E/S/C/O/P Monographs

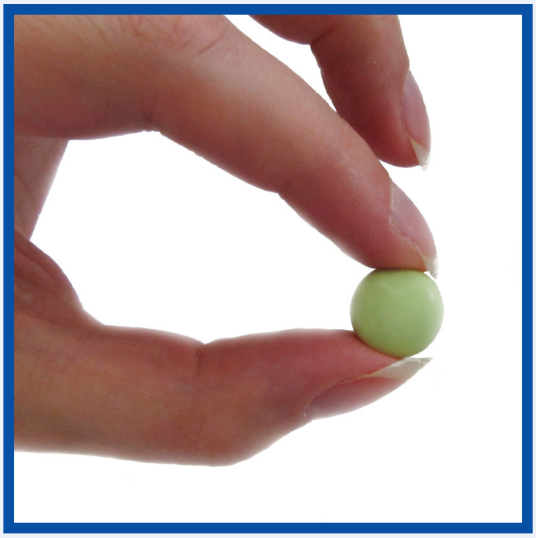
Online Series

The Scientific Foundation for Herbal Medicinal Products

Fumariae herba

Fumitory

2018



E/S/C/O/P

European Scientific Cooperative On Phytotherapy

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E/S/C/O/P
MONOGRAPHS

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

FUMARIAE HERBA
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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 978-1-901964-58-5

Fumariae herba - Fumitory

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

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Edited by Simon Mills and Roberta Hutchins
Cover photographs by H. Zell [CC BY-SA 3.0] via Wikimedia Commons (*Fumaria officinalis*)
and Martin Willoughby
Cover and text design by Martin Willoughby
Typeset in Optima by Roberta Hutchins

Plant illustrated on the cover: *Fumaria officinalis*

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.

Dr. Tankred Wegener
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
CCl_4	carbon tetrachloride
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
DMSO	dimethyl sulfoxide
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
Pgp	P-glycoprotein
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
TC	total cholesterol
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

FUMARIAE HERBA

2018

Fumitory

DEFINITION

Fumitory consists of the whole or fragmented, dried aerial parts of *Fumaria officinalis* L. harvested in full bloom. It contains not less than 0.4 per cent of total alkaloids, expressed as protopine ($C_{20}H_{19}NO_5$; M_r 353.4) and calculated with reference to the dried drug.

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

CONSTITUENTS

The main characteristic constituents are isoquinoline alkaloids (0.3-1.3%) of the protopine, spirobenzylisoquinoline, protoberberine, benzophenanthridine and indenbenzazepine types, the principal ones being protopine and fumarophycine together with sinactine, sanguinarine, fumarofine and others. Over 20 alkaloids have been identified [Manske 1938; MacLean 1969; Hermansson 1973; Murav'eva 1975; Forgacs 1982, 1986; Mardirossian 1983; Sener 1985; Sousek 1999; Suau 2002; Sturm 2006; Paltinean 2016; Gorecki 2010; Blaschek 2016].

Other constituents include flavonol glycosides such as quercitrin, isoquercitrin, rutin, quercetin 3,7-diglucoside, quercetin 3-arabinoglucoside and their aglycones [Massa 1971; Torck 1971; Păltinean 2017], aliphatic acids (fumaric and malic acids), several hydroxycinnamoylmalic acids (a total of 1.3%), and hydroxycinnamic acids including caffeic, coumaric, sinapic and ferulic acids [Boegge 1995; Sousek 1999, Ivanov 2014].

CLINICAL PARTICULARS

Therapeutic indications
Digestive complaints (e.g. stomach ache, nausea, vomiting, feeling of fullness, flatulence) due to hepatobiliary disturbance [Fablet 1963; Colson 1967; Roux 1967; Salembier 1967; Warembourg 1967; Dornier 1968; Devin 1969; Heully 1969; Fiegel 1971; Roux 1977; Zacharewicz 1979; Bradley 1992; Gorecki 2010; Blaschek 2016].

Posology and method of administration

Dosage

Adult daily dose: 4-6 g of the drug as an aqueous dry extract [Fablet 1963; Colson 1967; Roux 1967, 1977; Salembier 1967; Warembourg 1967; Dornier 1968; Devin 1969; Heully 1969; Fiegel 1971; Zacharewicz 1979] or infusion [Bradley 1992; Gorecki 2010; Barnes 2007; Blaschek 2016]; other equivalent preparations, e.g. liquid extract (1:1, ethanol 25%V/V) and tincture (1:5, ethanol 45% V/V) [Bradley 1992; Barnes 2007].

Method of administration
For oral administration.

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

Contra-indications
Biliary obstruction.

Special warnings and special precautions for use
In cases of gallstones, fumitory should not be used without medical advice.

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 and lactation without medical advice.

Effects on ability to drive and use machines
None known.

Undesirable effects
None known.

Overdose
No toxic effects reported.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

In vitro experiments

Effects on smooth muscle
An alkaloid-rich dry extract (not further specified) had a biphasic effect on isolated muscle, increasing resting tone at low concentrations (10^{-5} to 5×10^{-5} g/mL), and reducing the amplitude of spontaneous contractions at concentrations above 5×10^{-4} g/mL in isolated rabbit jejunum and 10^{-3} g/mL in isolated rat duodenum. The extract had a concentration-dependent smooth muscle-relaxing effect on barium chloride-induced contractions of isolated rat duodenum (EC_{50}: 10^{-4} g/mL), with approximately 5% of the effect of papaverine. At 10^{-5} to 10^{-4} g/mL the extract induced muscle contraction in isolated rat uterus, the effect being less pronounced at higher concentrations. In isolated dog saphenous vein it antagonized noradrenaline-induced contractions (EC_{50}: 8.5×10^{-6} g/mL), as did papaverine and protopine (EC_{50}: 2.9×10^{-5} and 2.3×10^{-5} g/mL respectively). In contrast, the extract increased spontaneous venous contraction within a concentration range of 10^{-6} to 10^{-4} g/mL [Reynier 1977].

An aqueous dry extract (not further specified) exhibited cholecystokinetic activity on isolated bile duct and Oddi's sphincter from pigs, as shown by contraction of the bile duct and relaxation of its Oddi's sphincter from a concentration of 10^{-4} g/mL. The extract at 5×10^{-4} g/mL inhibited morphine-induced contraction of Oddi's sphincter. In contrast, pure protopine at 10^{-5} to 10^{-7} g/mL had a strong contractile effect on Oddi's sphincter [Kimura 1972].

Neuroprotective effects
An alkaloid–rich extract (ethyl acetate; not further specified) was tested for the inhibition of acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE). The extract exhibited inhibitory activities against both enzymes with IC_{50} values of 39.23 ± 1.96 µg/mL and 40.32 ± 1.08 µg/mL respectively. The isolated alkaloids parfumidine and sinactine did not show any inhibitory activity on these enzymes but inhibited propyl oligopeptidase activity with IC_{50} values of 99 ± 5 µM and 53 ± 2 µM respectively [Chlebek 2016].

In another study, an alkaloid-rich extract (ethanol; not further specified) exhibited AChE inhibition with an IC_{50} value of 0.26 ± 0.01 mg/mL as compared to galanthamin with an IC_{50} value of 0.31 ± 0.05 mg/mL [Vrancheva 2016].

Other effects
Ethanolic extracts (not further specified) showed radical-scavenging activities in various assays such as DPPH and ABTS, as well as antioxidant capacity in CUPRAC, FRAP, lipid peroxidation and ferric reduction [Ivanov 2014; Khamtache-Abderrahim 2016].

An aqueous extract (not further specified) was tested in an *Agrobacterium tumefaciens*–induced potato disk tumour assay. The activity was similar to the positive control camptothecin (both 100%), compared to water as the negative control [Pehlivan Karakas 2012].

Protopine and allocryptopine induced a concentration-dependent increase in CYP1A1 mRNA in HepG2 cells after 24 h treatment. Both alkaloids induced a concentration-dependent increase of CYP1A1 and CYP1A2 mRNA in human hepatocytes, whereas the activation of the aryl hydrocarbon receptor in the induction of CYP1A mRNA levels by either protopine or allocryptopine was mild or negligible. Neither protopine nor allocryptopine caused an increase in CYP1A protein and activity levels in both cell types [Vrba 2011].

In vivo experiments

Hepatobiliary effects
No significant variations in bile flow were observed after intravenous administration of an aqueous dry extract (not further specified) to rats at 25, 50 and 100 mg/kg in the bile fistula model [Boucard 1966a, 1966b]. When the extract (50 mg/kg) was administered intravenously 30 minutes before or at the same time as sodium dehydrocholate (25 mg/kg), increases in bile flow 1 hour later were 45% and 28% respectively, compared to 66% when the choleretic agent was given alone [Boucard 1966b]. Under similar conditions, the increase in bile flow of 77% after sodium dehydrocholate (25 mg/kg) was reduced by simultaneous administration of the fumitory dry extract, to 55% (25 mg/kg of sodium dehydrocholate + 25 mg/kg of extract), 43% (25 mg/kg of sodium dehydrocholate + 50 mg/kg of extract) and 35% (25 mg/kg of sodium dehydrocholate + 100 mg/kg of extract) [Boucard 1966a]. A reduction in bile secretion induced by oral administration of 10 mg/kg of sodium azide was almost completely antagonized by simultaneous oral administration of the extract at 100 mg/kg [Boucard 1966b].

The same extract was administered intravenously to bile duct-cannulated dogs at 20 or 50 mg/kg. In dogs with low biliary output (0.09-0.20 mL/hour/kg) increases in bile flow of 29-218% were observed, while those with a high biliary output (0.63-1.38 mL/hour/kg) were characterized by reductions of 27-41%. Similar effects were observed with the extract in the presence of the choleretic agent sodium dehydrocholate, administered intravenously [Giroux 1966].

The choleretic activity of an aqueous dry extract (not further specified) intravenously administered at 40 mg/kg was confirmed in both normal rats and sodium azide-induced hypocholeretic rats in the bile fistula model. On the other hand, increased bile secretion induced by sodium hydrocholate was not reduced by intravenous administration of the extract at 40 mg/kg [Kimura 1972].

Intraduodenal administration of an alkaloid-rich dry extract (not further specified) to bile duct-cannulated rats at 200 mg/kg produced, not only an increase of 23% in bile flow, but also increases in biliary-excreted bilirubin and cholesterol of 33% and 20% respectively, in comparison to control. Under the same conditions protopine at 6 mg/kg produced comparable effects, while sodium dehydrocholate at 25 mg/kg had an effect only on the excreted volume [Reynier 1977].

The effect of an aqueous dry extract (not further specified) on

experimental cholelithiasis, induced by a diet supplemented with cholesterol-cholic acid, was evaluated in mice at two dosages, 0.2% and 0.4%, as an addition to their lithogenic diet. After 6 weeks of treatment the mean numbers of gallstones per mouse were significantly reduced ($p<0.05$), from 1.61 in the control group to 1.00 in the 0.2% group and 0.64 in the 0.4% group [Lagrange 1973].

Hepatoprotective effects
An aqueous dry extract (not further specified) was administered intravenously at 50 and 100 mg/kg b.w. to normal rats and to rats intoxicated with a single i.p. dose of carbon tetrachloride (CCl_4). Compared to controls 48 hours after administration of CCl_4, alkaline phosphatase activity was unchanged in excreted bile and serum, while in the liver it was significantly higher ($p<0.01$) in the group of CCl_4-intoxicated rats that received 50 mg/kg of extract and in each of the groups treated with 100 mg/kg of extract, indicating stimulation of hepatocytes [Guesnier 1974].

Cardiac effects of fumitory alkaloids
An extract comprising the total alkaloids (TAF, extracted with sulphuric acid and purified by ion exchange), administered intravenously to mice at 1-1.5 mg/kg, slowed the heart rate by 14-22% for 90 minutes. Cardiac fibrillation in mice induced by a normally lethal intravenous dose of calcium chloride was inhibited by TAF at 5 mg/kg i.v., enabling 50% of the animals to survive and delaying deaths of the other animals longer than in the control group ($p<0.001$); protopine at the same dose level did not influence survival, but 15% of animals survived after cryptopine at 10 mg/kg. TAF administered intravenously to rabbits prior to an arrhythmogenic dose of adrenaline prevented arrhythmia in 50% of the animals at 0.5 mg/kg and 90% at 1 mg/kg. Under the same conditions protopine was ineffective at 0.5 mg/kg but prevented arrhythmia in 40% of animals at 1 mg/kg, while cryptopine was ineffective at both dose levels [Gorbunov 1977].

A study in dogs demonstrated that TAF at 1-2 mg/kg i.v. prevented or substantially reduced ischaemic shifts caused by experimental occlusion of the coronary artery, while 5.5 mg/kg prevented arrhythmia induced by ligation of the intraventricular branch of the left coronary artery [Gorbunov 1980].

Diuretic activities
An ethanolic extract (not further specified) produced a significant ($p<0.05$) increase in urine volume of rats, 24 h after oral administration of a single dose of 250 mg/kg b.w. The extract also significantly ($p<0.05$) increased the urinary excretion of sodium and potassium [Paltinean 2017].

Neuropharmacological activities
An ethanolic extract (not further specified) administered i.p. to mice at doses of 200 and 500 mg/kg b.w. significantly ($p<0.01$) decreased the number of movements in the actophotometer assay, and also significantly ($p<0.01$) increased the time spent in the open arm and the number of entrances into the open arms in the elevated plus-maze test [Sharma 2014].

Pharmacological studies in humans

Amphocholeretic effect
In a study carried out 7-10 days after choledochostomy (establishment of external drainage from the bile duct) in 25 patients, bile flow was measured before and after a single oral dose of 1500 mg of an aqueous dry extract (not further specified). The extract had an amphocholeretic effect, promoting bile secretion if it was below the normal threshold and inhibiting bile secretion if it was excessive [Salembier 1967]. In a subsequent study of this type, daily oral administration of 4 × 250 mg of the same extract to 20 post-choledochostomy patients for an average of 12 days produced similar effects on bile secretion, increasing weak bile flow and reducing elevated bile flow; antispasmodic and biliary analgesic effects were also observed [Devin 1969].

In an open study, the effect on choleresis of a single dose of an aqueous dry extract (not further specified) was investigated in 20 healthy volunteers. They received either 500 mg of the extract in physiological serum (12 subjects) or placebo (8 subjects) through an intraduodenal probe. Monitoring of bile secretion for 30 minutes confirmed that the extract facilitated normalization of bile flow by increasing or decreasing the flow in relation to the baseline secretion [Heully 1969].

Clinical studies
In a randomized, double-blind, cross-over study 30 patients with various biliary disorders including dyskinesia, cholecystitis and post-cholecystectomy syndrome, which had previously been treated for 2 years without success, were treated with 6 × 250 mg of an aqueous dry extract (not further specified) or placebo daily for 14 days and consecutively vice versa in a second 14-day phase. The group taking the extract during the first phase experienced a significant reduction ($p<0.01$) in the intensity of symptoms (right upper abdominal pains, postprandial pains, flatulence, nausea, vomiting, stomach rumblings, impaired sleep and headaches) and this lasted throughout the subsequent placebo phase. In the other group the intensity of symptoms increased during the second week of placebo treatment and then declined significantly ($p<0.01$) during treatment with the extract in the second phase [Zacharewicz 1979].

In an open study 45 patients, previously treated for 2 years without success for dyskinesia of the biliary tract, post-cholecystectomy syndrome, chronic cholecystitis or cholangitis, received 4 × 250 mg of an aqueous dry extract (not further specified) daily for 16 days and were given a follow-up examination 14 days later. The overall improvement in symptoms (right upper abdominal pains, postprandial pains, flatulence, nausea, vomiting, stomach rumblings, impaired sleep and headaches) was very good in 32 (71%) and moderate in 7 patients, while no effect was apparent in the remaining 6 [Zacharewicz 1979].

Daily treatment of 105 patients with biliary disorders of various origin (dyskinesia, hepatomegaly, gallstone complaints and post-cholecystectomy symptoms) with 6 × 250 mg of an aqueous dry extract (not further specified) for 2 weeks to 6 months led to substantial improvements in, or complete absence of, symptoms (right upper abdominal pains, nausea, retching, occasional vomiting and poor tolerance of food) in more than 80% of patients [Fiegel 1971].

The efficacy of an aqueous dry extract (not further specified) was evaluated in five observational studies involving a total of 286 patients, treated in most cases with 750-1500 mg/day for 1-3 months. The patients could be classified into six groups: biliary dyskinesia (n=90), biliary lithiasis (n=23), migraine (frequently associated with concomitant nausea or vomiting; n=106), hepatobiliary insufficiency (n=29), post-cholecystectomy symptoms (n=29) and jaundice following viral hepatitis (n=9). Global efficacy assessed by the physicians was excellent or good in 75%, 100%, 83%, 75%, 72% and 66% of patients in the respective groups [Fablet 1963; Colson 1967; Roux 1967; Warembourg 1967; Dornier 1968].

Thirty-one patients suffering from diarrhoea or chronic constipation of biliary origin were given 1000 or 1500 mg of an aqueous dry extract (not further specified) respectively.

Improvement was excellent or good in 71% of cases after treatment periods of at least 15 days [Roux 1977].

Pharmacokinetic properties
No data available.

Preclinical safety data

Single dose toxicity
The acute intraperitoneal LD_{50} of an aqueous dry extract (not further specified) was 1.91 g/kg b.w. in mice and 1.88 g/kg in rats [Cahen 1964].

Repeated dose toxicity in rats
No delayed growth, changes in vital organs or haematological abnormalities were evident in rats following 3 months of oral treatment with an aqueous dry extract (not further specified) at 2.4 g/kg/day [Cahen 1964].

Inhibition of hERG Channel
An extract (dichlormethane/ethanol; not further specified) did not show inhibitory activity in a hERG (human Ether-a-go-go Related Gene) screening based on semi-automated voltage-clamp system using *Xenopus* oocytes [Kratz 2016].

Clinical safety data
Over 500 individuals have participated in open and controlled studies with fumitory aqueous dry extracts (not further specified), taking 750-1500 mg/day for up to 6 months. The tolerability of the treatments was very good [Salembier 1967; Devin 1969; Heully 1969; Zacharewicz 1979; Fiegel 1971; Fablet 1963; Colson 1967; Dornier 1968; Roux 1967, 1977; Warembourg 1967]. Minor adverse events occurred in a very few cases involving gastrointestinal discomfort and/or an allergic reaction with pruritis [Fablet 1963; Roux 1967].

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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	Online Series, 2018
ANGELICAE RADIX	Angelica Root	Supplement 2009
ANISI FRUCTUS	Aniseed	Online Series, 2014
ARNICAE FLOS	Arnica Flower	Second Edition, 2003
ARCTII RADIX	Burdock Root	Online Series, 2016
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	Online Series, 2018
ECHINACEAE PURPUREAE HERBA	Purple Coneflower Herb	Supplement 2009
ECHINACEAE PURPUREAE RADIX	Purple Coneflower Root	Supplement 2009
ELEUTHEROCOCCI RADIX	Eleutherococcus	Supplement 2009
EQUISETI HERBA	Equisetum stem	Online Series, 2018
EUCALYPTI AETHEROLEUM	Eucalyptus Oil	Second Edition, 2003
FILIPENDULAE ULMARIAE HERBA	Meadowsweet	Online Series, 2015
FOENICULI FRUCTUS	Fennel	Second Edition, 2003
FRANGULAE CORTEX	Frangula Bark	Online Series, 2017
FUMARIAE HERBA	Fumitory	Online Series, 2018
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	Online Series, 2016
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	Online Series, 2018
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	Online Series, 2017
LIQUIRITIAE RADIX	Liquorice Root	Second Edition, 2003
LUPULI FLOS	Hop Strobile	Second Edition, 2003
MALVAE FLOS	Mallow Flower	Online Series, 2016
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
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PASSIFLORAE HERBA	Passion Flower	Second Edition, 2003
PAULLINIAE SEMEN	Guarana Seed	Supplement 2009
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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	Online Series, 2016
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	Online Series, 2017
RATANHIAE RADIX	Rhatany Root	Online Series, 2017
RHAMNI PURSHIANI CORTEX	Cascara	Online Series, 2015
RHEI RADIX	Rhubarb	Online Series, 2018
RIBIS NIGRI FOLIUM	Blackcurrant Leaf	Online Series, 2017
ROSAE PSEUDO-FRUCTUS	Dog Rose Hip	Supplement 2009
ROSMARINI FOLIUM	Rosemary Leaf	Second Edition, 2003
RUSCI RHIZOMA	Butcher's Broom	Online Series, 2017
SALICIS CORTEX	Willow Bark	Online Series, 2017
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	Online Series, 2018
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
UNCARIAE TOMENTOSAE CORTEX	Cat's Claw Bark	Online Series, 2018
URTICAE FOLIUM/HERBA	Nettle Leaf/Herb	Online Series, 2018
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
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