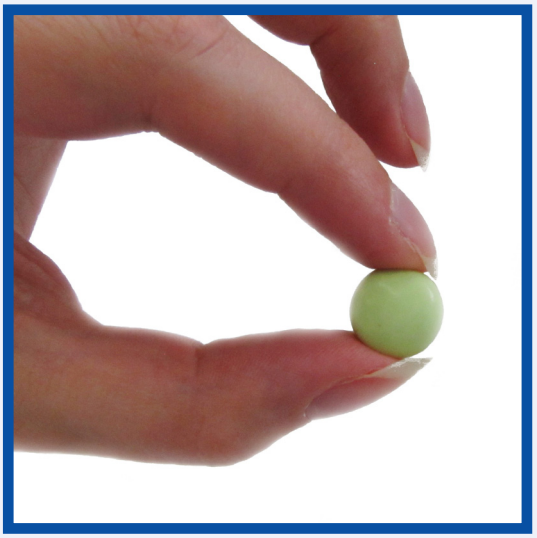
E/S/C/O/P Monographs

Online Series

The Scientific Foundation for Herbal Medicinal Products

Hydrastis rhizoma
Goldenseal rhizome

2013



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

HYDRASTIS RHIZOMA
Goldenseal rhizome

2013

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 978-1-901964-07-3

Hydrastis rhizoma - Goldenseal rhizome

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 photograph by Simon Mills (*Hydrastis canadensis*)
Cover and text design by Martin Willoughby
Typeset in Optima by Roberta Hutchins

Plant illustrated on the cover: *Hydrastis canadensis*

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

HYDRASTIS RHIZOMA 2013

Goldenseal rhizome

DEFINITION

Goldenseal rhizome consists of the whole or cut, dried rhizome and root of *Hydrastis canadensis* L. It contains not less than 2.5 per cent of hydrastine ($C_{21}H_{21}NO_6$; M_r 383.4) (dried drug) and not less than 3.0 per cent of berberine ($C_{20}H_{19}NO_5$; M_r 353.4) (dried drug).

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

CONSTITUENTS

Isoquinoline alkaloids (2.4 – 7%) [Blaschek 2007; Barnes 2007; Upton 2001; Galeffi 1997; Bradley 1992]:

- protoberberine alkaloids: berberine (2.5 – 4.5%), berberastine (2 – 3%), canadine (0.5 – 1%), corypalmine and isocorypalmine.
- phthalylisoquinoline alkaloids: hydrastine (1.5 – 4%), hydrastidine and isohydrastidine.
- benzylisoquinoline alkaloids: candaline and canadinic acid.

Quinic acid derivatives (up to 2.5%), mainly 5-O-(4′-[β-D-glucopyranosyl] trans-feruloyl)quinic acid [McNamara 2004] and methylated luteolin 7-methyl ethers [Hwang 2003].

CLINICAL PARTICULARS

Therapeutic indications

Digestive disorders such as dyspeptic complaints and gastritis; as an adjuvant in menorrhagia and dysmenorrhoea [Blaschek 2007; Barnes 2007; Mills 2013; Bradley 1992].

Efficacy in these indications is plausible on the basis of human experience and long-standing use.

Posology and method of administration

Dosage

0.5-1 g of the drug as a decoction three times daily; 0.3-1 mL of a liquid extract (1:1, ethanol 60%) three times daily [Bradley 1992; Barnes 2007]. Preparations accordingly.

Method of administration
For oral administration.

Duration of administration
No restriction. If symptoms persist or worsen, medical advice should be sought.

Contraindications
None known.

Special warnings and special precautions for use
None required.

Interaction with other medicaments and other forms of interaction
Investigations in healthy volunteers with goldenseal rhizome revealed significant interactions with drugs that are metabolized by cytochrome P450 3A4/5 (e.g. midazolam) and 2D6 (e.g. debrisoquin) [Gurley 2005; Gurley 2008a; Gurley 2008b].

Pregnancy and lactation
The product should not be used during pregnancy or lactation [Blaschek 2007; Barnes 2007; Upton 2001; Mills 2013; Bradley 1992].

E/S/C/O/P
MONOGRAPHS

Effects on ability to drive and use machines
None known.

Undesirable effects
None reported.

Overdose
Although no case reports are available, exaggerated reflexes, depression, delirium, vomiting and cyanosis have been mentioned [Blaschek 2007; Barnes 2007].

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

The pharmacodynamics of the key constituents berberine and hydrastine have been studied thoroughly. The following pharmacological activities have been demonstrated [Simeon 1989; Mills 2013; Upton 2001]:

For berberine:
- antibacterial, antifungal, antiparasitic
- antidiarrhoeal, intestinal antisecretory
- antiarrhythmic, positive inotropic
- cytotoxic, antitumoral
- cholagogue, choleretic

For hydrastine:
- choleretic
- sedative
- antibacterial
- vasoconstrictive

In vitro experiments

Antimicrobial and antiviral activity
A 95% ethanolic extract of goldenseal rhizome exhibited antimicrobial activity against *Staphylococcus aureus, Klebsiella pneumoniae, Mycobacterium smegmatis* and *Candida albicans* with an MIC of 1 mg/mL [Gentry 1998].

A 70% ethanolic extract of goldenseal rhizome (standardized to 10 mg/mL berberine) showed antimicrobial activity against *Staphylococcus aureus* and *Streptococcus sanguis* with MICs of 0.12 mg/mL and 0.5 mg/mL (expressed as berberine) respectively. The bactericidal activity was evaluated in a contact test: the extract at 10 mg/mL was bactericidal within 4 to 30 min against the test strains compared to 0.5 - 4 min for hydrogen peroxide at 30 mg/mL [Scazzocchio 2001; Villinski 2003].

A 95% methanolic extract of goldenseal rhizome inhibited the growth of 15 strains of *Helicobacter pylori* with an MIC_{50} range of 12.5-50 µg/mL [Mahady 2003].

In a screening of herbal extracts for antibacterial activity against *H. pylori* and *Campylobacter jejuni* a goldenseal rhizome extract (ethanol 45%; DER 1:3) showed inhibition of both organisms [Cwikla 2010].

A methanolic (100%) extract of goldenseal rhizome showed antimicrobial activity against *Streptococcus mutans* and *Fusobacterium nucleatum* with MICs of 250 µg/mL and 62.5 µg/mL respectively. A bioguided fractionation of the extract led to the isolation of berberine (MIC: 125 µg/mL and 15.6 µg/mL, respectively) and 6-C-methylluteolin 7-methyl ether (MIC: 250 µg/mL and 375 µg/mL, respectively) as active compounds [Hwang 2003].

A 50% ethanolic extract of goldenseal rhizome completely inhibited influenza A growth in RAW 264.7 cells from a concentration of 2.5 µM of berberine (IC_{50} = 0.22 µM) compared to pure berberine (IC_{50} 0.01 µM) and amantadine (IC_{50} 27 µM) [Cecil 2011].

Smooth muscle relaxant activity
A 70% ethanolic extract of goldenseal rhizome dose-dependently inhibited the contractions induced by adrenaline on rabbit aorta strips (IC_{50} 0.88 µM, calculated as berberine). The activity of the isolated alkaloids berberine, canadine and canadaline was less pronounced (IC_{50} 2.6 – 5.2 µM) [Palmery 1996].

An extract of goldenseal rhizome providing berberine at 2.45 µM significantly ($p<0.01$) inhibited the contractions of rabbit prostate strips induced by noradrenaline or phenylephrine [Baldazzi 1998].

A 70% ethanolic extract of goldenseal rhizome induced relaxation in bladder detrusor muscle strips comparable to isoproterenol (88% of the isoproterenol-evoked response). Propranolol reduced this response by 69% suggesting that β-adrenergic stimulation was not the only mechanism [Bolle 1998].

A 70% ethanolic extract of goldenseal rhizome dose-dependently inhibited spontaneous contractions of uterine strips of non-pregnant rats (IC_{50} 10 µg/mL) and contractions induced by serotonin (IC_{50} 19.9 µg/mL), oxytocin (IC_{50} 10.5 µg/mL) and acetylcholine (IC_{50} 10 µg/mL). The extract also relaxed carbachol precontracted guinea-pig trachea (EC_{50} 1.6 µg/mL). The effect was partially antagonized by timolol, suggesting again that β-adrenergic stimulation was not the only mechanism [Cometa 1998].

In another study using the same guinea-pig trachea model the relaxant effect of a 70% ethanolic extract of goldenseal rhizome was confirmed (EC_{50} 1.5 µg/mL). The EC_{50} value of isolated alkaloids was also determined: hydrastine (72.8 µg/mL), berberine (34.2 µg/mL), canadine (11.9 µg/mL) and canadaline (2.4 µg/mL). Timolol antagonized the effect of canadine and canadaline but not that of berberine and hydrastine, while an adenosine receptor antagonist (xanthine amine congener) antagonized the effect of canadaline and hydrastine, but not of berberine and canadine. Extract concentrations from 0.01 to 0.1 µg/mL significantly ($p<0.01$) potentiated the relaxant effect of isoprenaline [Abdel-Haq 2000].

Antioxidant activity
A 70% ethanolic extract of goldenseal rhizome showed an antioxidant activity in the ABTS assay in a dilution of 1:1000. The effect was comparable to 40 µM trolox [Pereira da Silva 2000].

Immunomodulating activity
A 50% ethanolic extract of goldenseal rhizome reduced the production of TNF-α and the interleukins 6, 10 and 12 in lipopolysaccharide-stimulated macrophages in a dose-dependant manner [Clement-Kruzel 2008].

A 50% ethanolic extract of goldenseal rhizome significantly ($p<0.05$) inhibited the production of TNF-α and PGE_2 in influenza A infected RAW 264.7 cells at a concentration corresponding to 25 µM of berberine [Cecil 2011].

Influence on cytochrome P450
Serial dilutions (from 100% to 1.56%) of 21 commercial ethanolic herbal extracts and tinctures were analyzed for their ability to inhibit CYP3A4 via a fluorometric microtiter plate assay. An ethanolic extract of goldenseal rhizome gave the strongest inhibition with a calculated IC_{50} of 0.03% [Budzinski

2000]. In the same assay an aqueous extract of two commercial products (product 1 containing 450 mg goldenseal rhizome powder per capsule; product 2 containing 250 mg extract, standardised to 10% alkaloids, and 65 mg rhizome powder per capsule) gave an IC_{50} of 3.03 and 3.23 mg/mL, respectively [Budzinski 2008].

A commercial extract of goldenseal rhizome (containing approximately 17 mM berberine and hydrastine) inhibited CYP2C9 (diclofenac 4-hydroxylation), CYP2D6 (bufuralol 1'-hydroxylation) and CYP3A4 (testosterone 6β-hydroxylation) in human hepatic microsomes. The inhibition of CYP3A4 was non-competitive with an apparent Ki (= dissociation constant of inhibitor) of 0.1% extract [Chatterjee 2003].

An aqueous and ethanolic extract of goldenseal rhizome (equivalent to 20 µM berberine plus hydrastine) exerted more than 50% inhibition of the activity of CYP2C8 (paclitaxel 6α-hydroxylation), CYP2D6 (dextromethorphan O-demethylation) and CYP3A4 (midazolam 1-hydroxylation and testosterone 6β-hydroxylation) in human hepatic microsomes. CYP2E1 activity (p-nitrophenol hydroxylation) was inhibited by 20 µM berberine, but was not affected by either the extracts or hydrastine (20 µM). The extracts, as well as berberine and hydrastine, stimulated human P-glycoprotein (Pgp) ATPase activity at about 50% of the activity of verapamil (20 µM) [Etheridge 2007]. Goldenseal rhizome tea (containing 0.2% hydrastine and 1.0% berberine) had a greater stimulatory effect on Pgp ATPase than verapamil (20 µM) [Budzinski 2008].

In contrast to the previous study, CYP2E1 activity (p-nitrophenol hydroxylation) was inhibited by berberine (4 µM, 11% decrease), hydrastine (4 µM, 64% decrease) and by a 50% ethanolic extract of goldenseal rhizome (corresponding to 1.7 µM berberine and 1.2 µM hydrastine, 55% decrease). Inhibition of CYP2E1 appeared to be competitive with a Ki of 18 µM, 2.8 µM and 0.1%, respectively [Raner 2007].

In vivo experiments

Antidiabetic activity
Goldenseal rhizome, incorporated into the diet at 6.25% for 9 days, significantly ($p<0.05$) reduced hyperphagia and polydipsia in streptozotocin-diabetic mice [Swanston-Flat 1989].

Immunomodulating activity
Goldenseal rhizome extract (not further specified) was administered to rats for 6 weeks (1 g/l of drinking water). At days 0, 14 and 28 the antigen KLH (keyhole limpet haemocyanin) was injected. The treated group showed a significant ($p<0.05$) increase in the primary IgM response during the first 2 weeks, whereas the IgG levels in treated and control rats were identical [Rehman 1999].

Lipid-lowering activity
Berberine (1.8 mg/animal) or goldenseal rhizome extract (125 µL/animal, equivalent to 0.9 mg berberine) was administered intraperitoneally to hyperlipidaemic hamsters once per day for 24 days. Goldenseal significantly ($p<0.001$) reduced total plasma cholesterol by 31%, LDL-cholesterol by 25% and triglycerides by 33% compared to control. The activity of berberine was almost identical [Abidi 2006].

Anti-carcinogenic activity
Oral administration of a 90% ethanolic extract (not further specified; 0.06 mL three times daily for 4 months) to mice chronically fed p-dimethylaminoazobenzene (0.06% in the diet) and phenobarbital (0.05% in the diet) markedly reduced the liver tumour incidence and the elevation of serum phosphatases and transferases. This was confirmed histopathologically by a decrease of necrosis, vascular congestion, fibrosis and damage to intracellular organelles in livers of the treated mice [Karmakar 2010].

Pharmacological studies in humans

In a randomized, cross-over study 12 healthy volunteers received a goldenseal rhizome extract (900 mg, 3 times daily) for 28 days. Probe drug cocktails (midazolam and caffeine, chlorzoxazone and debrisoquin) were administered before and at the end of supplementation. Determination of cytochrome P450 activity 1A2, 2D6, 2E1 and 3A4/5 revealed a significant ($p<0.05$) inhibition (approximately 40%) of CYP2D6 and CYP3A4/5 [Gurley 2005].

In a cross-over study, the pharmacokinetics of indinavir were characterized in 10 healthy volunteers before and after treatment with goldenseal rhizome (1140 mg, twice daily for 28 days). No significant differences in peak concentration or oral clearance were observed, suggesting that interactions with drugs metabolized by CYP3A4 are unlikely [Sandhu 2003]. However indinavir is less suitable as a probe for assessing changes in CYP3A4/5 activity due to its high oral bioavailability [Gurley 2005].

In a randomised, cross-over study the effect of treatment with a standardized goldenseal rhizome extract (1070 mg, containing 24.1 mg isoquinoline alkaloids, 3 times daily for 14 days) on digoxin pharmacokinetics was determined in 20 healthy volunteers. No clinically relevant effects on digoxin pharmacokinetics were observed. When compared to rifampin (= rifampicin) and clarithromycin, goldenseal rhizome does not seem to be a potent modulator of P-glycoprotein [Gurley 2007].

Sixteen healthy volunteers received a goldenseal rhizome extract, corresponding to 132 mg hydrastine and 77 mg berberine per day, for 14 days. Midazolam (8 mg, per os) was admistered 1 day before and on the last day of treatment. Comparison of pre- and post-treatment midazolam pharmacokinetic parameters revealed significant inhibition of CYP3A: AUC(0-∞): 108 vs. 175 ng*h/mL ($p<0.001$); apparent oral clearance normalised to body weight: 1.3 vs. 0.8 l/h/kg ($p<0.001$); $T_{1/2}$ elimination: 2.0 vs. 3.2 h ($p<0.001$) and C_{max}: 51 vs. 71 ng/mL ($p<0.05$)[Gurley 2008b]. In a comparable study, debrisoquin (5 mg, orally) was administered before and at the end of goldenseal treatment (same product, same dose). Comparison of pre- and post-treatment urinary recovery ratios of debrisoquin revealed significant ($p<0.05$) inhibition of CYP2D6: 0.71 vs. 0.37 [Gurley 2008a].

Clinical studies
No data available.

Pharmacokinetic properties
No data available for goldenseal rhizome.

Pharmacokinetics in animals
After oral administration of berberine sulphate to rats at doses of up to 1 g/kg body weight only very small amounts of berberine were detected in a few tissues. As anticipated for a quaternary alkaloid, examination of the intestines revealed that berberine was neither well absorbed nor destroyed [De Smet 1992].

After oral administration of berberine to rats at a lower dose of 40 mg/kg, berberine, four metabolites and their glucuronide conjugates were found in plasma, bile and urine. Berberine reached its peak plasma concentration (10 µg/l) after 2 hours and was eliminated within 12 hours (AUC(0-∞): 37 ng*h/mL). However, the peak plasma concentration and AUC(0-∞) values

of the metabolites were much higher: e.g. AUC(0-∞) of 1880 ng*h/mL for the main metabolite berberrubine. About 34% of the oral dose was absorbed from the gastrointestinal tract within 1 hour. [Zuo 2006].

Intravenous administration of berberine to rats at 10 mg/kg resulted in $T_{1/2}$ elimination of 0.3 h and AUC0-∞ of 265 µg*min/mL (plasma)/1470 µg*min/mL (bile). Only a small amount of berberine was detected in urine. Berberine was rapidly transported from blood into liver and bile (via P-glycoprotein) and metabolised with phase I demethylation (CYP450) and phase II glucuronidation [Tsai 2004].

The cumulative urinary and biliary excretion of berberine after i.v. administration of 2 mg/kg to rabbits was 4.9% and 0.5% of the administered dose respectively (AUC: 0.84 µg*h/mL) [Chen 1995].

Berberine was given orally to dogs in a single dose of 280 mg/kg body weight and resulted in a C_{max} of 15.5 µg/mL, T_{max} of 3.7 h and AUC0-∞ of 777 µg*h/mL. At this high dose vomiting occurred within 1 h [Upton 2001].

Pharmacokinetics in humans
In an uncontrolled study, 56 patients with congestive heart failure received 1.2 g berberine per day orally for 2 weeks. Peak plasma levels were reached in about 2.4 h ranging from 0.07 to 0.19 mg/l [Zeng 1999].

After oral administration of berberine to 5 volunteers at a dose of 900 mg/day for 3 days, 3 sulphate-conjugated metabolites were isolated and identified in the urine [Pan 2002].

An oral dose of 300 mg berberine was given 3 times daily for 2 days to 12 healthy volunteers. In their urine 7 metabolites could be identified: phase I metabolites formed by cleavage of the dioxymethylene ring or by demethylation, most of them were conjugated with glucuronic or sulphuric acid (phase II metabolites) [Qiu 2008].

Preclinical safety data

Acute and repeated dose toxicity
The oral LD_{50} of an extract of goldenseal rhizome in mice was 1620 mg/kg body weight [Blaschek 2007; Mills 2013].

The oral LD_{50} of berberine in mice was 329 mg/kg body weight. Oral doses of up to 100 mg/kg of berberine sulphate have been well tolerated in animal studies without permanent effects. However, prolonged administration caused organ damage and death after 8 to 10 days [De Smet 1992; Mills 2013].

The LD_{50} values of hydrastine in rats were 1000 mg/kg body weight (oral), 1270 mg/kg (subcutaneous) and 104 mg/kg (intraperitoneal) [Blaschek 2007].

Chronic toxicity
In a two-year toxicity study goldenseal rhizome powder (3.9% berberine, 2.8 hydrastine and 0.2% canadine) was administered to male and female rats and mice at up to 25% of the feed. The primary finding was an increase in liver tumours in rats and mice at the highest dose (25%) [Dunnick 2011].

Reproductive toxicity
In a preliminary experiment, non-pregnant, female rats were dosed by oral gavage with a liquid extract of goldenseal rhizome (45% ethanol; 333 mg/mL goldenseal; standardized to 9.3 mg/mL berberine and 8.4 mg/mL hydrastine) at incremental doses for 8 days. The maximum dose of 1.86 g/kg body weight/day was non-maternotoxic. This dose was administered daily to female rats on either gestation days (GD) 1-8 or GD 8-15. Controls received an equivalent dose of ethanol. On GD 20, foetuses were weighed and examined for signs of external, internal, or skeletal malformations: differences between the treated and control group could not be demonstrated. When rat embryos were explanted and cultured with the extract at concentrations from 0.5 to 6 µL/mL, growth retardation and embryotoxicity were demonstrated in a dose-dependent manner. A possible poor absorption of orally administered goldenseal could explain the discrepancy between the in vivo and in vitro results [Yao 2005].

Berberine was administered in the feed and by gavage to pregnant rats on GD 6-20 and to pregnant mice on GD 6-17. A mortality of 33% of the mice exposed to 792 mg/kg/day berberine by gavage was observed. The following NOAEL (no observed adverse effect level) and LOAEL (lowest observed adverse effect level) values were determined [Jahnke 2006]:

	LOAEL (mg/kg/day)	NOAEL (mg/kg/day)
Rat maternal toxicity	420	223
Rat developmental toxicity	>792	792
Mouse maternal toxicity	666	450
Mouse developmental toxicity	792	666

Clinical safety data

In an 11 year old girl with diabetic ketoacidosis, the degree of hypernatraemia and hyperosmolality was enhanced after intake of 500 mg goldenseal (not further specified) 2 to 3 times daily for 2 weeks, but a causal relationship could not be demonstrated [Bhowmick 2007].

REFERENCES

Abdel-Haq H, Cometa MF, Palmery M, Leone MG, Silvestrini B and Saso L. Relaxant effects of *Hydrastis canadensis* L. and its major alkaloids on guinea-pig isolated trachea. Pharmacol Toxicol 2000;87:218-22. http://dx.doi.org/10.1034/j.1600-0773.2000.d01-77.x

Abidi P, Chen W, Kraemer FB, Li H, Liu J. The medicinal plant goldenseal is a natural LDL-lowering agent with multiple bioactive compounds and new action mechanisms. J Lipid Res 2006;47:2134-47. http://dx.doi.org/10.1194/jlr.M600195-JLR200

Baldazzi C, Leone MG, Casoni ML and Tita B. Effect of the major alkaloid of *Hy-drastis canadensis* L., berberine, on rat prostate strips. Phytother Res 1998;12:589-91. http://dx.doi.org/10.1002/(SICI)1099-1573(199812)12:8<589::AID-PTR347>3.0.CO;2-I

Barnes J, Anderson LA, Phillipson JD. Golden Seal. In: Herbal Medicines 3rd ed. London, The Pharmaceutical Press, 2007:337-9.

Bhowmick SK, Hundley OT, Rettig KR. Severe hypernatremia and hyperosmolality exacerbated by an herbal preparation in a patient with ketoacidosis. Clinical Pediatrics 2007;46:831-4. http://dx.doi.org/10.1177/0009922807303042

Blaschek W, Ebel S, Hackenthal E, Holzgrabe U, Keller K, Reichling J, Schulz V, editors. Hydrastis. In: Hagers Enzyklopädie der Arzneistoffe und Drogen 6th ed., Band8, WVG Stuttgart 2007:615-24.

Bolle P, Cometa MF, Palmery M and Tucci P. Response of rabbit detrusor muscle to total extract and major alkaloids of *Hydrastis canadensis*. Phytother Res 1998;12:S86-8. http://dx.doi.org/10.1002/(SICI)1099-

1573(1998)12: 1+<S86::AID-PTR259>3.0.CO;2-C

Bradley P. Golden seal root. In: British Herbal Compendium - A handbook of scientific information on widely used plant drugs, Volume 1. Bournemouth: British Herbal Medicine Association, 1992:119-20.

Budzinski JW, Foster BC, Trudeau VL, Drouin CE, Bafi-Yeboa N, Arnason JT. The interaction of selected phytochemicals, HIV drugs, and commercial-source herbal teas and capsules with human cytochrome P450 3A4 and P-glycoprotein. Pharm Biol 2008;46:53-65. http://dx.doi.org/10.1080/13880200701729844

Budzinski JW, Foster BC, Vandenhoek S and Arnason JT. An *in vitro* evaluation of human cytochrome P450 3A4 inhibition by selected commercial herbal extracts and tinctures. Phytomedicine 2000;7:273-82. http://dx.doi.org/10.1016/S0944-7113(00)80044-6

Chatterjee P and Franklin MR. Human cytochrome P450 and metabolic-intermediate complex formation by goldenseal extract and its methylenedioxyphenyl components. Drug Metabolism and Disposition 2003;31:1391-7. http://dx.doi.org/10.1124/dmd.31.11.1391

Cecil CE, Davis JM, Cech NB, Laster SM. Inhibition of H1N1 influenza A virus growth and induction of inflammatory mediators by the isoquinoline alkaloid ber-berine and extracts of goldenseal (*Hydrastis canadensis*). Int Immunopharmacol 2011;11:1706-14. http://dx.doi.org/10.1016/j.intimp.2011.06.002

Chen CM, Chang HC. Determination of berberine in plasma, urine and bile by HPLC. J Chromatogr B 1995;665:117-23. http://dx.doi.org/10.1016/0378-4347(94)00517-9

Clement-Kruzel S, Hwang SA, Kruzel MC, Dasgupta A and Actor JK. Immune modulation of macrophage pro-inflammatory response by goldenseal and *Astragalus* extracts. J Med Food 2008;11:493-8. http://dx.doi.org/10.1089/jmf.2008.0044

Cometa MF, Abdel-Haq H and Palmery M. Spasmolytic activities of *Hydrastis canadensis* L. on rat uterus and guinea-pig trachea. Phytother Res 1998;12:S83-5. http://dx.doi.org/10.1002/(SICI)1099-1573(1998)12:1+<S83::AID-PTR258>3.0.CO;2-O

Cwikla C, Schmidt K, mattias A, Bone KM, Lehman R, Tiralongo E. Investigations into the antibacterial activities of phytotherapeutics against *Helicobacter pylori* and *Campylobacter jejuni*. Phytother Res 2010;24:649-56. http://dx.doi.org/10.1002/ptr.2933

De Smet PAGM. Berberine. In: Adverse effects of herbal drugs, Volume 1. Springer-Verlag, Berlin 1992:97-104.

Dunnick JK, Singh B, Nyska A, Peckham J, Kissling GE, Sanders JM. Investigating the potential for toxicity from long-term use of the herbal products, goldenseal and milk thistle. Toxicol Pathol 2011;39:398-409. http://dx.doi.org/10.1177/0192623310394211

Etheridge AS, Black SR, Patel PR, So J, Mathews JM. An *in vitro* evaluation of cytochrome P450 inhibition and P-glycoprotein interaction with goldenseal, *Ginkgo biloba*, grape seed, milk thistle, and ginseng extracts and their constituents. Planta Med 2007;73:731-41. http://dx.doi.org/10.1055/s-2007-981550

Galeffi C, Cometa MF, Tomassini L and Nicoletti M. Canadinic acid: a new alkaloid from *Hydrastis canadensis*. Planta Medica 1997;63:194. http://dx.doi.org/10.1055/s-2006-957649

Gentry EJ, Jampani HB, Keshvarz-Shokri A, Morton MD, Vander Velde D, Telikepalli H and Mitscher LA. Antitubercular natural products: berberine from the roots of commercial *Hydrastis canadensis* powder. Isolation of inactive 8-oxotetrahydrothalifendine, canadine, β-hydrastine, and two new quinic acid esters, hycandic acid esters-1 and-2. J Nat Prod 1998;61:1187-93. http://dx.doi.org/10.1021/np9701889

Goldenseal rhizome – Hydrastis rhizoma. European Pharmacopoeia, Council of Europe.

Gurley BJ, Gardner SF, Hubbard MA, Williams DK, Brooks Gentry W, Khan IA and Shah A. In vivo effect of goldenseal, kava kava, black cohosh, and valerian on human cytochrome P450 1A2, 2D6, 2E1 and 3A4/5. Clin Pharm Ther 2005;77(5):415-26. http://dx.doi.org/10.1016/j.clpt.2005.01.009

Gurley BJ, Swain A, Barone GW, Williams DK, Breen P, Yates CR, Stuart LB, Hubbard MA, Tong Y and Cheboyina S. Effect of goldenseal and kava kava supplementation on digoxin pharmacokinetics in humans. Drug Metabolism and Disposition 2007;35:240-5. http://dx.doi.org/10.1124/dmd.106.012708

Gurley BJ, Swain A, Hubbard MA, Hartsfield F, Thaden J, Williams DK, Gentry WB, Tong Y. Supplementation with goldenseal (*Hydrastis canadensis*), but not kava kava (*Piper methysticum*), inhibits human CYP3A activity *in vivo*. Clin Pharmacol Ther 2008b;83:61-69. http://dx.doi.org/10.1038/sj.clpt.6100222

Gurley BJ, Swain A, Hubbard MA, Hartsfield F, Williams DK, Barone G et al. Clinical assessment of CYP2D6-mediated herb-drug interactions in humans: effects of milk thistle, black cohosh, goldenseal, kava kava, St John's wort, and *Echinacea*. Mol Nutr Food Res 2008a;52:755-63. http://dx.doi.org/10.1002/mnfr.200600300

Hwang BY, Roberts SK, Chadwick LR, Wu CD and Kinghorn AD. Antimicrobial constituents from goldenseal against selected oral pathogens. Planta Medica 2003;69:623-7. http://dx.doi.org/10.1055/s-2003-41115

Jahnke GD, Price CJ, Marr MC, Myers CB and George JD. Developmental toxicity evaluation of berberine in rats and mice. Birth Defect Res (part B) 2006;77:195-206. http://dx.doi.org/10.1002/bdrb.20075

Karmakar SR, Biswas SJ, Khuda-Bukhsh AR. Anti-carcinogenic potentials of a plant extract (*Hydrastis canadensis*): I. Evidence from *in vivo* studies in mice (*Mus musculus*). Asian Pac J Cancer Prev 2010;11:545-51.

Mahady GB, Pendland SL, Stoia A and Chadwick LR. *In vitro* susceptibility of *Helicobacter pylori* to isoquinoline alkaloids from *Sanguinaria canadensis* and *Hydrastis canadensis*. Phytother Res 2003;17:217-21. http://dx.doi.org/10.1002/ptr.1108

McNamara CE, Perry NB, Follett JM, Parmenter GA and Douglas JA. A new glucosyl feruloyl quinic acid as a potential marker for roots and rhizomes of goldenseal, *Hydrastis canadensis*. J Nat Prod 2004;67:1818-22. http://dx.doi.org/10.1021/np049868j

Mills S, Bone K. Berberis bark and Hydrastis root. In: Principles and practice of phytotherapy. 2nd Edition Edinburgh, 2013:404-424.

Palmery M, Cometa MF and Leone MG. Further studies of the adrenolytic activity of the major alkaloids from *Hydrastis canadensis* L. on isolated rabbit aorta. Phytother Res 1996;10:S47-9.

Pan JF, Zhu DY, Zhang H, Zeng JF, Jiang SH, Ren JY. Identification of three sulphate-conjugated metabolites of berberine chloride in healthy volunteers' urine after oral administration. Acta Pharmacol Sin 2002;23:77-82.

Pereira da Silva A, Rocha R, Silva CML, Mira L, Duarte MF and Florêncio MH. Antioxidants in medicinal plant extracts. A research study of the antioxidant capacity of *Crataegus*, *Hamamelis* and *Hydrastis*. Phytother Res 2000;14:612-6. http://dx.doi.org/10.1002/1099-1573(200012)14:8<612::AID-PTR677 >3.0.CO;2-T

Qiu F, Zhu Z, Kang N, Piao S, Qin G, Yao X. Isolation and identification of urinary metabolites of berberine in rats and humans. Drug Metab Dispos 2008;36:2159-65. http://dx.doi.org/10.1124/dmd.108.021659

Raner GM, Cornelious S, Moulick K, Wang Y, Mortenson A, Cech NB. Effects of herbal products and their constituents on human cytochrome $P450_{2E1}$ activity. Food Chem Toxicol 2007;45:2359-65. http://dx.doi.org/10.1016/j.fct.2007.06.012

Rehman J, Dillow JM, Carter SM, Chou J, Le B and Maisel AS. Increased production of antigen-specific immunoglobulins G and M following *in vivo* treatment with medicinal plants *Echinacea angustifolia* and *Hydrastis canadensis*. Immunology Letters 1999;68:391-5. http://dx.doi.org/10.1016/S0165-2478(99)00085-1

Sandhu RS, Prescilla RP, Simonelli TM and Edwards DJ. Influence of goldenseal root on the pharmacokinetics of indinavir. J Clin Pharmacol 2003;43:1283-8. http://dx.doi.org/10.1177/0091270003258660

Scazzocchio F, Cometa MF, Tomassini L and Palmery M. Antibacterial activity of *Hydrastis canadensis* extract and its major isolated alkaloids. Planta Medica 2001;67:561-4. http://dx.doi.org/10.1055/s-2001-16493

Simeon S, Rios JL and Villar A. Pharmacological activities of protoberberine alkaloids. Plantes Med Phytother 1989;23:202-50.

Swanston-Flatt SK, Day C, Bailey CF and Flatt PR. Evaluation of traditional plant treatments for diabetes: studies in streptozotocin diabetic mice. Acta Diabetol Lat 1989;26:51-5. http://dx.doi.org/10.1007/BF02581196

Tsai PL, Tsai TH. Hepatobiliary excretion of berberine. Drug Metab Dispos 2004;32:405-12. http://dx.doi.org/10.1124/dmd.32.4.405

Upton R. Goldenseal root – *Hydrastis canadensis*. American Herbal Pharmacopoeia 2001.

Villinski JR, Dumas ER, Chai HB, Pezzuto JM, Angerhofer CK, Gafner S. Antibacterial activity and alkaloid content of *Berberis thunbergii*, *Berberis vulgaris* and *Hydrastis canadensis*. Pharm Biol 2003;41:551-7. http://dx.doi.org/10.1080/13880200390500768

Yao M, Ritchie HE and Brown-Woodman PD. A reproductive screening test of goldenseal. Birth Defects Research (Part B) 2005;74:399-404. http://dx.doi.org/10.1002/bdrb.20055

Zeng X and Zeng X. Relationship between the clinical effects of berberine on severe congestive heart failure and its concentration in plasma by HPLC. Biomed Chromatogr 1999;13:442-4. http://dx.doi.org/10.1002/(SICI)1099-0801(199911)13:7<442::AID-BMC908>3.0.CO;2-A

Zuo F, Nakamura N, Akao T, Hattori M. Pharmacokinetics of berberine and its main metabolites in conventional and pseudo germ-free rats determined by liquid chromatography / ion trap mass spectrometry. Drug Metab Dispos 2006;34:2064-72. http://dx.doi.org/10.1124/dmd.106.011361

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	Supplement 2009
ALOE CAPENSIS	Cape Aloes	Second Edition, 2003
ALTHAEAE RADIX	Marshmallow Root	Second Edition, 2003
ANGELICAE RADIX	Angelica Root	Supplement 2009
ANISI FRUCTUS	Aniseed	Second Edition, 2003
ARNICAE FLOS	Arnica Flower	Second Edition, 2003
BALLOTAE NIGRAE HERBA	Black Horehound	Supplement 2009
BETULAE FOLIUM	Birch Leaf	Second Edition, 2003
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	Second Edition, 2003
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
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	Second Edition, 2003
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	Supplement 2009
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	Second Edition, 2003
ORTHOSIPHONIS FOLIUM	Java Tea	Online Series, 2014
PASSIFLORAE HERBA	Passion Flower	Second Edition, 2003
PAULLINIAE SEMEN	Guarana Seed	Supplement 2009
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	Second Edition, 2003
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	Second Edition, 2003
UVAE URSI FOLIUM	Bearberry Leaf	Online Series, 2012
VACCINII MACROCARPI FRUCTUS	Cranberry	Supplement 2009
VALERIANAE RADIX	Valerian Root	Supplement 2009
VIOLAE HERBA CUM FLORE	Wild Pansy	Supplement 2009
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 978-1-901964-07-3