Evidence for Self-Medication
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Promoted to the highest evidence class: meta-analysis supports the evidence for EA 575® in treating acute cough

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In self-limiting diseases such as acute respiratory infections, patients primarily expect relief of their symptoms, the aim being to reduce suffering and thus improve their quality of life. The results of a meta-analysis of two studies conducted in line with recognized scientific standards show that the positive effects of the dry ivy leaf extract EA 575® are visible and subjectively noticeable not only in the assessment of those administering the treatment, but also in the evaluation by the participating patients.

Family practices and pharmacies are the first points of contact for patients with acute cough due to acute respiratory infection or bronchitis. In most cases, viruses cause such an infection, so the use of antibiotics is not indicated [1, 2]. Over-the-counter cough medications containing ivy are a widely used treatment option. A systematic review [2] examined the efficacy and tolerability of ivy leaves in the treatment of adults and children with acute cough.

Ivy preparations with different compositions show slight improvement in cough symptoms and are safe to use

An independent systematic review from 2021 [2] evaluated all available randomised controlled trials (RCTs), controlled clinical trials (CCTs), and observational studies (OS) that investigated ivy leaf mono- or combination preparations in the treatment of cough in the context of acute respiratory tract infections in adults and children. The aim of the review was to analyse the efficacy and safety of ivy extracts for respiratory tract infections. The authors selected eleven studies whose bias risk was evaluated in different categories according to the Cochrane risk-of-bias tools. The overall result always corresponds to the worst individual result. In addition to five non-randomised studies, six RCTs were assessed (**Fig. 1**). Only two studies were consistently rated as having a low risk of bias. They were conducted in 2016 and 2019 and fulfilled the specified inclusion criteria. In both studies, the study preparation was the dry ivy leaf extract EA 575® (Prospan® Cough Syrup)* [3, 4].

The systematic review does not differentiate between studies conducted with different active substances (**Fig. 1**). The authors therefore conclude, despite the difficulty of comparing data, that ivy preparations can lead to at least a slight reduction in cough symptoms. The authors consider serious side effects to be unlikely. No quantitative evaluation of the two studies was performed that met all criteria of scientific standards. The authors report statistically significant differences in these studies in favour of ivy treatment on treatment day 3 using the Bronchitis Severity Scale (BSS) and a visual analogue scale (VAS). A significant improvement in cough frequency using the Verbal Category Descriptive (VCD) during this period is also mentioned [2].

Dry ivy leaf extract EA 575® shows significant improvement in various cough markers

Building on this large-scale systematic review, the two studies with special ivy extract EA 575®, which were assigned a low bias risk, were quantitatively analysed separately in a meta-analysis and summarised [5]. Individual data are included in this meta-analysis for evidence synthesis through pooled quantification of effect sizes from both RCTs. These allow more precise analyses of the distribution of effect sizes, such as the comparison of the frequencies of complete remission of cough at the end of therapy with EA 575® or placebo.

Both studies together included 390 patients aged 18 to 75 years who had acute cough (Study A) or bronchitis (Study B).

* Prospan® (e.g.: DE, AU, BE, CA, FR, GR, HK, KR, NL, NZ, PL, SE, USA, ZA), Abrilar (e.g.: BR, CL, CO, SG), Athos (AR), Panoto-s (MX), Prospanex (CH), Prospantus (e.g.: ES)

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Fig. 1. Cochrane assessment of bias risk for six randomised controlled trials (RCTs) based on five areas. [According to 2]
D1: Bias risk due to the randomisation process, D2: Bias risk due to deviations from the planned intervention, D3: Bias risk due to missing outcome data, D4: Bias risk in the measurement of the outcome, D5: Bias risk due to bias in the selection of the reported result

They were randomly assigned to one of the verum (n = 228) or placebo (n = 162) groups. The treatment period comprised seven days and a follow-up on day 14. The study drug product was the dry ivy leaf extract EA 575® or placebo, each taken three times a day.

The endpoint was the severity of the cough. It was recorded by the doctors with the internationally validated Bronchitis Severity Score (BSS) and by the patients with a Visual Analogue Scale (VAS) and a Verbal Rating Score (VRS) to assess the subjective cough severity.

Severity of bronchitis significantly improved after only two days of treatment

Statistically significant differences in the BSS total score between the two treatment arms were seen after just two days (difference of 0.9 score points, $p < 0.001$) and increased until the end of treatment (mean difference 2.4 score points, $p < 0.001$).; **Fig. 2A**). The score reduction for placebo after 7 days was comparable to that for EA 575® after 4 days (placebo 6.2 and EA 575® 6.1 score points). This results in a treatment advantage of three days over placebo after four days of treatment. Similarly, an improvement in the AUC (area under the curve) of the BSS was observed throughout the treatment period (**Fig. 2B**).

Whether the statistically significant difference is also relevant for the patients was checked by means of a responder analysis. In the absence of a defined minimal important difference (MID) for the BSS, the Institute for Quality and Efficiency in Health Care (IQWiG) criterion was used to determine clinical relevance. This states that an improvement of at least 15% of the range of the scale used is a change detectable with sufficient certainty [6]. For the BSS, this corresponds to an improvement of at least 3.15 points. Here, an improvement of 4 points was conservatively defined as the threshold. Accordingly, 93.4% of the EA 575® patients and 76.5% of the placebo patients were considered responders at the end of therapy. The difference was statistically significant ($p < 0.01$).

Severity of cough significantly improved

In terms of cough severity, determined as the AUC of scores obtained with a VAS, there was a treatment group difference of 1501 (95% CI 1070–1932; $p < 0.001$) score points/hour after the 7-day administration (**Fig. 2C**). Lower values are equivalent to a less pronounced cough severity.

The subjective well-being of the patients significantly improved

At baseline, more than 90% of patients described their cough as moderate to severe. This proportion of severely affected patients decreased to 14.5% on day 7 and 11.5% on day 14 in

Study	EA 575®	Placebo	Mean difference (95%-CI)	p
A) Improvement in the BSS at the end of therapy (score points)				
Study A	8,5 ± 0,3	5,7 ± 0,3	2,8 (1,9–3,7)	< 0,001
Study B	8,6 ± 0,2	6,7 ± 0,3	1,9 (1,0–2,7)	< 0,001
Meta-analysis	8,6 ± 0,2	6,2 ± 0,2	2,4 (1,8–3,0)	< 0,001
B) AUC of the BSS in the treatment period (points × time)				
Study A	1160,2 ± 38,9	1449,2 ± 38,1	289,0 (182,4–395,6)	< 0,001
Study B	1154,6 ± 31,0	1374,2 ± 43,7	219,6 (114,6–324,6)	< 0,001
Meta-analysis	1157,4 ± 24,8	1411,7 ± 28,9	254,3 (179,5–329,2)	< 0,001
C) AUC of cough severity in the treatment period (mm × time)				
Study A	7952,6 ± 222,1	9757,0 ± 218,5	1804 (1191–2417)	< 0,001
Study B	8399,5 ± 177,9	9597,0 ± 250,6	1198 (593–1802)	< 0,001
Meta-analysis	8176,0 ± 142,3	9677,0 ± 166,3	1501 (1070–1932)	< 0,001

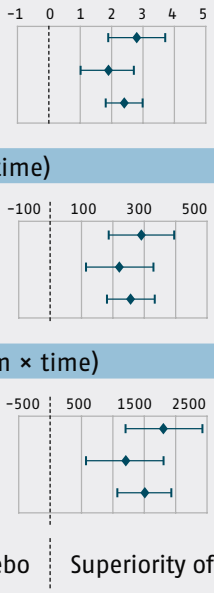
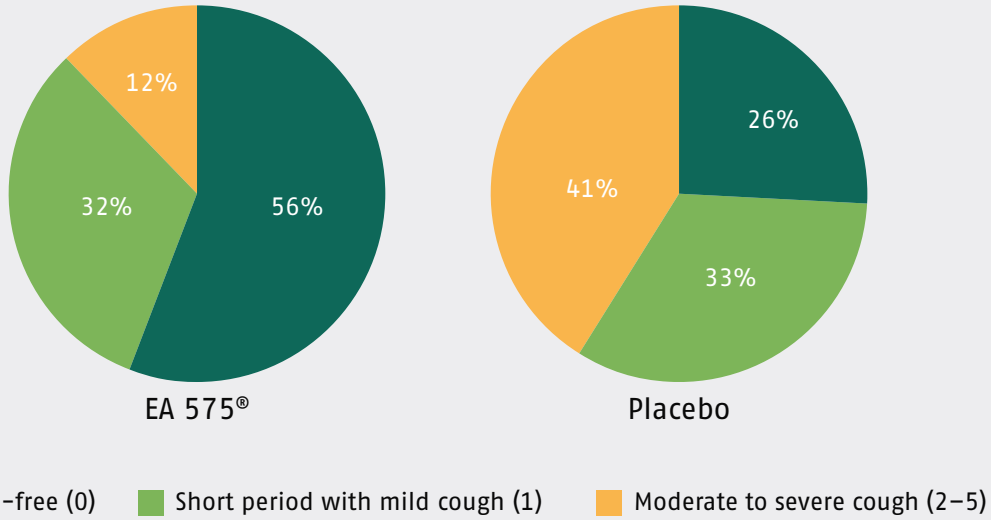


Fig. 2. Forest plots of the main results from the meta-analysis [mean values and mean differences between the treatment groups with 95% confidence interval (CI) as well as statistical significance level of the differences (p)]. The superiority of EA 575® is statistically significant and clear for all outcomes (according to [5]).
A) Improvement in BSS (Bronchitis Severity Score) at the end of treatment. B) Area under the curve (AUC) of BSS during the treatment period. C) AUC of cough severity VAS during the treatment period.



Legend for the Verbal Rating Score (VRS)
0: no coughing
1: sporadic short period of mild coughing without strain
2: several short periods of coughing without much strain
3: frequent coughing that does not interfere with normal daily life or sleep
4: strong and very frequent coughing that interferes with normal daily life or sleep
5: torturous constant coughing lasting over 24 hours

Fig. 3. Assessment of cough severity (VRS) at the end of the observation period on day 14 [5]

participants treated with EA 575®. 56.2% of participants in the verum group were completely cough-free and 32.3% showed only short periods of coughing. This is in marked contrast to the results of the placebo group, where at the end of the observation period (day 14) 41.1% still reported moderate to severe cough and 33.1% of patients reported a mild cough (**Fig. 3**). In this group, 25.8% of those treated were symptom-free.

Summary

This meta-analysis increases the level of evidence regarding the efficacy of EA 575® for treating cough in adults. This is done by increasing the precision of estimates for the expected effect sizes compared to the individual studies through the use of appropriate meta-analytical methods. The superiority of EA 575® over placebo can be shown in all parameters studied, for example the BSS (**Fig. 2**). Consequently, the meta-analysis elevates the dry ivy leaf extract EA 575® to the highest level of clinical evidence (evidence level Ia). In self-limiting diseases such as acute respiratory tract infections, patients primarily expect relief of their symptoms, the aim being to reduce suffering and thus increase their quality of life. A subjectively noticeable treatment effect is therefore an important factor for evaluating therapy options in this indication area. The results of this meta-analysis show that the positive effects of EA 575® are not only visible in scores assessed by the treating practitioners, but also in therapy assessments by the patients, and are thus also subjectively noticeable for the patients. This highlights the clinical relevance of the data. Therapy with EA 575® leads to significantly faster symptom reduction on average.

The investigation of safety-relevant aspects such as adverse events showed no relevant differences between EA 575® and placebo.

At the end of the observation period, almost 90% of the EA 575® patients reported feeling „good“ or „very good“ under therapy with the study drug product.

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