Echinacea: A Critical Review

Introduction

Echinacea preparations are among the most popular herbal remedies worldwide. They are very well known and the general public cherishes their therapeutic value Key markets are some European markets such as Germany, North America and also some Asian countries, notably Indonesia. “Echinacea” comprises different species and different parts of the plant. The species and the plant parts vary in their composition of constituents, not only quantitatively but also qualitatively. It is thus of utmost importance to clarify which Echinacea species (*E. purpureae, E. angustifolia, E. pallida*), plant part (herb, root or both) and also what method of preparation (drying, alcoholic extraction or pressing out the juice from fresh plants) is used, if one wants to evaluate effects of Echinacea preparations.
The plant originates from the United States of America and was used by the Native Indians used for treating insect and snake bites, for feverish illnesses and to enhance wound healing (1). Today, rational use refers to the immune stimulating properties of the plant material and therefore it seems essential to correlate the phytochemical properties of the different plant materials and preparation methods with the respective clinical and preclinical data.

1. Monographs:

Echinacea purpurea (L.) herb

Echinacea purpurea (L.) is the only species monographed in a Pharmacopoeia, not counting the homoeopathic monographs. The draft “Purple Coneflower Herb - Echinaceae purpureae herba” is published in Pharmeuropa (2) and is expected to become an official monograph of the Pharmacopoeia Europaea in the near future. The definition of the drug is “Dried, whole or cut flowering aerial parts of *Echinacea purpurea* (L.) Moench.” It is evident, that the Pharmeuropa monograph follows the popular demand for cichoric acid as standardization. Cichoric acid is found only in *Echinacea purpurea* preparations which are either prepared from dried material or from fresh material which has been heat or steam treated. Fresh pressed juice preparations, following the traditional method of preparation performed by native Americans on the other hand does not contain cichoric acid. From the manufacturer ´s point of view the dried material is preferred, because processing is much easier. For the fresh pressed juice special equipment for pressing is needed, this has to be close to the fields and the timing of the pressing is crucial. The fresh plants will undergo microbiological contamination and spoilage very rapidly, if not treated with utmost care. Processing the dried material is much simpler and cheaper. The monograph uses phenolic compounds such as cichoric acid for the identity test as well as for the assay. There are no tests for other compounds, for example alkamides or fructofuranosides. These two substances are suitable marker substances to ensure the correct time of harvest at flowering stage (alkamides) and also the careful processing (fructofuranosides). The alkamides are found mainly in the flowerheads of Echinacea purpurea herba (1). Thus drug harvested from a “second cut” late in the year will contain cichoric acid, but no alkamides. The fructofuranosides undergo microbiological degradation very rapidly, they are therefore a marker for correct handling of the raw material (3).

The monograph of the World Health Organization (4) has the title “Herba Echinaceae purpureae” and the raw material is defined as fresh or dried aerial parts of *Echinacea purpurea* (L.) Moench harvested in full bloom. Notably the dosage recommendation considers only the *fresh* pressed juice: “6 – 9 ml expressed juice”. The chemical constituents listed include alkamides, caffeic acid derivatives and polysaccharides. The medicinal uses supported by clinical data given by the WHO monograph are orally in supportive therapy for colds and infections of the respiratory and urinary tract. It is stated that the beneficial effects are generally thought to be brought about by stimulation of the immune response.

The ESCOP monograph “Echinaceae purpureae herba” (5) also serves as a review of the current scientific and clinical data on Purple Coneflower Herb. The most important chemical constituents listed are alkamides, caffeic acid derivatives, polysaccharides, flavonoids, essential oil and polyacetylenes. The therapeutic indication of the ESCOP monograph is “Adjuvant therapy and prophylaxis of recurrent infections of the upper respiratory tract (common colds) and also of the urogenital tract.”
The dosage is given as “6 – 9 ml of pressed juice or other equivalent preparations at comparable dose”. This underlines the link to the German Commission E monograph “Echinaceae purpureae herba”, which only accepts the fresh pressed juice and its preparations.

The German Commission monograph “Echinaceae purpureae herba” (6) is strictest about the raw material. It is defined as “the fresh, above ground parts of *Echinacea purpurea* (LINNE) MOENCH harvested at flowering time, and the respective preparations”.

Echinacea purpurea (L.) root

Echinacea purpurea (L.) root is also monographed in the ESCOP, the therapeutic indication is: “Adjuvant therapy and prophylaxis of recurrent infections of the upper respiratory tract (common colds).”

The draft for the monograph “Purple Coneflower Root” (7) in the Pharmeuropa closely resembles the *Echinacea purpurea* herb monograph in Pharmeuropa, both test the identity using phenolic compunds and give an assay for total phenols, summarizing cichoric, caftaric and chlorogenic acid. Other components of *Echinacea purpurea* root, for example polysaccharides, alkamides or volatile oil are not considered.

The German Commission E states that the clinical data is not sufficient to recommend the use (8).

Echinacea angustifolia (DC.) root

Echinacea angustifolia (DC.) root was monographed in the German Pharmacopoeia 9 of 1986 (9), but this monograph was not transferred to the European Pharmacopoeia. In the comment of the monograph the frequent adulterations of the drug are mentioned. Instead of *Echinacea angustifolia, Echinacea pallida* or even *Parthenium integrifolium* L. was found in commercial samples.

The WHO monograph “Radix Echinaceae” includes both species, *Echinacea pallida* and *Echinacea angustifolia* root in one monograph (10). The authors mention that a considerable amount of commercial “*E. angustifolia”* cultivated in Europe, was in fact, “*E. pallida*”. Apparently the distinction still causes problems, for under “Microscopic characteristics” it says “The roots of the two species are very similar.” The description of powdered *E. pallida* is according to WHO currently unavailable.

The German Commission E states that the clinical data is not sufficient to recommend the use (11).

Echinacea angustifolia (DC.) herb

The German Commission E states that the clinical data is not sufficient to recommend the use (11).

Echinacea pallida (NUTT.) root

The German Commission E recommended *Echinacea pallida* root for the supportive therapy of common colds (12)

Echinacea pallida (NUTT.) root is monographed in the ESCOP (13). The indication is the same as for *Echinacea purpurea* root: “Adjuvant therapy and prophylaxis of recurrent infections of the upper respiratory tract (common colds).”

Echinacea pallida (NUTT.) herb

The German Commission E states that the clinical data is not sufficient to recommend the use (14).

2. Phytopharmaceutical differences between the species

The composition of Echinacea is complex, for a complete overview see (15). *Echinacae angustifolia* root is characterized through cynarin, which has not been found in other species (15). Both *Echinacea pallida* and *Echinacea angustifolia* contain echinacoside, which is not present in *Echinacea purpurea*. *Echinacea pallida* herb contains rutin as characteristic flavonoid and cichoric acid from the polyphenol group. *E. angustifolia* has only traces of cichoric acid. In *Echinacea purpurea* the cichoric acid content depends on the method of preparation, the cold pressed juice of the herb is virtually free of cichoric acid. All *Echinacea* species contain alkamides, the distribution in the different parts of the plant is important for the quality control. In *Echinacea purpurea* herb for example, the alkamides are found mainly in the flower heads.

3. Current data on clinical trials:

The evaluation of the scientific material on Echinacea is not simple, as many studies are performed with herbal preparations which are not standardized, or in other cases, studies are performed with indications that do not match the drug profile of Echinacea and the recommendations of the respective monographs.

The study of Taylor et al (16) for example used Echinacin®, a well-known *Echinacea purpurea* preparation made from the above ground parts harvested at flowering time. The randomized, double-blind, placebo-controlled trial investigated the effect of an *Echinacea purpurea* herb preparation on upper respiratory tract infections (URI) in children aged 2 to 11 years. The result was that severity and duration of the URIs were similar in the verum and placebo group. The negative outcome of the study thus may seem surprising, but on a closer look some peculiarities of the study set up are evident. The severity of the symptoms was recorded by the parents, giving a secondhand assessment. Furthermore, the children received the study medication only after two symptoms of an upper respiratory tract infection were noticed by the parents and confirmed by the study coordinator. In other studies with adults the patients were asked to take the medication when having the subjective feeling of a cold, rather than requiring two symptoms (17,18).
Interestingly, Taylor found a statistically significant reduction in the number of subsequent URIs in the verum group. The author concludes “It is conceivable that echinacea stimulated an immune response in study children that was too late to modify the URI for which it was given but provided a window of protection against another URI in the child.”

A short time ago, a study with a clearly negative outcome was published: A clinical trial with rhinovirus challenge and *Echinacea angustifolia* root as study medication gave no positive effects (19). The double blind, randomized and placebo-controlled study used different *Echinacea angustifolia* root preparations. The dosage used was determined by the recommendation of the German Commission E for *Echinacea pallida* root, as *Echinacea angustifolia* is not approved by the Commission E and has no dosage recommendation. The authors give no explanation for the unexpected outcome. Mark Blumenthal of the American Botanical Council commented that the extracts used in the study do not correlate with echinacea products that are available commercially to consumers, because they were produced in a university laboratory (20).

Another North American clinical trial failed to produce positive results. Barret et al investigated the effects of an unrefined mixture of powdered *Echinacea purpurea* herb, root and *Echinacea angustifolia* root (21).

A very recent double blind, randomized, placebo-controlled trial with an *Echinacea purpurea* extract standardized on alkamides, cichoric acid and polysaccharides gave very good results (22). The total daily symptoms scores were found to be significantly (23.1 %) lower in the echinacea group than in placebo. In a follow-up study (23) the same authors found significant and sustained increase in the number of circulating total white blood cells, monocytes, neutrophils and NK cells. The study medication prepared from freshly harvested *Echinacea purpurea* plants did not only decrease the total daily symptomatic score, but also changed the unspecific immune response, apparent in the blood parameters.

The very different results of these latest clinical trials cannot be explained with a single cause. Certainly the set-up of the study is one factor, that is to say the choice of subjects, instructions on how and when to take the medication etc.
Other causes for the varying results can be found in the study medication itself. Echinacea is not Echinacea, the species, plant part and mode of preparation are important factors. This conclusion is supported by a recently published Cochrane Database Review composed by Linde et al. on the effectiveness of Echinacea preparations for preventing and treating common cold examining 16 controlled clinical trials of single Echinacea preparations that had been carried out in recent years. The trials tested different species and different extracts – from the root, leaves or both – as well as different manufacturing methods for producing Echinacea preparations. Researchers only found positive effects for the early treatment of colds in adults for pressed juice preparations and alcoholic extracts prepared from the *aerial parts* of *Echinacea purpurea.* However, they were not able to demonstrate benefits from other preparations, plant parts (roots) or Echinacea species (*E. pallida, E. angustifolia*) used (24).

These findings demonstrate the importance of labelling Echinacea products with information about species, plant part and preparation method used.

Future research on chemically well-defined preparations would be desirable to enable further comparisons.

4. Mode of action of Echinacea preparations

Goel and Lovlin (22) have had positive results with an Echinacea purpurea preparation standardized on alkamides, cichoric acid and polysaccharides. In their latest clinical study the mode of action was to be clarified (23). This study was, as the previous one, randomized, double blind, placebo controlled. 62 persons participated, giving a self-assessment of cold symptoms. Additionally, blood parameters were monitored and the result was a significant and sustained increase in the number of circulating total white blood cells, monocytes, neutrophils and NK cells in the Echinacea group. The authors conclude “These results suggest that Echilin, by enhancing the non-specific immune response and eliciting free radical scavenging properties, may have led to a faster resolution of the cold symptoms.” As the study medication used contained alkamides, cichoric acid and polysaccharides it is not possible to pinpoint the effect to one chemical substance.

The polysaccharides of Echinacea have been widely investigated, especially in the fresh pressed juice of *Echinacea purpurea*. Blaschek et al. (25) determined the content of mono-, oligo- and polysaccharides to be 25 % of the dry matter of the fresh pressed juice. The two characteristic polysaccharides of the fresh pressed juice are an arabinogalactan (average MG appr. 70.000 Da) and a fructane (average MG appr. 6000 Da). A very similar polysaccharide isolated from plant cell cultures of Echinacea purpurea proved to activate macrophages to produce tumor necrosis factor (TNF-α), interleukin-1 (IL-1) and interferon-β2 (26). These results are coherent with the studies by Burger (27) who used *Echinacea purpurea* fresh pressed juice or dried fresh pressed juice. At very low concentrations of 0.012 µg / ml the fresh pressed juice of *Echinacea purpurea* induced human macrophages to produce significantly higher levels of IL-1, TNF- α, IL-6 and IL-10 than placebo. The author

concludes that these results are consistent with an immune activated antiviral effect. *Echinacea purpurea* fresh pressed juice preparations have no direct antiviral effect, but activate the unspecific immune system.

Bearing in mind the concentrations of the test substance is crucial when judging results of in-vivo or clinical studies. An example is the study of Cheminat et al on the antiviral effect of cichoric acid (28). Cheminat found an antiviral effect against vesicular stomatis virus at concentrations of 125 µg/ml pure cichoric acid. Comparing this to the results of Burger who worked with concentrations of 0.012 µg/ml fresh pressed juice and not with one purified compound, the relevance is clear. The difference in concentration alone is a factor of ten thousand. The concentration of cichoric acid in certain Echinacea preparation ranges from 2 – 5 %, so a factor of 20 to 50 has to be added to that. The value of the results using pure cichoric acid are especially conspicuous because traditional fresh pressed juice preparations do not contain cichorid acid in any larger amounts. During the pressing the cichoric acid is very rapidly degraded enzymatically. Only preparations from dried material or steamed plants will contain cichoric acid. But neither dried material nor steamed plants are in line with the monograph of the German Commission E. The enzymatic degradation of cichoric acid in Echinacea preparation was subject of intensive investigation by Nüsslein et al (29). The results support the absence of cichoric acid in cold fresh pressed juice of *Echinacea purpurea*. According to this study the polyphenol oxidases are responsible for the rapid degradation.

The clinical effects of alkamides have not been very well investigated; the bioavailability was shown in humans (30) and in Caco-2 cells (31).
The alkamides are easily detectable in any Echinacea preparation, for they cause a tingling sensation on the tongue. This was used as a quality criteria by the North American Indians (15).

All the above results support the multicomponent system theory of herbal extracts. Thus for *Echinacea purpureae,* for example, the “active substance” is the fresh pressed juice or preparations thereof, not any isolated substance. Nevertheless, the quality should be monitored and the specification of marker substances for example alkamides or fructofuranosides (3) is necessary to ensure consistent quality.

5. Analytical investigation

Considering the great impact of species, plant part and preparation method used on product efficacy of Echinacea preparation as well as to assess the conventions of product labelling an analytical investigation of various commercial ‘Echinacea‘ preparations was conducted. The investigation was done using different commercial preparations from Indonesia. In Indonesia Echinacea is very popular, market share is large, first and foremost because Echinacea is prescribed by doctors.

Looking at some of the commercial preparations on the market it is striking, that the declaration on the packages is very limited.

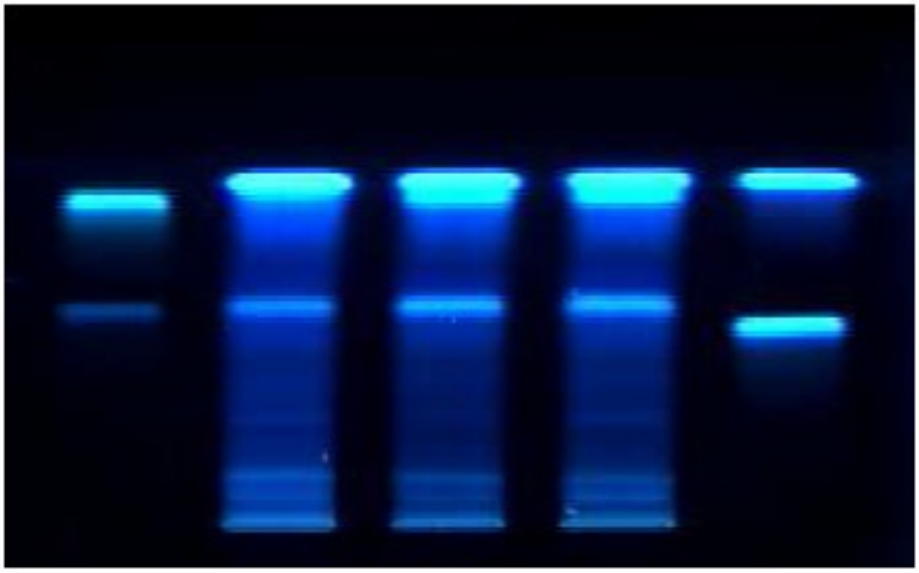
We investigated Imunos® (PT Lapi Laboratories) Imboost® and Imboost Force® (PT Soho Industri Pharmasi) and Immu-Cea® PT Interbat). None of the four preparations either declares the plant part or the Echinacea species used on the package.

Methods of preparation are declared only fragmentary. While Immu-Cea declares ‘Echinacea fresh juice’ as the ingredient and Imboost and Imboost Force disclose ‘Echinacea dry extract“ as raw material, Imunos solely refers to Echinacea. The drug – extract ratio is not stated for any of the preparations.

The analytical investigation to assess raw material (species, plant part, preparation method) used in the four commercial preparations was performed using TLC (thin layer chromatography) and HPLC (high performance liquid chromatography).

TLC analysis was done in comparison to a commercially available dried pressed juice preparation of *Echinacea purpurea* (EFLA®894; Frutarom Ltd, Switzerland).

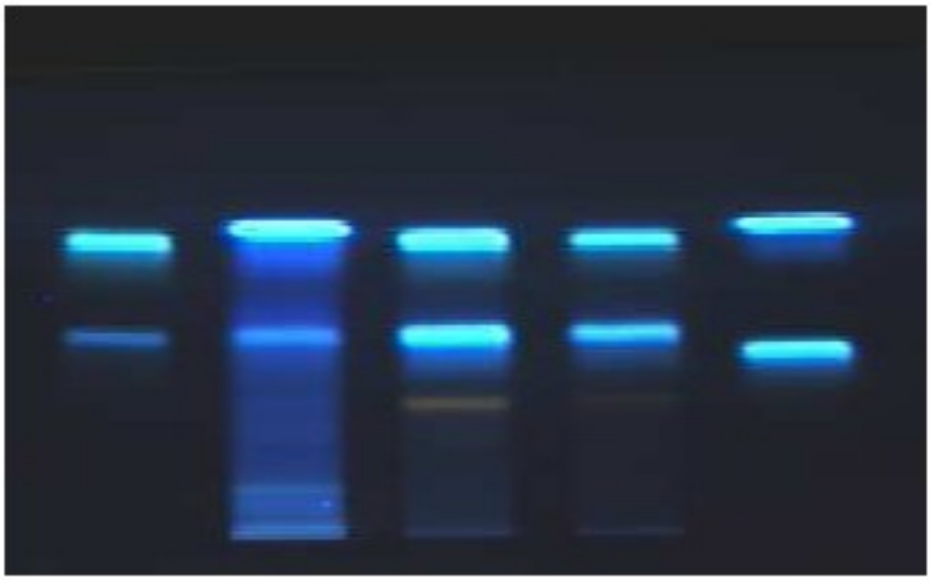
Figure 1: TCL of phenolic compounds of Imunos®



track 1: caftaric acid, cichoric acid (ascending)
track 2: Echinacea purp. hba succ. siccum EFLA®894
track 3: Imunos® tablets
track 4: Imunos® syrup
track 5: chlorogenic acid, caffeic acid (ascending)

For Imunos the pattern is very similar to the fresh pressed juice of *Echinacea purpurea*

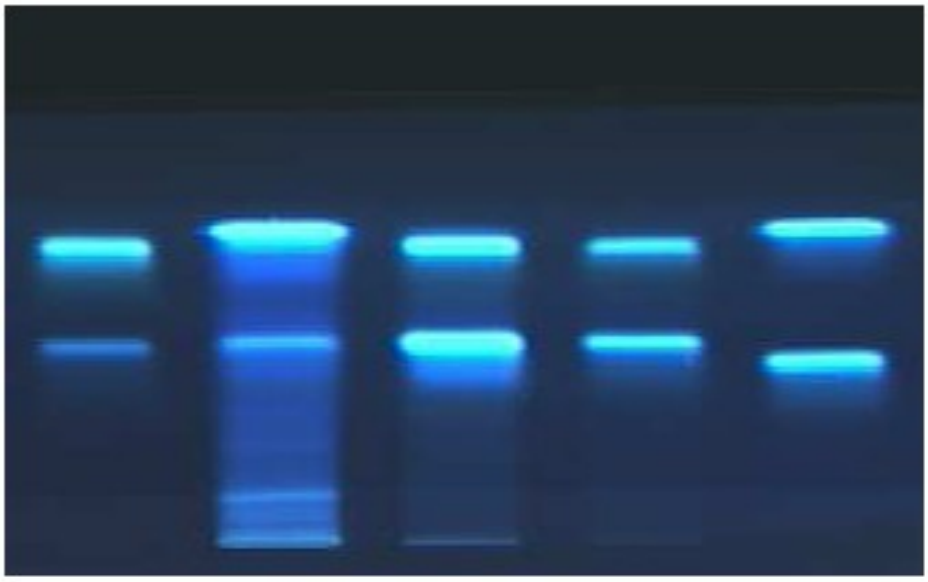
Figure 2: TCL of phenolic compounds of Imboost Force®



track 1: caftaric acid, cichoric acid (ascending)
track 2: Echinacea purp. hba succ. siccum EFLA®894
track 3: Imboost Force® tablets
track 4: Imboost Force® syrup
track 5: chlorogenic acid, caffeic acid (ascending)

Imboost Force contains Echinacea and black elderberry, therefore the TLC evaluation is not very specific. The orange rutin band may also be an elderberry component. The two pronounced blue bands in the upper third of the TLC are very similar to the fresh pressed juice of *Echinacea purpurea* in the second track. The finer bands in the lower half of the TLC are missing.

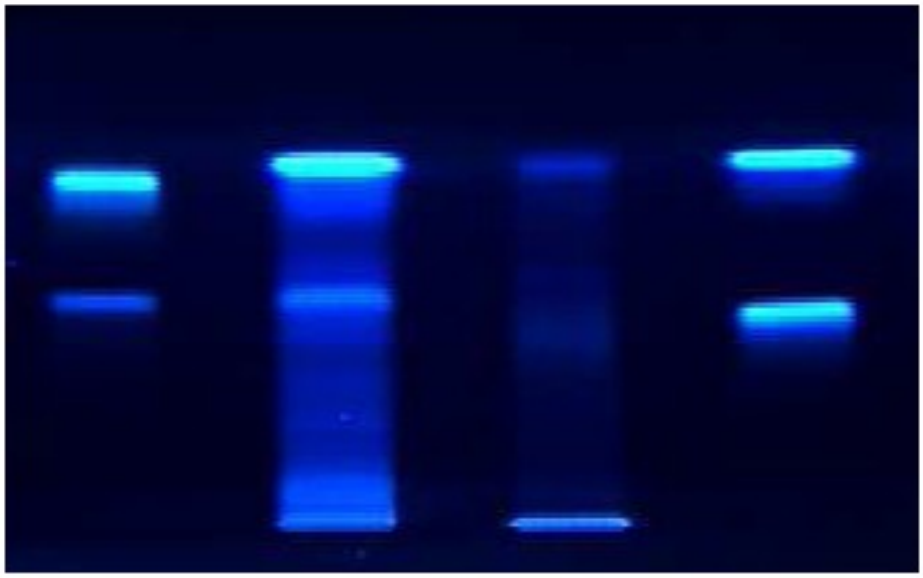
Figure 3: TCL of phenolic compounds of Imboost®



track 1: caftaric acid, cichoric acid (ascending)
track 2: Echinacea purp. hba succ. siccum EFLA®894
track 3: Imboost® tablets
track 4: Imboost® syrup
track 5: chlorogenic acid, caffeic acid (ascending)

Imboost tablets and syrup are similar in the TLC to Imboost Force, except for the orange band at appr. rf 0.5 which is present in Imboost Force, but not in Imboost.

Figure 4: TCL of phenolic compounds of Immu-Cea®

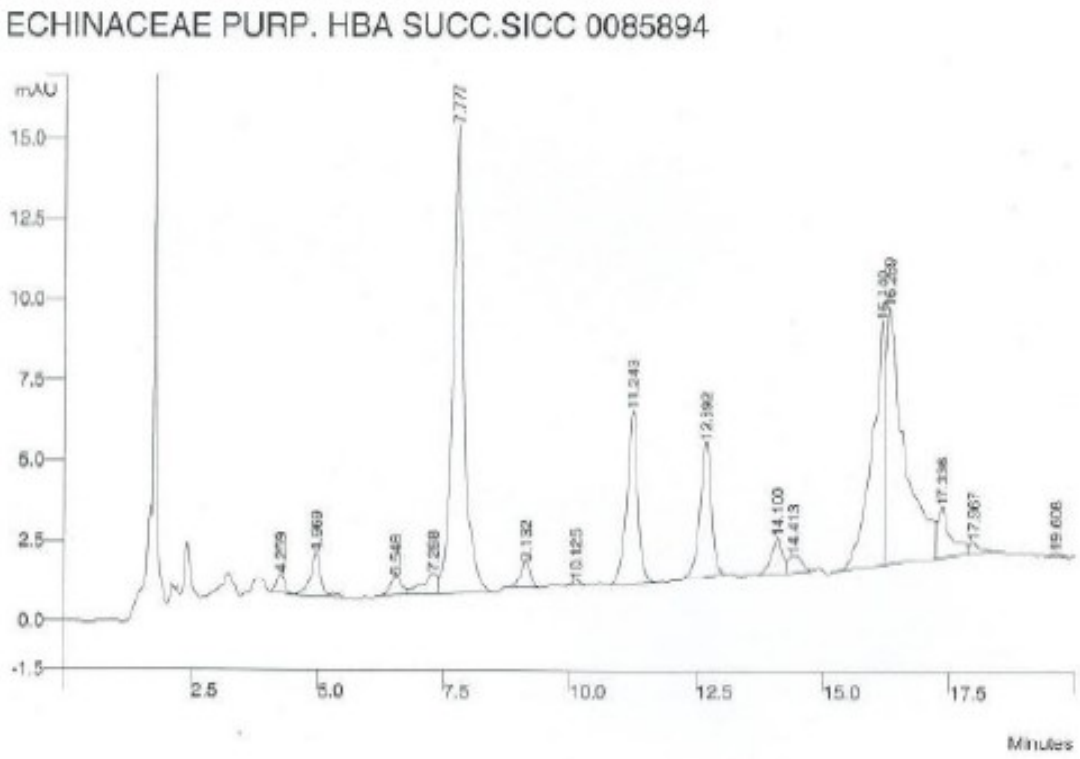


track 1: caftaric acid, cichoric acid (ascending)
track 2: Echinacea purp. hba succ. siccum EFLA®894
track 3: Immu-Cea® syrup
track 4: chlorogenic acid, caffeic acid (ascending)

Immu-Cea shows a very different picture in the TLC. The characteristic blue bands in the upper half of the chromatogram are missing almost completely. The reason could either be a totally different raw material or advanced degradation of the preparation. As Immu-Cea was tested as syrup, this might be possible.

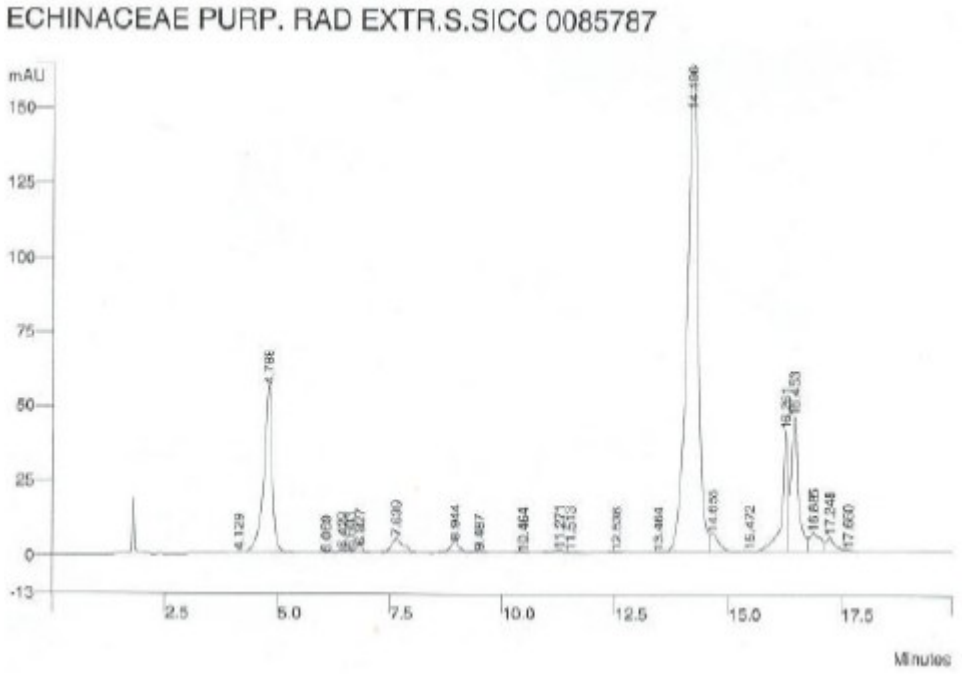
HPLC analysis was done in comparison to a commercially available dried pressed juice preparation of *Echinacea purpurea* (EFLA®894; Frutarom Ltd, Switzerland) as well as a to a preparation of *Echinacea purpureae root* (EFLA®787; Frutarom Ltd, Switzerland).

Figure 5: HPLC chromatogram of *Echinacea purpurea* dry pressed juice (aerial parts)



The peaks at 4.9, 7.7, 11.2 and 12.6 minutes are characteristic for fresh pressed juice of *Echinacea purpurea* Moench (EFLA®894).

Figure 6: HPLC chromatogram of *Echinacea purpurea* root extract



The peaks at 4.7 and 14.1 minutes are characteristic for *Echinacea purpurea* root preparations.

Figure 7: HPLC chromatogram of Imunos tablets

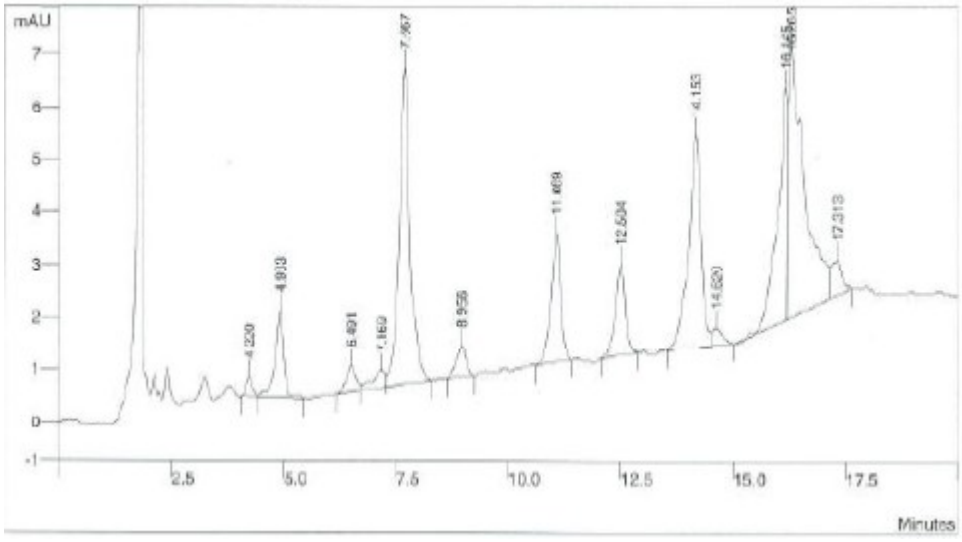
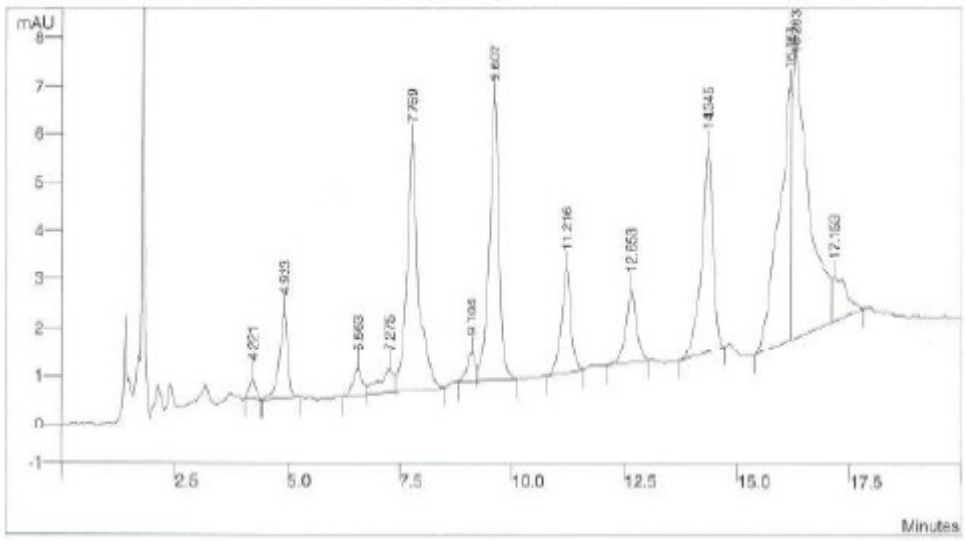


Figure 8: HPLC chromatogram of Imunos syrup



The HPLC chromatograms of the Imunos tablets and the syrup (Figure 7 and 8) have the same characteristic peaks as the *Echinacea purpurea* fresh pressed juice preparation. The peaks at 4.9, 7.5 respectively 7.7, 11.0 respectively 11.2 and 12.5 respectively 12.6 minutes are congruent with the chromatogram of EFLA®894.

Figure 9: HPLC chromatogram of Imboost Force tablets

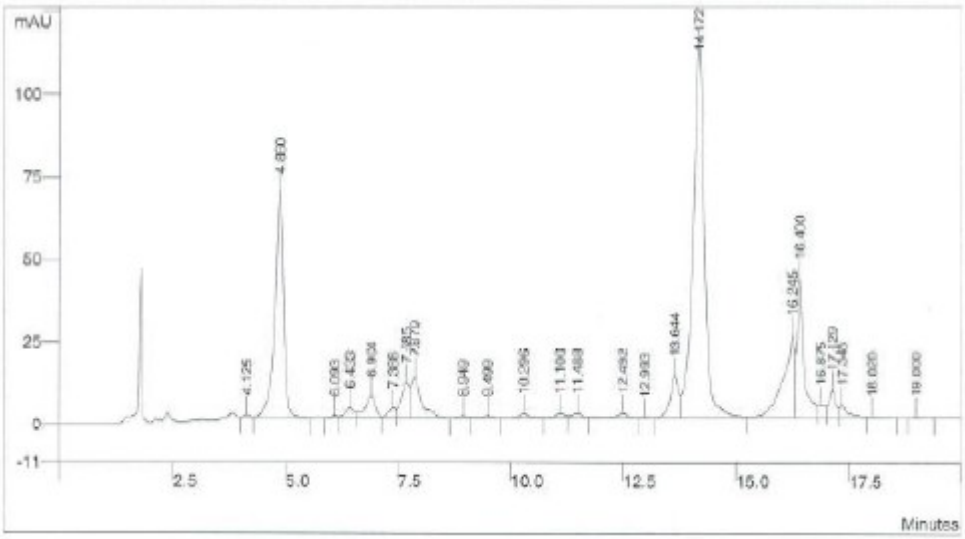
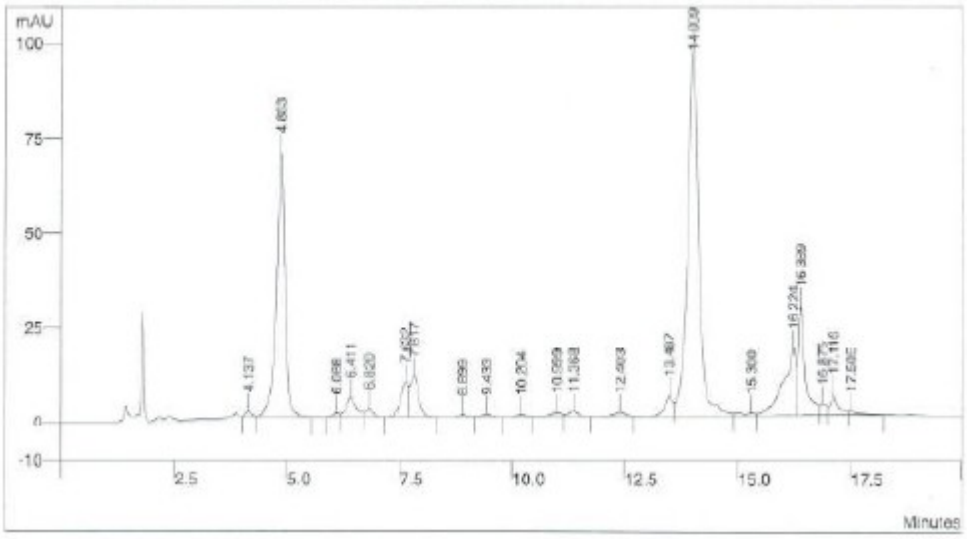


Figure 10: HPLC chromatogram of Imboost Force syrup



The fingerprint chromatogram of both, Imboost Force tablets and syrup are strikingly similar to the HPLC chromatogram of Echinacea purpurea root (Figure 6). The baseline separation is excellent and the two most prominent peaks at 4.8 and 14.1 resp. 14.0 minutes are identical with the peaks of the root extract. The peaks typical for the fresh pressed juice are only very minor.

Figure 11: HPLC chromatogram of Imboost tablets

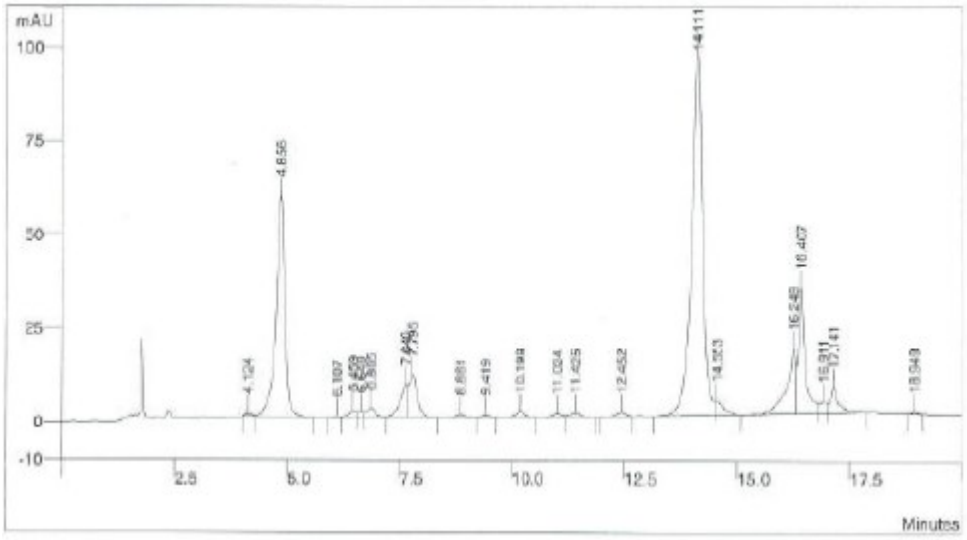
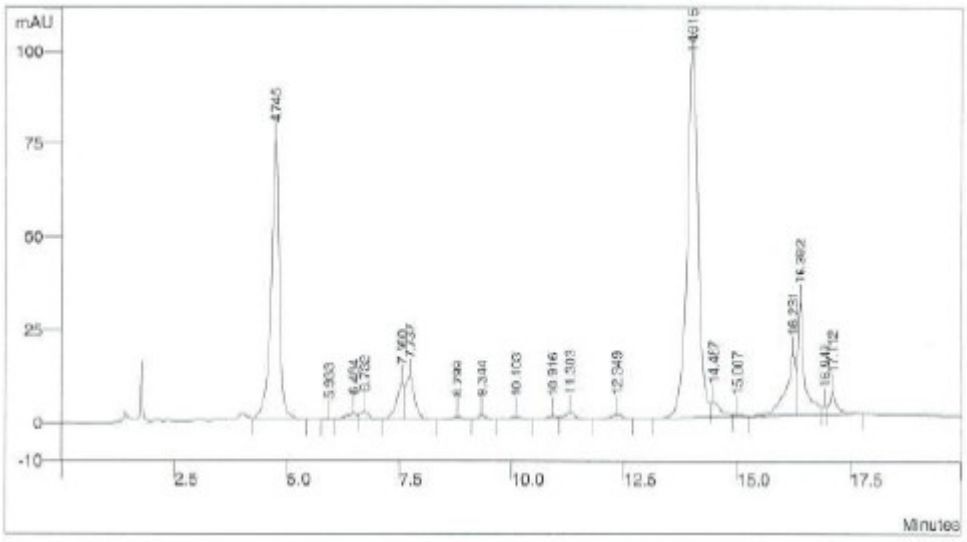
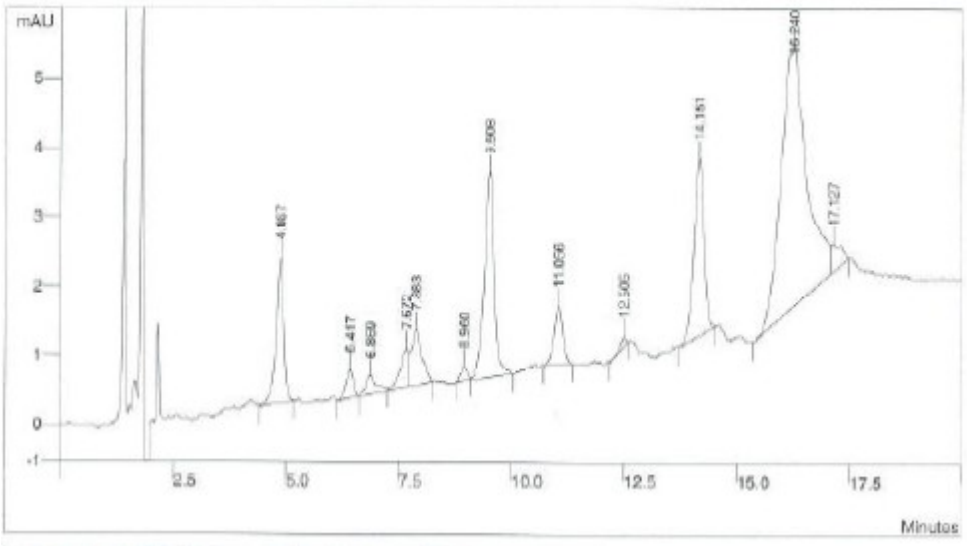


Figure 12: HPLC chromatogram of Imboost syrup



The HPLC chromatograms of Imboost tablets and syrup are very similar to the chromatograms of Imboost Force, even though Imboost Force contains black elderberry and Echinacea while Imboost only contains Echinacea. The baseline separation is excellent and the two most prominent peaks at 4.8 resp. 4.7 and 14.1 resp. 14.0 minutes are identical with the peaks of the root extract. The peaks typical for the fresh pressed juice are only very minor.

Figure 13: HPLC chromatogram of Immu-Cea syrup



The HPLC chromatogram of Immu-Cea syrup has two peaks typical for *Echinacea purpurea* root preparations: at 4.8 and 14.1 minutes. The peak at 9.5 minutes cannot be assigned to either *Echinacea purpurea* root preparations or fresh pressed juice preparations of the herb. Three peaks are congruent with the *Echinacea purpurea* herba fresh pressed juice: 7.6, 11.0 and 12.5 minutes, although the intensity is a lot less than in the reference chromatogram of the EFLA®894 fresh pressed juice preparation.

Summary of the analytical investigations:

Imunos syrup and tablets both match the profile of *Echinacea purpurea* herba fresh pressed juice preparation in the TCL as well as in the HPLC chromatograms suggesting this being the single raw material used for the preparation.
TLC profiles of Imboost and Imboost Force do not completely match the profile of the applied *Echinacea purpurea* fresh pressed juice reference. Particularly the HPLC profile closely resembles the profile of *Echinacea purpurea* radix, hinting the product being either solely composed of a dry extract of *Echinacea purpurea* root or a mixture of herb and root.
Immu-Cea finally, labelled as an Echinacea fresh juice preparation, depicts a very different TLC and HPLC profile compared to the dried fresh press juice reference. While characteristics of both *Echinacea purpurea* root and aerial parts can be found raw material profile is difficult to match more precisely. Differences in the profile found could be due to a different manufacturing process applied or other species of raw material used but cannot be identified more precisely in the analytical approach chosen for this market analysis.

Conclusion:

Considering the results of this review consumer and clinicians need to realise that the efficacy of Echinacea preparations differs greatly depending on the species, the part of plant as well as the preparation method utilised. Latest research concludes that only pressed juice preparations and alcoholic extracts of the aerial parts of *Echinacea purpurea* are believed to mediate positive effects.
An analytical investigation using TLC, HPLC of various Indonesian market products containing ‘Echinacea’ revealed that not all commercial preparation seem to comply with these findings of evidence based medicine. According to the analytical data found the Echinacea preparation Imunos, manufactured by PT Lapi, most closely resembles the constituent profile of an *Echinacea purpurea* dry pressed juice preparation, not showing any evidence of containing root material.
Moreover, the analysis revealed insufficient product labelling, lacking information about Echinacea species, plant part or preparation method used in the preparation.

Manufacturers of Echinacea preparations need to recognize the importance of labelling Echinacea preparations more precisely with information about the extract and raw material used and start communicating the differences to customers and clinicians.

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