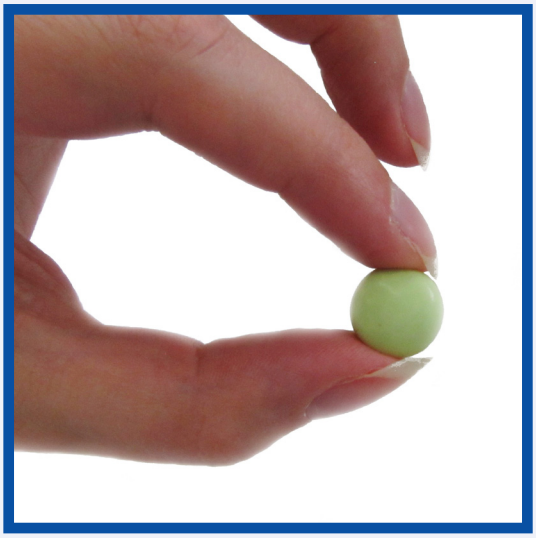
E/S/C/O/P Monographs

Online Series

The Scientific Foundation for Herbal Medicinal Products

Pelargonii radix
Pelargonium Root

2015



E/S/C/O/P
European Scientific Cooperative On Phytotherapy

www.escop.com

E/S/C/O/P
MONOGRAPHS

***The* Scientific Foundation for**
Herbal Medicinal Products

PELARGONII RADIX
Pelargonium Root

2015

E/S/C/O/P
European Scientific Cooperative
On Phytotherapy

ESCOP Monographs were first published in loose-leaf form progressively
from 1996 to 1999 as Fascicules 1-6, each of 10 monographs

Second Edition, completely revised and expanded

Second Edition, Supplement 2009

ONLINE SERIES

ISBN 978-1-901964-38-7

Pelargonii radix - Pelargonium Root

Published by the European Scientific Cooperative on Phytotherapy (ESCOP)
Notaries House, Chapel Street, Exeter EX1 1EZ, United Kingdom
www.escop.com

Important Note: Medical knowledge is ever-changing. As new research and clinical experience broaden our knowledge, changes in treatment may be required. In their efforts to provide information on the efficacy and safety of herbal drugs and herbal preparations, presented as a substantial overview together with summaries of relevant data, the authors of the material herein have consulted comprehensive sources believed to be reliable. However, in view of the possibility of human error by the authors or publisher of the work herein, or changes in medical knowledge, neither the authors nor the publisher, nor any other party involved in the preparation of this work, warrants that the information contained herein is in every respect accurate or complete, and they are not responsible for any errors or omissions or for results obtained by the use of such information. Readers are advised to check the product information included in the package of each medicinal preparation they intend to use, to be certain that the information contained in this publication is accurate and that changes have not been made in the recommended dose or in the contraindications for administration.

Edited by Simon Mills and Roberta Hutchins
Cover photographs by Stickpen (Own work) [Public domain],
via Wikimedia Commons (*Pelargonium sidoides*) and Martin Willoughby
Cover and text design by Martin Willoughby
Typeset in Optima by Roberta Hutchins

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
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
MW	molecular weight
NBT	nitro blue tetrazolium
NF-κB	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 oxalacetate 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-*O*-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

2015

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 ($C_6H_6O_3$; 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 (afzelechin, catechin and gallocatechin); phenolic acids (gallic acid and its methylester); hydroxycinnamic 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
Symptoms of upper respiratory tract infections including common cold, such as blocked or runny nose, sore throat and cough [Timmer 2013, Kamin 2010a-b, Brendler 2009, Bachert 2009, Agbabiaka 2008, Matthys 2010a/2007c/2003, Lizogub 2007, Chuchalin 2005, Bereznoy 2003].

Posology and method of administration

Dosage

Ethanolic extract (1:8-11; 12% V/V)
Adults and children over 12 years: 2.5-7.5 mL daily [Timmer 2013, Kamin 2010a, Brendler 2009, Bachert 2009, Agbabiaka 2008, Matthys 2007b-c/2003, Lizogub 2007, Chuchalin 2005, Heil 1994].
Children aged 6-12 years: 1.25–2.5 mL daily [Timmer 2013, Kamin 2010a, Brendler 2009, Agbabiaka 2008, Matthys 2007b, Bereznoy 2003, Haidvogl 1996, Heil 1994].
Children aged 2-6 years: 0.6-1.25 mL daily [Timmer 2013, Kamin 2010a, Brendler 2009, Agbabiaka 2008, Matthys 2007b, Haidvogl 1996, Heil 1994].

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 [Teschke 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 will 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) [Kayser 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 adhesion of *Streptococcus pyogenes* (Sp) to human Hep-2 epithelial cells dose-dependently by up to 46% ($p<0.001$) while the adhesion 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 [Janecki 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 (EC_{50} 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 EC_{50} values of 4.4 and 12.5 µg/mL (compared to the reference sodium stibogluconate, EC_{50} 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 (LC_{50} > 1 mg/mL for the extracts; LC_{50} > 0.2 mg/mL for the pure compounds) [Kolodziej 2002].

The cytotoxicity of scopoletin, 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 IC_{50} values of 22.1 and 9.5 µM respectively (compared to cisplatin: IC_{50} 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 EC_{50} of 6.6 µg/mL and corresponding to a selectivity index of 84 (CC_{50}/ EC_{50}). 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 a EC_{50} of 2.8 µg/mL [Theisen 2012].

The extract exhibited a free radical scavenging activity in the DPPH assay (IC_{50} 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 TJ356 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) [Rezaizadehnajafi 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 mono-preparations 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 Bronchitis 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 1.5mL 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% [Dome 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)

Number of patients	Duration (days)	Control	BSS decrease after treatment	
			Verum	Control
205 adults	7	placebo	7.7 points	5.3 points
220 adults & children	7	placebo	4.4 points	2.9 points
60 children (6-12 y.)	7	AcC	7[1] points	6[1] points
213 children (6-12 y.)	7	AcC	6.7 points	6.6 points
205 adults	7	-	3.3 points	-
1042 children (up to 12 y.)	14	-	5.4 points	-

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 therapy with 1.5 mL of the liquid extract 3 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)

Number of patients	Duration (days)	Control	TSS decrease after treatment	
			Verum	Control
124 children (6-10 y.)	6	placebo	6.8 points	3.4 points
78 children (6-10 y.)	6	placebo	6.7 points	3.6 points
60 children (6-10 y.)	10	gargle	5[1] points	3[1] points
1000 (2-35 years)	7	-	11[1] points	-

[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 (88 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 oral administration 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-hepatoxicity. 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 psychomotor 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 2003].

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) [Bachert 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 [Schapowal 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].

REFERENCES

Adewusi EA, Afolayan AJ. Safety evaluation of the extract from the roots of *Pelargonium reniforme* Curtis in male wistar rats. Afr J Pharm Pharmacol 2009;3:368-73.

Agbabiaka TB, Guo R, Ernst E. *Pelargonium sidoides* for acute bronchitis: a systematic review and meta-analysis. Phytomedicine 2008;15:378-85. http://dx.doi.org/10.1016/j.phymed.2007.11.023.

Arora RB, Mathur CN. Relationship between structure and anti-coagulant activity of coumarin derivatives. Brit J Pharmacol 1963;20:29-35.

Bachert C, Schapowal A, Funk P, Kieser M. Treatment of acute rhinosinusitis with the preparation from *Pelargonium sidoides* EPs 7630: a randomised, double-blind, placebo-controlled trial. Rhinology 2009; 47:51-8.

Beil W and Kilian P. EPs 7630, an extract from *Pelargonium sidoides* roots inhibits adherence of Helicobacter pylori to gastric epithelial cells. Phytomedicine 2007, 14 (Suppl VI):5-8. http://dx.doi.org/10.1016/j.phymed.2006.11.024

Bereznoy VV, Riley DS, Wassmer G, Heger M. Efficacy of extract of *Pelargonium sidoides* in children with acute non-group A beta-hemolytic streptococcus tonsillopharyngitis: a randomised, double-blind, placebo-controlled trial. Alternative Therapies 2003;9:68-79.

Brendler T, van Wijk BE. A historical, scientific and commercial perspective on the medicinal use of *Pelargonium sidoides* (Geraniaceae). J Ethnopharmacol 2008;19:420-33. http://dx.doi.org/10.1016/j.jep.2008.07.037

Brendler T. Umckaloabo: from a patent remedy to a modern herbal pharmaceutical based on *Pelargonium sidoides* with clinically proven efficacy. Am Chem Soc 2009;295-319

Brown D. *Pelargonium sidoides* extract (EPs7630): alternative treatment of acute upper respiratory tract infections. Natural Medicine Journal 2009;1:1-6.

Chuchalin AG, Berman B, Lehmacher W. Treatment of acute bronchitis in adults with a *Pelargonium sidoides* preparation (EPs 7630): a randomised, double-blind, placebo-controlled trial. Explore 2005;1:437-45 (http://dx.doi.org/10.1016/j.explore.2005.08.009).

Conrad A, Hansmann C, Engels I, Daschner FD; Frank U. Extract of *Pelargonium sidoides* (EPs 7630) improves phagocytosis, oxidative burst, and intracellular killing of human peripherial blood phagocytes in vitro. Phytomedicine 2007a, 14 (Suppl VI):46-51. http://dx.doi.org/10.1016/j.phymed.2006.11.016

Conrad A, Jung I, Tioua D, Lallemand C, Carrapatoso F, Engels I, Daschner FD; Frank U. Extract of *Pelargonium sidoides* (EPs 7630) inhibits the interaction of group A-streptococci and host epithelia *in vitro*. Phytomedicine 2007b, 14 (Suppl VI):52-9. http://dx.doi.org/10.1016/j.phymed.2006.11.018 (= Z Phytotherapie 2008;29:19-22)

de Boer HJ, Hagemann U, Bate J, Meyboom RHB. Allergic reaction to medicines derived from *Pelargonium* species. Drug Safety 2007,30:677-80. http://dx.doi.org/10.2165/00002018-200730080-00004

Dome L, Schuster R. Umckaloabo – eine phytotherapeutische Alternative bei akuter Bronchitis im Kindesalter? Ärztezeitschrift für Naturheilverfahren 1996;37:216-22.

Haidvogl M, Schuster R, Heger M. Akute Bronchitis im Kindesalter, Multizenter-Studie zur Wirksamkeit und Verträglichkeit des Phytotherapeutikums Umckaloabo. Z Phytother 1996;17:300-13.

Heil C, Retermann U. Atemwegs- und HNO-Infektionen. TW Pädiatrie 1994;7:523-5.

Janecki A, Conrad A, Engels I, Frank U, Kolodziej H. Evaluation of an aqueous-ethanolic extract from *Pelargonium sidoides* (EPs® 7630) for its activity against group A-streptococci adhesion to human Hep-2 epithelial cells. J Ethnopharmacol 2011;133:147-52. http://dx.doi.org/10.1016/j.jep.2010.09.018

Kamin W, Maydannik V, Malek FA, Kieser M. Efficacy and tolerability of EPS 7630 in children and adolescents with acute bronchitis. A randomised, double-blind, placebo-controlled multicenter trial with a herbal drug preparation from *Pelargonium sidoides* roots. Int J Clin Pharmacol Ther 2010a;48:184-91. http://dx.doi.org/10.5414/CPP48184

Kamin W, Maydannik VG, Malek FA, Kieser M. Efficacy and tolerability of EPS 7630 in patients (aged 6-18 years old) with acute bronchitis. A

randomised, double-blind, placebo-controlled clinical dose-finding study. Acta Pædiatrica 2010b;99:537-43 http://dx.doi.org/10.1111/j.1651-2227.2009.01656.x

Kamin W, Ilyenko L, Malek F, Kieser M. Treatment of acute bronchitis with EPs 7630: randomized, controlled trial in children and adolescents. Pediatrics International 2012;54:219-26. http://dx.doi.org/10.1111/j.1442-200X.2012.03598.x

Kayser O, Kolodziej H, Kiderlen AF. Immunomodulatory Principles of *Pelargonium sidoides*. Phytother Res 2001;15:122-6. http://dx.doi.org/10.1002/ptr.785

Kayser O, Kolodziej H. Antibacterial Activity of Extracts and Constituents of *Pelargonium sidoides* and *Pelargonium reniforme*. Planta Med 1997;63:508-10. http://dx.doi.org/10.1055/s-2006-957752

Kayser O, Kolodziej H. Highly Oxygenated Coumarins from *Pelargonium sidoides*. Phytochemistry 1995;39:1181-5. http://dx.doi.org/10.1016/0031-9422(95)00166-5

Koch E and Biber A. Treatment of rats with the *Pelargonium sidoides* extract EPs 7630 has no effect on blood coagulation parameters or on the pharmacokinetics of warfarin. Phytomedicine 2007, 14 (Suppl VI):40-5. http://dx.doi.org/10.1016/j.phymed.2006.11.026

Kolodziej H, Kayser O, Gutmann M. Arzneilich verwendete Pelargonien aus Südafrika. Dtsch Apoth Ztg 1995;135:853-64.

Kolodziej H, Kayser O, Woerdenbag HJ, van Uden W, Pras N. Structure – cytotoxicity of a series of natural and semi-synthetic simple coumarins as assessed in two human tumour cell lines. Z Naturforsch 1997;52c, 240-4.

Kolodziej H, Kayser O. *Pelargonium sidoides* DC. — Neueste Erkenntnisse zum Verständnis des Phytotherapeutikums Umckaloabo. Z Phytother 1998;19:141-51.

Kolodziej H. Traditionally used Pelargonium Species: Chemistry and Biological Activity of Umckaloabo Extracts and their Constituents. Curr Topics Phytochem 2000;3:77-93.

Kolodziej H. *Pelargonium reniforme* and *Pelargonium sidoides*: their botany, chemistry and medicinal use. In: Lis Balchin M Ed. Geranium and Pelargonium. Taylor and Francis, London and New York, 2002:262-90.

Kolodziej H, Kayser O, Radtke OA, Kiderlen AF, Koch E. Pharmacological profile of extracts of Pelargonium sidoides and their constituents. Phytomedicine 2003a;10 (Suppl.IV):18-24. http://dx.doi.org/10.1078/1433-187X-00307

Kolodziej H, Schulz V. Umckaloabo — Von der traditionellen Anwendung zum modernen Phytotherapeutikum. Dtsch Apoth Ztg 2003b;143:1303-12.

Kolodziej H. Fascinating metabolic pools of Pelargonium sidoides and Pelargonium reniforme, traditional and phytomedicinal sources of the herbal medicine Umckaloabo. Phytomedicine 2007a;14(Suppl VI):9-17. http://dx.doi.org/10.1016/j.phymed.2006.11.021

Latté KP, Kayser O, Tan N, Kaloga M, Kolodziej H. Unusual coumarin patterns of Pelargonium species forming the origin of the traditional herbal medicine Umckaloabo. Z Naturforsch 2000;55c:528-33.

Lizogub VG, Riley DS, Heger M. Efficacy of a *Pelargonium sidoides* preparation in patients with the common cold: a randomised, double-blind, placebo-controlled clinical trial. Explore 2007;3:573-84. http://dx.doi.org/10.1016/j.explore.2007.09.004

Loew D und Koch E. Differenzierte Risikobetrachtung mit dem Beispiel eines pflanzlichen Arzneimittels. Z Phytotherapie 2008;29:28-36. http://dx.doi.org/10.1055/s-2008-1064945

Luna LA, Bachi ALL, Novaes e Brito RR, Eid RG, Suguri VM, Oliveira PW, Gregorio LC, Vaisberg M. Immune responses induced by *Pelargonium sidoides* extract in serum and nasal mucosa of athletes after exhaustive exercise: modulation of secretory IgA, IL-6 an IL-15. Phytomedicine 2011;18:303-8. http://dx.doi.org/10.1016/j.phymed.2010.08.003

Matthys H, Eisebitt R, Seith B, Heger M. Efficacy and safety of an extract of *Pelargonium sidoides* (Eps 7630) in adults with acute broncitis. A randomised, double-blind, placebo-controlled trial. Phytomedicine 2003;10 (Suppl.IV):7-17. http://dx.doi.org/10.1078/1433-187X-00308

Matthys H and Heger M. EPs 7630-solution – an effective therapeutic option in acute and exacerbating bronchitis. Phytomedicine 2007a;14(Suppl VI):65-8. http://dx.doi.org/10.1016/j.phymed.2006.11.017

Matthys H, Kamin W, Funk P, Heger M. *Pelargonium sidoides* (EPs 7630) in the treatment of acute bronchitis in adults and children. Phytomedicine 2007b;14(Suppl VI):69-73. http://dx.doi.org/10.1016/j.phymed.2006.11.015

Matthys H, Heger M. Treatment of acute bronchitis with a liquid herbal drug preparation from *Pelargonium sidoides* (EPS 7630): a randomised, double-blind, placebo-controlled, multicentre study. Current Medical Research & Opinion 2007c;23:323-31. http://dx.doi.org/10.1185/030079906X167318

Matthys H, Lizogub VG, Malek FA, Kieser M. Efficacy and tolerability of EPS 7630 tablets in patients with acute bronchitis: a randomised, double-blind, placebo-controlled dose-finding study with a herbal drug preparation from *Pelargonium sidoides*. Current Medical Research & Opinion 2010a;26:1413-22. (http://dx.doi.org/10.1185/03007991003798463)

Matthys H, Lizogub VG, Funk P, Malek FA. P*elargonium sidoides* bei akuter Bronchitis – Gesundheitsbezogene Lebensqualität und Therapiebeurteilung aus Patientensicht unter Behandlung mit EPs 7630. Wien Med Wochenschr 2010b;160/21-22:564-70. http://dx.doi.org/10.1007/s10354-010-0847-5

Matthys H, Pliskevich DA, Bondarchuk OM, Malek FA, Tribanek M, Kieser M. Randomised, double-blind, placebo-controlled trial od EPS 7630 in adults with COPD. Respiratory Medicine 2013;107:691-701. http://dx.doi.org/10.1016/j.rmed.2013.02.011

Neugebauer P, Mickenhagen A, Siefer O, Walger M. A new approach for pharmacological effects on ciliary beat frequency in cell cultures – exemplary measurements under *Pelargonium sidoides* extract (Eps 7630). Phytomedicine 2005;12:46-51. http://dx.doi.org/10.1016/j.phymed.2003.11.005

Nöldner M and Schölz K. Inhibition of lipopolysaccharide-induced sickness behaviour by a dry extract from the roots of *Pelargonium sidoides* (EPs 7630) in mice. Phytomedicine 2007, 14 (Suppl VI):27-31. http://dx.doi.org/10.1016/j.phymed.2006.11.013 (= Z Phytotherapie 2008;29:23-6)

Pelargonium root – Pelargonii radix. European Pharmacopoeia, Council of Europe.

Rezaizadehnajafi L, Wink M. EPs7630 from *Pelargonium sidoides* increases stress resistance in *Caenorhabditis elegans* probably via the DAF-16/FOXO pathway. Phytomedicine 2014;21:547-50. http://dx.doi.org/10.1016/j.phymed.2013.10.027

Schapowal A, Heger M. EPs 7630 Lösung (Umckaloabo®) bei Sinusitis. Z Phytother 2007;28:58-65. http://dx.doi.org/10.1055/s-2007-981621

Schoetz K, Erdelmeier C, Gerner S, Hauer H. A detailed view on the constituents of EPs 7630. Planta Med 2008;74:667-74. http://dx.doi.org/10.1055/s-2008-1074515

Tahan Fand Yaman M. Can the *Pelargonium sidoides* root extract

EPs® 7630 prevent asthma attacks during viral infections of the upper respiratory tract in children? Phytomedicine 2013;20:148-50. http://dx.doi.org/10.1016/j.phymed.2012.09.022

Teschke R, Frenzel C, Wolff A, Herzog J, Glass X, Schulze J, Eickhoff A. Initially purported hepatotoxicity by *Pelargonium sidoides*: the dilemma of pharmacovigilance and proposals for improvement. Ann Hepatol 2012a,11(4):500-12.

Teschke R, Frenzel C, Schulze J, Eickhoff A. Spontaneous reports of primarily suspected herbal hepatotoxicity by *Pelargonium sidoides*: was causality adequately ascertained? Regul Tox Pharmacol 2012b;63:1-9 (http://dx.doi.org/10.1016/j.yrtph.2012.02.009)

Thäle C, Kiderlen A, Kolodziej H. Anti-infective mode of action of EPs 7630 at the molecular level. Planta Medica 2008;74:675-81. http://dx.doi.org/10.1055/s-2008-1034324

Theisen LL, Muller CP. EPs® 7630 (Umckaloabo), an extract from *Pelargonium sidoides* roots, exerts anti-influenza virus activity *in vitro* and *in vivo*. Antiviral Research 2012;94:147-56. http://dx.doi.org/10.1016/j.antiviral.2012.03.006

Timmer A, Günther J, Motschall E, Rücker G, Antes G, Kern WV. *Pelargonium sidoides* extract for treating acute respiratory tract infections (Review). Cochrane Database for Systematic Reviews 2013, Issue 10 http://dx.doi.org/10.1002/14651858.CD006323.pub3

Williamson E, Driver S, Baxter K, editors. Pelargonium. In: Stockley's herbal medicines interactions. Pharmaceutical Press 2009:309-10.

E/S/C/O/P
MONOGRAPHS

MOST RECENT VERSIONS

Title	Common name	Publication
ABSINTHII HERBA	Wormwood	Second Edition, 2003
AGNI CASTI FRUCTUS	Agnus Castus	Second Edition, 2003
AGRIMONIAE HERBA	Agrimony	Supplement 2009
ALCHEMILLAE HERBA	Lady's Mantle	Online Series, 2013
ALLII SATIVI BULBUS	Garlic	Second Edition, 2003
ALOE BARBADENSIS	Barbados Aloes	Online Series, 2014
ALOE CAPENSIS	Cape Aloes	Online Series, 2014
ALTHAEAE RADIX	Marshmallow Root	Second Edition, 2003
ANGELICAE RADIX	Angelica Root	Supplement 2009
ANISI FRUCTUS	Aniseed	Online Series, 2014
ARNICAE FLOS	Arnica Flower	Second Edition, 2003
BALLOTAE NIGRAE HERBA	Black Horehound	Online Series, 2015
BETULAE FOLIUM	Birch Leaf	Online Series, 2015
BOLDI FOLIUM	Boldo Leaf	Second Edition, 2003
CALENDULAE FLOS	Calendula Flower	Second Edition, 2003
CAPSICI FRUCTUS	Capsicum	Supplement 2009
CARVI FRUCTUS	Caraway Fruit	Second Edition, 2003
CARYOPHYLLI AETHEROLEUM	Clove Oil	Online Series, 2014
CENTAURII HERBA	Centaury	Online Series, 2015
CENTELLAE ASIATICAE HERBA	Centella	Supplement 2009
CHELIDONII HERBA	Greater Celandine	Second Edition, 2003
CIMICIFUGAE RHIZOMA	Black Cohosh	Online Series, 2011
CINNAMOMI CORTEX	Cinnamon	Second Edition, 2003
COLAE SEMEN	Cola	Online Series, 2014
CRATAEGI FOLIUM CUM FLORE	Hawthorn Leaf and Flower	Second Edition, 2003
CRATAEGI FRUCTUS	Hawthorn Berries	Supplement 2009
CUCURBITAE SEMEN	Pumpkin Seed	Supplement 2009
CURCUMAE LONGAE RHIZOMA	Turmeric	Second Edition, 2003
CURCUMAE XANTHORRHIZAE RHIZOMA	Javanese Turmeric	Supplement 2009
CYNARAE FOLIUM	Artichoke Leaf	Supplement 2009
ECHINACEAE ANGUSTIFOLIAE RADIX	Narrow-leaved Coneflower Root	Supplement 2009
ECHINACEAE PALLIDAE RADIX	Pale Coneflower Root	Supplement 2009
ECHINACEAE PURPUREAE HERBA	Purple Coneflower Herb	Supplement 2009
ECHINACEAE PURPUREAE RADIX	Purple Coneflower Root	Supplement 2009
ELEUTHEROCOCCI RADIX	Eleutherococcus	Supplement 2009
EUCALYPTI AETHEROLEUM	Eucalyptus Oil	Second Edition, 2003
FILIPENDULAE ULMARIAE HERBA	Meadowsweet	Online Series, 2015
FOENICULI FRUCTUS	Fennel	Second Edition, 2003
FRANGULAE CORTEX	Frangula Bark	Second Edition, 2003
FUMARIAE HERBA	Fumitory	Supplement 2009
GENTIANAE RADIX	Gentian Root	Online Series, 2014
GINKGO FOLIUM	Ginkgo Leaf	Second Edition, 2003
GINSENG RADIX	Ginseng	Second Edition, 2003
GRAMINIS RHIZOMA	Couch Grass Rhizome	Supplement 2009
GRINDELIAE HERBA	Grindelia	Online Series, 2015
HAMAMELIDIS AQUA	Hamamelis Water	Online Series, 2012
HAMAMELIDIS CORTEX	Hamamelis Bark	Online Series, 2012
HAMAMELIDIS FOLIUM	Hamamelis Leaf	Online Series, 2012
HARPAGOPHYTI RADIX	Devil's Claw Root	Supplement 2009
HEDERAE HELICIS FOLIUM	Ivy Leaf	Second Edition, 2003
HIPPOCASTANI SEMEN	Horse-chestnut Seed	Second Edition, 2003
HYDRASTIS RHIZOMA	Goldenseal rhizome	Online Series, 2013
HYPERICI HERBA	St. John's Wort	Second Edition, 2003
JUNIPERI PSEUDO-FRUCTUS	Juniper	Second Edition, 2003
LAVANDULAE FLOS/AETHEROLEUM	Lavender Flower/Oil	Supplement 2009
LICHEN ISLANDICUS	Iceland Moss	Second Edition, 2003
LINI SEMEN	Linseed	Second Edition, 2003

LIQUIRITIAE RADIX	Liquorice Root	Second Edition, 2003
LUPULI FLOS	Hop Strobile	Second Edition, 2003
MALVAE FLOS	Mallow Flower	Supplement 2009
MARRUBII HERBA	White horehound	Online Series, 2013
MATRICARIAE FLOS	Matricaria Flower	Second Edition, 2003
MELALEUCAE AETHEROLEUM	Tea Tree Oil	Supplement 2009
MELILOTI HERBA	Melilot	Second Edition, 2003
MELISSAE FOLIUM	Melissa Leaf	Online Series, 2013
MENTHAE PIPERITAE AETHEROLEUM	Peppermint Oil	Second Edition, 2003
MENTHAE PIPERITAE FOLIUM	Peppermint Leaf	Second Edition, 2003
MENYANTHIDIS TRIFOLIATAE FOLIUM	Bogbean Leaf	Online Series, 2013
MILLEFOLII HERBA	Yarrow	Supplement 2009
MYRRHA	Myrrh	Online Series, 2014
MYRTILLI FRUCTUS	Bilberry Fruit	Online Series, 2014
OLIBANUM INDICUM	Indian Frankincense	Supplement 2009
ONONIDIS RADIX	Restharrow Root	Online Series, 2015
ORTHOSIPHONIS FOLIUM	Java Tea	Online Series, 2014
PASSIFLORAE HERBA	Passion Flower	Second Edition, 2003
PAULLINIAE SEMEN	Guarana Seed	Supplement 2009
PELARGONII RADIX	Pelargonium Root	Online Series, 2015
PIPERIS METHYSTICI RHIZOMA	Kava-Kava	Second Edition, 2003
PLANTAGINIS LANCEOLATAE FOLIUM/HERBA	Ribwort Plantain Leaf/Herb	Online Series, 2013
PLANTAGINIS OVATAE SEMEN	Ispaghula Seed	Second Edition, 2003
PLANTAGINIS OVATAE TESTA	Ispaghula Husk	Second Edition, 2003
POLYGALAE RADIX	Senega Root	Second Edition, 2003
PRIMULAE RADIX	Primula Root	Second Edition, 2003
PRUNI AFRICANAE CORTEX	Pygeum Bark	Supplement 2009
PSYLLII SEMEN	Psyllium Seed	Second Edition, 2003
RATANHIAE RADIX	Rhatany Root	Supplement 2009
RHAMNI PURSHIANI CORTEX	Cascara	Online Series, 2015
RHEI RADIX	Rhubarb	Second Edition, 2003
RIBIS NIGRI FOLIUM	Blackcurrant Leaf	Second Edition, 2003
ROSAE PSEUDO-FRUCTUS	Dog Rose Hip	Supplement 2009
ROSMARINI FOLIUM	Rosemary Leaf	Second Edition, 2003
RUSCI RHIZOMA	Butcher's Broom	Second Edition, 2003
SALICIS CORTEX	Willow Bark	Second Edition, 2003
SAMBUCI FLOS	Elder flower	Online Series, 2013
SALVIAE OFFICINALIS FOLIUM	Sage Leaf	Second Edition, 2003
SALVIA TRILOBAE FOLIUM	Sage Leaf, Three-lobed	Online Series, 2014
SENNAE FOLIUM	Senna Leaf	Second Edition, 2003
SENNAE FRUCTUS ACUTIFOLIAE	Alexandrian Senna Pods	Second Edition, 2003
SENNAE FRUCTUS ANGUSTIFOLIAE	Tinnevelly Senna Pods	Second Edition, 2003
SERENOAE REPENTIS FRUCTUS (SABAL FRUCTUS)	Saw Palmetto Fruit	Second Edition, 2003
SERPYLLI HERBA	Wild Thyme	Online Series, 2014
SOLIDAGINIS VIRGAUREAE HERBA	European Golden Rod	Second Edition, 2003
SILYBI MARIANI FRUCTUS	Milk Thistle Fruit	Supplement 2009
SYMPHYTI RADIX	Comfrey Root	Online Series, 2012
TANACETI PARTHENII HERBA	Feverfew	Online Series, 2014
TARAXACI FOLIUM	Dandelion Leaf	Second Edition, 2003
TARAXACI RADIX	Dandelion Root	Second Edition, 2003
THYMI HERBA	Thyme	Second Edition, 2003
TORMENTILLAE RHIZOMA	Tormentil	Online Series, 2013
TRIGONELLAE FOENUGRAECI SEMEN	Fenugreek	Second Edition, 2003
URTICAE FOLIUM/HERBA	Nettle Leaf/Herb	Second Edition, 2003
URTICAE RADIX	Nettle Root	Online Series, 2015
UVAE URSI FOLIUM	Bearberry Leaf	Online Series, 2012
VACCINII MACROCARPI FRUCTUS	Cranberry	Supplement 2009
VALERIANAE RADIX	Valerian Root	Supplement 2009
VERBASCI FLOS	Mullein Flower	Online Series, 2014
VIOLAE HERBA CUM FLORE	Wild Pansy	Online Series, 2015
VITIS VINIFERAE FOLIUM	Red Vine Leaf	Supplement 2009
ZINGIBERIS RHIZOMA	Ginger	Supplement 2009

E/S/C/O/P Monographs

Online Series

The Scientific Foundation for Herbal Medicinal Products

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.

E/S/C/O/P
European Scientific Cooperative On Phytotherapy

www.escop.com

ISBN 978-1-901964-38-7