



Polinacea™

Echinacea angustifolia

The most innovative immunobooster from Echinacea

.....
A patented* unique *Echinacea angustifolia* extract

.....
Triple standardization in different components

.....
Pharmacological data support its efficacy

.....
A safe product, devoid of any side effect

■ Historical tradition of the use of *Echinacea angustifolia* is related to the tribes of Native Americans as most of them commonly used to treat themselves with preparations of this plant. Back then, Echinacea was used for a variety of maladies including wounds, burns, insect bites, toothaches infections and snake bites, coughs and general inflammatory conditions.¹⁻³

Following the European colonization of the new continent, Echinacea began to be a **popular remedy** among settlers, too. It was described in the National Formulary of the United States from 1916 to 1950. Besides the prevalent use of synthetic drugs at the time, the use of Echinacea still remained popular in the last century, until its consumption as a **dietary supplement** gained interest after receiving approval by DHSEA in the US.

According to the National Institute of Allergy and Infectious Diseases, the US population has 1 billion colds every year. Echinacea, known for its immunostimulatory effects, is the most common nutraceutical consumed in the US to treat and prevent common cold.⁴

A number of scientific data are available in literature referring to different preparations obtained from the most relevant Echinacea species, the indications being generally prevention and treatment of **common cold, flu and upper respiratory infections**. The available clinical evidences have been recently reviewed by Barret,⁵ who concluded that the globality of the data supports the use of Echinacea in the treatment of acute

respiratory inflammations, reflecting the most widespread utilization. Other studies demonstrated the stimulation of various immune cells *in vitro*.⁶

Polinacea™ is a new immunomodulating *E. angustifolia* standardized extract. Through direct action on T cells, it increases the immune functions when compared to very well known Echinacea based specialties sold as drug in Europe.⁷ Besides the **immunoboosting effect**, Echinacea based preparations had also a role in the reduction of the inflammatory processes. The phenolic compound, i.e. **echinacoside**, is reported to be responsible for this effect.⁸ Considering the multiplicity of activities referred to Echinacea the biological effects may not be attributed to a single component: the standardized extract from *E. angustifolia* developed and patented* by Indena has a triple standardization that makes it different from all other Echinacea derivatives.



Chemical profile

Polinacea™ is a standardized extract from *E. angustifolia* selected variety wild and cultivated by Indena. The extract is obtained from its roots. It contains **echinacoside** ($\geq 2\%$), and a very **unique high molecular weight polysaccharide** (Fig. 1) characterized by a backbone of a partially carboxymethylated and partially acetylated polygalacturonic acid with a hairy region of rhamnogalacturonan ($\geq 5\%$), named IDN 5405.

IDN 5405 is a polysaccharide that has been highlighted for the first time in the root of *E. angustifolia*.

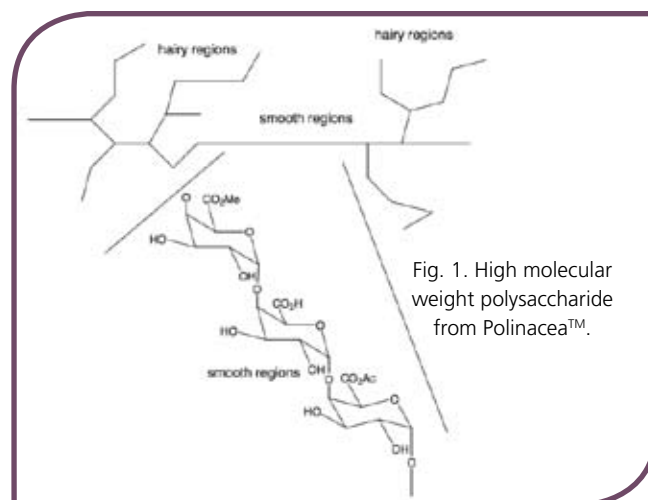


Fig. 1. High molecular weight polysaccharide from Polinacea™.

Table 1. Triple standardization of Polinacea™.

Standardized compound	Chemical nature	Content (%)
Echinacoside	Caffeic acid derivative	$\geq 2\%$
IDN 5405	High molecular weight polysaccharide	$\geq 5\%$
Isobutylamides	Amides	$\leq 0.1\%$

Polinacea™ has a unique triple standardization in the following components: **echinacoside** (Fig. 2), a polyphenol derived from caffeic acid use as a marker of the extract; **IDN 5405**, a high molecular weight polysaccharide of ca. 20,000 Da. identified for the very first time in the *E. angustifolia* root alone; Polinacea™ is also standardized to be **devoid of isobutylamides** ($\leq 0.1\%$) since these compounds show CB2 mediated immunosuppressive activity.⁹

On the other hand, by virtue of a direct (mediated by cannabinoid receptor CB2) and indirect (FAAH-fatty acid amide hydrolase-mediated) cannabinomimetic activity, isobutylamides show anti-inflammatory and pain relief action, a complementary activity compared to the high molecular weight polysaccharides of Polinacea™.¹⁰ Thus, while Polinacea™ is more indicated to **prevent cold**, Echinacea preparations rich in isobutylamides might be useful to treat this condition.

Echinacea angustifolia root extract with a unique triple standardization

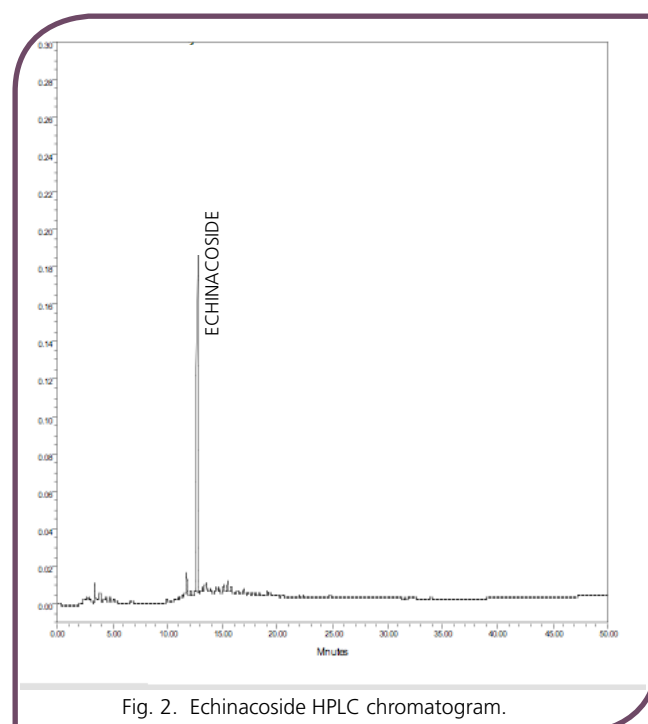


Fig. 2. Echinacoside HPLC chromatogram.



Pharmacology

Polinacea™ can be considered a very good immune response improver on the basis of the results obtained in several experimental models. In order to avoid an unspecific response of the immune competent cells for the *in vitro* studies, samples of Polinacea™ have been purified from lipopolysaccharides (LPS) of bacterial origin, which are a possible contaminant of the raw drug utilized for the extraction. LPS, in fact, are reported to produce a non specific immune response on macrophages.

In immunocompetent mice challenged with *Leishmania*

major (one of the most representative experimental animal models utilized to check the immunoboosting capability of drugs), Polinacea™ reduced by over 25% the experimentally induced leishmaniasis (mortality at week 1).

Moreover, Polinacea™ orally administered at the dose of 1g/kg day for 7 days was effective (30%) in counteracting the mortality induced by *Candida albicans* in immunocompetent mice; even in the case of Cyclosporin-immunosuppressed mice, Polinacea™ was able to prevent animal death by 40% (Table 2).

Table 2. Effect of oral administration of Polinacea™ on survival in normal and immunosuppressed mice infected with *Candida albicans*.

Treatment	n	Survivors
<i>Candida albicans</i>	10	0
<i>Candida albicans</i> + Polinacea™ (1g/kg day x 7 days)	20	6*
<i>Candida albicans</i> + Cyclosporin A (1g/kg day x 7 days)	10	0
<i>Candida albicans</i> + Cyclosporin A + Polinacea™ (1g/kg day x 7 days)	10	4*

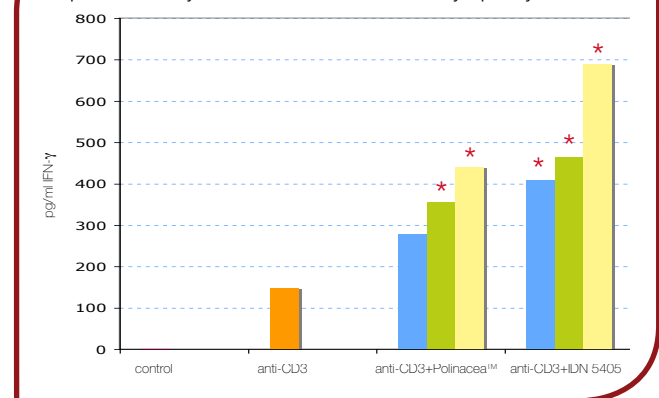
* p < 0.01 vs control

Polinacea™ intraperitoneally administered at the dose of 0.1g/kg day was effective in counteracting mortality induced by *Candida albicans*. This effect was also supported by the fact that LPS (lipopolysaccharides) administered at a dose (2 µg/kg day) corresponding to the amount administered in LPS-containing Polinacea™ was practically ineffective.

In the same animal model, a reference product (the best selling European Echinacea), compared to a placebo, has not given statistically significant results.

In terms of mechanism of action, the hypothesis of a direct action on T cells can be done: Polinacea™ and IDN 5405 have been both deprived of LPS (responsible of non specific immune response). They have been shown to dose dependently stimulate anti-CD3-treated isolated T lymphocytes to produce and release interferon-γ (IFN-γ) (Fig. 3).

Fig. 3. Effect of Polinacea™ and IDN5405 on IFN-g production by anti-CD3-treated human T lymphocytes.



Anti-CD3 are reported to affect immune responses by inducing immune regulation.¹¹ These results have been paralleled by a good response in terms of cell proliferation of T lymphocytes.

Safety profile

The studies conducted on Polinacea™ (oral acute and sub-acute toxicity) indicate that the product has no toxic effect at all being the LD₅₀ > 2000 mg/kg. No signs of any clear toxicological effect were seen at any of the dose levels investigated (the high dose 1g/kg/day may be considered the

“no observed adverse effect level”- NOAEL in the study). This specific characteristic entitles Polinacea™ to be considered a high profile candidate as a “functional ingredient” in the enhanced food category.

Botanical profile

Echinacea angustifolia DC (narrow leaved-purple cone-flower) is one of the "coneflowers", a group of Native American wildflowers from Asteraceae family, characterized by spiny flowering heads and with an elevated receptacle which forms the "cone". The species is an herbaceous perennial, flowering late spring-mid summer, with vertical taproots, occurring in dry prairies, barrens, rocky sandy soil from Texas to Saskatchewan, from western Iowa to Minnesota.^{12,13} Knowledge about many of the **popular medicinal plants** from North America in common use today derives from the Native Americans. Of all the indigenous medicines introduced by Native Americans, *Echinacea* spp. may be one of the most typical and tangible example.¹⁴ Samples of *Echinacea* spp. have been found in archeological digs of Lakota Sioux village sites from 1600s and most of the

information we have on the ethnobotany of *Echinacea* spp. come from Native American tribes. For medicinal purpose, three different species are widely collected or cultivated: *Echinacea angustifolia* DC, *E. pallida* (Nutt.) Nutt. and *E. purpurea* (L.) Moench. The first two species are often confused; in particular the more abundant and easily cultivated *E. pallida* is traded under the name of the more popular *E. angustifolia*.¹⁵

Indena's Quality Control by **morphological** and **chemical examination** is able to distinguish the two species, avoiding contamination of the extract due to the considerable differences of the root lipophilic constituents. Moreover, Indena, in order to improve the consistency and quality, since many years has established plantations to provide its factories with selected plants of *E. angustifolia*.

Conclusive remarks

The studies conducted on Polinacea™ revealed its immune boosting capacity besides the presence of LPS activating macrophages. The positive results on the *in vivo* T cells suggest Polinacea™ is **effective** when employed as **immunostimulant**. It is likely that the activity played on the T cells is due to the presence of the high molecular weight polysaccharide IDN 5405.

A few milestones about Polinacea™:

- selected cultivated *Echinacea angustifolia* plants
- innovative extraction procedure
- unique triple standardization
- low level of isobutylamides
- direct immunological effect on T cells
- well tolerated in acute and subacute toxicity

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