Echinacea purpurea

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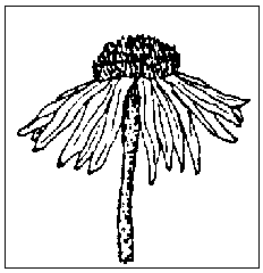
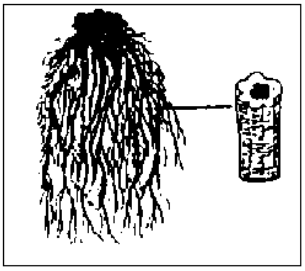
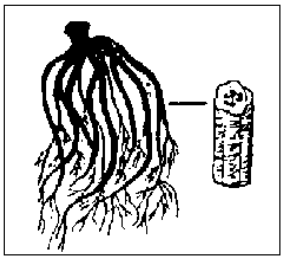
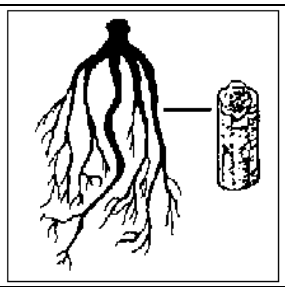
The knowledge of pharmacological effects of different preparations of Echinacea purpurea has been used for the medical treatment of several complaints for centuries now. Historical traces are going back to the North-American Indians. Actually, the majority of investigations has been carried through with cold pressed juice of the aerial parts of Echinacea purpurea. Recent studies have proved the stimulation of the non-specific immune system as the main action of this pressed juice. In fact, none of the identified compounds of the polar and lipophilic fraction could have been determined to be solely responsible for this activity. Several compounds as alkamides, polysaccharides and glycoproteins are discussed to be potentially part of the "active principle". Since immunomodulation is a pharmacological effect, most of the clinical studies have focused on treatment and prevention of common cold and infections of the upper respiratory and the urinary tract. Recent clinical studies have provided data on the therapeutic effectiveness of pressed juice of Echinacea purpurea, while other, probably also beneficial Echinacea purpurea preparations are not that well documented.

Echinacea for Pharamceutical Use			
	Echinacea purpurea L..Moench	Echinacea pallida Nutt.	Echinacea angustifolia DC.
Wuchshöhe	60-180cm	30-100cm	10-60cm
Grundblattform	eiförmig	lanzettlich	lanzettlich
Zungenblüten Lange	hängend 2-4cm	hängend 4-9cm	±abstehend 2-4cm
Köpfchen			
Pollen-farbe Größe	gelb 18-25µm	weiß 25-32µm	gelb 19-36µm
Chromosomenzahl	2n=22	2n=44	2n=22
Wurzelsystem			

(R.Bauer H.Wagner Echinacea Handbuch fur Aerzte , Apotheker und andere Naturwissenschaftler 1990)

Introduction

Echinacea preparations represent the most popular herbal immunostimulants in North Ame-rica and in Europe [1]. Echinacea products are derived from Echinacea purpurea (L.) Moench, E. angustifolia DC. and E. pallida (Nutt.) Nutt.. While from E. purpurea both, aerial and underground parts are used, the only plant parts used from E. angustifolia and E. pallida are the roots. In North America, encapsulated powders from roots and aerial parts from E. purpurea and E. angustifolia are used, but also tinctures and extracts. In Europe the major products are prepared from the pressed juice of Echinacea purpurea aerial parts, or from hydroalcoholic extracts of E. pallida or E. purpurea roots [2,3].

The medicinal use of Echinacea can be traced back to the American Indians, who regarded Echinacea as among the most favourable remedies to treat wounds, snake bites, headache and the common cold [4]. In the middle of the 20th century, Echinacea purpurea has been introduced as a medicinal plant to Europe, where it has been used against infections and for stimulation of the immune response.

The constituents of Echinacea purpurea, as of any other plant, cover a wide range of polarity, from polar polysaccharides and glycoproteins, via medium polar caffeic acid derivatives to the rather lipophilic alkamides. Therefore, preparations prepared with solvents of different polarity are likely to be chemically different. So they have to be discussed individually regarding pharmacological activity and clinical efficacy.

Tab.1 lists the pharmacological effects of different preparations from Echinacea purpurea. It is evident that most actions are directed towards the stimulation of the non-specific immune system. Therefore, Echinacea seems to be effective not in a specific way but more general in the enhancement of the unspecific first line defence system of our body. Pharmacological studies have also shown that some constituents like cichoric acid, alkamides, and glyco-proteins/polysaccharides possess immunomodulatory and other activities, like stimulation of phagocytosis, induction of cytokins from macrophages and antioxidant activity [5]. However, no clinical studies have so far been undertaken with pure compounds, besides a preliminary investigation with polysaccharides [6]. Therefore the total native extracts have still to be regarded as the „active principles„ of Echinacea preparations. Bioavailability has only been shown for alkamides [7]. Analysis of caffeic acid derivatives is possible in principle as well. However, it is rather unlikely that they can be found undecomposed, as studies with cichoric acid from horsetail have shown [8]. Glycoproteins can be analysed by an EIA, which however is not

Tab. 1 : Pharmacological effects of preparations which have been prepared from Echinacea purpurea

Pressed juice from E. purpurea aerial parts:
- stimulation of phagocytosis (in vitro) [30,31]
- induction of cytokins in macrophages [32]
- activation of PMN (oxidative burst) [33]

Hydroalcoholic extract from E. purpurea aerial parts:
- stimulation of phagocytosis (in vitro and in vivo) [34,35]

Hydroalcoholic extract from E. purpurea roots:
- antioxidant activity [36]
- stimulation of phagocytosis [37]
- inhibition of hyaluronidase [38]
- interferon mediated antiviral activity [39,40]
- stimulation of splenocytes in mice [39]
- induction of cytokins in vitro and in vivo [39]
- stimulation of NK activity in humans [41]
- stimulation of NK cells and monocytes in mice [42]

freely available [9]. A routine and specific analytical method for the active polysaccharides has not yet been developed.

Analytical investigations have shown, that the content of alkamides depends on the used plant part and the harvesting season, and that cichoric acid is enzymatically decomposed during processing. Alkamides are especially accumulated in the flowerheads and there in the tubulous flowers and achenes. Their content is low at the beginning of the vegetation period and becomes high at the end (see Fig.1) [10]. Therefore the date and mode of harvest play an important role for the quality of Echinacea preparations. Cichoric acid occurs in especially high concentrations in the flowerheads (liguls) and in the roots of E. purpurea (1.2-3.1% and 0.6-2.1%, respectively). Less is present in the leaves and stems. The content depends also on the season and the stage of development of the plant, being highest at the beginning of the vegetation period and decreasing during the growth of the plant (Fig. 1). Cichoric acid regularly undergoes rapid decomposition during the preparation of tinc-tures or expressed juices. It has been found that enzymatic degradation occurs during the extraction process and that a phenoloxidase is mainly responsible [11,12]. In order to provide a consistent quality of Echinacea preparations, the products should be characterized by HPLC analysis of the polar and lipophilic constitutents [13].

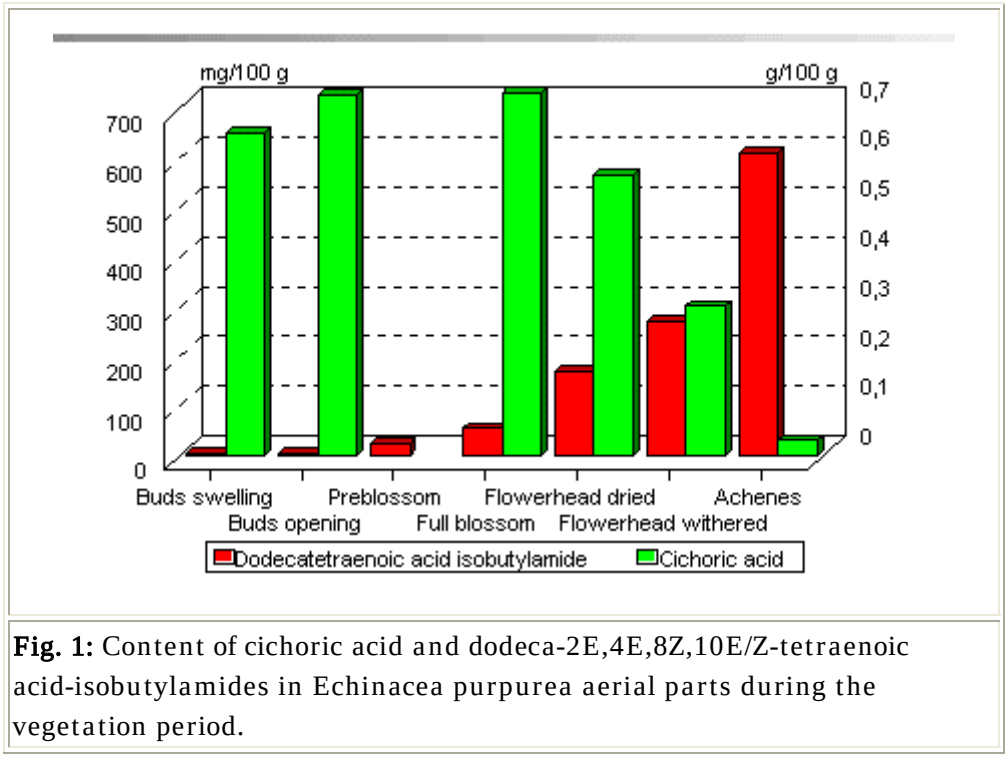


Fig. 1: Content of cichoric acid and dodeca-2E,4E,8Z,10E/Z-tetraenoic acid-isobutylamides in Echinacea purpurea aerial parts during the vegetation period.

Research into pharmacology and therapeutic effectiveness

Clinical studies have been mainly oriented to the treatment and prevention of common cold and infections of the upper respiratory and the urinary tract, since immunomodulation is a pharmacological, but not a therapeutic effect. Positive effects have been demonstrated in clinical studies for a pressed juice preparation from the aerial parts of E. purpurea, for the hydroalcoholic extracts of E. purpurea roots and for a 95:5 mixture of hydroalcoholic extracts of E. purpurea aerial parts and roots [15-21,23,24]. In case of the pressed juice from E. purpurea aerial parts, clinical studies have only been performed with the cold pressed juice and not with heated materials. Due to enzymatic degradation, classically prepared cold pressed juices are void of cichoric acid, while heat

treated juices contain up to 0.4 % of cichoric acid [13]. Therefore, the activity of cold pressed juices must be derived from other compounds, like alkamides, polysaccharides or glycoproteins [14].

In a placebo controlled double blind study on 108 patients with frequent upper respiratory tract infections the efficacy of treatment with E. purpurea pressed juice (orally 2x4 mL daily over 8 weeks) was tested. A tendency to less (19 = 35,2 % versus 14 = 25,9 %) and less severe infections has been observed in the verum group. Especially in patients which started the study with a T4/T8 ratio of < 1.5, a reduction of the duration of the disease was achieved (5.34 days instead of 7.54 days) [15]. Years later Grimm and Müller [16] reported the same study and stated that the prophylactic effect of the verum and the placebo was not statistically significant.

A single centre clinical trial was carried out to investigate the therapeutic efficacy of a pressed juice preparation of Echinacea purpurea aerial parts in 120 patients with initial symptoms of acute, uncomplicated upper airways infection [17]. The verum group (n = 60) received cold pressed Echinacea purpurea pressed juice, stabilized with 20 % (V/V) ethanol, the placebo group (n = 60) coloured diluted ethanol. The medication was started at initial signs of common cold. Patients took 20 drops every two hours at the first day, and then 20 drops three times daily for 10 days. The intention-to-treat analysis revealed that 24 out of 60 patients (40.0 %) in the verum group, but only 36 out of 60 (60.0 %) in the placebo group, developed a 'real', fully pressed common cold (p = 0.044). In the sub-group of patients with a 'real' cold, the median time for improvement was 4 days in the verum group (n = 24), while it was 8 days in the placebo group (n = 36) [17].

This effect was confirmed recently in a similar placebo controlled double blind study [18]. The verum group (n = 41) received cold pressed juice EC31J0 from Echinacea purpurea aerial parts stabilized with 20 % (V/V) ethanol, the placebo goup (n = 39) coloured diluted ethanol. The medication was also started at initial signs of a common cold. The dosage was 2 x 5 ml daily for 10 days. Eight characteristic symptoms of common cold were measured according to the Jackson Score. In the verum group 85.4 % of the patients developed a full expression of common cold, in the placebo group 97.4 % of the patiens (p = 0.055). The median of days of illness was 6 days in the verum group and 8 days in the placebo group (p = 0.021) (Tab.2).

Tab. 2 : Doubleblind, randomized, placebo-controlled study of efficacy and tolerability of a 10 days treatment with Echinacea purpurea pressed juice (EC31J0) in patients with acute common cold [18, 43]

	Verum (n = 41)	Placebo (n = 39)	p
Days of illness (median) in patients with full expression of common cold; (one-sided 95 CI)	6.0 (6.0;∞)	9.0 (8.0;∞)	21
Number of patients with full expression of common cold	35 (85.4 %)	38 (97.4 %)	55

In another recent double blind study, 42 triathlets received 8 ml of a cold pressed juice preparation from Echinacea purpurea aerial parts (EC31). After four weeks the number of immunocompetent cells was slightly increased in the verum group. After a competition, which led to a temporary immunosuppression, a significant increase of interleukin 6 was meassured in the urin of the verum group only. The concentration of soluble IL-2 receptors was significantly reduced.

In the two months after the competition, common colds were registered only in the placebo group [19].

A randomized, double-blind, placebo controlled study was undertaken to investigate the efficacy and safety of different doses and preparations of Echinacea purpurea in the treatment of common cold [20,21]. 246 of 559 recruited healthy, adult volunteers caught a common cold and took 3 times daily 2 tablets of either Echinaforce (6.78 mg E. purpurea crude extract based on 95 % herb and 5 % root), Echinacea purpurea concentrate (48.27 mg E. purpurea crude extract based on 95 % herb and 5 % root), special Echinacea purpurea radix preparation (29.60 mg E. purpurea crude extract based on roots only) or placebo until they felt healthy again but not longer than 7 days. The primary endpoint was the relative reduction of the complaint index defined by 12 symptoms during common cold according to the doctor's record. Echinaforce and its concentrated preparation were significantly more effective than the special Echinacea extract or placebo. All treatments were well tolerated. Among the Echinacea groups the frequency of adverse events was not significantly higher than in the placebo group.

Tan [22] reported three cases of positive results in immunosuppressed patients after oral Echinacea therapy (hydroalcoholic extract from the aerial parts (95 %) and the roots (5 %) (DEV = 5.9:1) of E. purpurea. In the case of a 12 year old girl with chronic respiratory tract infections, bacterial otitis media and sinusitides, the symptoms were reduced and the time until the next exacerbation was prolonged. In the case of a 50 years old diabetic lady, who suffered frequently from common colds and vaginal infections, an improvement of symptoms could be achieved as well. Also a 22 year old man with chronic fatique syndrom could achieve relief of his common cold like symptoms.

A placebo controlled double blind study has been performed to prove the therapeutic effectiveness of an hydroalcoholic extract of E. purpurea roots (55 % ethanol; drug extract ratio DER 5:1) on 180 patients with the common cold [23]. A score of symptoms, like irritated nose, frontal headache, lymphnode swelling, coated tongue, and rale, was evaluated at the beginning of the study and after 3-4 and 8-10 days. The dose equivalent of 900 mg root/day (3 x 60 drops) caused a significantly faster reduction of symptoms compared to the placebo group and compared to a group treated with 450 mg/day (3 x 30 drops) only (see Fig. 2).

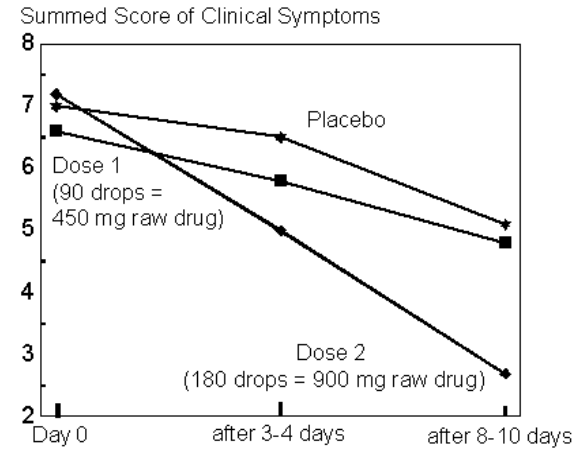


Fig. 2 : Placebo controlled double blind study with an alcoholic extract of E. purpurea roots on 180 patients with common cold [23]. Test preparation: 55 % ethanolic tincture (DER 5:1); Dose 1: 90 drops = 450 mg raw drug, Dose 2: 180 drops = 900 mg raw drug. Rated symptoms: irritated nose, frontal headache, lymphnode swelling, coated tongue, rale.

A double-blind, placebo-controlled randomized trial with 302 healthy volunteers has recently been performed with solutions in 30 % ethanol of Echinacea root extracts for the prevention of upper respiratory tract infections by Melchart et al. [24]. Ethanolic extracts from Echinacea purpurea

roots (96 % ethanolic extract, DER 11:1), Echinacea angustifolia roots (96 % ethanolic extract, DER 11:1), or placebo (coloured ethanolic solution), were given orally for 12 weeks (2 times daily 50 drops = 1 ml) from Monday to Friday each. The time until the first upper respiratory tract infection (time to event) was measured. Secondary outcome measures were the number of participants with at least 1 infection, global assessment, and adverse effects. As a result it was observed, that the time until occurrence of the first upper respiratory tract infection was 66 days (95 % confidence 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 = .49). In the placebo group, 36.7 % had an infection. In the treatment groups, 32.0 % 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. It was concluded, that a prophylactic effect of the investigated echinacea extracts could not be shown in this study and that future studies with much larger sample sizes would be needed to prove this effect. From a practical point of view it may be added, that neither the ethanolic extract from Echinacea purpurea roots, nor the extract from E. angustifolia roots represent commercial extracts or products which are on the market.

In another randomized, single-blind, and placebo-controlled study with 32 subjects (17 male and 15 female, ages 18 to 71 years), the efficacy of an anti-cold remedy including vitamin C and E. purpurea root extract in the treatment of the common cold was investigated. Evaluation parameter was the duration of the illness based on rhinorrea (nasal drip) and the number of paper tissues used daily by each patient. The length of the common cold was 3.37 days in the verum-treated and 4.37 days in the placebo-treated group of patients ($p < 0.01$). Also, the number of tissues used was significantly different between the two groups (882 treated, 1168 placebo). The preparation was found to be useful and safe for the treatment of the common cold [25].

For reviews of clinical studies with Echinacea preparations see [26] and [27]. As a consequence of the activity demonstrated by pharmacological and clinical studies, preparations from the pressed juice of E. purpurea aerial parts (6 - 9 ml pressed juice, corresponds to 12-18 g of fresh plants or 200 - 400 mg dried juice) have been approved as effective drugs in Germany for the internal adjuvant therapy of relapsing infections of the respiratory and derivative urinary tract, and externally for poorly healing superficial wounds. Extracts of E. purpurea roots have not yet been accepted but could also be effective in the treatment of the common cold [28].

Toxicology and adverse effects

Only few data exist on side effects and toxicological risks of echinacea preparations. The acute toxicity of E. purpurea root extract and E. purpurea aerial parts pressed juice has been shown to be extremely low. Adverse effects on oral administration of the cold pressed juice of Echinacea purpurea aerial parts for up to 12 weeks are infrequent and consist mainly of unpleasant taste (see Tab. 3). Even in long-term treatment, the pressed juice of E. purpurea was well-tolerated [29]. Mutagenicity studies exhibited no results indicating tumour initiating properties. All clinical reports provide indications of a good tolerability. However, allergy to plants of the Compositae family is a contraindication. Because of lack of experience echinacea preparations should also not be used in cases of progredient syste-mic diseases like tuberculo-sis, leuko-ses, collage-no-ses, and multiple sclerosis, AIDS, HIV infection, and other autoimmune diseases-. According to German Commission E monograph, the metabolic condition in diabetics may decline upon parenteral application.

Tab. 3: Adverse events in 1231 patients with relapsing respiratory and urinary infections treated for 4-6 weeks with a *Echinacea purpurea* pressed juice preparation (Echinacin lozenges) [29].

	No. of patiens	% of total
Unpleasant taste	62	1.70
Nausea/vomiting	6	0.48
Recurrent infection	5	0.41
Sore throat	3	0.24
Abdominal pain	3	0.24
Diarrhoea	3	0.24
Difficulty in swallowing	2	0.16
Other single reports	19	1.54

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