Potential of Plant-Based Medicine: Examples from a Swiss Practitioner

Andreas G. Schapowal MD, PhD, DSc (hon)

Specialist in oto-rhino-laryngology, allergology and clinical immunology, psychosomatic and psychosocial medicine, phytotherapy

Switzerland

NVF-Webinar: Phytotherapy Excellence
May 16th, 2023

Andreas G. Schapowal
MD, PhD, DSc (hon)

Number of medicines approved by Swissmedic

according to drug code on March 31th, 2023

	Number	%
Total	**11,382**	**100**
Herbal medicines - traditional approval according to EU monographs (HPMC)	**441**	**3.87**
Anthroposophic medicines	460	4.04
Homeopathic medicines	636	5.58
Tibetan medicines	5	0.04
Ayurvedic medicines	1	0.008

Number of medicines approved on the specialty list (SL)

paid by general health insurance on March 31th, 2023

	Number	%
Total	**10,119**	**100**
Herbal medicines – approval with proven efficacy, safety, usefulness, cost-effectiveness	**133**	**1.31**
Complementary medicines	157	1.55

Andreas G. Schapowal
MD, PhD, DSc (hon)

Petasites hybridus
Butterbur leaf extract Ze 339 in allergic rhinitis

Cultivation (Petzell®, leaves)
Good agricultural practice

CO_2-extract
Good manufacturing practice

Pharmacology

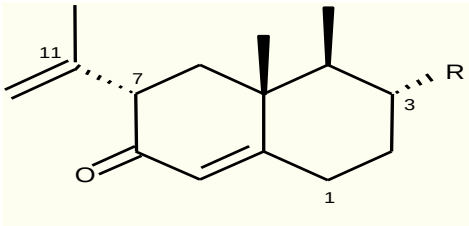
Clinical trials
Proof of principle
Ze 339 vs. cetirizine
Ze 339 vs. placebo, dose-finding
Ze 339 vs. placebo and fexofenadine
Ze 339 vs. placebo and desloratadine
Good clinical practice

Post marketing studies
Good pharmacovigilance practice

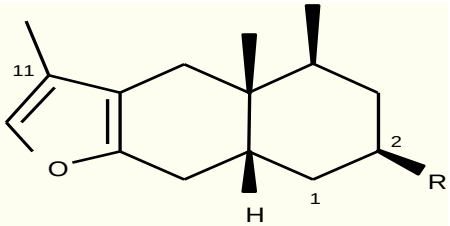
Andreas G. Schapowal
MD, PhD, DSc (hon)

Pharmacological active constituents

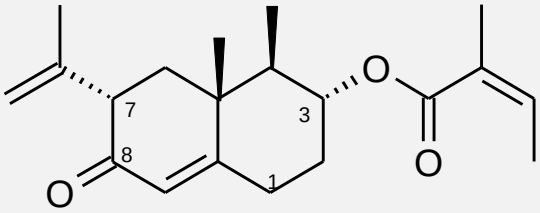
Petasin isomers (group of sesquiterpenes)



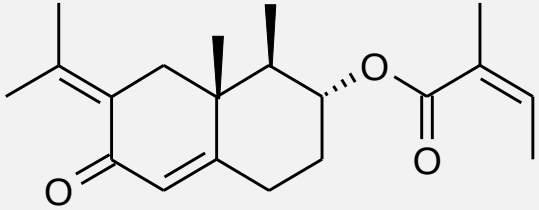
petasin chemovariety



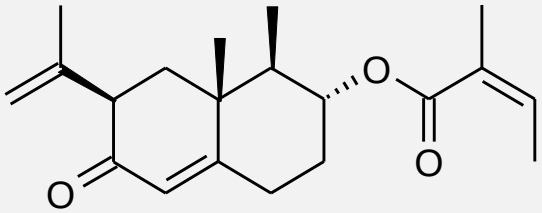
furanopetasin chemovariety



petasin



isopetasin

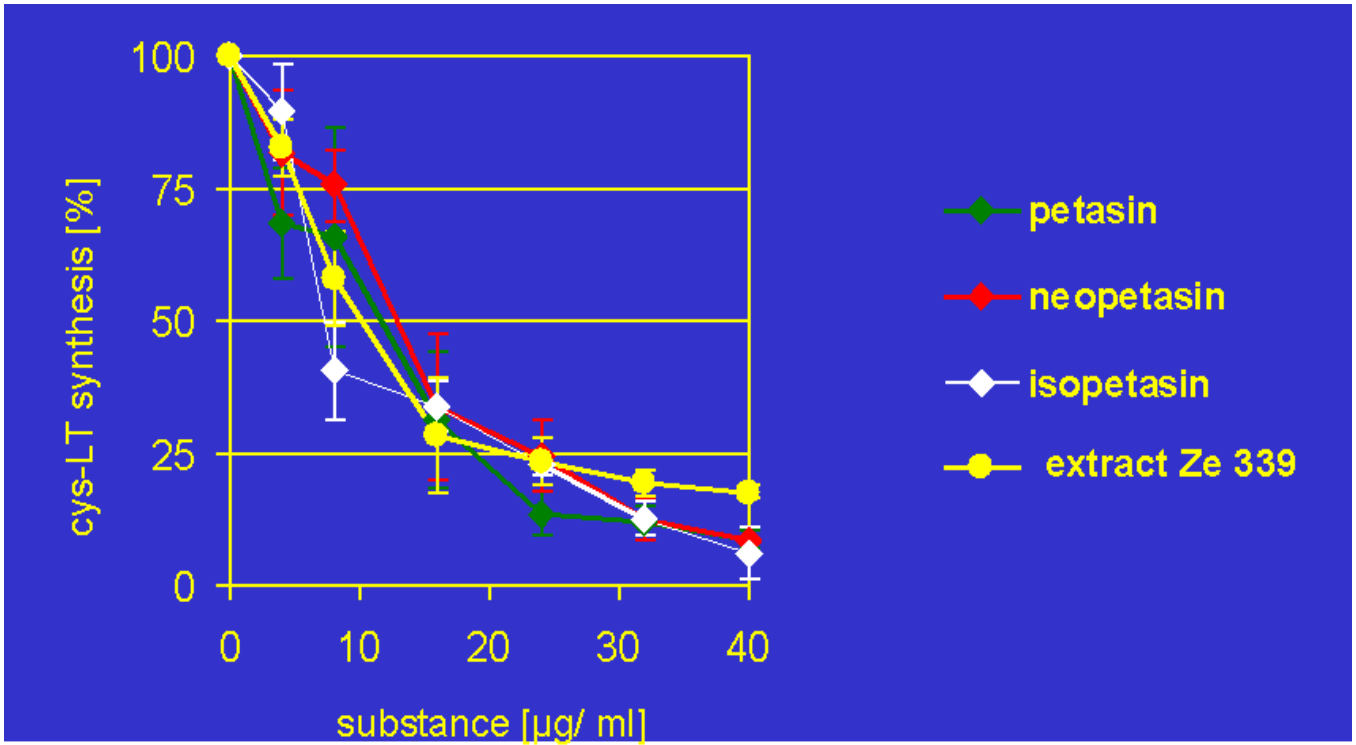


neopetasin

Role of petasin in the potential antiinflammatory activity of a plant extract of petasites hybridus

OAR Thomet, UN Wiesmann, A Schapowal,
C Bizer, HU Simon

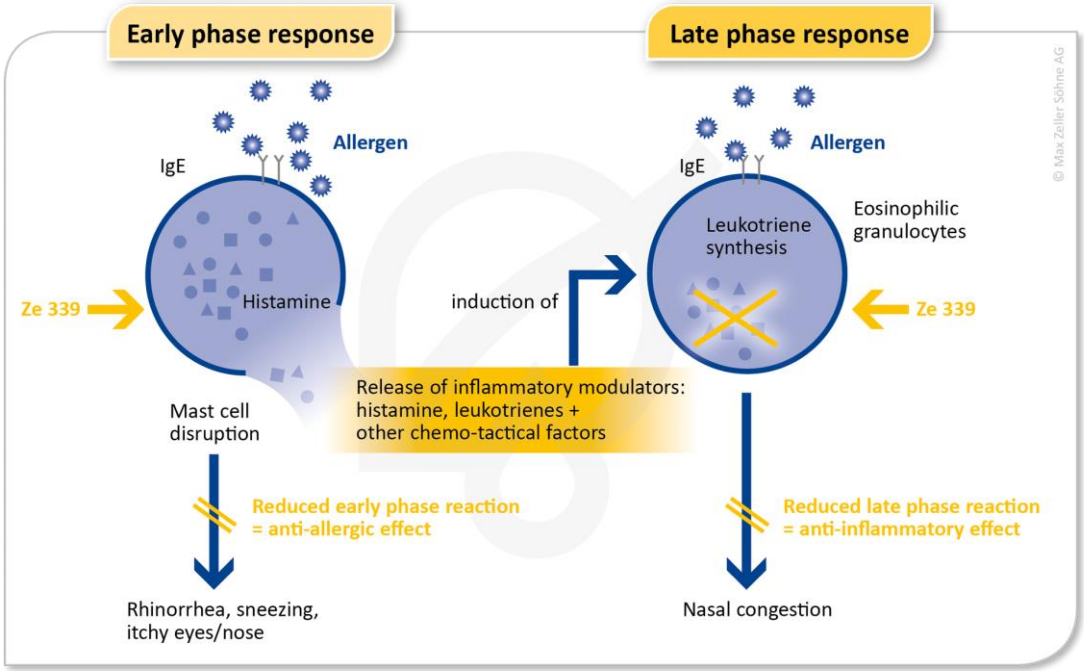
Biochemical Pharmacology 2001; 61: 1041-47



Andreas G. Schapowal
MD, PhD, DSc (hon)

Ze 339 – Mode of action

Ze 339 affects the early and the late phase allergic reaction

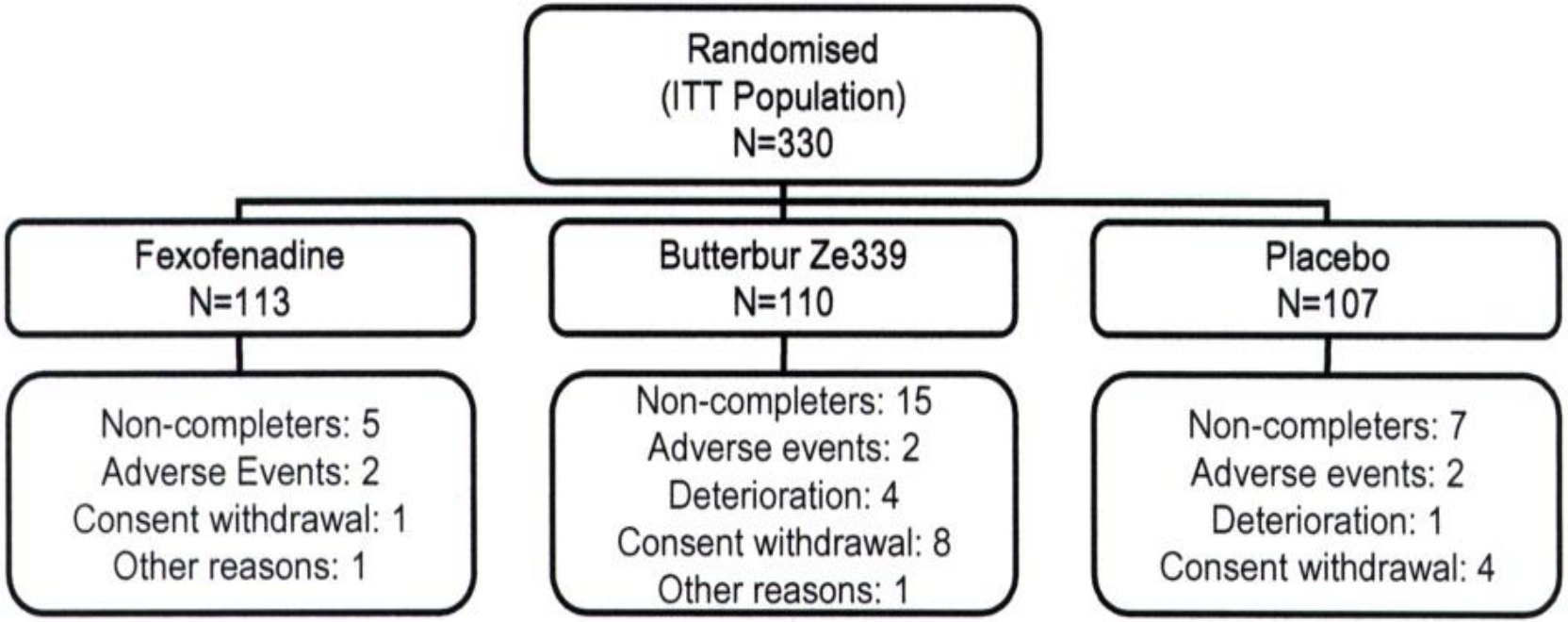


Thomet et al. *Biochemical pharmacology* (2001); 61: 1041-1047
Thomet et al. *Clin Exp Allergy* (2001); 31: 1310-1320
Thomet et al. *Int Immunopharmacol* (2002) 2:997-1006
Gex-Collet C. et al. *J Investig Allergol Clin Immunol* (2006); 16; 3: 156-161
Dumitru et al. *J Allergy Clin Immunol* (2011); 127; 6: 1515-1521

- In the early phase of allergic rhinitis, Ze 339 **blocks the release of inflammatory mediators** such as leukotrienes and histamines by inhibition of mast cell degranulation. This results in **reduced rhinorrhea, sneezing and itching**.
- No binding to the histamine receptor = no sedation
- In the late phase of allergic rhinitis, Ze 339 **by inhibition of the synthesis of leukotrienes** reacts anti-inflammatory. This results in **reduced congestion of the nose**.

Treating intermittend allergic rhinitis: a prospective, randomized, placebo and antihistamine-controlled study of p. hybridus extract Ze 339

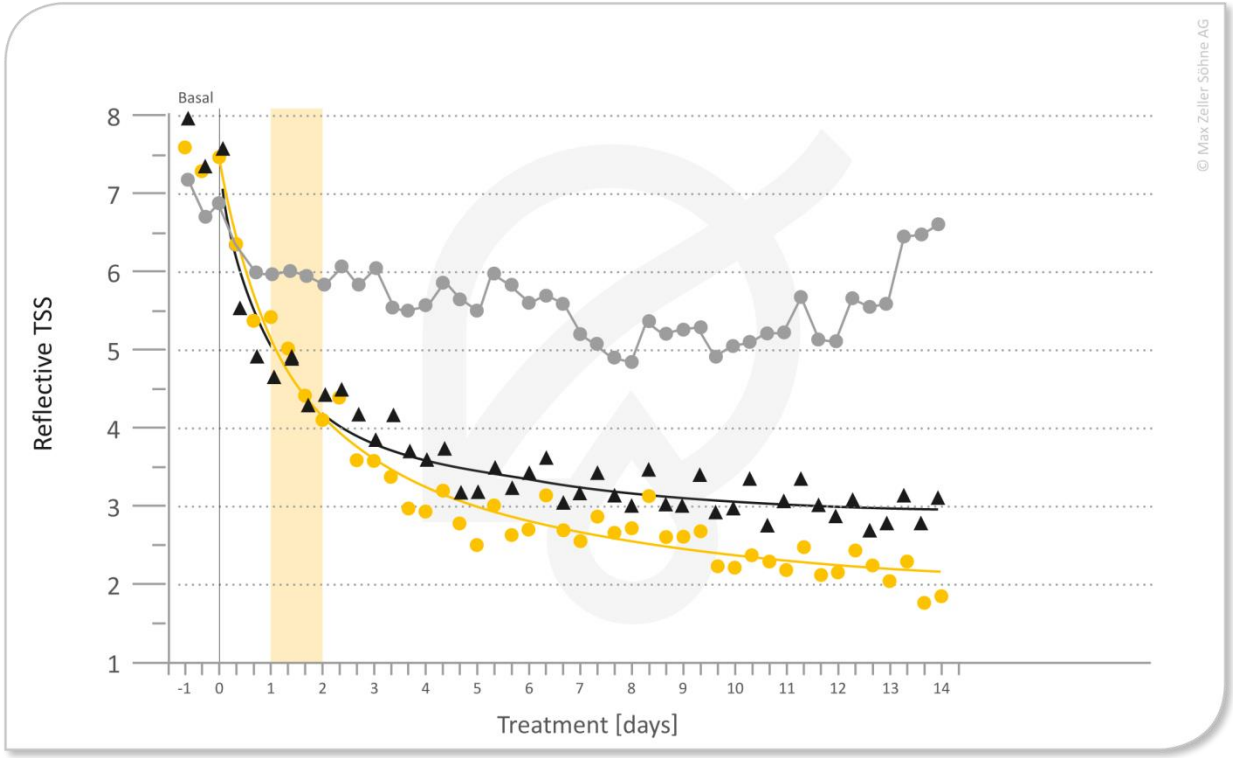
A. Schapowal et al.: Phytother Res 2005; 19, 530-537



Andreas G. Schapowal
MD, PhD, DSc (hon)

Efficacy of Ze 339 vs. fexofenadine and placebo

Improvement of the Total Symptom Score (TSS)



[1] Schapowal et al. Phytother Res 2005; 19: 530-537

Placebo

Ze 339

Fexofenadine

TSS = rhinorrhea+ nasal congestion + itchy nose + sneezing + red eyes

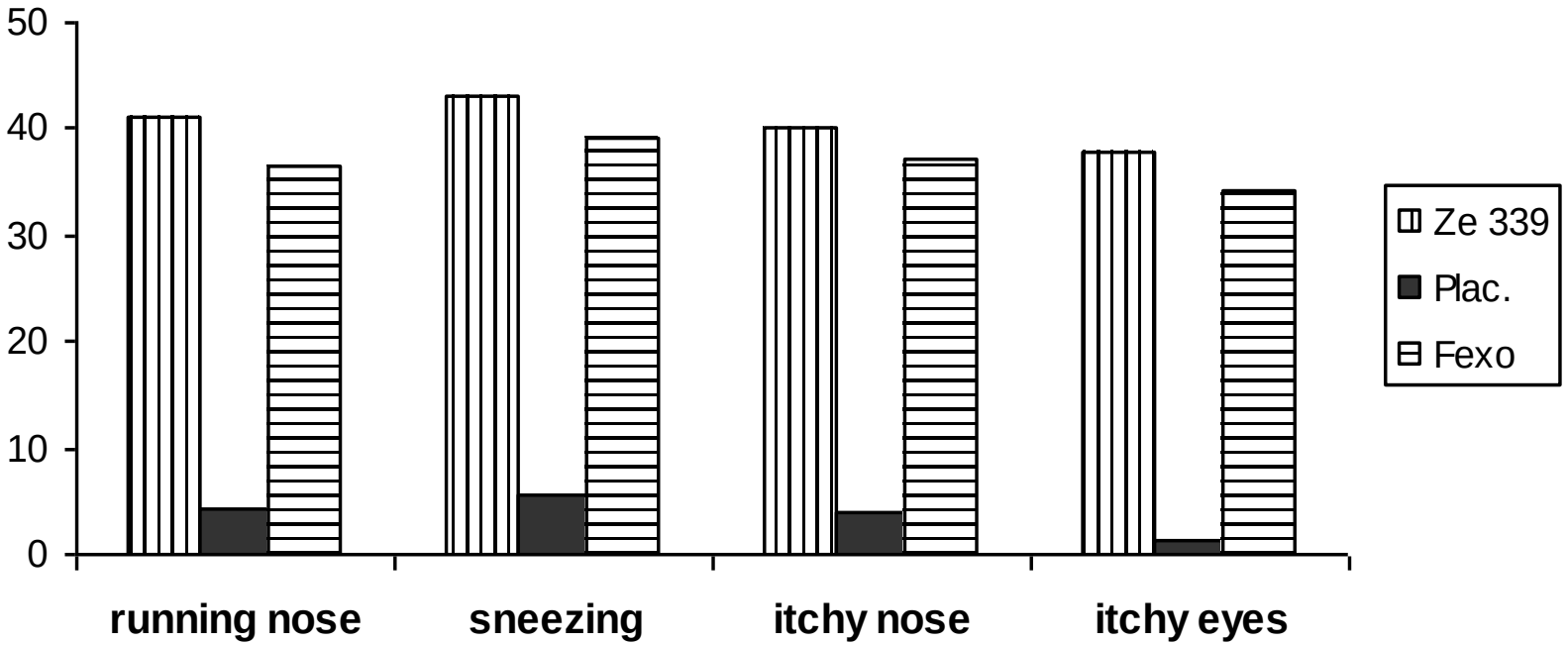
Ze 339 and fexofenadine are equally superior to placebo.

The treatment with Ze 339 caused very few adverse events, comparable to placebo.

Andreas G. Schapowal
MD, PhD, DSc (hon)

Treating intermittent allergic rhinitis: a prospective, randomized, placebo and antihistamine-controlled study of P. hybridus extract Ze 339

A. Schapowal et al.: Phytother Res 2005; 19: 530-537



Improvement vs. baseline (%)

Andreas G. Schapowal
MD, PhD, DSc (hon)

Petasites hybridus
Butterbur

- Composition 1 tablet Ze 339: 20 - 40 mg CO_2-extract (Ze 339) from the leaves of *Petasites hybridus* (L.) Gaertn., B. Mey. et Scherb. corresponding to 8 mg petasins (DER 50-100:1)
- Indication: For the treatment of symptoms of allergic rhinitis and its symptoms in the eyes, nose and throat
- Dosage: Adults and adolescents from 12 years 2 - 3 x 1 tabl
- Studies: 4 RCTs

- Schapowal A on behalf of Petasites Study Group. Randomised controlled trial of butterbur and cetirizine for treating seasonal allergic rhinitis. BMJ 2002; 324: 144 – 146
- Schapowal A on behalf of Petasites Study Group. Butterbur Ze 339 for the treatment of intermittent allergic rhinitis. Dose-dependent efficacy in a prospective, double-blind, placebo-controlled study. Arch Otolaryngol Head Neck Surg. 2004; 130: 1381 – 1386
- Schapowal A on behalf of Petasites Study Group. Treating intermittent allergic rhinitis a prospective, randomized, placebo and antihistamine-controlled study of Butterbur extract Ze 339. Phytother Res 2005; 19: 530 – 537
- Dumitru A et al. Petasol butenoate complex (Ze 339) relieves allergic rhinitis–induced nasal obstruction more effectively than Desloratadine. JACI 2011; 127(6): 1515-1521

- EbM level: 2

Andreas G. Schapowal
MD, PhD, DSc (hon)

Oenothera biennis
Evening primrose

- Composition 1 capsule: 1000 mg of evening primrose oil with at least 80 mg of gamolenic acid
- Indication: Supportive treatment and symptomatic relief of atopic, eczematous skin diseases with accompanying itching
- Dosage: adults 2 x 2–3 caps, children from 1-12 years 2 x 1-2 caps.
- Studies: 2 meta-analyses (9 resp. 26 RCTs)

- Morse PF, Horrobin DF, Manku MS, et al. Meta-analysis of placebo-controlled studies of the efficacy of Epogam in the treatment of atopic eczema. Relationship between plasma essential fatty acid changes and clinical response. Br J Dermatol. 1989;121:75-90
- Morse NL, Clough PM. A meta-analysis of randomized, placebo-controlled clinical trials of Efamol evening primrose oil in atopic eczema. Where do we go from here in light of more recent discoveries? Curr Pharm Biotechnol. 2006; 7: 503-524

- EbM level: 1

Andreas G. Schapowal
MD, PhD, DSc (hon)

Vitex agnus castus
Chaste tree

- Composition 1 tablet Ze 440: 20 mg dry extract of chaste tree fruits
- Indication: Premenstrual complaints, cycle disorders
- Dosage: 1 x 1 tablet
- Studies:

- Berger D et al. Efficacy of Vitex agnus castus L. extract Ze 440 in patients with pre-menstrual syndrome (PMS). Arch Gynecol Obstet 2000; 264:150–153
- Falch BS, Bitzer J, Polasek W. Die Behandlung des prämenstruellen Syndroms (PMS) mit dem Vitex-agnus-castus-Extrakt Ze 440: Eine Therapiebeobachtung. Therapiewoche 2003; 19: 287-288
- Schellenberg R. Treatment for the premenstrual syndrome with agnus castus fruit extract: prospective, randomised, placebo controlled study. BMJ 2001; 322: 134-137
- Schellenberg R et al. Dose-dependent efficacy of the Vitex agnus castus extract Ze 440 in patients suffering from premenstrual syndrome. Phytomedicine 2012; 19: 1325–1331
- van Die M et al. Vitex agnus-castus Extracts for Female Reproductive Disorders: A Systematic Review of Clinical Trials. Planta Med 2013; 79: 562–575

- EbM level: 2

Andreas G. Schapowal
MD, PhD, DSc (hon)

Cimicifuga racemosa
Black cohosh

- Composition 1 tablet Ze 450: 6.5 mg/ 13 mg dry root extract
- Indication: Complaints during menopause (hot flashes, sweating, sleep disorders, nervousness, mood swings)
- Dosage: Ze 450 uno/- forte 1 x 1
- Studies:

- Lopatka L et al. Die Traubensilberkerze in der Behandlung menopausaler Beschwerden – Ergebnisse einer Therapiebeobachtung mit Cimifemin® uno. Journal für Menopause 2007; 2: 3-7
- Schellenberg R et al. Dose-Dependent Effects of the Cimicifuga racemosa Extract Ze 450 in the Treatment of Climacteric Complaints: A Randomized, Placebo-Controlled Study. Evidence-Based Complementary and Alternative Medicine 2012, doi:10.1155/2012/260301
- Drewe J et al. The effect of a Cimicifuga racemosa extracts Ze 450 in the treatment of climacteric complaints – an observational study. Phytomedicine 2013; 20: 659-666

- EbM level: 2

Andreas G. Schapowal
MD, PhD, DSc (hon)

Crataegus
Hawthorn

- Composition 1 film tablet: 450 mg dry extract of hawthorn leaves with flowers, corresponding to at least 6% flavonoids
- Indication: Declining cardiac output, which is associated with a slight limitation in exercise capacity (NYHA 2)
- Dosage: adults 2 x 1 tablet
- Studies:

- Pittler MH et al. Hawthorn Extract for Treating Chronic Heart Failure: Meta-analysis of Randomized Trials. Am J Med. 2003; 114: 665-674
- Pittler MH et al. Hawthorn extract for treating chronic heart failure. The Cochrane database of systematic reviews (online) 2008: CD005312

- EbM level: 1

Andreas G. Schapowal
MD, PhD, DSc (hon)

Hedera helix
Ivy

- Composition 5 ml cough syrup: 35 mg ivy dry leaf extract
- Indication: Excessive formation of thick phlegm, cold cough
- Dosage: Toddlers from 2 years 3 x 2.5 ml, school children from 6 years and adolescents 3 x 5 ml, adults 3 x 7.5 ml syrup
- Studies:

- Bolbot Y et al. Comparing the efficacy and safety of high-concentrate (5 – 7,5:1) ivy leaves extract and Acetylcysteine for treatment of children with acute bronchitis. Drugs of Ukraine 2004
- Mansfeld HJ et al. Therapie des Asthma bronchiale mit Efeublätter-Trockenextrakt. MMW 1998; 140(39): 16-30
- Fazio S et al. Tolerance, safety and efficacy of Hedera helix extract in inflammatory bronchial diseases under clinical practice conditions: a prospective, open, multicentre postmarketing study in 9657 patients. Phytomedicine 2009; 16(1): 17-24

- EbM level: 2

Andreas G. Schapowal
MD, PhD, DSc (hon)

Hypericum perforatum
St. John´s wort

- Composition 1 tablet Ze 117: 250/500 mg St. John's wort dry extract
- Indication: For depressed mood, mood lability, inner restlessness, anxiety, states of tension and the associated difficulty falling asleep and sleeping through the night
- Dosage: adults and adolescents from 12 years 2 x 250 mg/1 x 500 mg
- Studies: 18 RCTs, 2 meta-analyses

- Linde K, Mulrow CD, Berner M, Egger M. St John‘s wort for depression. Cochrane Database Syst Rev 2005;2:CD000448
- Schrader E, Meier B, Brattstroem A: Hypericum Treatment of mild-moderate depression in a placebo-controlled study. A prospective, double-blind, randomized, placebo-controlled, multicenter study. Human Psychopharmacol 1998; 13: 163-169
- Schrader, E. Equivalence of St John's wort extract (Ze 117) and fluoxetine: a randomized, controlled study in mild-moderate depression. Internat Clin Psychopharmacol 2000; 15: 61-68
- Woelk H. Comparison of St John's wort and imipramine for treating depression: randomised controlled trial. BMJ 2000; 321: 536-539
- Brattstroem A. Long-term effects of St. John’s wort (Hypericum perforatum) treatment: A 1-year safety study in mild to moderate depression. Phytomedicine 2009; 16: 277-283

- EbM level: 1

Andreas G. Schapowal
MD, PhD, DSc (hon)


Valeria officinalis / Humulus lupulus

Valerian / Hop

- Composition 1 tablet Ze 91019: 250/500 mg dry extract from valerian root, 60/120 mg dry extract from hop cones
- Indication: Difficulty falling asleep and sleeping through the night as well as restless sleep
- Dosage: adults and adolescents from 12 years 2-3 tbl Ze 91019 250 mg resp. 1-1 ½ Ze 91019 500 mg one hour before bedtime, children from 6 years 1 Ze 91019 250 mg bzw. ½ Ze 91019 250 mg
- Studies:

- Morin CM et al. Valerian-Hops Combination and Diphenhydramine for Treating Insomnia: a Randomized Placebo-Controlled Clinical Trial. Sleep 2005; 28(11): 1307-1313
- Koetter U et al. A Randomized, Double Blind, Placebo-Controlled, Prospective Clinical Study to Demonstrate Clinical Efficacy of a Fixed Valerian Hops Extract Combination (Ze 91019) in Patients Suffering from Non-Organic Sleep Disorder. Phytotherapy Research 2007; DOI: 10.1002/ptr.2167

- Valerian acts like endogenous adenosine and increases the willingness to sleep
- Hops acts like endogenous melatonin and supports rhythmicity
- Both extracts complement each other in the therapy of sleep disorders of non-organic origin (ICD 10: F51.0 - F51.2)

- EbM level: 2

Andreas G. Schapowal
MD, PhD, DSc (hon)

Petasites hybridus/Valeria officinalis/Passiflora/Melissa officinalis Butterbur/valerian/passionflower/lemon balm

- Composition 1 tablet Ze 185: 90 mg dry extract from butterbur roots, 90 mg valerian roots, 90 mg passionflower herb, 60 mg lemon balm leaves
- Indication: Nervousness, states of tension and restlessness, exam anxiety, which manifests itself e.g. in spasmodic gastrointestinal complaints, increased irritability, occasional problems falling asleep and sleeping through the night
- Dosage: adults and children from 6 years 3 x 1 tablet
- Studies:

- Gerhard U et al. Die sedative Akutwirkung eines pflanzlichen Entspannungsdragées im Vergleich zu Bromazepam. Schweiz. Rundschau Med (PRAXIS) 1991; 80 (52): 1481-1486
- Schellenberg R et al. Pflanzlicher Tagestranquilizer Ze 185 und Oxazepam im klinischen und neurophysiologischen Vergleich bei Patienten mit psychovegetativen Beschwerden. Zeitschrift Phytotherapie 2004; 25: 289-295
- Melzer M et al. Fixed herbal drug combination with and without Butterbur (Ze 185) for the treatment of patients with somatoform disorders: randomized, placebo-controlled, pharmaco-clinical trial. Phytother Res 2009; 23(9):1303-1308

- EbM level: 2




Andreas G. Schapowal
MD, PhD, DSc (hon)

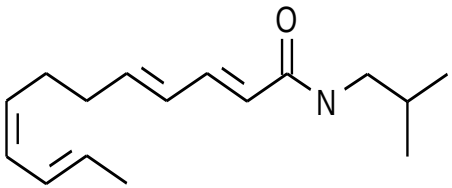
Echinacea purpurea
Red coneflower

- North American Indians used the root and herb to aid in healing wounds, fevers, insect bites, and snake bites
- Used in Europe since the beginning of the 20th century, E. purpurea for about 70 years
- Ingredients: phenols (caffeic acid, cichoric acid), essential oils, flavonoids, polyacetylene, alkylamides, fatty acids (palmitic acid, linoleic acid), polysaccharides, glycoproteins
- Different distribution in herb and root, e.g. main ingredients in the herb cichoric acid and alkamides, in roots also glycoproteins with cytokine-inducing effect

Andreas G. Schapowal
MD, PhD, DSc (hon)

Effects of the well-known components of Echinacea

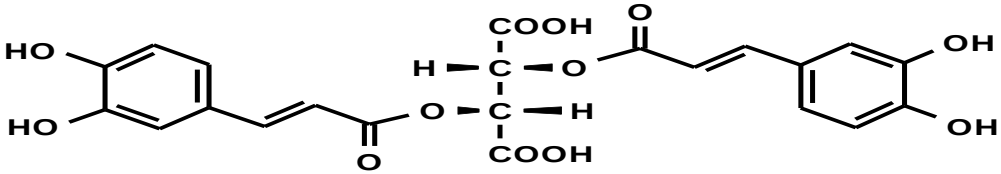
Alkamids



- Stimulation of phagocytosis (Bauer et al. 1989)
- Activation of makrophages (Goel et al. 2002)
- Inhibition of PG- and LT synthesis (Bauer et al. 1994)
- Expression of TNF-α via CB2 and other signal transduction ways (Gertsch et al. 2004)

Caffeic acid derivates

- Inhibition of hyaluronidase (Orinda et al. 1973)
- Free radical scavenging properties (Facino et al. 1995)
- Inhibition of inflammation (Speroni et al. 2002)



1,2-dicaffeoyl-tartaric acid
(cichoric acid)

Glycoproteins/Polysaccharids

- Activation of makrophages (Beuscher et al. 1995)
- Stimulation of antibody production (Beuscher & Kopanski 1987)
- Complement stimulation (Alban et al. 2002)

Andreas G. Schapowal
MD, PhD, DSc (hon)

Echinace purpurea

EF tablets

(Echinacea purp. herba 380 mg + Echinacea purp. radix 20 mg)

3 x 2 tablets daily, children from 4 – 12 years 3 x 1 tablets for **preventive**

3-5 x 2 Tab, children from 4 years 3-5 x tgl. 1 tab for **curative**

EF forte® tablets

(Echinacea purp. herba 1140 mg + Echinacea purp. radix 60 mg)

Adults and adolescents from 12 years 2 x 1 tablet daily **preventive**

Adults and adolescents from 12 years 2 x 2 tablets daily **curative**

EF sore throat spray: Echinacea purpurea + Salvia officinalis

(1 ml solution: 863 mg Echinacea purp. herba +
46 mg Echinacea purp. radix tincture +
430 mg ticture from fresh sage leaves)

Adults and adolescents from 12 years 6-10 x 2 puffs daily

Prevention of recurrent respiratory tract infections and complications

Adv Ther (2015) 32:187–200
DOI 10.1007/s12325-015-0194-4

REVIEW

Echinacea Reduces the Risk of Recurrent Respiratory Tract Infections and Complications: A Meta-Analysis of Randomized Controlled Trials

Andreas Schapowal · Peter Klein · Sebastian L. Johnston

To view enhanced content go to www.advancesintherapy.com
Received: February 4, 2015 / Published online: March 18, 2015

ABSTRACT

Introduction: Respiratory tract infections are common, and these infections occur frequently in children, susceptible adults, and older persons. The risk for recurrences and complications relates not only to the presence of viruses but also to immune function. Therefore, modulation of the immune system and antiviral interventions such as echinacea might reduce the risk of recurrences and possibly the development of complications.

Methods: MEDLINE, EMBASE, CAplus, BIOSIS, CABA, AGRICOLA, TOXCENTER, SCISEARCH, NAHL, and NAPRALERT were searched for clinical trials that studied recurrent respiratory infections and complications on treatment with echinacea extracts in a generally healthy population. Two independent reviewers selected randomized, placebo-controlled studies of high methodological quality and a Jadad score of ≥4. Relative risks (RRs) with 95% confidence intervals (CIs) were calculated according to a fixed effect model.

Results: Six clinical studies with a total of 2458 participants were included in the meta-analysis. Use of echinacea extracts was associated with reduced risk of recurrent respiratory infections (RR 0.649, 95% CI 0.545–0.774; $P < 0.0001$). Ethanolic extracts from echinacea appeared to provide superior effects over pressed juices, and increased dosing during acute episodes further enhanced these effects. Three independent studies found that in individuals with higher susceptibility, stress or a state of immunological weakness, echinacea halved the risk of recurrent respiratory infections (RR 0.501, 95% CI 0.380–0.661; $P < 0.0001$). Similar preventive effects were observed with virologically

Electronic supplementary material The online version of this article (doi:10.1007/s12325-015-0194-4) contains supplementary material, which is available to authorized users.

A. Schapowal (✉)
Allergy Clinic, Landquart, Switzerland
e-mail: andreas@schapowal.ch

P. Klein
d.s.h. Statistical Services Gmbh, Rohrbach, Germany

S. L. Johnston
Airway Disease Infection Section, National Heart and Lung Institute, Imperial College London, London, UK

S. L. Johnston
MRC & Asthma UK Centre in Allergic Mechanisms of Asthma, Imperial College London, London, UK

Schapowal A, Klein P, Johnston SL: Advances in Therapy 2015; 32:187-200

Andreas G. Schapowal
MD, PhD, DSc (hon)

Prevention of recurrent respiratory tract infections and complications

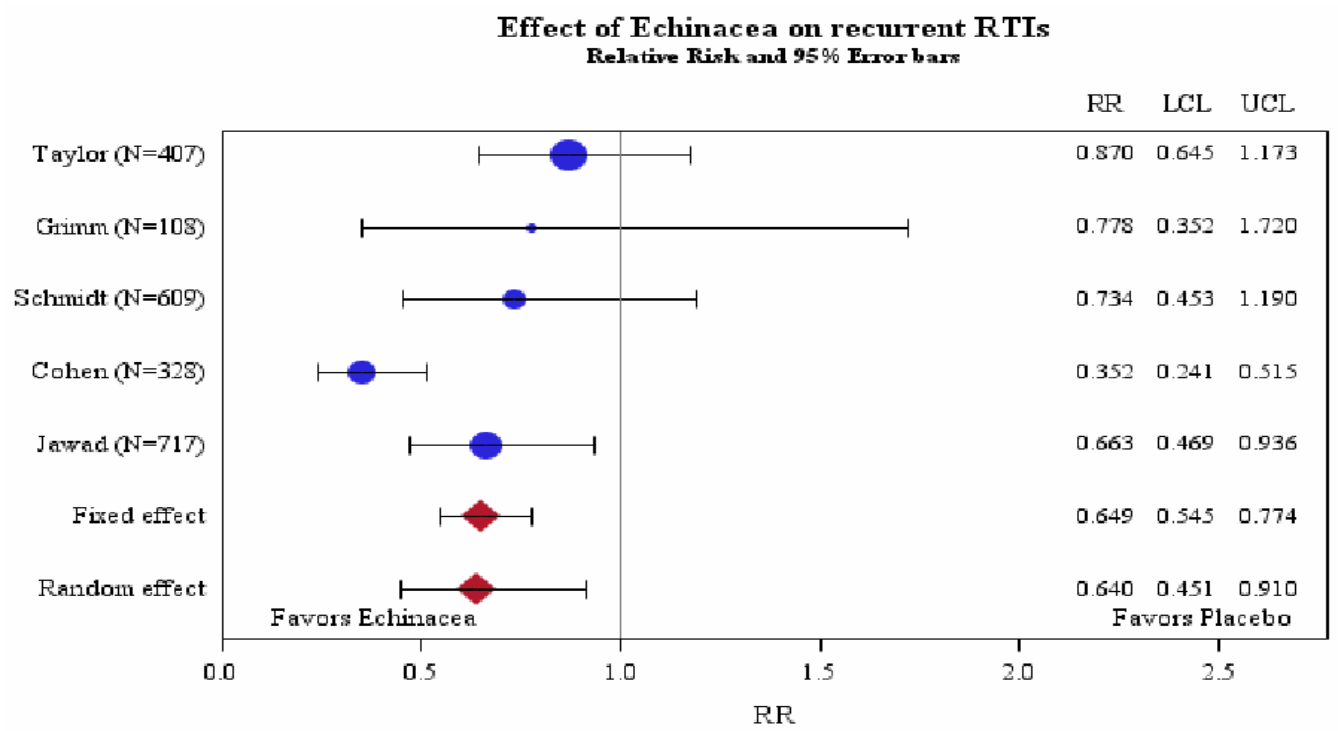
Study design:
6 clinical studies with high quality – Jadad ≥ 4 – included, n = 2546

Study	Echinacea species	Extraction method	Supplement	Duration of treatment /observation [mts]	Daily Dosis / amount of Echinacea [mg]	Patient number	Cold definition	Jadad Score
Schmidt (1990)	EA	Ethanolic extract	Eupatorium / Baptisia	2	1 x 12 ml 1440 mg[1]	609	Patient reported - Confirmed by physician	4
Grimm (1999) / Schoeneberger (1996)	EP	Pressed-juice	-	2	2 x 4 ml 6200 mg[2]	108 / 66 with weak immune response	Patient reported - Confirmed by physician	5
Melchart (1998) 3-arm study	EP EA	Ethanolic extract Ethanolic extract	- -	3	2 x 50 drops 1800 mg[3] 2 x 50 drops 1800 mg[3]	99 (90 placebo) 100 (90 placebo)	Patient reported - Confirmed by physician	4
Cohen (2004)	EP + EA	Glycerol extract	Propolis + Vitamin C	3	2 – 4 x 5 – 7.5 ml 500 - 1500 mg	328	Patient reported - Confirmed by physician	4
Taylor (2003) / Weber (2005)	EP	Pressed juice	-	10d / 4	7.5 – 10 ml 7500 – 10000 mg	407 / 401	Study staff confirmed	5
Jawad (2012)	EP + EP	Ethanolic extract	-	4	2.7 – 4.5 ml 2400 – 4000 mg	717 717	Patient reported – confirmed by Jackson method Virally confirmed infections	5

Schapowal A, Klein P, Johnston SL: Advances in Therapy 2015; 32:187-200

Andreas G. Schapowal
MD, PhD, DSc (hon)

Prevention of recurrent respiratory tract infections

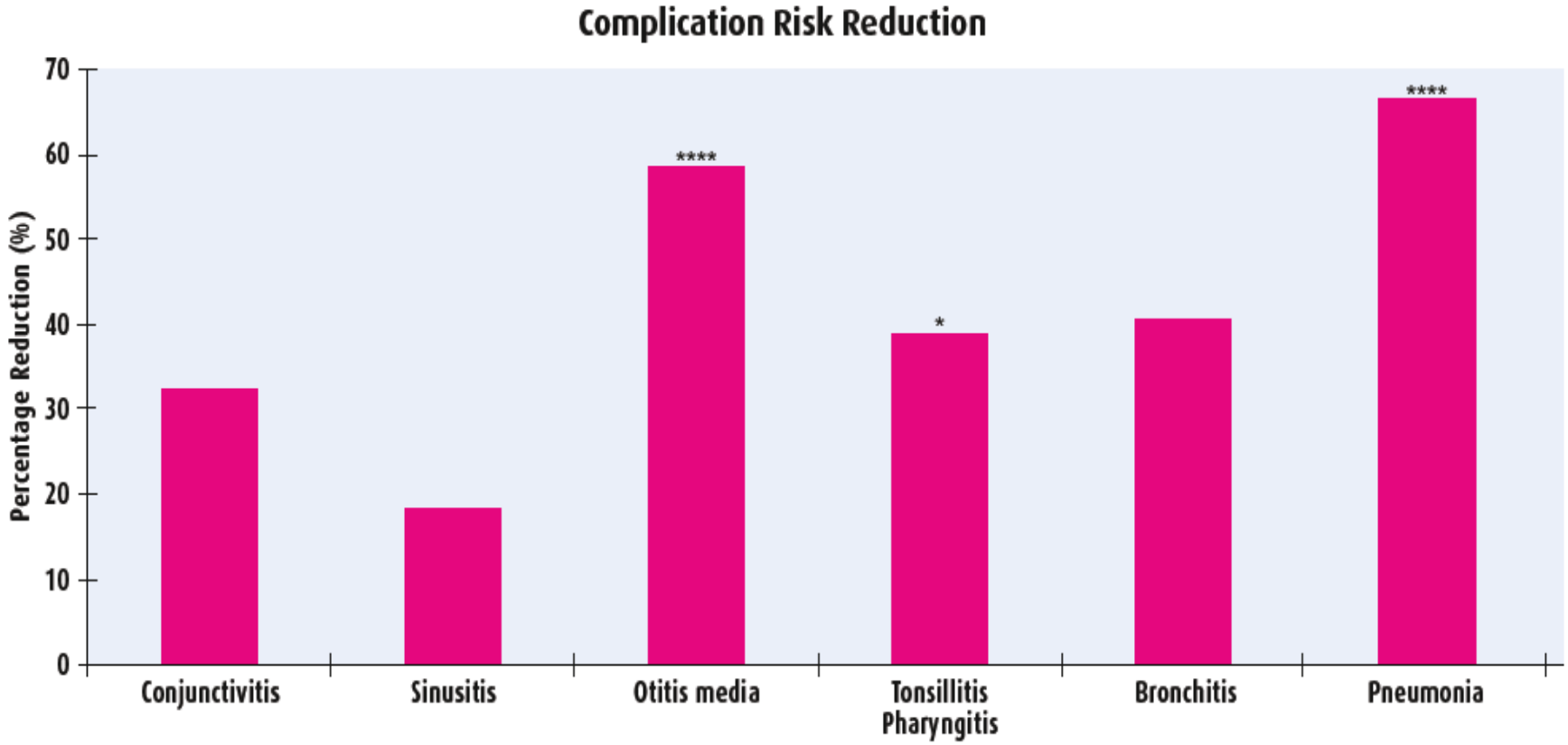


Recurrent respiratory tract infections were significantly reduced with Echinacea by **35%**, RR = 0.649**,** 95% CI 0.545 – 0.774, p < 0.0001
Heterogenity: RR=0.858 with pressed juices (n.s.), RR=0.542 with lipophilic extracts (p<0.0001)
EF: Reduction by 58 %, RR=0.420, 95% CI 0.222-0.796, p = 0.005

Schapowal A, Klein P, Johnston SL: Advances in Therapy 2015; 32:187-200

Andreas G. Schapowal
MD, PhD, DSc (hon)

Reduction of complications of respiratory tract infections

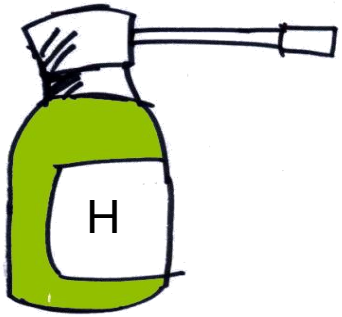


Schapowal A, Klein P, Johnston SL: Advances in Therapy 2015; 32:187-200

Andreas G. Schapowal
MD, PhD, DSc (hon)

Echinacea/Sage or Chlorhexidine/Lidocaine for treating acute sore throats: a randomized double-blind trial

Schapowal, A., D. Berger, P. Klein, A. Suter:
Eur J Med Res 2009; 14: 406-412



Andreas G. Schapowal
MD, PhD, DSc (hon)

Echinacea/Salvia sore throat spray

863.3 mg/ml Echinace purpurea tincture from fresh flowering herb, DER 1:12; 45.5 mg/ml E. purpurea tincture from fresh roots, DER 1:11; 430.0 mg/ml tincture from fresh sage leaves, DER 1:17; extraction agent ethanol 57.3 %

Collunosol®, Sanofi AG

1 mg Chlorhexidini gluconas, 2 mg Lidocaini hydrochlorinum in 1 ml spray (glycerol, saccharin, aromatics, ethanol 5 %)

Andreas G. Schapowal
MD, PhD, DSc (hon)

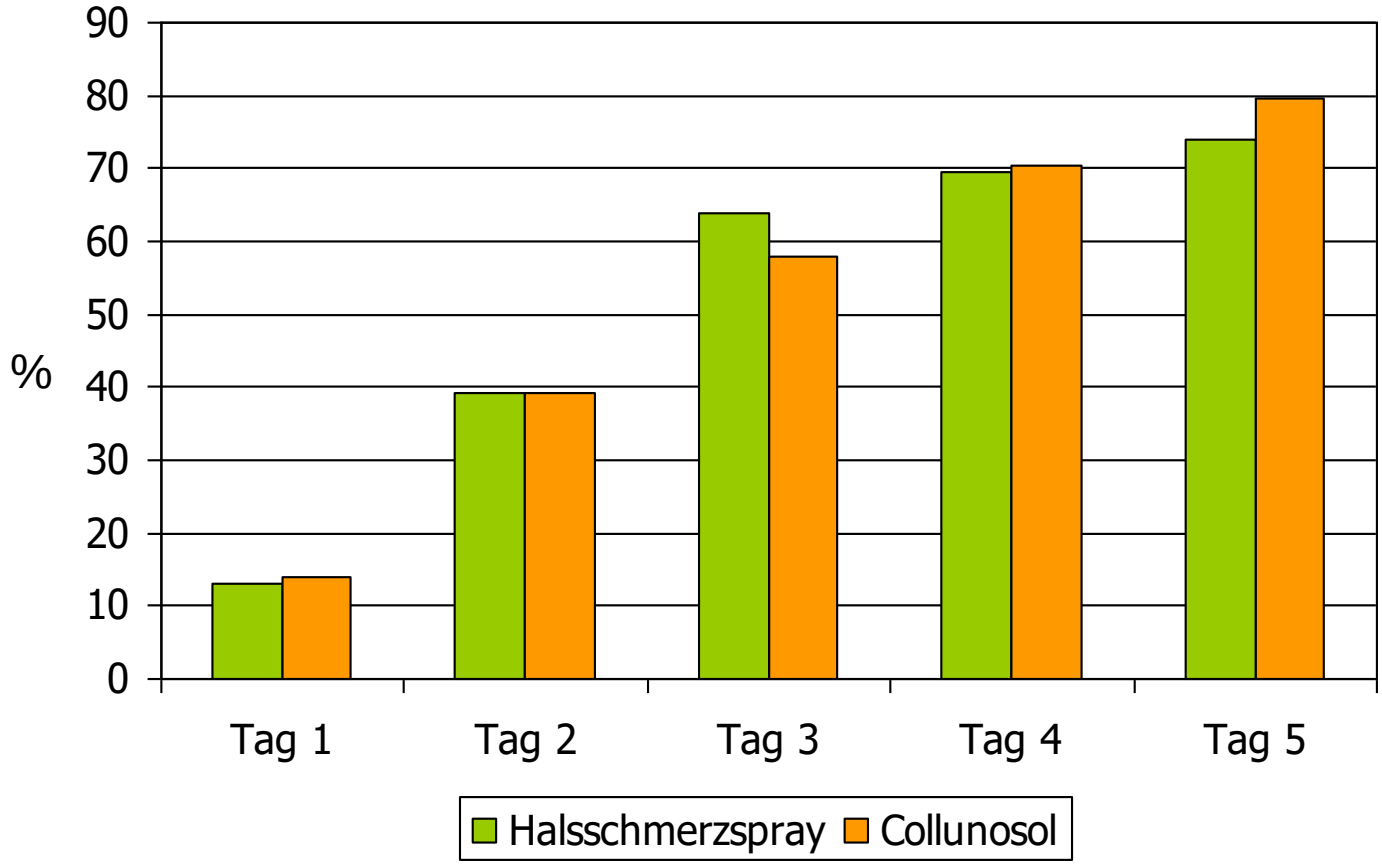
Synergistic effects of Echinacea/Salvia sore throat spray

	Echinacea	Salvia
antibacterial	++	++
antiviral	+++	+
anti-inflammatory	++	++
immunomodulating	+++	+

Additional: cooling and refreshing effect of peppermint oil

Andreas G. Schapowal
MD, PhD, DSc (hon)

Responder rates over 5 days



No significant differences in 50 % symptom reduction (day 1 p=0.5083, day 2 p=0.4968, day 3 p=0.2408, global day 1 – 3 p=0.3928, U-test). **No inferiority in the main target criterion responder rate day 1 - 3** of EF sore throat spray versus Collunosol.
Also on day 4 (p=0.5374) and day 5 (p=0.7857) no significant differences.

EF sore throat spray

Approval from Swissmedic and market launch in 2009

Health insurance eligibility 2010

Indication

For the treatment of painful inflammation and infections of the mouth and throat such as angina, sore throat, difficulty swallowing, swollen tonsils, swelling and redness, soreness and hoarseness

Thank you very much for your attention!

andreas@schapowal.ch