90 YEARS 1933-2023

RESEARCH DOSSIER

Echinacea purpurea (L.) Moench
DRY EXTRACT 4%

Ekin ACT®

the activity of mountain
Echinacea for the immune system

1-Botanical information:

Echinacea purpurea (L.) Moench, commonly called **purple coneflower**, is a perennial herb in the botanical family of Asteraceae (Compositae or Daisy/Sunflower family); native to North American prairies and mountains, it is now cultivated worldwide in temperate regions (1-3). The typical habitat for Echinacea spp. is open and sunny fields, barren lands, with rocky to sandy-clay soils, up to an altitude of 1.500 mt (4).

Echinacea grows up to 120 cm, with a taproot, a simple, empty, hirsute stem, lanceolate or linear-lanceolate leaves (10-20 cm long and 1.5-10 cm broad), cone-shaped flowers (inflorescences), with purple/reddish florets. Blooming time is late spring to mid-summer (the epigeous part dries up and dies in fall) (1-3). The herb has a characteristic odor, mild and aromatic; the taste is initially sweet, but quickly it becomes bitter, followed by a tingling sensation on the tongue (3).

It is used for ornamental purposes too; it appeared in German and English gardens since the end of the 18th century (5).

The genus name comes from the Greek word "echinos" meaning "sea urchin" or "hedgehog", after the shape of the spiky seedheads. The Echinacea genus includes several species, very similar among them from a morphologic point of view, that have been differentiated only in recent years (3), hence the importance of the DNA barcoding test to confirm the correct identification. Moreover, it is known that some Echinacea species may be confused or adulterated with *Parthenium integrifolium* (1). Current herbal preparations, which have become very popular in Western Countries, have tended to prefer *E. purpurea* over other species; also, the majority of scientific studies have focused on purple coneflower (14).

2- Parts used:

The plant material consists of the dried flowering aerial part of *Echinacea purpurea* (L.) Moench. The drug is DNA certified

EPO DNA® CERTIFIED EXTRACTS

to prevent possible adulteration with similar species of Echinacea by design (some species are cheaper than others) or default (some species look truly alike); it comes exclusively from an Italian cultivation chain in the Alps (Valle Giudicaria, Trento): the mountain crop is probably contributing to its rich phytochemical profile.

MOUNTAIN CROP IN VALLE GIUDICARIA

WATCH OUR VIDEO:
https://www.youtube.com/watch?v=6VHz6sG4osI

3-Active constituents:

Aerial parts of *E. purpurea* contain (1): water-soluble polysaccharides; volatile oil (under 0.08-0.32%), including germacrene alcohol, borneol, bornyl acetate, pentadeca-8-en-2-on, germacrene D, caryophyllene, caryophyllene epoxide; alkamides; flavonoids, tannins and phenolic acids (i.e. chicoric, caftaric and chlorogenic acids) are also present.

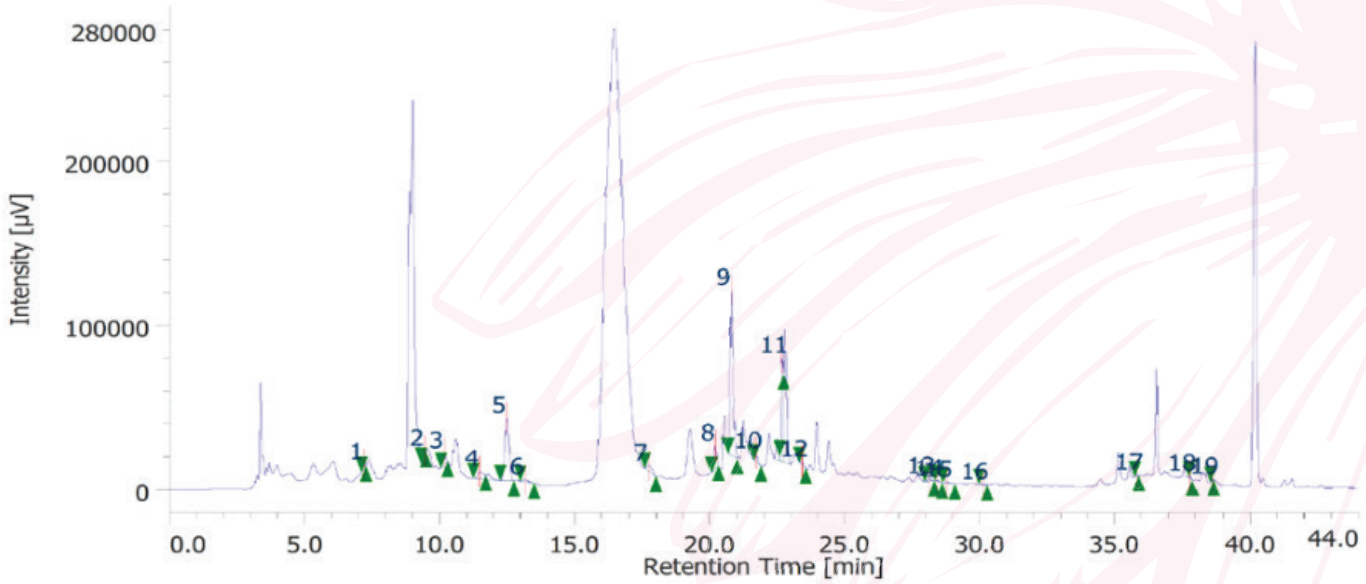

Figure 1. HPLC-DAD Chromatogram related to the analysis of phenolic compounds of EkinACT®. 1. and 2. Gallic acid (sum of the two peaks); 3. 3-hydroxytyrosol; 4. Caftaric acid; 5. Catechin; 6. Chlorogenic acid; 7. Epicatechin; 8. Caffeic acid; 9. Syringic acid; 10. Chicoric acid; 11. Coumaric acid; 12. Ferulic acid; 13. Rutin; 14. Benzoic acid; 15. Quercetin; 16. Cinnamic acid; 17. Naringenin; 18. Hesperitin; 19. Flavone.

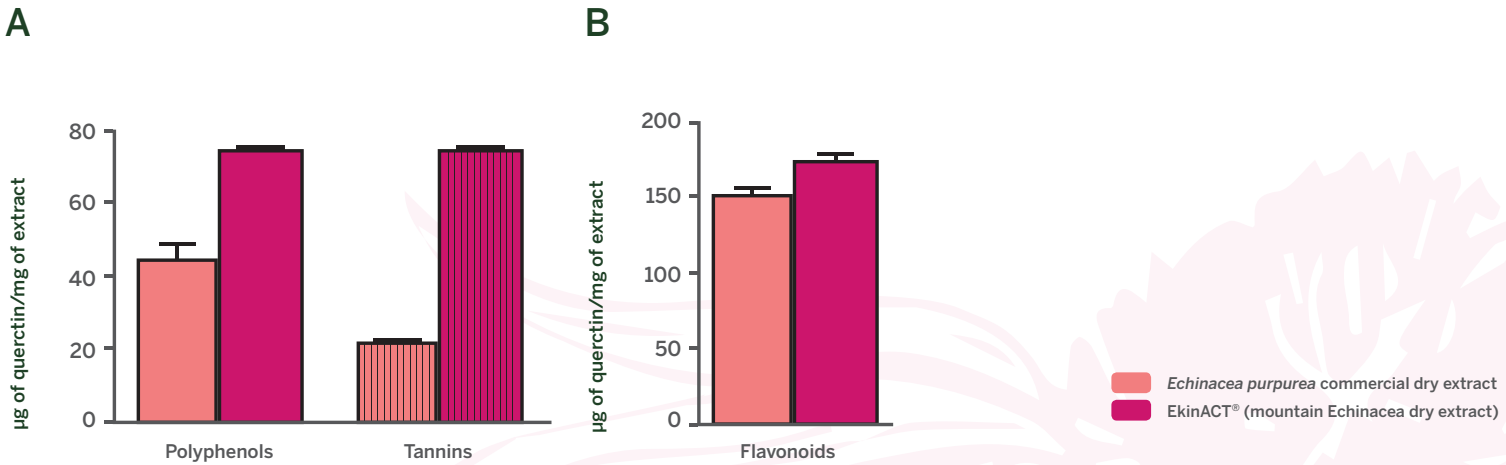

Figure 2. Levels of total polyphenols, tannins, and flavonoids in EkinACT® compared to a commercial dry extract of *Echinacea purpurea* (L.) Moench. Total polyphenols and tannins are expressed as tannic acid equivalents per mg of extract **(A)** while total flavonoids as quercetin equivalents per mg of extract **(B)**.

E. purpurea from mountain crops (EkinACT®) has a peculiar phytochemical profile: caftaric acid, chicoric acid, ferulic acid, 2-hydroxytirosol and catechin are particularly abundant compared to a commercial sample of *Echinacea purpurea*, while coumaric acid and rutin were absent in the latter.

Compounds	Concentration [µg/mg of the sample]	
	ECH	EC
Benzoic acid	0.040 ± 0.001	0.034 ± 0.001
Caffeic acid	0.330 ± 0.001	0.384 ± 0.003
Caftaric acid	3.154 ± 0.137	1.560 ± 0.050
Catechin	1.565 ± 0.014	0.341 ± 0.001
Chicoric acid	16.480 ± 0.041	7.663 ± 0.095
Chlorogenic acid	0.290 ± 0.001	0.239 ± 0.001
Cinnamic acid	0.027 ± 0.002	0.013 ± 0.001
Coumaric acid	0.065 ± 0.009	nd

Compounds	Concentration [µg/mg of the sample]	
	ECH	EC
Epicatechin	0.361 ± 0.013	0.573 ± 0.002
Ferulic acid	0.433 ± 0.001	0.246 ± 0.003
Gallic acid	0.371 ± 0.034	0.247 ± 0.040
Hesperitin	0.012 ± 0.001	0.016 ± 0.001
2-Hydroxytyrosol	5.440 ± 0.558	2.201 ± 0.001
Quercetin	0.005 ± 0.001	0.005 ± 0.001
Rutin	0.008 ± 0.001	nd
Syringic acid	0.139 ± 0.001	0.158 ± 0.001

nd: not detected

Table 1. Phenolic composition of EkinACT® (ECH) compared to a commercial sample of *Echinacea purpure* Dry Extract (EC)

4-Galenic forms:

In scientific studies, an ethanol extract of aerial parts of the dried plant or roots or an aqueous "pressed juice" have habitually been used (14).
EkinACT® is a dry extract of *E. purpurea* (L.) Moench flowering aerial parts, standardized to contain **4% phenolic acids**, **expressed as the sum of chicoric, caftaric and chlorogenic acids** (according to the HPLC official method of EP and USP).

5-Regulatory status:

Included in the Italian positive list, Decree 10 August 2018 plants, Annex 1 updated on 9 January 2019, 26 July 2019, 4 August 2021, 1 August 2022 and 13 December 2023
https://www.salute.gov.it/portale/temi/p2_6.jsp?id=1424&area=Alimenti%20particolari%20e%20integratori&menu=integratori

Included in the Therapeutic Goods (Permissible Ingredients) Determination that specifies those ingredients that may be contained in a medicine that is listed in in the Australian Register of Therapeutic Goods and requirements in relation to the inclusion of those ingredients in such medicines.
https://www.tga.gov.au/about-tga/legislation/legislation-and-legislative-instruments/therapeutic-goods-determinations#indications

6-Traditional uses:

Ethnobotanical studies, made by WHO, report, among the documented empirical uses of Echinacea spp., the use against snakebites, to heal wounds and as a primitive antibiotic (3). In experimental studies, antiviral, anticancer activity, and immunomodulatory effects have been described for different Echinacea species (3, 8). As extensively reported by Catanzaro et al. in a recent review (2018), several modulatory effects on the immune system have been demonstrated on both innate and acquired immunity. Studies suggest that Echinacea stimulates immune functions in both healthy and immune-suppressed animals. In macrophages, phagocytosis process and cytokine production (increased TNF-Ð, IL-1, IFN-ß) have been enhanced following treatment with Echinacea extracts; moreover, increased leukocytes mobility as well as activation of natural killer cells have also been reasonably demonstrated in animals and humans (11). Different Echinacea preparations are documented in the literature, however, no clear results emerged, due to the huge difference in terms of products tested and efficacy studies carried out. Fresh or dry herb, dried rhizome and roots, and alcoholic extracts are commercially available, often combined with Ginseng, Goldenseal, or Garlic (11). Echinacea preparations belong to the best-selling botanical drugs in the USA and Europe (11). The traditional use is also continuously supported by literature data. A systemic review carried out by Cochrane collaboration grouped 33 clinical trials with 4631 subjects for which common cold prevention activity was evaluated considering different preparations of Echinacea spp. Thanks to that, Echinacea is nowadays prescribed as a remedy for the short-term prevention and treatment of the common cold (9, 13). EkinACT® has a very rich chemical profile, as previously shown. In an unpublished preclinical study EkinACT® was able to modulate the immune response by increasing macrophage phagocytosis in a range of 30% - 40%, compared to control cells, so confirming the traditional use to boost the immune system; EkinACT® was also tested under inflammatory conditions induced by LPS (lipopolysaccharide): it counteracts the phagocytosis reduction induced by LPS and the increase of Nitric Oxide (NO). Moreover, EKINact® has good radical scavenger activity and protects cells from oxidative stress damage.

Furthermore, there are many studies highlighting the antiviral activity of Echinacea spp. against rhinovirus, influenza virus, respiratory syncytial virus, coronavirus, calicivirus, and herpes virus. However, results are controversial, and no clear mechanism of action and effects were found so far. It seems that the antiviral activity synergistically acts together with the anti-inflammatory properties of Echinacea (14).

7-Safety and warnings:

EMA does not recommend the use of Echinacea preparations, as for all immunostimulant agents, in cases of progressive systemic diseases, such as tuberculosis, diseases of the white blood cells system, multiple sclerosis, AIDS, HIV infections, and other immune diseases (9). Atopic patients and those with asthma should be cautious since rare allergic reactions have been reported (8-9, 12). Moreover, EMA reported that **the use in children (under 12 years of age) and during pregnancy and lactation is not recommended** due to a lack of adequate data. Echinacea may cause light allergic reactions if administered to sensitive subjects with known allergies to other members of the Asteraceae family (8-9). The EkinACT® suggested dose in adults is 300-600 mg/die.

8- References:

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9- Summary of the main clinical studies (source: NOL Database, www.foodchainid.com):

Table 2. **MAIN APPLICATION: IMMUNITY (UPPER RESPIRATORY TRACT)**

REFERENCE	DESIGN	SUBJECTS	SUPPLEMENTATION	RESULTS
ADULTS				
Hoheisel et al., 1997	Randomized, double-blind, placebo-controlled study	n = 120 Adults with symptoms of common cold	Group 1: 20 drops of a preparation containing 80 g of pressed juice from *E. purpurea*/100 g every 2 h for the first day, and thereafter 3 times /day Group 2: placebo 10 days	The median time taken to achieve recovery improvement was significantly shorter in the supplemented group in comparison to placebo ($p < 0.0001$).
Melchart et al., 1998	Three-armed, randomized, double-blind, placebo-controlled trial	n = 302 Volunteers with acute illness	Group 1: 100 drops/day of ethanolic extract of *E. purpurea roots* (DER = 1:11 in 30% alcohol) Group 2: 100 drops of ethanolic extract of E. *angustifolia roots* Group 3: placebo 12 weeks	The time until occurrence of the first upper respiratory tract infection was 66 days (95% confi- dence interval [CI],61-72 days) in the *E. angustifolia* group, 69 days (95% CI, 64-74 days) in the *E. purpurea* group, and 65 days (95% CI, 59-70 days) in the placebo group ($p = 0.49$). In the placebo group, 36.7% had an infection. In the treatment groups, 32% in the *E. angustifolia* group (relative risk compared with placebo, 0.87; 95% CI, 0.59-1.30) and 29.3% in the *E. purpurea* group (relative risk compared with placebo, 0.80; 95% CI, 0.53-1.31) had an infection. Participants in the treatment groups believed that they had more benefit from the medication than those in the placebo group ($p = 0.04$).
Grimm et al., 1999	Randomized, double-blind, placebo-controlled clinical study	n = 128 Adults with history of colds	Group 1: 8 mL /day of *Echinacea purpurea* fluid extract (22% ethanol, made from fresh expressed juice of whole flower roots) Group 2: placebo 8 weeks	The average number of colds and respiratory infections per patient was 0.78 in the Echinacea group, and 0.93 in the placebo group [difference = 0.15; 95% CI (-0.12, 0.41), $p = 0.33$]. Median duration of colds and respiratory infections was 4.5 days in the Echinacea group and 6.5 days in the placebo group (95% CI: -1, +3 days; $p = 0.45$). There were no significant differences between treatment groups in the number of infections in each category of severity
Brinkeborn et al., 1999	Randomized, double-blind, placebo-controlled clinical study	n = 246 Healthy adult volunteers with caught and common cold	Group 1: Echinaforce® 6 tablets/day (40.68 mg/d of *E. purpurea* crude extract) Group 2: Echinacea concentrate preparation, 6 tablets/day (289.62 mg/d of extract) Group 3: *E. purpurea* extract preparation, 6 tablets/day (177.6 mg/d of crude extract based on root only) Group 4: placebo From onset of the first symptoms until symptoms relief but for no longer than 7 days	Echinaforce® ($p = 0.02$) and Echinacea concentrate ($p = 0.003$) were significantly more effective than placebo for reducing the complaint associated with the cold. Only a tendency has been measured for the special *Echinacea purpurea* extract ($p = 0.06$).

MAIN APPLICATION: IMMUNITY (UPPER RESPIRATORY TRACT)

REFERENCE	DESIGN	SUBJECTS	SUPPLEMENTATION	RESULTS
ADULTS				
Schulten et al., 2001	Randomized, double-blind, placebo-controlled trial	n = 80 Patients with first signs of a cold	Group 1: 10 mL /day of *E. purpurea* (Echinacin® EC31J0: pressed juice from fresh flowering purple coneflower (1.7–2.5: 1) stabilized by ethanol) Group 2: placebo 10 days	In group 1 the median time of illness was 6.0 days compared to 9.0 days in the placebo group, assigning zero time for patients without a complete picture (one-sided p = 0.0112).
Yale et al, 2004	Randomized, double-blind, placebo-controlled study	n = 128 Subjects with frequent common cold episodes	Group 1: 300 mg/day of *E. purpurea* (freeze-dried pressed juice from the aerial portion of the plant) Group 2: placebo Until cold symptoms were relieved or until the end of 14 days	No significant difference was observed, at dosage tested, between treatment groups for either total symptom scores or mean individual symptom scores (p range = 0.29 - 0.90). The time to resolution of symptoms was not statistically different (p = 0.73).
Goel et al., 2004	Randomized, double-blind, placebo-controlled study	n = 282 Subjects with frequent common cold episodes	Group 1: Freshly harvested *E. purpurea* (Echinilin®), 10 doses (i.e. 40 mL of extract) the first day of cold symptoms and 4 doses (i.e. 16 mL of extract)/d for the next 6 days) Group 2: placebo 7 days	Total daily symptom scores were 23.1% lower in Echinacea group than in placebo (p < 0.01). 50% and 95% of the subjects in the intervention group showed at least a 50% reduction of their maximum total daily symptom scores by day 4 and 7, respectively, whereas this effect wasn't evident in the placebo group until approximately 5.5 days.
Sperber et al., 2004	Randomized, double-blind, placebo-controlled study	n = 48 Healthy adults	Group 1: 2.5 mL 3 times per day of pressed juice of the above-ground plant parts of E. purpurea placed in a 22% alcohol base (EchinaGuard®) Group 2: placebo 14 days	Colds developed in 58% of echinacea recipients and 82% of placebo recipients (p = 0.114, by Fisher's exact test). Administration of echinacea before and after exposure to rhinovirus did not decrease the rate of infection; however, because of the small sample size, statistical hypothesis testing had relatively poor power to detect statistically significant differences in the frequency and severity of illness.
Schoop et al., 2006	Open, phase 4, multicenter observational study	n = 80 Physically active subjects	1 tablet of Echinaforce Forte® tablets twice daily which corresponds to 18.6 mg dry mass of *E. purpurea* (DER of 95% herba = 1:12 and 5% root = 1:11) 8 weeks	Most investigators (97.5%) rated the treatment as having "very good" or "good" tolerability. About 75% of patients and investigators rated its efficacy during a common cold as "very good" or "good," and 71% of subjects were free of cold episodes.

MAIN APPLICATION: IMMUNITY (UPPER RESPIRATORY TRACT)

REFERENCE	DESIGN	SUBJECTS	SUPPLEMENTATION	RESULTS
ADULTS				
Hall et al., 2007	Randomized placebo-controlled, double-blinded study	n = 32 Non-smoking, active adults	Group 1 (E): 8 capsules/d of standardized *Echinacea purpurea* extract (Nature's Way®) Group 2 (C): placebo 4 weeks	Both groups demonstrated significant exercise induced reductions in s-IgA (C - 69%; E - 43%) and the secretion rate of s-IgA (C - 79%; E - 53%) at the beginning of the study ($p < 0.05$). Following the 4-week intervention, only the control group experienced the post intervention decrease in s-IgA (C - 45%; E + 7%) and the secretion rate of s-IgA (C - 45%; E - 7%). Further, while there was no significant difference in the number of URTI between groups, the reported duration was significantly different (C 8.6 days vs. E 3.4 days).
O'Neil et al., 2008	Randomized, double-blind, placebo-controlled study	n = 90 Healthy volunteers	Group 1: 3 capsules twice daily of *E. purpurea* (300 mg/capsule) Group 2: placebo 8 weeks	Individuals in the echinacea group reported 9 sick days per person during the 8-week period, whereas the placebo group reported 14 sick days ($z = -0.42$; $p = 0.67$). Mild adverse effects were noted by 8% of the echinacea group and 7% of the placebo group ($p = 0.24$).
Jawad et al., 2012	Randomized double-blind, placebo-controlled study	n = 755 Subjects that experienced ≥ 2 colds per year	Group 1: 3 x 0.9 mL/d (i.e. 2400 mg/d) of an alcohol extract from freshly harvested *E. purpurea* (95% herba and 5% root) called Echinaforce® or 5 x 0.9 mL/d (i.e. 4000 mg/d) of extract during acute stages of colds Group 2: placebo 4 months	Echinacea reduced the total number of cold episodes (149 vs. 188, $p < 0.05$), cumulated episode days within the group (650 vs. 872, $p < 0.05$), and pain-killer medicated episodes ($p < 0.05$). Echinacea inhibited virally confirmed colds and especially prevented enveloped virus infections ($p < 0.05$).

MAIN APPLICATION: IMMUNITY (UPPER RESPIRATORY TRACT)

REFERENCE	DESIGN	SUBJECTS	SUPPLEMENTATION	RESULTS
CHILDREN				
Taylor et al., 2003	Randomized, double-blind, placebo-controlled trial	n = 407 Children 2 to 11 years old with upper respiratory tract infection (URIs)	Group 1: 7.5 mL/d of pressed *E. purpurea* juice for children 2-5 years old during a URI or 10 mL/day of pressed *E. purpurea* juice for children 6-11 years old during a URI Group 2: placebo Maximum of 10 days	Results didn't show significant difference in duration between URIs treated with *E. purpurea* or placebo (p = 0.89). Moreover, no difference was found in the overall estimate of severity of URI symptoms between the groups (p = 0.69). In addition, no significant differences were observed between the groups for peak severity of symptoms (p = 0.68), number of days of peak symptoms (p = 0.97), number of days of fever (p = 0.09) or parental global assessment of severity of the URI (p = 0.67).
Weber et al., 2005	Randomized, double-blind, placebo-controlled trial	n = 401 Children with at least 2 symptoms of acute URI (cough, fever, nasal congestion, runny nose, sneezing)	Group 1: 87.75 mg twice a day for children 2-5 years or 117 mg twice a day for children 6-11 years of non-alcohol *E. purpurea* liquid (Echinacin®) (ratio fresh plant/dried pressed juice = 31.5-53.6:1) Group 2: placebo Maximum of 10 days	Results showed that among children who had at least one URI, 69.2% of children who received the placebo developed a second URI versus only 55.8% of those who received *E. purpurea*. Moreover, *E. purpurea* supplementation was associated with a 28% decreased risk of subsequent URI (p = 0.01). Thus, E. purpurea may be effective to reduce the occurrence of subsequent URIs in children
Abdel-Naby Awad2020	Prospective comparative study	n = 300 Children with recurrent tonsillitis	Group 1: no treatment Group 2: 10 mg/kg/day Azithromycin (AZT) over 6 consecutive days every month for 6 months Group 3: 10 mg/kg/d Azithromycin (AZT) + 5 ml 3 times daily of oral suspension of *Echinacea purpurea* for 10 consecutive days every months for 6 months	Group 2 and group 3 had significant less number of tonsillitis attacks and severity of assessed symptoms during 6 months of prophylactic treatment with significant better results in group 3 (i.e. AZT plus Echinacea) compared to group 2 (i.e. AZT alone).
Ogal et al., 2021	Randomized, blind, controlled study	n = 200 Healthy children aged 4-12 years	Group 1: 400 mg of *Echinacea purpurea* extract (Echinaforce®) 3 times daily. Group 2: vitamin C 2 x 2 months separated by 1-week treatment break.	Echinacea prevented 32.5% of respiratory tract infections (RTI) episodes resulting in an odds ratio of OR = 0.52 [95% CI 0.30-0.91, p = 0.021]. Six children (5.8%) with Echinacea and 15 children (15.3%) with vitamin C required 6 and 24 courses of antibiotic treatment, respectively (reduction of 76.3%, p < 0.001). A total of 45 and 216 days of antibiotic therapy were reported in the two groups, respectively (reduction of 80.2% (p < 0.001). Eleven and 30 events of RTI complications (e.g., otitis media, sinusitis or pneumonia) occurred with Echinacea and vitamin C, respectively (p = 0.0030). Echinacea significantly prevented influenza (3 vs. 20 detections, p = 0.012) and enveloped virus infections (29 vs. 47 detections, p = 0.0038). Finally, 76 adverse events occurred with Echinacea and 105 events with vitamin C (p = 0.016), only three events were reported possibly related with Echinacea.

Table 3. SECOND APPLICATION: IMMUNITY (NATURAL DEFENSES STIMULATION)

REFERENCE	DESIGN	SUBJECTS	SUPPLEMENTATION	RESULTS
CHILDREN				
Schwarz et al., 2002	Randomized, double-blind, placebo- controlled crossover trial	n = 40 Healthy male volunteers	Group 1: 12 mL/d of freshly expressed juice of *Echinacea purpurea* herbs (harvested without roots and containing 22% (v/v) ethanol) Group 2: placebo 2 treatment periods of 14 days	*Echinacea purpurea* herbs did neither enhance phagocytic activity of polymorphonuclear leukocytes nor that of monocytes when compared with placebo. *Echinacea purpurea* herbs did not influence the production TNF-alpha and IL-1beta by LPS- stimulated monocytes. Unexpectedly, *Echinacea purpurea* herbs decreased serum ferritin concentration ($p = 0.0005$). All other laboratory and safety data remained unchanged.
Schwarz et al., 2005	Randomized, double-blind, placebo- controlled crossover trial	n = 40 Healthy male volunteers	Group 1: 12 mL/d of freshly pressed juice of *E. purpurea* herbs (Esberitox® Mono) Group 2: placebo 2 treatment periods of 14 days	After 1 week of treatment with *E. purpurea* extracts, the mean value of the total number of lymphocytes decreased compared to baseline (-6%, $p = 0.033$). Moreover, treatment for 1 and 2 weeks with *E. purpurea* extracts had only minor effects on 2 subtypes of lymphocytes. Indeed, no significant changes were found for the *E. purpurea* extracts supplementation for the T-and B-lymphocytes, CD4+ and CD8+ T-lymphocytes ("naive" and "memory"-T-lymphocytes and NK cells). However, a significant difference for the number of CD8+ T-lymphocytes and NK cells was shown: a decrease in *E. purpurea* extracts supplementation period and an increase in the number of these cells in the placebo period were found.
Goel et al., 2005	Randomized, double-blind, placebo-controlled trial	n = 150 Adults with a history of common cold in the previous year	Group 1: Doses of 5 mL of *E. purpurea* (Echinilin®) diluted with water: 8 doses on the first day and 6 doses/d from day 2 to day 7 Group 2: placebo 7 days	Results showed a decrease in total daily symptomatic score in the *E. purpurea* supplemented group compared to the placebo group ($p < 0.05$). These effects of *E. purpurea* were associated with a significant and sustained increase in the number of circulating total white blood cells ($p < 0.01$ and $p = 0.04$ after 2- and 7-days treatment), monocytes ($p < 0.01$ and $p= 0.01$ after 2- and 7-days treatment), neutrophils ($p < 0.01$ and $p = 0.02$ after 2- and 7-days treatment) and NK cells (CD4+and CD16+).
Woelkart et al., 2006	Randomized, crossover trial	n = 10 Healthy volunteers	Group 1: 4 mL of a standardized *E.purpurea* tincture (Echinaforce®) Group 2: 12 mL of *E. purpurea* tablets(Echinaforce®) Group 3: placebo Single dose	Both *E. purpurea* preparations led to the same effects on the immune system according to the concentration of pro-inflammatory cytokines TNF-alpha and IL-8. 23 hours after oral application a significant down-regulation of TNF-alpha and IL-8 in LPS pre-stimulated whole blood was found. However, no significant changes in the concentration of IL-6 were observed ($p > 0.05$).
Brush et al., 2006	Randomized, double-blind, placebo- controlled investigation	n = 16 Healthy subjects	Group 1: 7.5 mL twice daily of herbal extract of *Echinacea purpurea* Group 2: *Astragalus* tincture Group 3: *Glycyrrhiza* tincture Group 4: Three herbs combination tincture 7 days	The results demonstrate that *Echinacea*, *Astragalus* and *Glycyrrhiza* herbal tinctures stimulated immune cells as quantified by CD69 expression on CD4 and CD8 T cells. This activation took place within 24 h of ingestion and continued for at least 7 days. In addition, these three herbs had an additive effect on CD69 expression when used in combination.
Zwickey et al., 2007	Randomized, double-blind, placebo-controlled pilot study	n = 14 Subjects	Group 1: 7.5 mL twice daily of herbal extract of *Echinacea purpurea* Group 2: *Astragalus* extract Group 3: *Glycyrrhiza* extract Group 4: Combination 7 days	CD25 expression on T cells was significantly increased for subjects ingesting *Echinacea* at 24 h with notable increases in activation from *Astragalus* and *Glycyrrhiza* ($p < 0.05$). CD25 expression remains elevated with daily use of *Echinacea* for at least 7 days.

Table 4. THIRD APPLICATION: SPORT (PERFORMANCE)

REFERENCE	DESIGN	SUBJECTS	SUPPLEMENTATION	RESULTS
Whitehead et al.,2007	Double-blind, placebo-controlled clinical study	n = 24 Men aged 24.9 ffl 4.2 years	Group 1: 8000 mg/d of *Echinacea purpurea* extract (ECH) Group 2: placebo (PLA) 28 days	The EPO increased significantly in ECH at 7 days (ECH: 15.75 ffl 0.64, PLA: 10.01 ffl 0.73 mU/mL), 14 days (ECH: 18.88 ffl 0.71, PLA: 11.02 ffl 0.69 mU/mL), and 21 days (ECH: 16.06 ffl 0.55, PLA: 9.20 ffl 0.55 mU/mL). VO2max increased significantly in ECH (ECH: 1.47 ffl 1.28, PLA: -0.13 ffl 0.52%). Running economy improved significantly in ECH as indicated by a decrease in submaximal VO2max during the first 2 stages of the GXT (stage 1: ECH -1.50 ffl 1.21, PLA 0.60 ffl 1.95%;stage 2: ECH -1.67 ffl 1.43, PLA 0.01 ffl 1.03%).
Whitehead et al.,2012	Double-blinded, placebo-controlled clinical study	n = 24 Men aged 24.9 ffl 4.2 years	Group 1: 8000 mg/d of *Echinacea purpurea* extract (ECH) Group 2: placebo (PLA) 28 days	A significant increase in erythropoietin was showed in the ECH group at 7 days (ECH: 15.75 ffl 0.64, PLA: 10.01 ffl 0.73 mU/mL), at 14 days (ECH: 18.88 ffl 0.71, PLA: 11.02 ffl 0.69 mU/mL) and at 21 days (ECH: 16.06 ffl 0.55, PLA: 9.20 ffl 0.55 mU/mL). Moreover, VO2max increased significantly in ECH group (ECH: 1.47 ffl 1.28, PLA: -0.13 ffl 0.52%). Running economy also improved in ECH. Indeed, a decrease in submaximal VO2max during the first 2 stages of the graded exercise tests was observed (stage 1: ECH -1.50 ffl 1.21, PLA 0.60 ffl 1.95%; stage 2: ECH -1.67 ffl 1.43, PLA 0.01 ffl1.03%).
Baumann et al.,2014	Double-blind, placebo-controlled clinical study	n = 16 Trained endurance runners	Group 1: 8000 mg/d of *Echinacea purpurea* extract (ECH) Group 2: placebo 6 weeks	Results didn't show significant differences in VO2max, hematocrit (Hct) and hemoglobin (Hb) between the ECH and placebo groups before or after supplementation. Moreover, supplementation with ECH didn't improve VO2max (67.37 ffl 4.62 vs. 67.23 ffl 5.82 mL/kg/min), Hct (43.57 ffl 2.38 vs. 42.85 ffl 1.46%) or Hb (14.93 ffl 1.27 vs. 15.55 ffl 0.80 g/dL) compared to baseline measurements.
Stevenson et al.,2016	Randomized, double-blind, placebo-controlled clinical study	n = 45 Endurance athletes	Group 1: Regular dose (RD) of 8000 mg/d of echinacea-based dietary supplement (EBS) (*E. purpurea*) Group 2: Double dose (DD) of 16 000 mg/d of echinacea-based dietary supplement (EBS) (E. purpurea) Group 3: placebo 35 days	There was a significant increase in VO2max for endurance-trained men in PLA (increase of 2.8 ffl 1.5 mL/kg/min, p = 0.01) and RD of EBS (increase of 2.6 ffl 1.8 mL/kg/min, p = 0.04), but not in DD of EBS (p = 0.96). Importantly, there was no difference in the change in VO2max between PLA and RD of EBS. For endurance-trained women, VO2max did not change in either treatment (PLA: -0.7 ffl 1.7 mL/kg/min/, p = 0.31; RD of EBS: -0.2 ffl 2.4 mL/kg/min, p = 0.80). There were no significant changes in any blood parameter across visits for any treatment group.
Martin et al., 2019	Randomized, blind, placebo-controlled study	n = 24 Recreationally active males with above-average aerobic fitness	Group 1: 8000 mg.day-1 of *Echinacea purpurea* Group 2: placebo 6 weeks	There were no significant interaction, group, or time effects observed for EPO or erythropoietic status markers for any of the measurement points ($p \leq 0.05$). The present study indicated that 6 weeks of oral *E. purpurea* supplementation in recreationally active males with above average aerobic fitness did not enhance EPO or erythropoietic status.

ESTRATTI PIANTE OFFICINALI

Via Stadera 19, 20141 Milano, MI, Italy

Phone:+39.02.89557.1
Fax.+39.02.89557490
E-mail: epo@eposrl.com

CERTIFICATIONS

EPO is certified according to **ISO 9001-2015**, **ISO 14001:2015**, **21CFR111-GMP for dietary supplements**, **Kosher**, **Halal** and **Organic standards**.

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