanalisi indica che sarebbero necessari ulteriori studi rigorosi di adeguata numerosità per stabilire l'effetto clinico dell'Echinacea[28].

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26 *Harrison - Principi di medicina interna, McGraw-Hill, 2007.*

27 "Extracts Echinacea is a herbal preparation that is frequently used to treat the common cold. **A total of 322 articles related to echinacea and colds, including 9 placebo-controlled clinical trials, were identified using the Medline and PubMed databases**. Eleven features of experimental design that affect the accuracy of the measurement of features of interest, the probability of a chance relationship, bias, and blinding were used to evaluate the 9 placebo-controlled studies. The criteria were validated case definition, quantifiable hypothesis, sample-size calculation, randomized assignment, double blinding, proof of blinding, measurement of compliance, measurement of drop-out rate, analysis by intention to treat, description of the methods of analysis, and measurement of probability. Equal weight was given to each criterion, since failure to meet any one of them could potentially invalidate the findings of a clinical trial. Results: **Of the 9 studies, 2 met all 11 criteria. The results of both studies were judged to be negative by the people who performed the studies. Of the remaining 7 studies, 6 were judged to have positive results, and 1 was judged to have negative results**. The criterion most commonly not met was proof of blinding. **This structured review suggests that the possible therapeutic effectiveness of echinacea in the treatment of colds has not been established**." *(Caruso TJ, Gwaltney JM Jr. Treatment of the common cold with echinacea: a structured review. Clin Infect Dis. 2005 Mar 15;40(6):807-10. Epub 2005 Feb 18).*

28 "…We included randomized controlled trials that compared mono-preparations of Echinacea with a placebo, no treatment, or another treatment for the prevention or treatment of common colds. Trials on combinations of Echinacea and other herbs were excluded. (…) **Sixteen trials including a total of 22 comparisons of an Echinacea preparation and a control group (19 with placebo, 2 with no treatment, 1 with another herbal preparation) met the inclusion criteria**. **All trials except one were described as double-blind. The majority had reasonable to good methodological quality**. Three comparisons investigated prevention of colds and 19 comparisons tested treatment of colds. A variety of different Echinacea preparations were used. None of the three comparisons in the prevention trials showed an effect over placebo. **Comparing an Echinacea preparation with placebo as treatment, a significant effect was reported in nine comparisons, a trend in one, and no difference in six**. More than one trial was available only for preparations based on the aerial parts from Echinacea purpurea.

Una successiva metanalisi (luglio 2007) ha valutato l'azione dell'Echinacea sull'incidenza e sulla durata della malattie da raffreddamento delle prime vie aeree (sindromi influenzali o febbrili con interessamento delle vie respiratorie superiori). Sono stati inclusi 14 studi clinici controllati, i quali indicano che l'echinacea riduce l'incidenza di queste patologie del 58% ($p<0,001$) e la durata del singolo fatto infettivo di 1,4 giorni ($p<0,01$). Gli effetti avversi segnalati si sono limitati a sporadici casi di reazioni allergiche cutanee. La metanalisi conferma che gli estratti di Echinacea riducono in misura significativa l'incidenza e la durata delle malattie infettive delle prime vie aeree[29].

Attività cicatrizzante. L'impiego storico dell'Echinacea in medicina è rappresentato dal trattamento locale delle ulcerazioni e di talune patologie dermatologiche, e si basa sulla semplice osservazione della capacità della pianta di accelerare la rigenerazione tissutale e di ridurre i rischi di infezione. Secondo il Benigni (1963) "l'azione locale si manifesta con una inibizione della jaluronidasi da cui deriva la stabilizzazione degli acidi jaluronici che vengono così sottratti all'azione depolimerizzante dell'enzima. Ne consegue un ritardo dell'assorbimento delle sostanze iniettate nei tessuti, una diminuita possibilità di diffusione dei germi infettanti che tendono perciò a localizzarsi nel punto in cui è avvenuta l'infezione e, infine, un accumulo di mucopolisaccaridi (acidi glicuronici in particolare e dialtre sostanze PAS-positive) atti a fornire il materiale istoplastico che verrà utilizzato nel corso dei processi riparativi e rigenerativi dei tessuti". Gli effetti benefici dell'Echinacea nella guarigione di ferite e nella prevenzione di infezioni sistemiche conseguenti a ferite o traumi, sono dovuti – oltre all'attività immunomodulante aspecifica – all'inibizione delle ialuronidasi, che idrolizzando i glicosaminoglicani nei tessuti sottocutanei permettono a microorganismi o veleni di raggiungere i vasi ematici e diffondere nell'organismo, nonché all'inibizione degli enzimi elastasici. La somministrazione della droga sembra invece non influire sulla modulazione del rilascio di

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Authors' conclusions: Echinacea preparations tested in clinical trials differ greatly. There is some evidence that preparations based on the aerial parts of Echinacea purpurea might be effective for the early treatment of colds in adults but results are not fully consistent. **Beneficial effects of other Echinacea preparations, and for preventative purposes might exist but have not been shown in independently replicated, rigorous randomized trials**." *(Linde K, Barrett B, Wölkart K, Bauer R, Melchart D. Echinacea for preventing and treating the common cold. Cochrane Database Syst Rev.2006 Jan 25;(1):CD000530).*

[29] "Echinacea is one of the most commonly used herbal products, but controversy exists about its benefit in the prevention and treatment of the common cold. Thus, **we did a meta-analysis evaluating the effect of echinacea on the incidence and duration of the common cold. 14 unique studies were included in the meta-analysis. Incidence of the common cold was reported as an odds ratio (OR) with 95% CI, and duration of the common cold was reported as the weighted mean difference (WMD) with 95% CI.** Weighted averages and mean differences were calculated by a random-effects model (DerSimonian-Laird methodology). Heterogeneity was assessed by the Q statistic and review of L'Abbé plots, and publication bias was assessed through the Egger weighted regression statistic and visual inspection of funnel plots. **Echinacea decreased the odds of developing the common cold by 58% (OR 0.42; 95% CI 0.25-0.71; Q statistic p<0.001) and the duration of a cold by 1.4 days (WMD -1.44, -2.24 to -0.64; p=0.01). Similarly, significant reductions were maintained in subgroup analyses limited to Echinaguard/Echinacin use, concomitant supplement use, method of cold exposure, Jadad scores less than 3, or use of a fixed-effects model. Published evidence supports echinacea's benefit in decreasing the incidence and duration of the common cold**." *(Shah SA, Sander S, White CM, Rinaldi M, Coleman CI. Evaluation of echinacea for the prevention and treatment of the common cold: a meta-analysis. Lancet Infect Dis. 2007 Jul;7(7):473-80).*

glucocorticoidi[30]. I derivati dell'acido caffeico sembrano, fra i componenti della droga, i più attivi nell'inibire le ialuronidasi: l'acido cicorico e l'acido caffarico risultano gli inibitori più potenti con una IC_{50} di 0,42 e 0,61 mM, rispettivamente, mentre la cinarina e l'acido clorogenico risultano più deboli (1,85 e 2,22 mM, rispettivamente)[31]. Buone evidenze supportano inoltre l'attività antijaluronidasica dell'echinacoside, uno dei principali componenti del fitocomplesso di *E. pallida*[32,33]. L'uso esterno dell'Echinacea trova pertanto indicazione nella cura delle ulcere, delle ferite infette e delle ustioni; preparazioni della droga sono impiegate anche nel trattamento di infiammazioni e piccole lesioni della mucosa orale e delle gengive.

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[30] "Healing of open skin wounds begins with an inflammatory response. Restraint stress has been well documented to delay wound closure, partially via glucocorticoid (GC)-mediated immunosuppression of inflammation. Echinacea, a popular herbal immunomodulator, is purported to be beneficial for wound healing. To test the hypothesis, an alcohol extract of E. pallida was administrated orally to mice for 3 days prior to, and 4 days post wounding with a dermal biopsy on the dorsum. Concomitantly, mice were exposed to 3 cycles of daily restraint stress prior to, and 4 cycles post wounding. **Echinacea accelerated wound closure in the stressed mice, but had no apparent wound healing effect for the non-stressed mice when compared to their respective controls**. To test if the positive healing effect is through modulation of GC release, plasma corticosterone concentrations were measured in unwounded mice treated with restraint stress and the herbal extract for 4 days. Plasma GC in restraint stressed mice gavaged with Echinacea was not different from mice treated with restraint only, but was increased compared to the vehicle control. This data suggests that **the improved wound healing effect of Echinacea in stressed mice is not mediated through modulation of GC signaling**." *(Zhai Z, Haney DM, Wu L, Solco AK, Murphy PA, Wurtele ES, Kohut ML, Cunnick JE. Alcohol extract of Echinacea pallida reverses stress-delayed wound healing in mice. Phytomedicine. 2009 Jun;16(6-7):669-78. Epub 2009 Mar 20).*

[31] *Facino RM, Carini M, Aldini G, Marinello C, Arlandini E, Franzoi L, Colombo M, Pietta P, Mauri P. Direct characterization of caffeoyl esters with antihyaluronidase activity in crude extracts from Echinacea angustifolia roots by fast atom bombardment tandem mass spectrometry. Farmaco 1993; 48: 1447-61).*

[32] "Phytochemical constituents of medicinal plants demonstrate inhibition of tissue and bacterial hyaluronidase. **Echinacoside is a caffeoyl conjugate of Echinacea with known anti-hyaluronidase properties**. The **purpose of this study was to investigate the wound healing effects of Echinacea on vocal fold wound healing and functional voice outcomes. Pig animal model**. Methods: Vocal fold injury was induced in 18 pigs by unilateral vocal fold stripping. The uninjured vocal fold served as control. Three groups of six pigs randomly received a topical application of 300, 600, or 1,200 mg of standardized Echinacea on the injured side. Animals were euthanized after 3, 10, and 15 days of wound healing. Phonation threshold pressure and vocal economy measurements were obtained from excised larynges. Treatment outcomes were examined by comparing the animals receiving treatment with a set of 19 untreated and 5 historical controls. Treatment effects on wound healing were evaluated by histologic staining for hyaluronan and collagen. **Treated larynges revealed improved vocal economy and phonation threshold pressure compared with untreated larynges. Histologically, treated vocal folds revealed stable hyaluronan content and no significant accumulation of collagen compared with control. Findings provide a favorable outcome of anti-hyaluronidase treatment on acute vocal fold wound healing and functional measures of voice**." *(Rousseau B, Tateya I, Lim X, Munoz-del-Rio A, Bless DM. Investigation of anti-hyaluronidase treatment on vocal fold wound healing. J Voice. 2006 Sep;20(3):443-51).*

[33] "Among the different species belonging to the Echinacea family, largely used in traditional medicine, Echinacea pallida, Echinacea purpurea and Echinacea angustifolia were investigated. (…) In particular, echinacoside, a caffeoyl derivative, is present in E. pallida and only in traces in E. angustifolia. It seems to have protective effects on skin connective tissue and to enhance wound healing. **The anti-inflammatory and wound healing activities of echinacoside, compared with the ones of the total root extract of E. pallida and E. angustifolia, were examined in rats, after topical application**. The tissues of the treated animals were evaluated after 24, 48 and 72 h treatment and excised for histological observation at the end of the experiment. **Results confirm the good anti-inflammatory and wound healing properties of E. pallida and of its constituent echinacoside, with respect to E. purpurea and control. This activity probably resides in the antihyaluronidase activity of echinacoside**." *(Speroni E, Govoni P, Guizzardi S, Renzulli C, Guerra MC. Anti-inflammatory and cicatrizing activity of Echinacea pallida Nutt. root extract. J Ethnopharmacol. 2002 Feb;79(2):265-72).*

Attività antinfiammatoria. *In vivo* è stata dimostrata una attività antinfiammatoria della frazione polisaccaridica dell'Echinacea in modelli sperimentali diversi di infiammazione nel ratto. La frazione è risultata attiva somministrata sia per via parenterale sia in applicazione topica[34]. Ricerche più recenti, mirate ad individuare i componenti attivi di *E. pallida,* evidenziano l'attività antiinfiammatoria della frazione lipofila del fitocomplesso, in particolare dei composti alchilamidici e chetonici, soprattutto attraverso un meccanismo di inibizione della produzione di PGE_2[35]. Estratti metanolici di *Echinacea pallida* radice hanno poi mostrato un'attività antiossidante i cui meccanismi includono azione scavenging dei radicali liberi e chelazione dei metalli di transizione[36], ed i caffeoil derivati presenti nella droga (p.e. echinacoside) hanno protetto il collagene dalla degradazione indotta dai ROS in modo dose-dipendente[37]. È infine importante sottolineare come, riguardo all'azione antiossidante, l'effetto più evidente si osserva con il fitocomplesso totale della droga, grazie agli effetti di sinergia che si sviluppano tra i componenti delle diverse frazioni[38].

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[34] *Tubaro A, Tragni E, Del Negro P, Galli CL, Della Loggia R. Anti-inflammatory activity of a polysaccharidic fraction of Echinacea angustifolia. J Pharm Pharmacol. 1987 Jul;39(7):567-569.*

[35] "…Researchers have been actively investigating which Echinacea constituent or groups of constituents are necessary for immune-modulating bioactivities. **Our prior studies indicate that alkylamides may play an important role in the inhibition of prostaglandin E2 (PGE(2)) production**. High-performance liquid chromatography fractionation, employed to elucidate interacting anti-inflammatory constituents from ethanol extracts of Echinacea purpurea, Echinacea angustifolia, Echinacea pallida, and Echinacea tennesseensis, identified fractions containing alkylamides and ketones as key anti-inflammatory contributors using lipopolysaccharide-induced PGE(2) production in RAW264.7 mouse macrophage cells. **Nitric oxide (NO) production and parallel cytotoxicity screens were also employed to substantiate an anti-inflammatory response**. **E. pallida showed significant inhibition of PGE(2) with a first round fraction, containing gas chromatography-mass spectrometry (GC-MS) peaks for Bauer ketones 20, 21, 22, 23, and 24, with 23 and 24 identified as significant contributors to this PGE(2) inhibition.** Chemically synthesized Bauer ketones 21 and 23 at 1 microM each significantly inhibited both PGE(2) and NO production. Three rounds of fractionation were produced from an E. angustifolia extract. GC-MS analysis identified the presence of Bauer ketone 23 in third round fraction 3D32 and Bauer alkylamide 11 making up 96% of third round fraction 3E40. Synthetic Bauer ketone 23 inhibited PGE(2) production to 83% of control, and synthetic Bauer alkylamide 11 significantly inhibited PGE(2) and NO production at the endogenous concentrations determined to be present in their respective fraction; thus, each constituent partially explained the in vitro anti-inflammatory activity of their respective fraction. From this study, two key contributors to the anti-inflammatory properties of E. angustifolia were identified as Bauer alkylamide 11 and Bauer ketone 23." *(LaLone CA, Rizshsky L, Hammer KD, Wu L, Solco AK, Yum M, Nikolau BJ, Wurtele ES, Murphy PA, Kim M, Birt DF. Endogenous levels of Echinacea alkylamides and ketones are important contributors to the inhibition of prostaglandin E2 and nitric oxide production in cultured macrophages. J Agric Food Chem. 2009 Oct 14;57(19):8820-30).*

[36] *Hu C, Kitts DD. Studies on the antioxidant activity of Echinacea root extract. J Agric Food Chem 2000;48: 1466-72.*

[37] *Sloley BD, Urichuk LJ, Tywin C, Coutts RT, Pang PKT, Shan JJ. Comparison of chemical components and antioxidant capacity of different Echinacea species. J Pharm Pharmacol 2001;53:849-57.*

[38] "Preparations of Echinacea are widely used as alternative remedies to prevent the common cold and infections in the upper respiratory tract. **After extraction, fractionation, and isolation, the antioxidant activity of three extracts, one alkamide fraction, four polysaccharide-containing fractions, and three caffeic acid derivatives from Echinacea purpurea root was evaluated by measuring their inhibition of in vitro Cu(II)-catalyzed oxidation of human low-density lipoprotein (LDL)**. The antioxidant activities of the isolated caffeic acid derivatives were compared to those of echinacoside, caffeic acid, and rosmarinic acid for reference. **The order of antioxidant activity of the tested substances was cichoric acid > echinacoside > or = derivative II > or = caffeic acid > or = rosmarinic acid > derivative I.** Among the extracts the 80% aqueous ethanolic extract exhibited a 10 times longer lag phase prolongation (LPP) than the 50% ethanolic extract, which in turn exhibited a longer LPP than the water extract. Following ion-exchange chromatography of the water extract, the majority of its antioxidant

Attività antivirale. L'Echinacea possiede attività antivirale. I virus più sensibili alla droga sembrerebbero essere l'*Herpes simplex* tipo 1 e l'influenza tipo A2. È noto che alcuni virus associati alle malattie delle vie aeree stimolano la secrezione di citochine proinfiammatorie. Uno studio ha valutato l'effetto di un estratto secco di *Echinacea purpurea* sulla produzione di citochine proinfiammatorie indotta dai virus in cellule epiteliali bronchiali umane. Si è visto che i Rhinovirus 1A e 14, i virus influenzali, il virus respiratorio sinciziale, gli adenovirus 3 e 11 e il virus dell'*Herpes simplex* tipo 1 inducevano la secrezione di IL6 e IL8 e che l'estratto di Echinacea la inibiva. Inoltre l'estratto mostrava una certa azione viruscida a livello delle membrane virali. Lo studio indica che le preparazioni a base di Echinacea possono ostacolare sia lo sviluppo delle infezioni virali[39] che la secrezione di citochine proinfiammatorie indotta da diverse tipologie di virus a livello dell'epitelio delle vie aeree[40]. L'efficacia terapeutica in alcune malattie virali potrebbe anche derivare da un concorso di attività antinfiammatoria, antiossidante ed immunomodulante. Uno studio *in vitro* ha

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activity was found in the latest eluted fraction (H2O-acidic 3). **The antioxidant activity of the tested Echinacea extracts, fractions, and isolated compounds was dose dependent. Synergistic antioxidant effects of Echinacea constituents were found when cichoric acid (major caffeic acid derivative in E. purpurea) or echinacoside (major caffeic acid derivative in Echinacea pallida and Echinacea angustifolia) were combined with a natural mixture of alkamides and/or a water extract containing the high molecular weight compounds. This contributes to the hypothesis that the physiologically beneficial effects of Echinacea are exerted by the multitude of constituents present in the preparations**." *(Dalby-Brown L, Barsett H, Landbo AK, Meyer AS, Mølgaard P. Synergistic antioxidative effects of alkamides, caffeic acid derivatives, and polysaccharide fractions from Echinacea purpurea on in vitro oxidation of human low-density lipoproteins. J Agric Food Chem. 2005 Nov 30;53(24):9413-23).*

39 "**We evaluated the antirhinovirus efficacy of a standardized preparation of Echinacea purpurea (Echinaforce(R)) in a 3-dimensional organotypic model of normal human airway epithelium (EpiAirway tissue)**. Individual replicate tissue samples, maintained as inserts in culture for 3 days or 3 weeks, were infected with rhinovirus type 1A (RV1A), Echinacea alone, a combination of the two, or medium only. None of the treatments affected the histological appearance or integrity of the tissues, all of which maintained a high level of cell viability and preservation of cilia. **RV infection resulted in increased mucopolysaccharide inclusions in the goblet cells, but this feature was reversed by Echinacea treatment. This result was confirmed by measurements of mucin secretion, which was stimulated by RV but reversed by Echinacea, suggesting that mucus production during colds could be ameliorated by Echinacea.** We did not find evidence of virus replication, although the RV-infected tissues secreted substantial amounts of the pro-inflammatory cytokines IL-6 and IL-8 (CXCL8), and this response was reversed by Echinacea treatment. These results confirmed previous findings derived from studies of bronchial and lung epithelial cell lines, namely, that RV infection results in a substantial inflammatory response in the absence of virus replication." *(Sharma M, Schoop R, Hudson J. The efficacy of Echinacea in a 3-D tissue model of human airway epithelium. Phytother Res. 2010 Jun;24(6):900-4.*

40 "Several viruses associated with upper respiratory diseases have been shown to stimulate the secretion of pro-inflammatory cytokines, including chemokines, sometimes in the absence of viral cytopathology. We **evaluated the ability of a standardized preparation of the popular herbal medicine Echinacea** (Echinaforce, an ethanol extract of herb and roots of E. purpurea) **to inhibit the viral induction of various cytokines in a line of human bronchial epithelial cells (BEAS-2B), and in two other human cell lines**. All of the viruses tested, **rhinoviruses 1A and 14**, **influenza virus, respiratory syncytial virus, adenovirus types 3 and 11, and herpes simplex virus type 1**, induced substantial secretion of IL-6 and IL-8 (CXCL8), in addition to several other chemokines, depending on the virus, although only viable viruses were able to do this. In every case however Echinacea inhibited this induction. The Echinacea preparation also showed potent virucidal activity against viruses with membranes, indicating the multi-functional potential of the herb. **These results support the concept that certain Echinacea preparations can alleviate "cold and flu" symptoms, and possibly other respiratory disorders, by inhibiting viral growth and the secretion of pro-inflammatory cytokines**." *(Sharma M, Anderson SA, Schoop R, Hudson JB. Induction of multiple pro-inflammatory cytokines by respiratory viruses and reversal by standardized Echinacea, a potent antiviral herbal extract. Antiviral Res. 2009 Aug;83(2):165-70. .*

esaminato l'effetto sia di un estratto idroalcolico sia del succo pressato di *Echinacea pallida* sugli Herpes virus di tipo 1 e 2, evidenziando una significativa azione antivirale di tipo dose dipendente. Il succo di *Echinacea pallida* aveva un'azione antivirale ancora più marcata rispetto all'estratto idroalcolico, mostrandosi attivo in ogni fase della replicazione virale[41]. Per tutti questi motivi, l'uso dell'Echinacea può essere utile in alcune infezioni virali che, in condizioni di immunodepressione, possono recidivare o assumere quadri clinici più marcati, quali p.e. le infezioni da *Herpes labialis*[42]. Uno studio recente ha mostrato come in pazienti anziani sottoposti a vaccino anti-influenzale, la somministrazione di tinture alcoliche di varie specie di Echinacea (angustifolia, pallida, purpurea, ecc.) nel periodo precedente la vaccinazione, abbia differenti effetti sul pattern di citochine prodotte. Le successive colture in vitro dei linfociti di pazienti trattati con le varie preparazioni di Echinacea hanno mostrato una riduzione della produzione di IL-2 e IFN-γ e alcune di esse (*E. angustifolia, purpurea*) un aumento di IL-10 rispetto ai controlli[43]. Siccome IL-10 pare sia necessaria per lo sviluppo di una sottoclasse specifica di anticorpi in risposta al vaccino (11), la somministrazione di Echinacea al momento del vaccinazione potrebbe favorire la risposta all'infezione stimolando la proliferazione di specifiche popolazioni cellulari.

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41 "**Hydroalcoholic extracts and pressed juice from Echinacea pallida** were phytochemically characterised by HPLC-MS analyses. Ferulic and caffeic acid derivatives were identified as major constituents. All tested extracts and pressed juice from Echinacea pallida exhibited a low cytotoxic activity on monkey kidney cells in vitro. **The inhibitory activity of echinacea against herpes simplex virus types 1 and 2 (HSV-1, HSV-2) was analysed with plaque reduction assays**. **All hydroalcoholic extracts exhibited high levels of antiviral activity against both types of herpesvirus in a dose-dependent manner.** Plaque formation was significantly reduced by more than 99 % or completely absent. **Pressed juice from E. pallida revealed the highest antiviral activity against HSV-1 and HSV-2 when compared to hydroalcoholic echinacea extracts and even highly diluted echinacea pressed juice still inhibited viral infectivity. Hydroalcoholic extracts were quite active against herpetic infection when HSV-1 or HSV-2 were pretreated with the extracts. In contrast, echinacea pressed juice revealed antiviral activity during all phases of the viral replication cycle. Additionally, echinacea pressed juice demonstrated protection of cells against viral infection.** In conclusion, hydroalcoholic Echinacea pallida extracts interfere with free herpesvirus but pressed juice is able to interact with herpesvirus inside and outside the cell as well as to protect cells against viral infection, probably by interfering with virus attachment. **Hydroalcoholic extracts and pressed juice from E. pallida demonstrated high selectivity indices, a necessary prerequisite for a potential topical treatment of herpetic infections**. Different types of echinacea preparations, such as commercial tinctures, tablets, and teas, are expected to offer different antiviral profiles." *(Schneider S, Reichling J, Stintzing FC, Messerschmidt S, Meyer U, Schnitzler P. Anti-herpetic Properties of Hydroalcoholic Extracts and Pressed Juice from Echinacea pallida. Planta Med. 2010;78(3):265-272*

42 *Ghaemi A, Soleimanjahi H, Gill P, Arefian E, Soudi S, Hassan Z. Echinacea purpurea polysaccharide reduces the latency rate in herpes simplex virus type-1 infections. Intervirology. 2009;52(1):29-34.*

43 "…Cells were cultured for 48 hours; following incubation, supernatants were collected and assayed for interleukin-2, interleukin-10, and interferon-gamma production, cytokines important in the immune response to viral infection. Four species (E. angustifolia, E. purpurea, E. simulata, E. tennesseensis) augmented IL-10 production, diminished IL-2 production, and had no effect on IFN-gamma production. Echinacea pallida suppressed production of all cytokines; E. paradoxa and E. sanguinea behaved similarly, although to a lesser extent. (…) **Our data support and extend previous research and indicate that tinctures from different Echinacea species have different patterns of immune modulation; further, they indicate that certain species may be efficacious in the immune response to viral infection**." *(Schneider S, Reichling J, Stintzing FC, Messerschmidt S, Meyer U, Schnitzler P. Anti-herpetic Properties of Hydroalcoholic Extracts and Pressed Juice from Echinacea pallida. Planta Med. 2010;78(3):265-272*

Attività sull'apparato urinario. Per la sua attività antiinfiammatoria e moderatamente antisettica, l'Echinacea viene utilizzata – sia da sola che insieme ad altri fitocomplessi – in caso di condizioni infiammatorie dell'apparato urinario, particolarmente quando un difficoltoso svuotamento della vescica può aumentare il rischio di infezioni delle basse vie urinarie, e in caso di candidosi.

Attività antibatterica. Diversi lavori scientifici riportano l'attività antibatterica del principale composto polifenolico isolato dalle radici di *E. pallida*, l'echinacoside. L'attività dell'echinacoside è particolarmente evidente sullo *Staphylococcus aureus*, e in misura inferiore anche sull'*Escherichia coli* e sulla *Pseudomosa aeruginosa*. L'estratto alcolico di *Echinacea angustifolia* ha dimostrato *in vitro* una attività inibente nei confronti del *Trichomonas vaginalis*[44]. Gli estratti di *Echinacea purpurea* si sono invece dimostrati efficaci nei confronti di *Streptococcus pyogenes*, *Hemophilus influenzae* and *Legionella pneumophila*, *Staphylococcus aureus* (meticillino-resistente) e *Mycobacterium smegmatis*[45].

Altre attività. È stata recentemente descritta un'attività citotossica diretta nei confronti di cellule cancerose per due composti isolati dall'estratto in n-esano delle radici di *E. pallida*[46].

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44 *Giusti E. Echinacea. Botanica, chimica, farmacologia e terapia. Erboristeria Domani, Novembre 1992, pag. 64-76.*

45 "Common symptoms of upper respiratory infections, such as sore throat, cough, and inflammation, are often caused by bacteria, sometimes as a complication of virus infection. Extracts of Echinacea purpurea (Asteraceae) have been advocated traditionally for use by individuals suffering from these symptoms, although the underlying basis for the beneficial effects of Echinacea is not known. **We hypothesized that Echinacea could inactivate certain respiratory bacteria and could also reverse inflammatory effects caused by these bacteria in epithelial cells**. In order to test this we used a commercial standardized extract of Echinacea purpurea (Echinaforce((R)), and a novel cytokine array system designed to measure simultaneously the levels of 20 different cytokines secreted by bronchial epithelial cell cultures in response to infection. **Streptococcus pyogenes (Group A Strep), which is often associated with sore throat and more severe pulmonary infections, was readily inactivated by Echinacea, which also completely reversed the cellular pro-inflammatory response. Hemophilus influenzae and Legionella pneumophila were also readily inactivated, and their pro-inflammatory responses reversed**. **Staphylococcus aureus (methicillin-resistant and sensitive strains) and Mycobacterium smegmatis were less sensitive to the bactericidal effects of Echinacea however, but their pro-inflammatory responses were still completely reversed. In contrast some other pathogens tested, including Candida albicans, were relatively resistant.** Thus Echinaforce((R)) exerts a dual action against several important respiratory bacteria, a killing effect and an anti-inflammatory effect. These results support the concept of using a standardized Echinacea preparation to control symptoms associated with bacterial respiratory infections." *(Sharma SM, Anderson M, Schoop SR, Hudson JB. Bactericidal and anti-inflammatory properties of a standardized Echinacea extract (Echinaforce((R))): Dual actions against respiratory bacteria. Phytomedicine. 2010; 17 (8-9):563-566.*

46 "**The n-hexane extracts of the roots of three medicinally used Echinacea species exhibited cytotoxic activity on human cancer cell lines, with Echinacea pallida found to be the most cytotoxic**. Acetylenes are present in E. pallida lipophilic extracts but essentially absent in extracts from the other two species. **In the present study, the cytotoxic effects of five compounds, two polyacetylenes (namely, 8-hydroxy-pentadeca-(9E)-ene-11,13-diyn-2-one (1) and pentadeca-(9E)-ene-11,13-diyne-2,8-dione (3)) and three polyenes (namely, 8-hydroxy-pentadeca-(9E,13Z)-dien-11-yn-2-one (2), pentadeca-(9E,13Z)-dien-11-yne-2,8-dione (4) and pentadeca-(8Z,13Z)-dien-11-yn-2-one (5)), isolated from the n-hexane extract of E. pallida roots by bioassay-guided fractionation, were investigated and the potential bioavailability of these compounds in the extract was studied**. Experimental approach: Cytotoxic effects were assessed on human pancreatic MIA PaCa-2 and colonic COLO320 cancer cell lines. Cell viability was evaluated by the WST-1 assay and apoptotic cell death by the cytosolic internucleosomal DNA enrichment and the caspase 3/7 activity tests. Caco-2 cell monolayers were used to assess the potential bioavailability of the acetylenes. Key results: The five compounds exhibited concentration-dependent cytotoxicity in both cell types, with a greater potency in the colonic cancer cells. Apoptotic cell death was found to be involved in the cytotoxic effect of the most active, compound 5. Compounds 2 and 5 were found to cross the Caco-2 monolayer with apparent permeabilities above 10 x 10(-6) cm s(-1). Conclusions and implications: **Compounds isolated from n-hexane extracts of E.**

Tollerabilità. L'Echinacea viene ritenuta una droga generalmente sicura. In rari casi sono stati riscontrati lievi disturbi gastrointestinali, vertigini e allergie cutanee in soggetti sensibili. La droga va pertanto usata con cautela in soggetti atopici. Per effetto della sua attività farmacologica, l'uso di *Echinacea sp.p.* è controindicato in pazienti in terapia immunosoppressiva (p.e. trapianti, malattie autoimmuni) e nei soggetti affetti da disturbi sistemici progressivi o patologie autoimmuni come AIDS/HIV, lupus, malattia tubercolare, sclerosi multipla, leucocitosi, patologie del tessuti connettivo, collagenosi[47]. Studi in vitro hanno evidenziato la capacità degli estratti di Echinacea di inibire in maniera significativa alcune isoforme del citocromo P450, tra cui CYP3A4; tale effetto, che appare correlato al contenuto in alchilammidi della droga[48], non sembra tuttavia essere clinicamente rilevante[49,50]. Infine, la somministrazione di preparazioni a base di Echinacea potrebbe potenziare l'effetto negativo sul fegato di farmaci epatotossici come paracetamolo, steroidi anabolizzanti, amiodarone, metotressato e chetoconazolo[51].

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pallida roots have a direct cytotoxicity on cancer cells and good potential for absorption in humans when taken orally." *(Chicca A, Pellati F, Adinolfi B, Matthias A, Massarelli I, Benvenuti S, Martinotti E, Bianucci AM, Bone K, Lehmann R, Nieri P. Cytotoxic activity of polyacetylenes and polyenes isolated from roots of Echinacea pallida. Br J Pharmacol. 2008 Mar;153(5):879-85).*

47 *ESCOP Monographs. Echinaceae pallida radix. The Scientific Foundation for Herbal Medicinal Products. 2nd edition, Thieme, 2003.*

48 *Toselli F, Matthias A, Gillam EM. Echinacea metabolism and drug interactions: the case for standardization of a complementary medicine. Life Sci. 2009 Jul 17;85(3-4):97-106.*

49 *Freeman C, Spelman K. A critical evaluation of drug interactions with Echinacea spp. Mol Nutr Food Res. 2008 Jul;52(7):789-98.*

50 *Heinrich M, Modarai M, Kortenkamp A. Herbal extracts used for upper respiratory tract infections: are there clinically relevant interactions with the cytochrome P450 enzyme system? Planta Med. 2008 May;74(6):657-60.*

51 *Kligler B. Echinacea. Am Fam Physician. 2003 Jan 1;67(1):77-80.*