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ONLINE SERIES

Pelargonii radix - Pelargonium Root
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Plant illustrated on the cover: Pelargonium sidoides
FOREWORD

It is a great pleasure for me to introduce the online era of ESCOP Monographs. Interest in herbal medicinal products continues to stimulate research on herbal substances and the body of knowledge in this field is steadily growing. ESCOP takes account of this by preparing new monographs and - as the only organisation in the field at the moment - particularly through regular revision of our published monographs. In order to provide readers and authorities with balanced compilations of scientific data as rapidly as possible, ESCOP Monographs will be published online from now on. This contemporary way of publishing adds further momentum to ESCOP’s endeavours in the harmonization of European standards for herbal medicinal products.

The Board of ESCOP wishes to express its sincere gratitude to the members of the Scientific Committee, external experts and supervising editors, and to Peter Bradley, the final editor of every monograph published up to March 2011. All have voluntarily contributed their time and scientific expertise to ensure the high standard of the monographs.

Liselotte Krenn
Chair of the Board of ESCOP

PREFACE

Over the 15 years since ESCOP published its first monographs, initially as loose-leaf documents then as two hardback books, ESCOP Monographs have achieved a reputation for well-researched, comprehensive yet concise summaries of available scientific data pertaining to the efficacy and safety of herbal medicinal products. The Second Edition, published in 2003 with a Supplement in 2009, covered a total of 107 herbal substances.

The monograph texts are prepared in the demanding format of the Summary of Product Characteristics (SPC), a standard document required in every application to market a medicinal product for human use within the European Union and ultimately providing information for prescribers and users of individual products.

As a change in style, literature references are now denoted by the name of the first author and year of publication instead of reference numbers; consequently, citations at the end of a monograph are now in alphabetical order. This is intended to give the reader a little more information and perspective when reading the text.

Detailed work in studying the pertinent scientific literature and compiling draft monographs relies to a large extent on the knowledge, skills and dedication of individual project leaders within ESCOP Scientific Committee, as well as invited experts. After discussion and provisional acceptance by the Committee, draft monographs are appraised by an eminent Board of Supervising Editors and all comments are taken into account before final editing and approval. In this way a wide degree of consensus is achieved, but it is a time-consuming process.

To accelerate the publication of new and revised monographs ESCOP has therefore decided to publish them as an online series only, commencing in 2011. We trust that rapid online access will prove helpful and convenient to all users of ESCOP Monographs.

As always, ESCOP is indebted to the many contributors involved in the preparation of monographs, as well as to those who provide administrative assistance and hospitality to keep the enterprise running smoothly; our grateful thanks to them all.
NOTES FOR THE READER

From 2011 new and revised *ESCOP Monographs* are published as an online series only. Earlier monographs are available in two books, *ESCOP Monographs Second Edition* (2003) and the Second Edition *Supplement 2009*, but are not available online for copyright reasons.

After purchase of a single monograph, the specific items to be downloaded are:

- Front cover
- Title page
- Verso
- Foreword and Preface
- Notes for the Reader
- Abbreviations
- The monograph text
- Back cover

Information on the member organizations and people involved in ESCOP’s activities can be found on the website (www.escop.com):

- Members of ESCOP
- Board of Supervising Editors
- ESCOP Scientific Committee
- Board of Directors of ESCOP
ABBREVIATIONS used in ESCOP monographs

AA   arachidonic acid
ABTS  2,2'-azino-bis(3-ethylbenzthiazoline-6-sulphonic acid)
ACE  angiotensin converting enzyme
ADP  adenosine diphosphate
ALAT or ALT  alanine aminotransferase (= SGPT or GPT)
ALP  alkaline phosphatase
anti-IgE  anti-immunoglobulin E
ASA  acetylsalicylic acid
ASAT or AST  aspartate aminotransferase (= SGOT or GOT)
ATP  adenosine triphosphate
AUC  area under the concentration-time curve
BMI  body mass index
BPH  benign prostatic hyperplasia
b.w.  body weight
cAMP  cyclic adenosine monophosphate
CI  confidence interval
C_max  maximum concentration of a substance in serum
CNS  central nervous system
CoA  coenzyme A
COX  cyclooxygenase
CSF  colony stimulating factor
CVI  chronic venous insufficiency
CYP  cytochrome P450
d  day
DER  drug-to-extract ratio
DHT  dihydrotestosterone
DNA  deoxyribonucleic acid
DPPH  diphenylpicrylhydrazyl
DSM  Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association)
ECG  electrocardiogram
ED_{50}  effective dose in 50% of cases
EDTA  ethylenediamine tetraacetate
EEG  electroencephalogram
EMA  European Medicines Agency
ENT  ear, nose and throat
ER  oestrogen receptor
ERE  oestrogen-responsive element
FSH  follicle-stimulating hormone
GABA  gamma-aminobutyric acid
Gal  galactose
GFR  glomerular filtration rate
GGTP  gamma-glutamyl transpeptidase
GOT  glutamate oxalacetate transaminase (= SGOT)
GPT  glutamate pyruvate transaminase (= SGPT)
GSH  glutathione (reduced)
GSSG  glutathione (oxidised)
HAMA  Hamilton Anxiety Scale
12-HETE  12-hydroxy-5,8,10,14-eicosatetraenoic acid
HDL  high density lipoprotein
HIV  human immunodeficiency virus
HMPC  Committee on Herbal Medicinal Products (of the EMA)
HPLC  high-performance liquid chromatography
5-HT  5-hydroxytryptamine (= serotonin)
IC_{50}  concentration leading to 50% inhibition
ICD-10  International Statistical Classification of Diseases and Related Health Problems, Tenth Revision
ICH  The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICSD  International Classification of Sleep Disorders
IFN  interferon
IL  interleukin
i.m.  intramuscular
iNOS  inducible nitric oxide synthase
INR  International Normalized Ratio, a measure of blood coagulation (clotting) tendency
i.p. intraperitoneal
IPSS International Prostate Symptom Score
i.v. intravenous
kD kiloDalton
KM Index Kuppermann Menopausal Index
kPa kiloPascal
LC-MS liquid chromatography-mass spectrometry
LD_{50} the dose lethal to 50% of animals tested
LDH lactate dehydrogenase
LDL low density lipoprotein
LH luteinizing hormone
5-LOX 5-lipoxygenase
LPS lipopolysaccharide
LTB_4 leukotriene B_4
M molar (concentration)
MAO monoamine oxidase
MBC minimum bactericidal concentration
MDA malondialdehyde
MFC minimum fungicidal concentration
MIC minimum inhibitory concentration
Mr molecular
MRS Menopause Rating Scale
MRSA methicillin-resistant Staphylococcus aureus
MTD maximum tolerated dose
MITT 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
MW molecular weight
NBT nitro blue tetrazolium
NF-kB necrosis factor kappa-B
NO nitric oxide
NOS nitric oxide synthase
n.s. not significant
NSAID non-steroidal anti-inflammatory drug
ovx ovariectomy or ovariectomized
ORAC oxygen radical absorbance capacity
PA pyrrolizidine alkaloid
PAF platelet activating factor
PCR polymerase chain reaction
PEG polyethylene glycol
PGE prostaglandin E
PHA phythaemagglutinin
p.o. per os
POMS profile of mood states
PVPP polyvinylpolypyrrolidone
RANKL receptor activator of nuclear factor kappa-B ligand
RNA ribonucleic acid
RT-PCR reverse transcription polymerase chain reaction
s.c. subcutaneous
SCI spinal cord injury
SERM selective oestrogen receptor modulator
SGOT or GOT serum glutamate oxalacetic transaminase (= ASAT or AST)
SGPT or GPT serum glutamate pyruvate transaminase (= ALAT or ALT)
SHBG sex hormone binding globulin
SOD superoxide dismutase
SSRI selective serotonin reuptake inhibitor
STAI state-trait anxiety inventory
t_1/2 elimination half-life
TBARS thiobarbituric acid reactive substances
TGF-β transforming growth factor-beta
TNF tumour necrosis factor
TPA 12-0-tetradecanoylphorbol-13-acetate
URT upper respiratory tract
URTI upper respiratory tract infection
UTI urinary tract infection
VAS visual analogue scale
VLDL very low density lipoprotein
PELARGONII RADIX

Pelargonium Root

DEFINITION

Dried, unpeeled, usually fragmented, underground organs of *Pelargonium sidoides* DC and/or *Pelargonium reniforme* CURT. It contains not less than 2.0 per cent of tannins, expressed as pyrogallol (C₆H₆O₃; Mr 126.1) (dried drug).

The material complies with the monograph of the European Pharmacopoeia [Pelargonium root].

CONSTITUENTS

Oligomeric and polymeric proanthocyanidins (mainly with catechin and gallocatechin units, approx. 9%); flavan-3-ols (aflzelechin, catechin and gallocatechin); phenolic acids (gallic acid and its methylester); hydroxycinamic acids (caffeic acid, p-coumaric acid); flavonoids (*P. reniforme*); highly oxygenated coumarins (approx. 0.05% for *P. sidoides* and 0.03% for *P. reniforme*) such as 7-hydroxy-5,6-dimethoxycoumarin (umckalin), 5,6,7-trimethoxycoumarin (TMC), 5,6,7,8-tetramethoxycoumarin and 6,8-dihydroxy-5,7-dimethoxycoumarin (DHDMC) (all characteristic for *P. sidoides*), 6-hydroxy-5,7-dimethoxycoumarin (fraxinol), 8-hydroxy-6,7-dimethoxycoumarin (fraxidin) and 5,6-dihydroxy-7-methoxycoumarin (isofraxetin) (characteristic for *P. reniforme*), 8-hydroxy-5,6,7-trimethoxycoumarin and 6,7,8-trihydroxycoumarin (present in both species), *P. sidoides* contains also coumarins as glycosides and sulfates [Kolodziej 1995,1998,2000,2003b, 2007, Kayser 1995, Latté 2000, Schoetz 2008].

CLINICAL PARTICULARS

Therapeutic indications


Dosage

**Ethanolic extract (1:8-11; 12% V/V)**


Method of administration

For oral administration.

Duration of administration

If symptoms persist or worsen, medical advice should be sought.

Contra-indications

None known.

Special warnings and special precautions for use

None required.

Interaction with other medicaments and other forms of interaction

None reported.
Pregnancy and lactation
No data available.

In accordance with general medical practice, the product should not be used during pregnancy or lactation without medical advice.

Effects on ability to drive and use machines
None known.

Undesirable effects
Gastro-intestinal complaints and allergic skin reactions [Agbabiaka 2008, Timmer 2013, Brendler 2009, Brown 2009]. Hepatotoxicity has been reported but causality for pelargonium could not be established [Tesche 2012a and 2012b].

Overdose
No toxic effects reported.

PHARMACOLOGICAL PROPERTIES
Almost all pharmacodynamic and clinical studies were performed with an ethanolic extract of P. sidoides root (1:9-11 or 1:8-10; 11% ethanol (m/m)) as an 80:20 mixture with glycerol 85%; this would be subsequently cited as the liquid extract.

Pharmacodynamic properties

In vitro experiments
Antibacterial effects
Methanolic extracts of the roots showed antibacterial activity against 8 bacteria: Staphylococcus aureus (Sa), Streptococcus pneumoniae, β-haemolytic Streptococcus, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa and Haemophilus influenzae (MIC values: 5 – 7.5 mg/mL). The ethyl acetate, butanol and remaining water fractions of these extracts gave MIC values from 0.6 to 2.5 mg/mL. From the 7 isolated compounds umckalin and DHDMC were the most potent (MIC values: 0.2-0.5 mg/mL) [Kayer 1997].

The liquid extract demonstrated antibacterial activity against several multiresistant strains of Sa (MIC 3.3 mg/mL). An 80% acetone extract (4:1; 12.5 µg/mL) inhibited the growth of Mycobacterium tuberculosis by 96% in the radiospirometric bioassay. In the Alamar blue assay the same extract exhibited an MIC of 100 µg/mL (compared to rifampicine MIC 0.06 µg/mL) [Kolodziej 2003a].

The liquid extract reduced the growth of Helicobacter pylori by 43% of the control value at a concentration of 100 µg/mL. The extract (50 and 100 µg/mL) significantly reduced (p<0.05) the quantity of bacteria attached to gastric epithelial AGS cells by 77% and 91% respectively; while amoxicillin (up to 64 µg/mL) was inactive. At the same concentrations the adherence to these cells was significantly reduced (p<0.05) [Beil 2007].

The same extract significantly reduced adherence of Streptococcus pyogenes (Sp) to human Hep-2 epithelial cells dose-dependently by up to 46% (p<0.001) while the adherence to decaying buccal epithelial cells was increased by 7-fold (p<0.001) [Conrad 2007b].

In another experiment the extract also inhibited the adhesion of Sp to Hep-2 cells but the polyphenol-free extract was inactive. When highly purified proanthocyanidin fractions from P. sidoides were evaluated, only the prodelphinidins showed anti-adhesive properties [Janiecki 2011].

Immunomodulatory properties
A methanolic extract, as well as petrol ether, ethyl acetate and butanol fractions thereof, reduced the intracellular survival of Leishmania donovani amastigotes within murine macrophages (EC50 2.7, <0.1, <0.1 and 3.3 µg/mL respectively). A bioassay-guided isolation led to the characterization of gallic acid and its methyl ester with EC50 values of 4.4 and 12.5 µg/mL (compared to the reference sodium stibogluconate, EC50 2.7 µg/mL). Isolated coumarins proved to be inactive at concentrations up to 25 µg/mL. This was possibly due to macrophage activation which was confirmed by detection of TNF-α and NO-inducing activity. The most potent NO inducers were gallic acid, umckalin and DHDMC (35-45% of the effect of LPS), whereas gallic acid and its methyl ester exhibited the strongest TNF-α-inducing potential (24 and 19% of LPS stimulus). Gallic acid also showed an interferon-like activity by reducing the cytopathogenic effect of encephalomyocarditis virus in fibroblasts [Kayser 2001].

The liquid extract (1 – 30 µg/mL) dose-dependently increased the release of NO, IL-1, IL-12 and TNF-α and changed the expression of the surface markers CD40 and CD119 in bone-marrow derived macrophages infected with Listeria monocytogenes [Thäle 2008].

The liquid extract (3 µg/mL) increased β-interferon secretion in MG-63 cells by 200% [Kolodziej 2003a].

Cytotoxic effects
In the brine shrimp lethality bioassay, neither pelargonium extracts nor phenolic constituents such as benzoic and cinnamic acid derivatives, hydrolysable tannins and C-glycosylflavones showed cytotoxic effects (IC50 > 1 mg/mL for the extracts; IC50 > 0.2 mg/mL for the pure compounds) [Kolodziej 2002].

The cytotoxicity of scopeotonin, umckalin and DHDMC was evaluated in a human small cell lung carcinoma line and in a human colorectal cancer cell line, using the micro culture tetrazolium assay. Only DHDMC showed a moderate cytotoxicity with IC50 values of 22.1 and 9.5 µM respectively (compared to cisplatin: IC50 of 1.0 and 2.7 µM respectively) [Kolodziej 1997].

Other effects
The liquid extract showed a dose-dependent anti-influenza virus activity with an EC50 of 6.6 µg/mL and corresponding to a selectivity index of 84 (CC50/EC50). The concentrations required for complete virus clearance (determined on 6 different strains) varied from 16 µg/mL up to 300 µg/mL. It was demonstrated that the extract had no virucidal activity but affected an early step in the virus life cycle (presumably viral entry into the host cell). A polyphenol-free extract had no activity while an oligo-/polymeric prodelphinidin fraction had an EC50 of 2.8 µg/mL [Theisen 2012].

The extract exhibited a free radical scavenging activity in the DPPH assay (IC50 14.7 ± 0.85 µg/mL) [Rezaizadehnajafi 2014].

The liquid extract (30 µg/mL) enhanced phagocytosis by 56% at 2 min (p<0.002) and oxidative burst (maximum increase of 120% after 4 min, p<0.001). The extract also enhanced intracellular killing, demonstrated by a significant reduction of surviving Candida albicans cells (maximum reduction of 31% after 120 min, p<0.001) [Conrad 2007a].

The liquid extract significantly (p<0.05) increased the ciliary beat frequency in human nasal epithelium cell cultures to 123% at 30 µg/mL and to 133% at 100 µg/mL, compared to the equilibration phase (100%) [Neugebauer 2005].
In vivo experiments
The liquid extract administered by inhalation to influenza-infected mice for 10 days significantly (p<0.003) increased survival without obvious toxicity (no difference in weight of lungs, liver, spleen and kidneys) [Theisen 2012].

In nematodes (Caenorhabditis elegans) pre-treated with 40, 50 and 100 µg/mL of the extract for 48 h before the addition of 20 µM juglone, a significant reduction (32% to 58%; p<0.001) in hsp-16.2::GFP activity (induced by oxidative stress) was observed as compared to controls. The same doses of the extract significantly increased the survival rate (22 – 24%; p<0.05) in the nematodes after the addition of a lethal dose of 300 µM juglone for 24 h. Application of the extract (50 µg/mL) to T.lept worms induced the migration of the transcription factor DAF-16 from cytosol to the nucleus (this is essential for the activation of the transcription of various genes mediating stress resistance) [Rezaizadehnejafai 2014].

Pre-treatment of mice with a single oral dose of liquid extract (400 µg/kg b.w.) significantly inhibited lipopolysaccharide-induced sickness behaviour (p<0.05) [Noldner 2007].

Studies in humans
All studies were performed with the liquid extract except a few where it was dried but no DER is given for the dry extract.

Pharmacological studies in humans
In a randomized, double-blind, placebo-controlled study 28 athletes received the liquid extract (4.5 mL daily) or placebo for 28 days. The relative salivary IgA level was significantly increased in the verum group (p<0.001) while nasal IL-15 (p<0.05), serum IL-15 (p<0.02) and serum IL-6 levels (p<0.05) were significantly decreased [Luna 2011].

Clinical Studies
In a systematic review and meta-analysis, 6 randomized clinical trials (Matthys 2003, Chuchalin 2005, Matthys 2007c, Blochin and 2 unpublished trials) met the inclusion criteria, of which 4 were suitable for statistical pooling. Only monopreparations containing the liquid extract used for the treatment of patients with acute bronchitis were included. Meta-analysis of the 4 placebo-controlled trials indicated that pelargonium significantly decreased the Bronchiectasis Severity Score (BSS assessing cough, sputum, rales/rhonchi, chest pain during coughing and dyspnoea) within 7 days of treatment (weighted mean difference: 2.80 points, 95% CI interval 2.44-3.15) [Agbabiaka 2008].

A Cochrane review evaluated 10 randomized clinical trials dealing with acute bronchitis in adults and children, sinusitis and the common cold in adults, and sore throat in children. The quality of 8 of the 10 studies was considered to be adequate for inclusion in the analysis (Chuchalin 2005, Matthys 2007c, Matthys 2010a, Lizogub 2007, Bachert 2009, Kamin 2010a, Kamin 2010b and Kamin 2012). It was concluded that based on the limited evidence from the few clinical trials with acceptable methodology, pelargonium may offer symptom relief in acute bronchitis in children and adults, and in rhinosinusitis and the common cold in adults [Timmer 2013].

Other clinical reviews, which assessed open as well as controlled studies, involved a total of 5400 patients. They all concluded that pelargonium is efficient in the treatment of upper respiratory tract infections [Brown 2009, Brendler 2009, Kolodziej 2002].

Acute bronchitis
In two randomized, double-blind, placebo-controlled, multicentre trials, patients (1-18 years) with acute bronchitis received the liquid extract (1-6 years: 3x0.5 mL; 6-12 years: 3x1 mL; 12-18 years: 3x1.5 mL daily) or placebo for 7 days. From baseline to day 7, the decrease in the BSS total score was significantly higher for the verum group compared to placebo:

Study 1 (n=200): 3.4±1.8 points versus 1.2±1.8 points (p<0.0001) [Kamin 2010a].

Study 2 (n=220): 4.4±1.6 points versus 2.9±1.4 points (p<0.0001) [Kamin 2012].

Treatment outcome and satisfaction with treatment were also significantly better compared to placebo (p<0.0001).

In three randomized, double-blind, placebo-controlled, multicentre studies patients with acute bronchitis received the liquid extract (1.5 mL 3 times daily) or placebo for 7 days. In all studies the decrease of BSS from baseline to day 7 was significantly higher for the verum group compared to placebo:

Study 1 (n=217): 7.6±2.2 points versus 5.3±3.2 points; p<0.0001 [Matthys 2007c]

Study 2 (n=124): 7.2±3.1 points versus 4.9±2.7 points; p<0.0001 [Chuchalin 2005]

Study 3 (n=468): 5.9±2.9 points versus 3.2±4.1 points; p<0.0001 [Matthys 2003]

In addition, the duration of illness was shorter and satisfaction with treatment was better with verum compared to placebo.

In a prospective, open, multicentre study, 205 patients (42±16 years) suffering from acute bronchitis, or an acute exacerbation of chronic bronchitis, were treated with 1.5 mL of the liquid extract, three times daily for 7 days. The total BSS decreased by 3.3±3.8 points and 60.5% of the patients assessed their health condition at the end of the study as much improved or free from symptoms [Matthys 2007a].

In a prospective, open, multicentre study, 2099 patients (<3 years: n = 78; 3-18 years: n = 420; >18 years: n = 1601) with acute bronchitis were treated with the liquid extract at an age-dependant dosage three times daily for a maximum of 14 days (<6 years: 0.5 mL; 6-12 years: 1 mL; >12 years: 1.5 mL). The mean BSS of all patients decreased from 7.1±2.9 points at baseline to 1.0±1.9 points at patient’s last visit. Subgroup analysis for children (<18 years, n = 498) and infants (<3 years) showed a decrease in mean BSS from 6.3±2.8 to 0.9±1.8 points and from 5.2±2.5 to 1.2±2.1 points, respectively [Matthys 2007b].

A prospective, open, multicentre study evaluated the treatment of 742 patients (<12 years) with acute bronchitis or acute exacerbations of chronic bronchitis. The children were treated with the liquid extract at a dosage according to their age for a maximum of 2 weeks: <2 years 0.75 mL daily, 2-6 years 1.5 mL daily and 6-12 years 3 mL daily. The overall BSS decreased significantly from 6.0±3.0 points to 1.4±2.1 points (p<0.001). The assessment of the individual symptoms (coughing, expectoration, difficulty in breathing, wheezing and chest pain) gave a response rate (remission and improvement) of more than 80% [Haidvogl 1996]. In a similar study with 259 children and the same treatment, all the individual symptoms showed remission or improvement rates of more than 80% [Dorn 1996].

In a randomized, double-blind, placebo-controlled, dose-finding study, 400 patients (6-18 years) with acute bronchitis received either 30 mg, 60 mg or 90 mg of the dry extract or placebo daily for 7 days. The decrease of total BSS from baseline to day 7 was significantly higher for the verum groups (60 mg, p=0.0004; 90 mg, p<0.0001) compared to placebo (4.4±2.4 and 5.0±1.9 points respectively versus 3.3±2.6 points) without relevant differences between these 2 verum dosages [Kamin 2010b].

In a randomized, double-blind, placebo-controlled, multicentre, dose-finding trial, 406 patients (>18 years) with acute bronchitis...
received either 30 mg, 60 mg or 90 mg of the dry extract or placebo daily for 7 days. The decrease of total BSS from baseline to day 7 was significantly higher for the verum groups (p<0.0001) compared to placebo (4.3±1.9, 6.1±2.1 and 6.3±2.0 points respectively, versus 2.7±2.3 points) without relevant differences between the 2 highest dosages [Matthys 2010a]. The HRQL (health-related quality of life) and PRO (patient-reported outcome) questionnaires, assessing the secondary outcome measures, demonstrated significantly (p<0.05 or p<0.0001) greater improvement in all three of the verum groups compared to placebo (physical score, impact of patient's sickness, duration of activity limitation, patient-reported treatment outcome, satisfaction with treatment) [Matthys 2010b].

According to two reviews, other studies also showed an improvement of the BSS with the liquid extract given at an age- dependant dosage three times daily (<6 years: 0.5 mL; 6-12 years: 1 mL; >12 years: 1.5 mL) [Kolodziej 2003b; Brendler 2009].

**TABLE 1. Clinical and surveillance studies in patients with acute bronchitis (Kolodziej 2003b)**

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Duration (days)</th>
<th>Control</th>
<th>BSS decrease after treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Verum</td>
</tr>
<tr>
<td>205 adults</td>
<td>7</td>
<td>placebo</td>
<td>7.7 points</td>
</tr>
<tr>
<td>220 adults &amp; children</td>
<td>7</td>
<td>placebo</td>
<td>4.4 points</td>
</tr>
<tr>
<td>60 children (6-12 y.)</td>
<td>7</td>
<td>AcC</td>
<td>71 points</td>
</tr>
<tr>
<td>213 children (6-12 y.)</td>
<td>7</td>
<td>AcC</td>
<td>6.7 points</td>
</tr>
<tr>
<td>205 adults</td>
<td>7</td>
<td>-</td>
<td>3.3 points</td>
</tr>
<tr>
<td>1042 children (up to 12 y.)</td>
<td>14</td>
<td>-</td>
<td>5.4 points</td>
</tr>
</tbody>
</table>

AcC = acetylcystein

1 result given as such in Kolodziej 2003b

**Chronic bronchitis**

In a randomized, double-blind, placebo-controlled trial, 200 patients (> 18 years) with a history of chronic bronchitis were allocated to a 24-week add-on treatment with 1.5 mL of the liquid extract three times daily or placebo, alongside a standardised baseline-treatment. Median time to exacerbation was significantly (p=0.005) prolonged with verum compared to placebo (57 versus 43 days). Analysis of the secondary endpoints showed fewer exacerbations, less patients with antibiotic use, improved quality of life and less days of inability to work [Matthys 2013].

**Tonsillopharyngitis**

In a randomized, double-blind, placebo-controlled trial, 143 patients (6-10 years) with acute non-group A β-haemolytic Streptococcus tonsillopharyngitis received the liquid extract (3 mL daily) or placebo for 6 days. The decrease of the Tonsillopharyngitis Severity Score (TSS; assessing sore throat, difficulty in swallowing, pharyngeal erythema and fever) from baseline to day 4 was significantly higher for the verum group compared to placebo (7.1±2.1 points versus 2.5±3.6 points; p<0.0001). Also, the severity of the symptoms was reduced and the duration of illness was shortened by at least 2 days [Bereznoy 2003].

According to two reviews, other studies also showed an improvement of the TSS with the liquid extract given in a dosage of 1 mL three times daily [Kolodziej 2003b; Brendler 2009].

**TABLE 2. Clinical and surveillance studies in patients with acute tonsillopharyngitis (Kolodziej 2003b)**

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Duration (days)</th>
<th>Control</th>
<th>TSS decrease after treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Verum</td>
</tr>
<tr>
<td>124 children (6-10 y.)</td>
<td>6</td>
<td>placebo</td>
<td>6.8 points</td>
</tr>
<tr>
<td>78 children (6-10 y.)</td>
<td>6</td>
<td>placebo</td>
<td>6.7 points</td>
</tr>
<tr>
<td>60 children (6-10 y.)</td>
<td>10</td>
<td>gargle</td>
<td>51 points</td>
</tr>
<tr>
<td>1000 (2-35 years)</td>
<td>7</td>
<td>-</td>
<td>111 points</td>
</tr>
</tbody>
</table>

1 result given as such in Kolodziej 2003b

**Rhinosinusitis**

In a randomized, double-blind, placebo-controlled, multicentre trial, 103 patients (18 – 60 years) with acute rhinosinusitis received the liquid extract (3 mL three times daily) or placebo for a maximum of 22 days. From baseline to day 7, the mean decrease in Sinusitis Severity Score (SSS; headache, maxillary pain, nasal obstruction and purulent nasal secretion) was 5.5 points in the verum group compared to 2.5 points in the placebo group (p<0.00001). Analysis of the secondary outcome measures showed a remission or major improvement in 30% of the patients in the verum group, compared to 5.8% in the placebo group (p<0.0001) [Bachert 2009].

In a randomized, double-blind, placebo-controlled trial, 272...
patients with acute sinusitis were treated with 3 mL of the liquid extract three times daily or placebo for a maximum of 3 weeks. In the verum group, the mean SSS decreased from 14.4±1.8 points at baseline to 7.4±3.2 points at the patient's last visit, while the baseline value of 13.9±1.7 points in the placebo group remained unchanged (p<0.0001) [Bachert 2005 in Brendler 2009].

In a prospective, open, multicentre study, 361 patients (1-94 years) with acute sinusitis or acute exacerbation of chronic sinusitis were treated with the liquid extract. Adults/children (<12 years) received 1.5/1 mL every hour up to 12 times daily on the first 2 days and thereafter 1.5/1 mL three times daily for 28 days. Patients with chronic sinusitis received prophylactic treatment for a further 8 weeks at 1.5/1 mL two times daily. The mean SSS of all patients decreased from 15.2±4.6 points at baseline to 2.4±3.2 points at day 28. Within 4 weeks 82.3% of the patients showed a complete remission or a clear improvement in symptoms [Schapowal 2007].

**Common cold**

In a randomized, double-blind, placebo-controlled, multicentre trial, 103 patients (18 – 55 years) with common cold (at least 2 major and 1 minor, or 1 major and 3 minor cold symptoms) received the liquid extract (1.5 mL three times daily) or placebo for 10 days. The decrease of the mean SSID (sum of symptom intensity differences) of the cold intensity score (CIS) from baseline to day 5 was significantly improved for the verum group (p<0.0001) compared to placebo (14.6±5.3 versus 7.6±7.5). The mean CIS decreased by 10.4±3.0 points in the verum group versus 5.6±4.3 points in the placebo group. After 10 days 78.8% of the patients in the verum group were free of symptoms (CIS = 0) versus 31.4% in the placebo group (p<0.0001) [Lizogub 2007].

**Upper respiratory tract infections**

A multicentre, post marketing surveillance study was carried out in 166 patients (1-19 years) with acute and chronic ear, nose, throat and respiratory tract infections. They were treated for up to 7 days (86 patients), 8 to 14 days (60 patients) and more than 14 days (16 patients) with the liquid extract at a dosage according to their age: 1-6 years 0.75–1.5 mL daily, 6-12 years 1.5–3 mL daily and >12 years 3–4.5 mL daily. The assessment of the subjective symptoms was performed by both physicians and patients/parents on a 4-point rating scale. The response rate (remission and improvement) was between 70% and 90% for the different symptoms such as coughing, fever, expectoration and pain [Heil 1994].

In a study investigating the prevention of asthma attacks during upper respiratory tract viral infections, 61 children received the liquid extract at a daily dosage according to their age: 1-5 years: 3x0.5 mL, 6-12 years: 3x1 mL and >12 years: 3x1.5 mL) or placebo for 5 days. After assessment of the symptoms, significant improvement (p<0.05) of cough frequency and nasal congestion was observed in the verum group, for fever and muscles aches there was no significant difference. The frequency of asthma attack was also significantly (p<0.05) reduced in the verum group [Tahan 2013].

In a prospective, open, multicentre study, 641 patients (10-60 years) were treated with the liquid extract at an age-dependant dosage for a maximum of 14 days. Improvement of symptoms was observed after 7 days (n=240) and 14 days (n=305). In 88.9% efficacy was assessed as “very good” or “good” [König 1995 in Brendler 2009].

**Pharmacokinetic properties**

No data available.

**Preclinical safety data**

No effect on thromboplastin time (TPT), partial TPT or thrombin time (TT) was observed in rats after oraladministration of the liquid extract (up to 500 mg/kg b.w, for 2 weeks), while treatment with warfarin (0.05 mg/kg b.w.) resulted in significant changes in TPT and partial TPT. The anticoagulant activity of warfarin was not influenced when warfarin (0.05 mg/kg b.w.) and the extract (500 mg/kg b.w.) were given concomitantly [Koch 2007].

The coumarins found in pelargonium root do not possess the structure required for anticoagulant activity [Arora 1963, Williamson 2009].

Toxicological studies in rats and dogs revealed a no observed effect level of more than 750 mg liquid extract/kg b.w. At a dose of 3 g/kg no signs of hepatotoxicity were found after morphological and histopathological examination. Incubation of human hepatocytes and hepatoma cells with 50 µg/mL extract confirmed the non-hepatotoxicity. Based on theoretical considerations the metabolism of 7-hydroxycoumarins (present in pelargonium root) by 3,4-epoxidation leading to formation of hepatotoxic metabolites is very unlikely [Loew 2008].

The effects of oral administration to rats of an aqueous extract (approx.16:1), at 100, 200 and 400 mg/kg b.w. for 21 days, on haematological and biochemical parameters, and on the organ body-weight ratio were investigated. Red blood cell count, haemoglobin, platelets, lymphocytes, total proteins, globulin and sodium levels were significantly increased, while the levels of alkaline phosphatase, chloride and uric acid were significantly reduced (p<0.05). No deaths or clinical signs were observed [Adewusi 2009].

**Clinical safety data**

The available data from clinical trials do not show an elevated risk of serious adverse events. However, gastrointestinal complaints such as nausea, vomiting, diarrhoea and heartburn, and allergic skin reactions with pruritus and urticaria, have been reported [Agbabiaka 2008, Timmer 2013, Brendler 2009, Brown 2009]. The following are adverse reports from clinical papers cited above.

Fifty one patients from the verum group (n=99) experienced 79 adverse events, compared to 40 patients with 46 adverse events in the placebo group (n=101). Most were gastrointestinal complaints and none were classified as serious. The incidence of suspected adverse reactions (events/day of exposure) was 0.001 [Matthys 2013].

Only 3 adverse events were observed in 2 of 111 patients in the verum group and all were classified as non-serious with no causal relationship with the medication [Kamin 2012].

A total of 59 adverse events were observed in 55 of 200 patients, for 8 events a causal relationship with the medication could not be excluded. None of the adverse events was classified as serious and most of the events were gastrointestinal complaints (17 patients in the verum group and 7 in the placebo group). The mean values of clinical laboratory parameters, such as different transferase enzymes, showed no group differences [Kamin 2010a].

At least one adverse event occurred in 47 of 217 patients (23 verum, 24 placebo), in 25 of 124 patients (15 verum, 10 placebo) and in 36 of 468 patients (20 verum, 16 placebo). All events were assessed as non-serious [Matthys 2007c, Chuchalin 2005, Matthys 2003].

Eighteen adverse events were observed in 16 of 205 patients,
all were assessed as non-serious [Matthys 2007a].

A total of 28 adverse events occurred in 26 of 2099 patients, of which 14 were in children (13/420 patients) and 4 in infants (3/78 patients). Most of them were coded as gastrointestinal disorders. For 9 adverse events a causal relationship to the medication could not be excluded, but was assessed as unlikely in 8 cases. In one child there was a hypersensitivity reaction possibly related to the medication [Matthys 2007b].

Only 8 of 742 patients (<12 years) experienced adverse events which were probably related to the medication. In 2 patients exanthema occurred and in one diarrhoea; in 2 patients psychosis/restlessness was reported [Haidvogl 1996].

In 152 of 806 patients 155 adverse events occurred, most of them classified as gastrointestinal disorders. No serious events were reported [Kamin 2010b, Matthys 2010a].

Adverse events occurred in 15 of 143 patients (1 verum; 14 placebo) and were not related to the medication [Bereznoy 2009].

At least one adverse event occurred in 8 of 103 patients. All events were assessed as non-serious. In 4 cases a causal relationship with the drug could not be excluded (3 gastrointestinal complaints and 1 allergic skin reaction) [Bacht 2009].

For 21 of 67 adverse events, in 17 of 361 patients, a causal relationship with the medication could not be excluded. Most of the events were gastrointestinal complaints [Schipowal 2007].

Adverse events occurred in 3 of 103 patients (2 verum; 1 placebo) and all were assessed as non-serious [Lizogub 2007].

In a study with 166 patients neither interactions nor undesirable effects were observed [Heil 1994].

In the period from 2002 to 2006, the Uppsala Monitoring Centre received 34 case reports of hypersensitivity reactions suspected to be associated with the use of pelargonium. In 14 of these reports, the description and timing of the event was indicative of an acute Coombs and Gell type I hypersensitivity reaction. Two of the patients needed treatment for circulatory failure or anaphylactic shock [de Boer 2007].

In two studies, a total of 28 spontaneous reports of primarily assumed hepatotoxicity associated with the use of pelargonium were assessed using the liver specific scale of the Council for International Organisations of Medical Sciences. None of the cases of liver disease generated a positive signal of safety concern since causality for pelargonium could not be established [Teschke 2012a and 2012b].

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The second edition of ESCOP Monographs, published as a hardback book in 2003 with a Supplement in 2009, has been widely acclaimed for its authoritative information on the therapeutic uses of herbal medicines. Monographs covering a total of 107 herbal substances include extensive summaries of pharmacological, clinical and toxicological data, and copious references to scientific literature form an important part of each text.

Although publication in the form of books was convenient in the past, ESCOP recognizes that online publication now offers a number of advantages, not least in facilitating rapid publication of individual monographs as soon as all stages of preparation have been completed. Commencing from 2011, therefore, new and revised monographs will be published online only.

The European legislative framework for herbal medicines has advanced considerably over the past decade. Directive 2004/24/EC introduced a simplified registration procedure for traditional herbal medicinal products in EU member states and imposed a 2011 deadline for the registration of certain products on the market. The Committee on Herbal Medicinal Products (HMPC), established in 2004 as part of the European Medicines Agency, has made substantial progress in the preparation of Community Herbal Monographs and associated documentation to provide a more harmonized approach to the scientific assessment of herbal medicinal products throughout the European Community.

Whether the evaluation of a herbal medicine is based on evidence of clinical efficacy (well-established use) or on experience and historical use of that product (traditional use) those involved at all levels of the regulatory process need access to detailed, reliable and structured summaries of the available efficacy and safety data. ESCOP monographs meet that requirement and offer an invaluable source of scientific information on herbal medicines to regulators, manufacturers, academics, researchers, health professionals and numerous others.