Meta-Analysis of Randomized, Double Blind, Controlled Studies Confirms the Efficacy and Safety of Esberitox in the Treatment of the Common Cold

Belal Naser[1,*], Jörg Schnitker[2], Christian Hentschel[3], Jennifer-Christin Kuchernig[1], Annette Holtdirk[2], Gerd Schöneberg[2], Petra Nicken[1], Klaus-Ulrich Nolte[1] and Hans-Heinrich Henneicke-von Zepelin[1]

[1]*Schaper & Brümmer GmbH & Co. KG, Salzgitter, Germany*

[2]*Dr. Jörg Schnitker (IAS), Bielefeld, Germany*

[3]*Internal Medicine, Allergology and Natural Therapy, Düsseldorf, Germany*

Abstract: Herbal medicines like Esberitox (TOX, wild indigo root stock, echinacea root, thuja tips and leaves) are used to treat common colds. Several randomized, controlled trials (RCT) document the efficacy and safety of TOX in this indication. So far its efficacy and safety has not been evaluated meta-analytically.

We included individual patient data from all 825 patients from 3 RCTs. 693 patients had been treated with TOX, 132 with placebo (PLA) (7-9 days). All symptom scores were adjusted to baseline and meta-analyzed regarding area under the curve (AUC), time to response (≥50% decrease of symptom score), response rate and duration of the cold.

The AUCs of the rhinitis score were 19.05 with TOX superior to 20.57 with PLA (p=0.020), bronchitis score 14.92 versus 16.16 (p=0.039) and well-being 208.4 versus 216.4 (p=0.008). Response rates were higher in TOX than PLA in all scores. The times to response showed an acceleration of the healing process of rhinitis (1.5 days, p=0.049), bronchitis (2 days) and pain (2 days, p=0.008). The duration of the cold was shortened by TOX by up to 2.3 days. The ADR-rate did not differ significantly (2.7% vs. 1.5%, p=0.41). Tolerability was good to very good in 98.4% (TOX) and 99.2% (PLA) (p=0.34). In conclusion, this meta-analysis confirmed the efficacy and tolerability of Esberitox at a higher level of evidence. It accelerates the improvement of cold symptoms by up to 2 days and shortens the duration of colds by up to 2.3 days.

Keywords: Metaanalysis, Common colds, Esberitox, Baptisia, Echinacea, Thuja.

1. INTRODUCTION

Common colds are defined as upper respiratory tract infections (URIs) that predominantly affect the nasal part of the respiratory mucosa [1]. Symptoms include sneezing and runny or congested nose. In addition to “rhinitis” symptoms, cough, sore throat, hoarseness, or expectoration are frequently reported. URIs are the most common acute illness, with more than 90% of the cases caused by viruses [2-4].

Rhinovirus, coronavirus, influenza virus, and respiratory syncytial virus are the four most common virus families that cause common colds [5]. Systematic reviews comparing antibiotic treatment to placebo for pediatric URIs concluded that antibiotics did not alter clinical outcome or reduce complication rates [6, 7]. Whereas symptomatic treatments might reduce symptom severity, they are unlikely to influence the overall duration of symptoms. Therefore, alternatives to antibiotic treatments have gained interest during recent years. Over-the-counter medicine, often herbal preparations, are widely used for the prevention and/or supportive treatment of URIs [3, 8-11].

Esberitox (an extract from a mixture of wild indigo root stock, echinacea root, and thuja tips and leaves) has been successfully used for decades to strengthen the immune system and to treat common colds in Europe, Asia, Australia, and the USA. Numerous *in vitro* and *in vivo* investigations evaluated the effects of this phytomedicine on the immune system, e.g., secretion of cytokines, spleen cell proliferation, antibody secretion [12, 13]. Overall, the pharmacodynamic effects seen are consistent with a stimulatory/modulatory effect on the immune system. The stimulation of the body’s defense [12, 13] is clinically evidenced by alleviation of the symptoms and shortening of the duration of illness in the case of viral colds and beyond this indication in the increase of antibody titer after hepatitis B vaccination [14].

Beside experimental analyses, several clinical studies regarding the efficacy and safety of the herbal remedy made from wild indigo, echinacea and thuja in viral common colds were carried out in the 1980s [15,

*Address correspondence to this author at the Department of Pharmacovigilance, Schaper & Brümmer GmbH & Co. KG, Bahnhofstraße 35, 38259 Salzgitter, Germany; Tel: +49 5341 307-174; Fax: +49 5341 307-82174; E-mail: belal.naser@schaper-bruemmer.de

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16]. GCP-compliant, randomized, controlled clinical studies (RCT) of this herbal remedy followed. In a prospective, mono-centric RCT, the efficacy in adult patients with symptoms of acute URI was statistically significantly superior to placebo [17]. Another RCT also proved the superiority to placebo in a multi-center setting [18]. Further multi-centric RCTs used similar inclusion and exclusion criteria, sample size, number of study centers, treatment duration, and the same diary questionnaire to assess the efficacy of the study medication in rhinitis, bronchitis, and well-being (data not published). These multi-center studies have been pooled in a meta-analysis, which is not only a classical one with aggregated data, but even better, uses an ANCOVA based on the individual patient data (IPD) from these studies. Such approach improves the precision of the estimate of efficacy [19]. The results of this meta-analysis may support the efficacy and safety of Esberitox in the treatment of URIs with a higher level of evidence, according to the Oxford Center for Evidence-Based Medicine[1].

2. MATERIAL AND METHODS

2.1. Selection of Studies

This meta-analysis was restricted to all GCP-compliant, double blind RCTs that used identical inclusion and exclusion criteria and identical questionnaires for the evaluation of cold symptoms and well-being to investigate the efficacy of Esberitox. One placebo-controlled RCT (SB-TOX 0495) [18] and two unpublished equivalence studies comparing similar product variants (SB-TOX 0794 and SB-TOX 1194) – all with ICH-E3-compliant study reports on file – met these criteria, included outpatients in general practices, had similar sample sizes, and examined the same treatment duration.

2.2. Randomization, Blinding and Ethics in the Included Studies

The method of randomization (sequence generation, allocation concealment, and implementation) and blinding has previously been described [18]. Pseudonymization in the studies had been performed using consecutive patient numbers. The legal procurements for protection of private data were met. The studies had been approved by the responsible Ethic committees before study onset.

[1]https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/

2.3. Process of Data Collection in the Included Studies

The studies' documentation in case report form (CRF) and the cold diaries included demography, cold anamnesis, diagnosis, general anamnesis, pre-existing conditions and comorbidity, medication at start of the study, and concomitant medication. The survey by the physician included clinical global impression (CGI), physical examination, laboratory (hematology, clinical chemistry), adverse events (definition see GCP) and assessment of the efficacy and tolerability. The patient survey in these three studies used a diary, which included a questionnaire of common cold symptoms, Welzel-Kohnen-color scales on well-being, body temperature, adverse events, and assessment of the efficacy and tolerability (see [18]).

2.4. Inclusion Criteria in the Included Studies

The studies had included outpatients aged 18 to 70 years with acute viral respiratory infection, who were willing to go to the planned control examinations and to fill out the diary. A written informed consent form for the voluntary participation in the trial had to be signed.

2.5. Exclusion Criteria in the Included Studies

The studies had excluded patients with the following diseases: influenza, acute respiratory infection that lasted for more than 3 days, more than one respiratory tract infection that did not heal within three weeks during the previous year, chronic diseases in the respiratory tract (e.g., chronic bronchitis, chronic sinusitis), fever >38.5°C, bacterial infections of the respiratory tract at the start of the study, and progressive systemic diseases such as tuberculosis, leucosis, connective tissue disease, multiple sclerosis, aids diseases, HIV-infection and other autoimmune diseases. Patients with inflammatory gastrointestinal diseases or absorption disorders (both if known) as well as previous organ transplantation also had been excluded.

In addition, patients with the following concomitant medications had been excluded: antibiotics within the last 7 days or the necessity to initiate an antibiotic therapy (except local antibiotics outside of the respiratory tract), immunosuppressive measures, other immunostimulants / immunomodulators during the last four weeks (including self-medication).

The following had been also not permitted: planned allergy tests (skin testing) or vaccination during the

study period, cytostatic therapy during the last 6 months, major internal diseases (e.g., severe decompensated organ diseases of the heart, liver or kidney, or diabetes mellitus), clinically relevant abnormalities in laboratory parameters (if known), anamnestic-known or acute dependence or abuse of alcohol or medicines, pregnancy or lactation, planned holidays or absence for several days from the place of residence during the study period, and anamnestic-known or current mental illness or disorder that may affect the patient's ability to understand the requirements of the exam, to participate in the exam, or to give informed consent. Also patients who were taking or who had taken an investigational medicinal product within the last 12 weeks prior to the start of treatment in the current study and patients who had already participated in that study had not been included.

2.6. Study Medication

The three studies investigated the herbal remedy Esberitox (TOX), which contains an alcoholic-aqueous extract from Herba Thujae occidentalis: Radix Echinaceae: Radix Baptisiae tinctoriae (corresponding to a daily dose of 18 – 24 mg Herba Thujae occidentalis: 67.5 - 90 mg Radix Echinaceae: 90 - 120 mg Radix Baptisiae tinctoriae). The placebo (PLA) of the study [18] served as comparator. The planned treatment duration was 8 ± 1 days.

2.7. Cold Diary and Clinical Visits

Clinical visits were carried out on day -1 (baseline), day 4 (or 3) and day 8 (± 1). The investigators documented the CGI on the severity (CGI-S) and the improvement (CGI-I) of the patients' diseases at these visits. During the treatment, the patients were supposed to document their cold symptoms in a diary continuously.

In the cold diary, 18 symptoms and 1 item assessing the overall severity of the cold were documented daily (range 0 = none to 9 = very severe). The cold scores (= average of the items) were: 1) rhinitis score (congested nose, runny nose, sniffling, frequency of handkerchief use, frequency of sneezing), 2) pain score (sore throat, headache, joint aches, dizziness, difficulties of swallowing), 3) bronchitis score (cough, hoarseness, expectoration, chest pain, shortness of breath), 4) fever score (night sweats, sweating during the day, chills), and 5) the "overall severity of the cold" as a single item. In addition, a total score (16 items without congested nose and chills) was meta-analyzed.

All symptom scores for all days were adjusted to baseline and evaluated regarding area under the curve (AUC). In patients with at least moderate severity of symptoms at baseline (score ≥ 4), time to response (response was defined as ≥ 50% decrease of symptom score), response rate, and duration of the cold (end of cold = symptom score in PLA at end of observation) were calculated.

Furthermore, the diaries contained the Welzel-Kohnen-color scales [20], validated to assess the well-being. The scales use the sum of 6 items (scale 1 = positive pole to scale 9 = negative pole): How are you today? How is your motivation today? Are you nervous or tense today? How is your mood today? How efficient are you today? How tired are you today?

Regarding safety, the physicians assessed the occurrence of adverse events (definition see GCP) or adverse drug reactions (definition see GCP) and the tolerability.

2.8. Statistics

All meta-analytical evaluations of the effect size were based on the ITT-collective, definition see [18]. The baseline-adjusted values of the AUCs of the rhinitis score (RS), the bronchitis score (BS), the well-being score (WB), and the mean CGI-S at day 4 (or 3) and day 8 (± 1) were the primary meta-analysis criteria. Additionally, response rates were calculated based on the cold scores (see above) and based on CGI-I, respectively (very much better or much better).

The synthesis of the effect sizes from the individual studies was carried out in this meta-analysis using two methods: (i) as covariance-analysis (ANCOVA) based on the individual patient data (IPD) and (ii) in a "classical" meta-analysis synthesizing the weighted means from the individual studies according to DerSimonian & Laird [21]. These are "naïve", i.e. non-standardized meta-analyses, which can be carried out in the "fixed effect model" (it is assumed that in the individual studies the same effects are present) and/or in the "random effects model" (differing effects in the studies are allowed), respectively. According to [18], that study's primary endpoint was also investigated in the current meta-analysis, i.e. the N(0,1)-transformed baseline-adjusted values of the four end points RS (A), BS (B), WB (C), and CGI-S (D) were summed to the

multiple endpoint A+B+C+D according to O'Brien [22]. As in the single study [18], this was evaluated in an hierarchical test procedure of the 4-fold, 3-fold, 2-fold, and 1-fold hypotheses according to Lehmacher [23] using one-tailed α=0.025. In brief, this hierarchical test procedure uses an algorithm that, in case of significant discrimination of the test groups in the 4-fold hypothesis at the predefined α-level, allows subsequent testing of the 3-fold hypotheses (A+B+D; A+C+D, B+C+D, A+B+C) at the same α-level. If there was significant discrimination of the test groups at any 3-fold hypothesis, testing of the subsequent 2-fold hypotheses (e.g. A+B, A+C and B+C for A+B+C) was allowed at the same α-level and so on for the 2-fold hypotheses and the 1-fold hypotheses [23].

Moreover, the time courses of the cold and well-being scores were analysed by ANCOVA considering baseline values and time as covariates for testing the factor treatment. All analyses used the statistical software SAS® version 9.4.

3. RESULTS

Data of all 825 patients with acute viral respiratory tract infection from 3 RCT- and GCP-conform studies were included in the meta-analysis. 693 patients had been treated with TOX and 132 patients with PLA. The pooled ITT-collective comprised 787 patients and served for the efficacy meta-analyses. 28 centers in Germany participated in the studies. TOX and PLA groups did not differ significantly regarding age, gender, smoking habits, and duration of the infection ≤ 3 days (Table **1**). 14 patients did not meet the entrance criterion '≤ 3 days' but were not excluded from the ITT data set considering their low proportion in the total sample and due to general ITT-principle. The body weight significantly differed between the groups in females but not in males. Females were heavier in the TOX than in the PLA group, which handicapped TOX regarding efficacy per kg body weight.

The ANCOVA of the primary target parameters showed significant differences between both groups in favor of TOX (Table **2**). The mean value of the AUC of rhinitis scores was 19.049 in the TOX group and 20.567 in the PLA group (Δ = -1.518¸ p = 0.020). The superiority of TOX also was statistically significant for the AUCs of the bronchitis score (14.916 vs. 16.162; Δ = -1.246; p = 0.039) and the score well-being (208.42 vs. 216.42; Δ = -8.00; p = 0.008). The difference in the CGI-S was in favor of TOX but not statistically significant (2.112 vs. 2.196, Δ = -0.085; p = 0.17).

The results of the classical meta-analysis [21] are in agreement with the aforementioned ANCOVA for comparing TOX vs. PLA. The differences for the baseline-adjusted rhinitis score (Δ = -1.517, p=0.020), bronchitis score (Δ= –1.256, p=0.037), and well-being score (Δ= -7.997; p=0.008, Table **3**) were significant in favor of TOX. By contrast, the difference in the CGI-S-score in favor of TOX was not statistically significant (Δ= –0.086, p=0.17).

Figure **1** presents the corresponding results of the multiple endpoint test procedure according to O'Brien / Lehmacher. All 4-fold, 3-fold, 2-fold, and all but one (CGI-S) of the 1-fold hypotheses revealed significant superiority of TOX to PLA.

Table 1: Patient Demography at Baseline. Mean Values, Standard Deviation (SD) or Frequencies

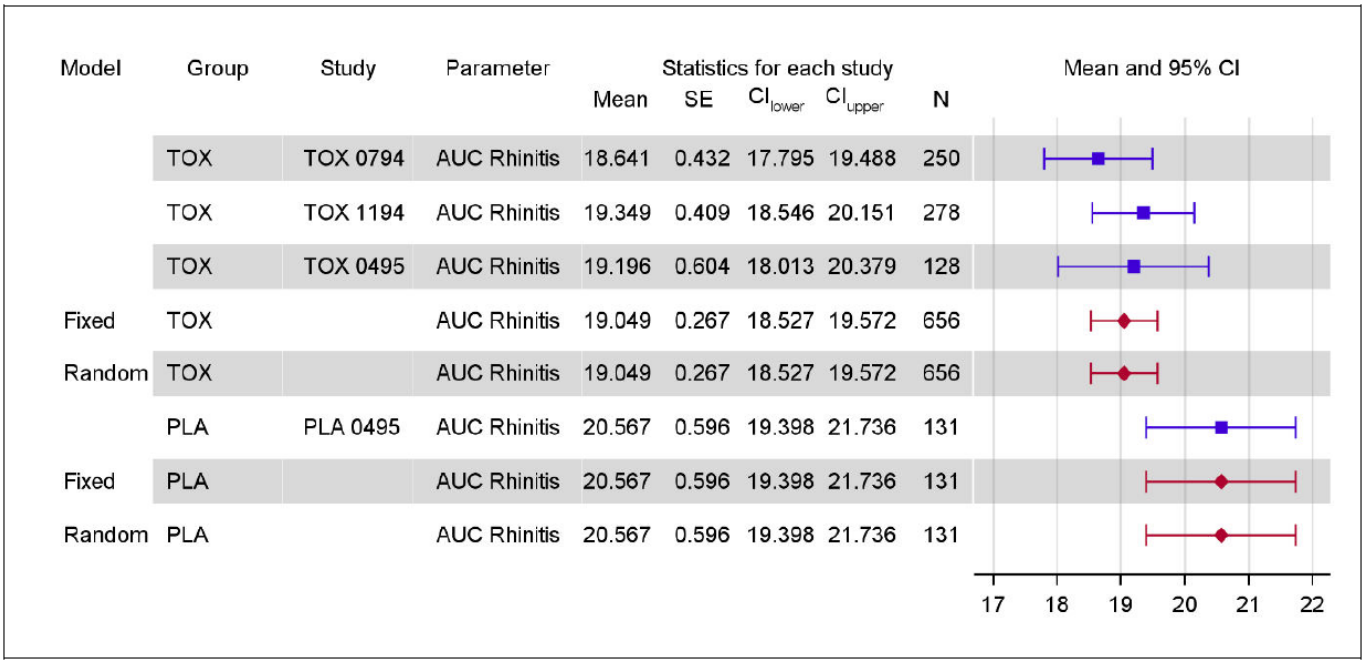
		TOX	PLA	Total collective	Comparison
N		693	132	825	
Age [Years] Mean±SD		41.3±14.2	39.1±13.6	41.0±14.1	p=0.1048
Sex	Male	287 (41.4%)	45 (34.1%)	332 (40.2%)	p=0.1158
	Female	406 (58.6%)	87 (65.9%)	493 (59.8%)	
Body weight [kg] Mean±SD	Male	79.9±11.9	78.6±10.2	79.8±11.7	p=0.4847
	Female	66.7±11.7	63.8±10.6	66.2±11.6	p=0.0365
Smoker	no	505 (72.9%)	100 (75.8%)	605 (73.3)	p=0.7757
	ex	44 (6.3%)	8 (6.1%)	52 (6.3%)	
	yes	144 (20.8%)	24 (18.2%)	168 (20.4%)	
Duration of cold symptoms before onset of therapy	≤3 Days	679 (98.0%)	132 (100.0%)	811 (98.3%)	p=0.0996
	>3 Days	14 (2.0%)	-	14 (1.7%)	

Table 2: ANCOVA of the primary meta-analysis criteria on the efficacy of Esberitox (TOX) in comparison to placebo (PLA). The treatment effect Δ is the difference of the least square means of the treatment groups adjusted to baseline; SE = standard error of the mean; CI = confidence interval with its lower limit LL and upper limit UL; p-value for Δ≠0. The results are based on the ITT-population comprising N=656 TOX and N=131 PLA patients.

Parameter	Mean TOX	Mean PLA	Δ	SE	95%-CI $_{LL}$	95%-CI $_{UL}$	p-value
AUC Rhinitis	19.049	20.567	–1.518	0.653	–2.799	–0.236	p=0.0204
AUC Bronchitis	14.916	16.162	–1.246	0.603	–2.429	–0.063	p=0.0390
AUC Well-being	208.42	216.42	–8.00	3.01	–13.90	–2.10	p=0.0080
AUC CGI-S	2.112	2.196	–0.085	0.062	–0.207	0.037	p=0.1729

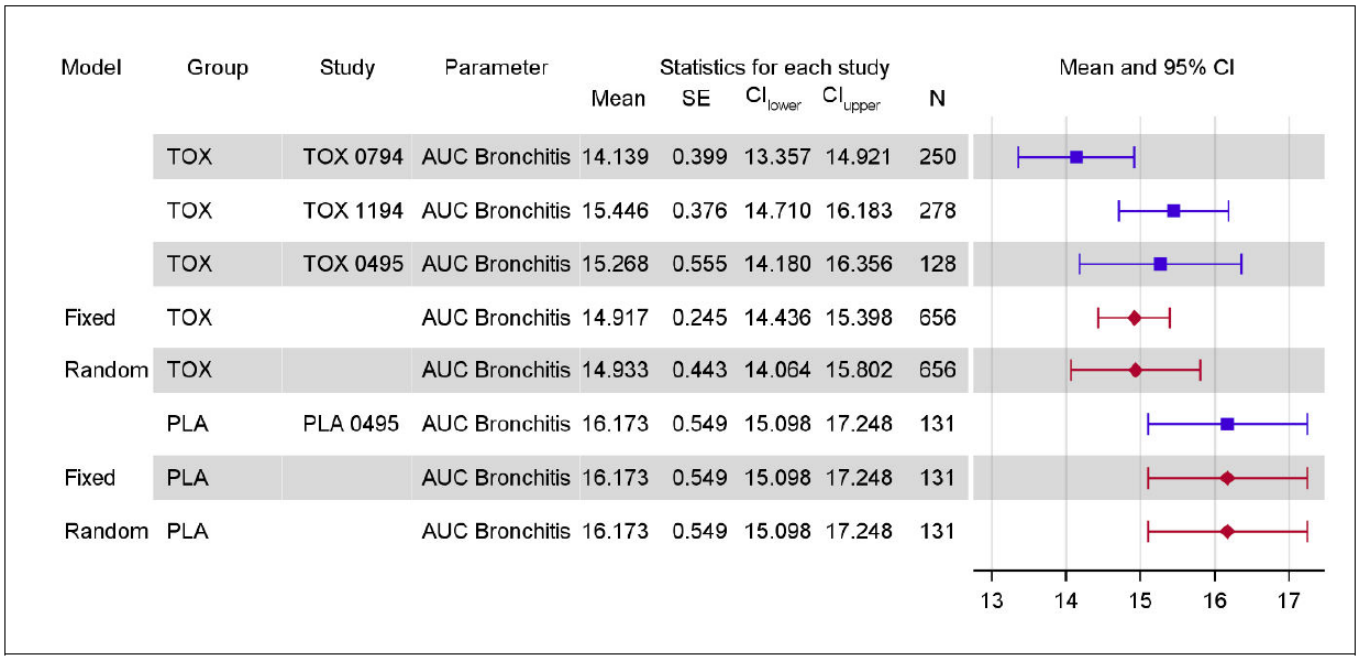
Table 3: Meta-Analysis of the Baseline-Adjusted Scores according to DerSimonian & Laird

A. Rhinitis Score. The difference of the means (19.049 – 20.567) calculates to Δ= –1.517 with 95%-CI ranging from –2.798 to –0.237 in the fixed effect model.



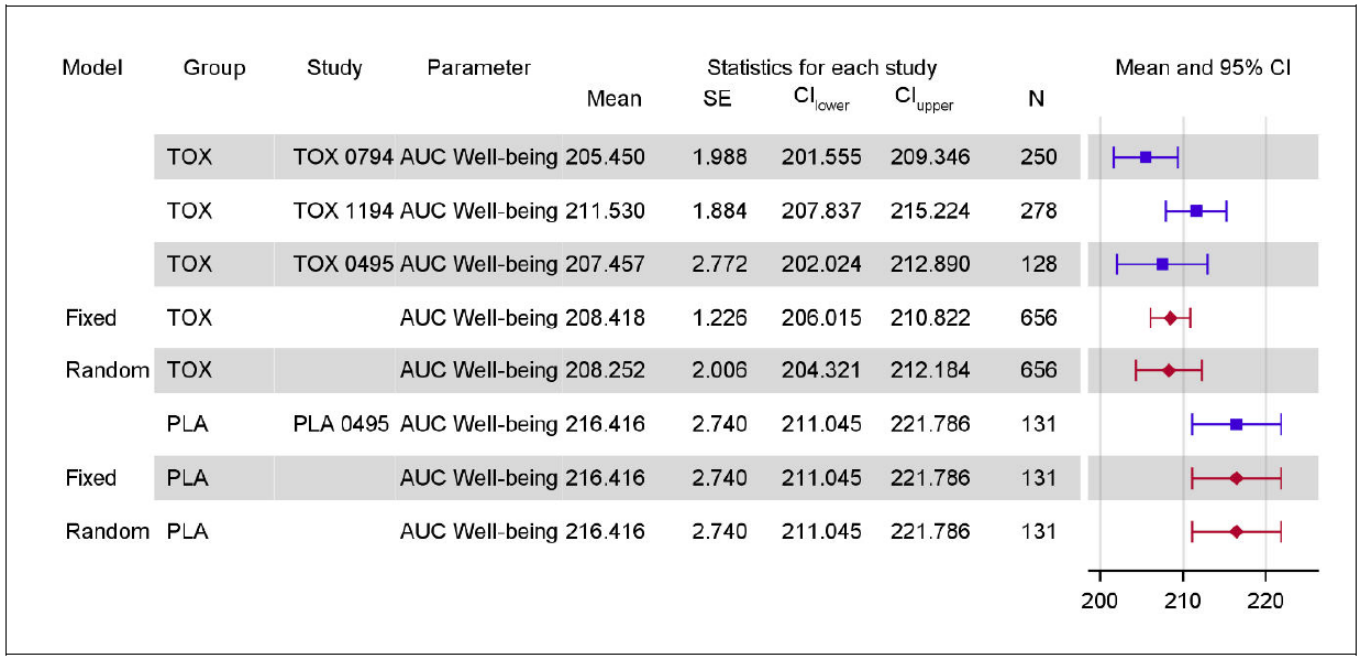
Model	TOX fixed		PLA fixed		TOX random		PLA random	
Heterogenicity	I^2=0.0% (p=0.4757)		I^2=0.0% (p=1.0000)					
Effect size	Mean	19.049	Mean	20.567	Mean	19.049	Mean	20.567
	Std. error	0.267	Std. error	0.596	Std. error	0.267	Std. error	0.596
	95%-CI $_{LL}$	18.527	95%-CI $_{LL}$	19.398	95%-CI $_{LL}$	18.527	95%-CI $_{LL}$	19.398
	95%-CI $_{UL}$	19.572	95%-CI $_{UL}$	21.736	95%-CI $_{UL}$	19.572	95%-CI $_{UL}$	21.736
Comparison TOX vs. PLA	p=0.0202				p=0.0202			

B. Bronchitis Score. The difference of the means (14.917 – 16.173) calculates to Δ= –1.256 with 95%-CI ranging from –2.434 to –0.078 in the fixed effect model.



Modell	**TOX fixed**		**PLA fixed**		**TOX random**		**PLA random**	
Heterogenicity	I^2=67.7% (p=0.0454)		I^2=0.0% (p=1.0000)					
Effect size	Mean	14.917	Mean	16.173	Mean	14.933	Mean	16.173
	Std. error	0.245	Std. error	0.549	Std. error	0.443	Std. error	0.549
	95%-CI $_{LL}$	14.436	95%-CI $_{LL}$	15.098	95%-CI $_{LL}$	14.064	95%-CI $_{LL}$	15.098
	95%-CI $_{UL}$	15.398	95%-CI $_{UL}$	17.248	95%-CI $_{UL}$	15.802	95%-CI $_{UL}$	17.248
Comparison TOX vs. PLA	p=0.0367				p=0.0789			

C. Well-being-Score. The difference of the means (208.418 – 216.416) calculates to Δ= –7.997 with 95%-CI ranging from –13.881 to –2.113 in the fixed effect model.



Modell	TOX fixed		PLA fixed		TOX random		PLA random	
Heterogenicity	I^2=60.6% (p=0.0789)		I^2=0.0% (p=1.0000)					
Effect size	Mean	208.418	Mean	216.416	Mean	208.252	Mean	216.416
	Std. error	1.226	Std. error	2.740	Std. error	2.006	Std. error	2.740
	95%-CI $_{LL}$	206.015	95%-CI $_{LL}$	211.045	95%-CI $_{LL}$	204.321	95%-CI $_{LL}$	211.045
	95%-CI $_{UL}$	210.822	95%-CI $_{UL}$	221.786	95%-CI $_{UL}$	212.184	95%-CI $_{UL}$	221.786
Comparison TOX vs. PLA	p=0.0077				p=0.0162			

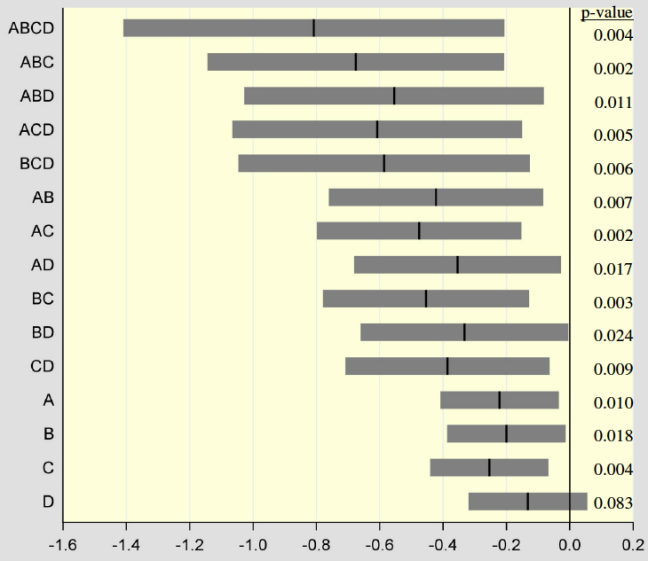


Figure 1: Multiple Endpoint Test Procedure according to O'Brien / Lehmacher. Statistics of sums of the N(0,1)-transformed baseline-adjusted AUC-values of A (rhinitis score), B (bronchitis score), C (total score well-being) and D (CGI-S) are shown, i.e. their mean group differences (bold line) and the corresponding 95%-confidence intervals (bars). Except the 1fold hypothesis D, all tests showed statistical significant superiority of TOX to PLA, simultaneously at α=0.025.

The response rates at the end of treatment were higher in TOX than PLA in all scores in patients with at least moderate severity (≥ 4) of the respective symptoms at baseline (onset of treatment), i.e. in the rhinitis score 84.3% vs. 75.4% (p=0.10), pain score 89.8% vs. 78.4% (p=0.020), bronchitis score 82.9% vs. 78.1% (p=0.51), and in the overall assessment of the severity of the cold 84.0% vs. 72.4% (p=0.003). The times to response were represented by Kaplan-Meier-Plots and compared using the Logrank-test. For example, in Figure **2** the TOX group starts with 300 patients on day 0 whose symptoms can improve on this day. 10 patients have a response (stable improvement of the rhinitis score by ≥ 50%) and the level increases by 10/300. On day 2, 290 patients remain without improvement. In 4 of them an improvement occurs; whereupon the level increases by 4/290 etc. The median time to response showed an acceleration of the healing process of 1.5 days with rhinitis (Figure **2**, p=0.049), 1 day with the overall assessment of the severity of the cold (p=0.007), 2 days with the bronchitis score (p=0.186), and 2 days with the pain score (Figure **2**, p=0.008).

The courses of the baseline-adjusted means of the cold scores (rhinitis, pain, bronchitis) and the well-being score (with at least moderate severity of the symptoms before the first application of the study medication, i.e. score ≥ 4) showed the superiority of TOX over PLA, too (Figure **3**). The calculated effect measure (average group difference of the baseline-adjusted means on the days 1 to 7 in the ANCOVA, i.e. LSmean ± SE) was -0.432 ± 0.193 for the rhinitis score (p=0.026), -0.484 ± 0.191 for the pain score (p=0.012), -0.518 ± 0.259 for the bronchitis score (p=0.047), -0.492 ± 0.249 for the fever score (p=0.0495), -0.225 ± 0.134 for the overall severity of the cold (p=0.094), -0.450 ± 0.197 for the total score (p=0.023) and -1.075 ± 0.535 for the well-being score (p=0.045). Moreover, the same symptom score (mean value) under PLA on day 7 was reached under TOX up to 2.3 days earlier. Thus, TOX shortened the duration of the cold by up to 2.3 days.

The CGI-I also showed significant superiority of TOX to PLA. This was most prominent at the intermediate clinical visit on day 4 with the CGI-I-based response rate of 55.6% (sum of very much better and much better) in the TOX group compared to 43.1% in the PLA group (Figure **4**). The superiority was still evident at the end of treatment with the CGI-S-based response rate of 89.1% in the TOX group compared to 85.8% in the PLA group (Figure **4**). The patients' self-assessments of efficacy also revealed a significant superiority of TOX to PLA (p=0.034) (Figure **4**).

While adverse events were observed more often under PLA than TOX (17.4% vs. 10.8%, p=0.03), the rate of adverse drug reactions did not significantly differ between TOX and PLA (2.7% vs. 1.5%, p=0.41). The

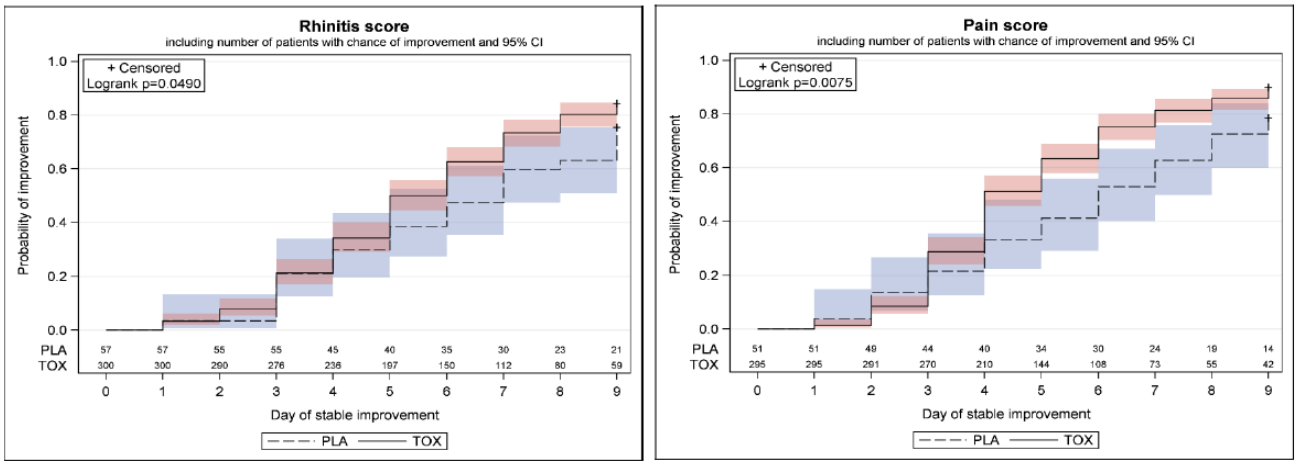


Figure 2: Kaplan-Meier-Plot of the “time to response" based on the rhinitis and pain scores with 95% confidence intervals and in patients with at least moderate severity of the respective symptoms at baseline. The times to response were compared using Logrank-test.

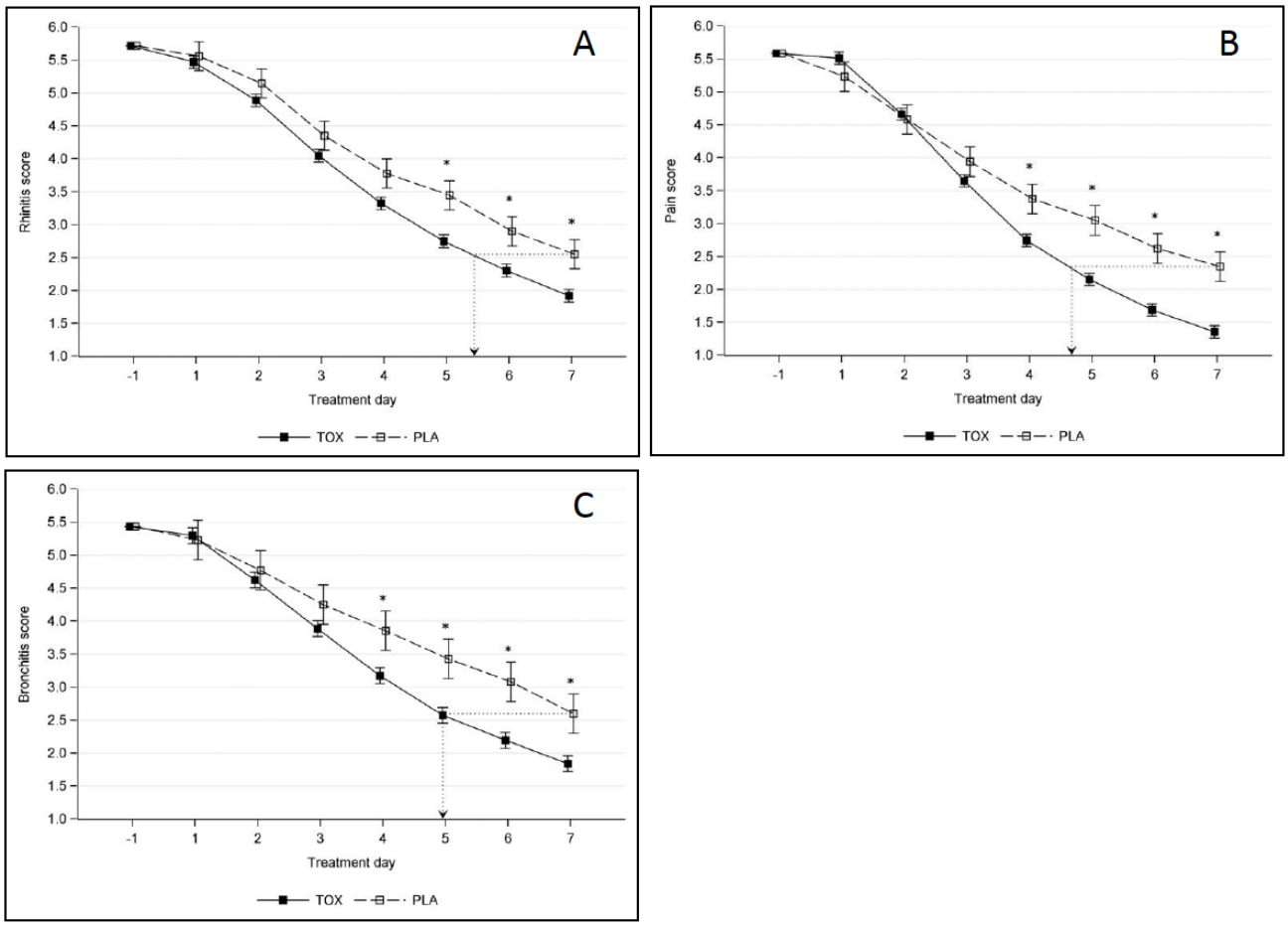


Figure 3: Scores over time. Baseline-adjusted means ± standard error are shown.

A) Rhinitis Score. Interaction with time: p=0.0546; direct treatment effect: p=0.0257; *: p<0.05

B) Pain Score. Interaction with time: p=0.0001; direct treatment effect: p=0.0117; *: p<0.05

C) Bronchitis Scores. Interaction with time: p=0.0033; direct treatment effect: p=0.0468; *: p<0.05.

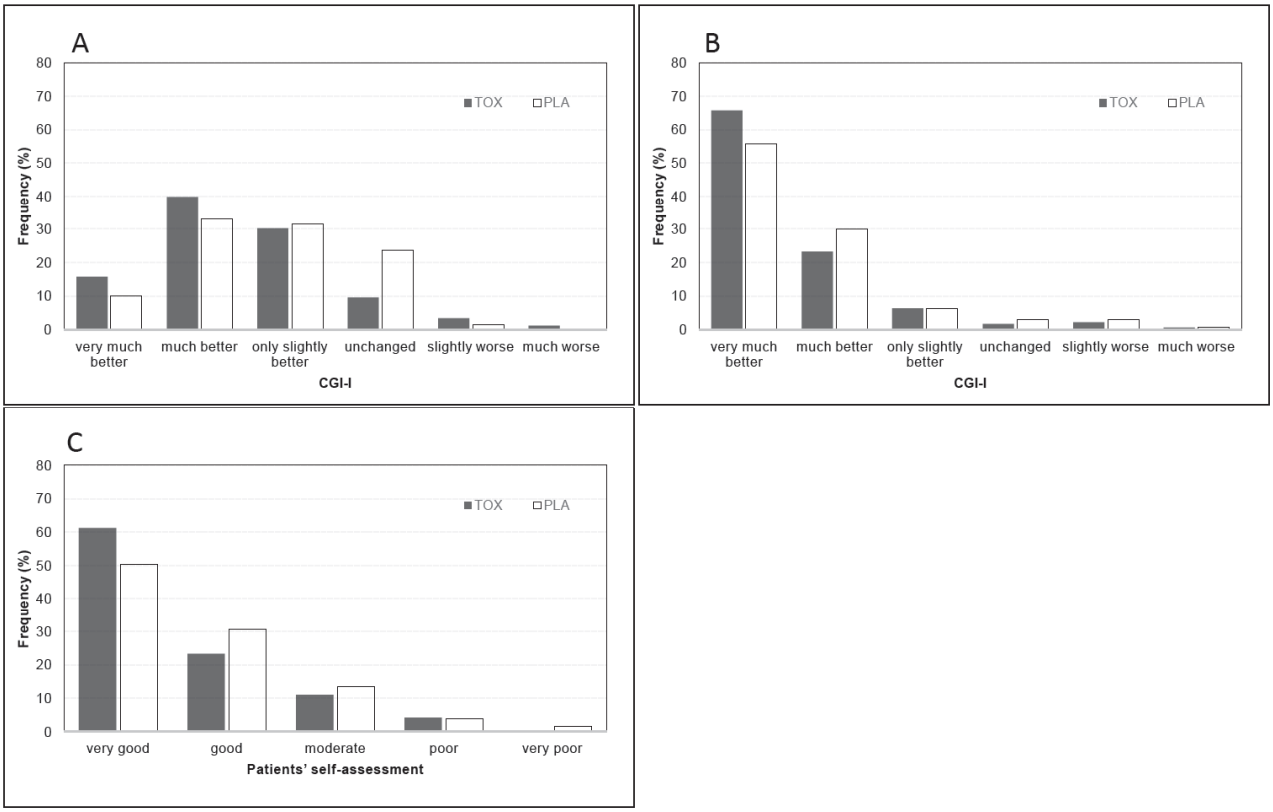


Figure 4: Clinical Global Impression of Improvement (CGI-I) at day 4 (**A**, p=0.0026, U-Test) and at day 8 (**B**, p=0.0330). Patients' self-assessment of efficacy (**C**, p=0.034).

physicians assessed the tolerability as good to very good in 98.4% of the TOX and in 99.2% of the PLA group without significant difference (p=0.34).

4. DISCUSSION

This meta-analysis of three RCTs provides further evidence for the efficacy of the herbal medicinal product Esberitox, containing a unique extract mixture of Echinacea, Thuja, and Baptisia, in the treatment of the common cold. It confirms the results of the RCT [18], which showed the superiority of the herbal remedy to placebo ($p < 0.05$). In that study, 263 patients were included and the effect size was 20.6% of the standard deviation in the ITT-population (90% CI: 0.04-41.1%) and 23.1% in the valid cases (90%-CI: 1.7-44.5%). In this current meta-analysis, 825 patients were included, and the ANCOVA showed the significant superiority of the herbal preparation to placebo regarding the AUCs of the rhinitis score (19.05 vs. 20.57; p=0.020), the bronchitis score (14.92 vs. 16.16; p=0.039) and well-being score (208.4 vs. 216.4; p=0.008).

Our meta-analysis is in agreement with the study [18] also regarding the faster reduction of symptoms and the shortening of the cold duration. According to this RCT, patients who suffered from at least a moderate severity of symptoms at baseline showed response rates (at least 50% improvement of the global score) of 55.3% in the herbal remedy group and 27.3% in the PLA group at day 5 ($p = 0.017$; NNT = 3.5). In our meta-analysis, the response rates were higher in the TOX group than in the PLA group regarding all scores; thereof, the pain score (89.8% with TOX vs. 78.4% with PLA (p=0.020) and the overall assessment of the severity of the cold (84.0% vs. 72.4%; p=0.003) were significant. The median time to response showed a significant acceleration of the healing process by 1 day with the overall assessment of the severity of the cold, by 1.5 days with rhinitis, and by 2 days with the pain score as well as non-significantly by 2 days with the bronchitis score.

Looking at symptom scores in the PLA group at the end of treatment (day 7), it can be stated that patients treated with TOX reached the same scores within shorter periods of time. In this context, the results of those patients with at least moderate symptoms at baseline are of particular interest. In these patients, the rhinitis reference score (day 7.0 in the PLA group) was reached at day 5.4 in the TOX group. Similar reductions were seen in other scores: the pain score was shortened from 7.0 to 4.7 days, the bronchitis

score from 7.0 to 5.0 days, the fever score from 7.0 to 5.1 days, the overall severity of the cold from 7.0 to 5.7 days, and the total score from 7.0 to 5.0 days. Hence, TOX can shorten the duration of a cold by up to 2.3 days.

In addition to the good efficacy, this meta-analysis confirms the very good safety of TOX.

Further placebo-controlled studies on the efficacy and safety of TOX in the treatment of common colds are available [15, 17]. They also confirmed the efficacy and safety of this phytomedicine [17]. This meta-analysis excluded those studies because they did not use the same questionnaire as in the three included studies. Two of the included studies have not been published yet, since they were originally performed for regulatory purposes only.

As a limitation of this meta-analysis, the sample size in the PLA group with 132 patients might seem to be small. However, this number provided sufficient power for proof of superiority and due to ethical reasons unsymmetrical proportions of randomization (693:132 equals about 5:1) are common in such cases. Moreover, we included studies with similar study design (double blind, randomized, controlled, and multicenter studies), which were carried out in general practices in Germany according to GCP-standard. The studies had identical inclusion and exclusion criteria, homogenous sample size and treatment duration, and used the same diary questionnaires for the assessment of efficacy in outpatients. To exclude possible bias we carried out the analysis in three steps. First, we investigated the studies for homogeneity without reference to placebo, which is a classical approach in naïve meta-analyses of studies. Secondly, we compared the results of the individual studies with placebo and finally we compared the pool of individual patient data (IPD) of the three studies with the placebo data. As the included studies do not have any substantial heterogeneity in the essential parameters (I^2-values, e.g. in Tables **3A-C**), a synthesis of the effect sizes by pooling the data of these three studies was feasible. This outweighs the potential limitation that only one of the studies had a placebo-control, which would have been a critical flaw in case of heterogeneity. In contrast, homogeneity circumvents the rule of thumb that a parallel group in the same place at the same time is necessary. Moreover, the current IPD-based meta-analysis investigated the same endpoint, which served as primary efficacy criterion in the placebo-controlled study [18]. The issue of multiple testing was kept under control by the multiple endpoint test procedure according to O'Brien and Lehmacher [22, 23], which preserves the overall α-level.

The strength of the current meta-analysis is that it was based on individual patient data. This allows more precision than in the classical approach using the method of DerSermonian & Laird [21], which summarizes aggregated data (e.g. weighted means and their standard deviations). To be noted is that both methods revealed very similar results in the current meta-analysis; this underlines the reliability of the findings.

Although it is known that viruses are the main causative agents and despite the fact that only a few patients with URI experience a bacterial infection, many patients presenting with URI symptoms are treated with antibiotics. In a study by Cochrane, it was found that antibiotics do not work for either the common cold or for acute purulent rhinitis, and many people are affected by antibiotic side effects [24]. Moreover, inappropriate use of antibiotics for colds contributes to the development of bacterial resistance to antibiotics. It is estimated that each year nearly 2 million people in the United States get an infection in a hospital, resulting in 90,000 deaths. Considering the increasing incidence of bacterial resistance and adverse events, antibiotic treatment is not justified in uncomplicated acute common cold, neither in adults nor in children.

Symptomatic treatment of acute viral URI to provide relief of the most prominent symptoms or syndromes may include decongestants, antihistamines, expectorants, warm saline gargles, lozenges, and/or cough suppression with antitussives (dextrometorphan, codeine). In cases of fever, severe headache, and malaise, NSAIDs may be useful although these agents may be associated with gastrointestinal problems. Additionally, one of the main concerns about anti-inflammatory therapy during URIs is the risk of prolonged viral shedding. While symptomatic treatments might reduce symptom severity, they are unlikely to influence the overall duration of symptoms. There is often no proven benefit of these medications over PLA, and the risk of side effects is great. [3, 10, 11, 25-28]. Also, vitamin C has been assessed by the Cochrane collaboration to have no effect on incidence and severity of URIs [29].

URI are the domain of over-the-counter medicine, often herbal preparations [3, 10, 11]. Echinacea

species are the most widely used herbals for the preventive and/or supportive treatment of common colds. The traditional use of these herbal substances were recently confirmed by the Committee on Herbal Medicinal Products (HMPC) [30, 31]. However, a recent review and metaanalysis on Echinacea found, that it is unlikely that all remedies made from this herbal substance shorten the duration of URI [32]. This issue is scientifically challenging. There are great variations in extracts and doses etc. so that even if one study finds benefit for one herbal extract or not, these findings cannot be extrapolated to other products on the market, especially, if the other product has more than one i.e. several components.

In contrary to herbal remedies containing Echinacea alone, Esberitox is made from Echinacea root in addition to two other herbal substances (wild indigo rootstock and arbor vitae tips and leaves), which also have been shown to stimulate the immune system. It shows pharmacodynamic effects, which are plausible in respect to the pathophysiology of respiratory tract infections, and is of clinical relevance in patients with such disorders as viral cold diseases, e.g. acute URIs. In short, the herbal combination has, amongst other things, pronounced stimulatory and co-stimulatory effects on cytokine and antibody secretion of spleen cells and macrophages *in vitro* and *in vivo* and induces proliferation of immune-competent cells. *In vivo* a restoration of immune-competence was observed in immune-compromised animals. Since it must be expected that the immune competence is impaired or stressed in viral infections, a normalization of the immunological network or an enhancement of the immune system response is considered as a meaningful approach for the treatment of respiratory tract infections, i.e. common colds. Not only in the present study but also in the past studies, the stimulation of the body's defenses was clinically evidenced by alleviation of the symptoms and shortening of the duration of illness [16-18, 33-36].

Several pharmacological and clinical trials have been conducted with this herbal combination, which have demonstrated its efficacy and safety in the treatment of common colds/URIs [15, 17]. A faster reduction of disease-associated symptoms and shortening of disease duration was demonstrated [18]. Neither adverse events nor interactions between this herbal combination and other medications were reported in the placebo-controlled study [17]. Clinically relevant changes in laboratory parameters were not seen in any of the active drug groups [17]. In another RCT adverse events were not related to the study medication and were equally distributed between both treatment groups [18]. In this RCT, adverse drug reactions were suspected in five patients in the placebo group and in two patients in the active treatment group, respectively.

5. CONCLUSION

This meta-analysis of RCTs confirms the good efficacy and tolerability of Esberitox on level 1a of evidence according to the Oxford Centre for Evidence-Based Medicine. The herbal medicine is significantly better than placebo in the treatment of colds. It can accelerate the improvement of cold symptoms by up to 2 days and shorten the duration of a cold by up to 2.3 days.

CONFLICT OF INTEREST

BN, JK, PN, KUN and HvZ are employees of Schaper & Brümmer GmbH & Co. KG. JS, AH, GS and ChH received fund from this company. However, all authors declare that these employments or funds have not had any impact on any of the contributions to this manuscript.

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