E/S/C/O/P Monographs

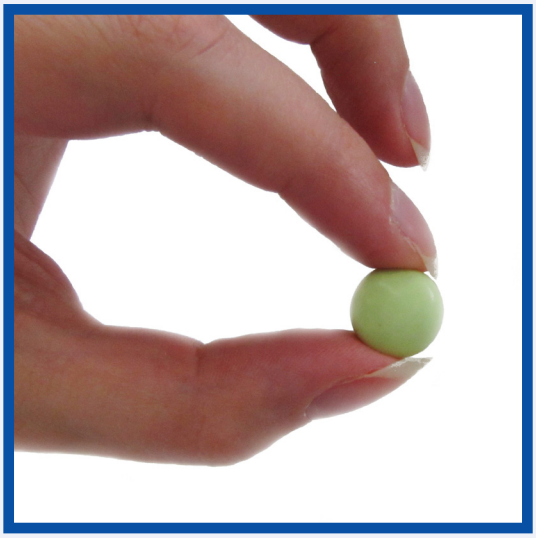
Online Series

The Scientific Foundation for Herbal Medicinal Products

Anisi fructus

Aniseed

2014



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

ANISI FRUCTUS
Aniseed

2014

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 978-1-901964-19-6

Anisi fructus - Aniseed

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 Charbelgereige [Public domain],
via Wikimedia Commons(*Pimpinella anisum*) and Martin Willoughby
Cover and text design by Martin Willoughby
Typeset in Optima by Roberta Hutchins

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

ANISI FRUCTUS

2014

Aniseed

DEFINITION

Aniseed consists of the whole dry cremocarp of *Pimpinella anisum* L. It contains not less than 20 ml/kg of essential oil.

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

Note: In The European Pharmacopoeia (Eds 1,2 and 3), the monograph for Anise Oil permits oils obtained by steam distillation from the fruits of *Pimpinella anisum* L. (aniseed) or *Illicium verum* L. (star anise). *Trans*-anethole is the predominant component of both oils, but the other components are not identical. The term 'anise oil' is therefore avoided in the following text and the terms 'essential oil' or 'oil' refer specifically to the essential oil from aniseed.

CONSTITUENTS

The essential oil (2-6%) contains predominantly *trans*-anethole (80-95%) with smaller amounts of estragole, *cis*-anethole, anisaldehyde and pseudoisoeugenyl-2-methylbutyrate [Blaschek 2007; Kubeczka 1976; Kubeczka 1978; Schultze 1987]; sesquiterpene and monoterpene hydrocarbons are also present [Kubeczka 1976; Scultze1987; Orav 2008].

Other constituents include flavonol glycosides [El-Moghazi 1979; Kunzemann 1977], phenolic acids [Schulz 1980; Baerheim-Svendsen 1951; El-Wakeil 1986], phenolic and hydroxyalkylglucosides [Dirks 1984; Fujimatu 2003] furanocoumarins [Ceska 1987; Kartnig 1969], hydroxycoumarins [Blaschek 2007] and fatty oil [Kartnig 1969].

CLINICAL PARTICULARS

Therapeutic indications
Dyspeptic complaints and mild spasmodic gastro-intestinal complaints, such as bloating, flatulence [Blaschek 2007; Czygan 2002; Weiss 1997; Pimpinella 1983; Sweetman 2011; Czygan 1992; Hänsel 1999].

In mild inflammation of the upper respiratory tract, as expectorant [Blaschek 2007; Czygan 2002; Weiss 1997; Pimpinella 1983; Sweetman 2011; Czygan 1992; Hänsel 1999].

In these indications the effects are plausible on the basis of human experience and longstanding use.

Posology and method of administration

Dosage

Adult average daily dose: 3 g of crushed fruits as an infusion or similar preparation [Czygan 2002; Pimpinella 1983].

Children, average daily dose: *0-1 year of age*, 0.5 g of crushed fruits as an infusion; *1-4 years of age*, 1 g; *4-10 years of age*, 2 g; *10-16 years of age*, the adult dose [Dorsch 2002].

Method of administration
For oral administration.

Duration of use
No restriction.

If symptoms persist, consult your doctor.

Contra-indications
Persons with known sensitivity to anethole should avoid aniseed.

E/S/C/O/P MONOGRAPHS

Special warnings and special precautions for use
Persons with known sensitivity to anethole should avoid aniseed [Newall 2002; Andersen 1978; Franks 1998]. The sensitizing potential of aniseed is considered low [Hausen 1988].

Interaction with other medicaments and other forms of interaction
None known. Experimental data on weak enzyme induction in rodents cannot be directly extrapolated to man [Marcus 1982].

Pregnancy and lactation
Aniseed may be used during pregnancy and lactation at the recommended dosage, as aqueous infusions only.

Preparations containing the essential oil [Tisserand 1995] or alcoholic extracts should not be used during pregnancy and lactation. Mild oestrogenic activity and antifertility effects of the essential oil and anethole (the major constituent of the essential oil) have been demonstrated *in vitro* and in rats [Dhar 1995].

Effects on ability to drive and use machines
None known.

Undesirable effects
Rare cases of contact dermatitis caused by anethole-containing toothpastes and cosmetic creams [Barnes 2007; Andersen 1978], occupational rhinoconjunctivitis and food allergy caused by working in a bakery making biscuits with aniseed [Garcia-Gonzales 2002] and repeated episodes of tongue angioedema in a patient after drinking aniseed liqueur [Garcia 2007].

Overdose
No toxic effects reported.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties
The medicinal use of aniseed is largely due to secretolytic, antispasmodic and secretomotor effects of its essential oil [Blaschek 2007].

In vitro experiments

Antimicrobial effects
An acetone extract of aniseed inhibited the growth of a range of bacteria including *Escherichia coli* and *Staphylococcus aureus*, and also exhibited antifungal activity against *Candida albicans* and other organisms [Gülcin 2003; Maruzella 1959].

Essential oil of aniseed inhibited the growth of *Escherichia coli* (MIC: 0.5% V/V), *Staphylococcus aureus* (MIC: 0.25%), *Salmonella typhimurium* (MIC: 2.0%) and *Candida albicans* (MIC: 0.5%) using the agar dilution method [Hammer 1999]. Antimicrobial activity of the oil has also been demonstrated in other studies [Ramadan 1972; Shukla 1987; Ibrahim 1991].

A methanolic dry extract of aniseed reduced the resistance of *Pseudomonas aeruginosa* to certain antibiotics when used in combination with the individual antibiotic (both the extract and antibiotic being at concentrations which did not inhibit growth when used alone; antibiotic concentrations were half their minimum inhibitory concentrations). The aniseed extract was particularly effective in combination with chloramphenicol, gentamicin, cephalexin, tetracycline or nalidixic acid against the standard strain of *P. aeruginosa*, causing almost complete inhibition of growth; it was less effective against a particularly resistant strain of *P. aeruginosa*, but inhibited growth by 74% in combination with tetracycline [Aburjai 2001].

The essential oil (0.0125-0.1%) concentration-dependently inhibited the growth of the fungi *Aspergillus flavus, A. parasiticus, A. ochraceus* and *Fusarium moniliforme*. The formation of mycotoxins (aflatoxins, ochratoxin A and fumonisin) in wheat infected with the fungi were also inhibited [Soliman 2002].

Secretolytic and expectorant effects
A modest increase in mucociliary transport velocity of isolated ciliated epithelium from the frog oesophagus was observed 90 seconds after application of 200 µl of an infusion from aniseed (4.6 g per 100 mL of water) [Müller-Limroth 1980].

Spasmolytic effects
The essential oil at 200 mg/litre produced complete relaxation of carbachol-induced contractions of isolated tracheal smooth muscle from the guinea pig. In contrast, the oil increased the contraction force in electrically-stimulated guinea pig ileal smooth muscle with an EC_{50} of 6-7 mg/litre (a positive inotropic effect) [Reiter 1985].

The essential oil (0.02 mL), an aqueous extract (0.6 mL, equivalent to 1.5 g of aniseed) and an ethanolic extract (0.1 mL, equivalent to 0.25 g of aniseed) exhibited relaxant effects on methacholine-induced contractions of guinea pig tracheal chains (prepared from rings of isolated tracheal smooth muscle). The bronchodilatory effects were significant ($p<0.05$, $p<0.005$, $p<0.001$ respectively) compared to those of controls (0.6 mL of saline for the essential oil and aqueous extract; 0.1 mL of ethanol for the ethanolic extract) [Boscabady 2001].

Local anaesthetic activity
Trans-anethole concentration-dependently reduced electrically-evoked contractions of rat phrenic nerve-hemidiaphragm, by 10.3% at 10^{-3} µg/mL, by 43.9% at 10^{-2} µg/mL, by 79.7% at 10^{-1} µg/mL and by 100% at 1 µg/mL [Ghelardini 2001].

Tumour-inhibiting activity
Anethole at a concentration below 1 mM has been shown to be a potent inhibitor of tumour necrosis factor (TNF)-induced cellular responses, such as activation of nuclear factor-kappa B (NF-κB) and other transcription factors, and also to block TNF-induced activation of the apoptotic pathway. This might explain the role of anethole in suppression of inflammation and carcinogenesis [Chainy 2000].

Oestrogenic activity
Dry extract of aniseed with hot water (DER 10:1) exhibited selective oestrogen receptor modulator (SERM)-like properties in various *in vitro* assays. At a concentration of 25 µg/mL, the extract caused a significant ($p<0.05$) increase in alkaline phosphatase activity. At 50 µg/mL it significantly ($p<0.05$) increased the formation of mineralized nodules [Kassi 2004].

The essential oil, and the pure isolated compound *trans*-anethol, exhibited extremely weak oestrogenic effect using the yeast oestrogen screen (YES) assay (yeast cells expressing the human oestrogen receptor) with an EC_{50} of 600 µg/mL for the essential oil and 625 µg/mL for *trans*-anethol. Relative potency compared to 17β-estradiol was 9.47×10^{-8} for the essential oil and 8.6×10^{-8} for trans-anethol [Tabanca 2004].

Using the same model, the potency of 17β-estradiol was found to be at least 10^5-10^6 times that of anethole, as well as for the other essential oil constituents [Howes 2002].

Antioxidant activity
The essential oil in concentrations of 2µM and 5µM inhibited the copper-catalyzed oxidation of human LDL by 40% and 71% respectively [Teissedre 2000]. An aqueous dry extract of

aniseed exhibited antioxidant activity in six different *in vitro* assays [Hinneburg 2006].

In vivo experiments

Secretolytic and expectorant effects
An emulsion of 2 drops of the essential oil, administered intragastrically to cats, caused hypersecretion of mucus in the air passages and stimulated ciliary removal of mucus (which had been inhibited by opium alkaloids) [VanDongen 1953].
A solution of the essential oil in 12% ethanol, administered intragastrically to anaesthetised guinea pigs at 50 mg/kg b.w., induced a 3- to 6-fold increase in respiratory tract fluid during the first 2 hours after administration; even 10 mg/kg caused a 2-fold increase [Boyd 1946]. A similar experiment in anaesthetised rats, dosed orally with the oil at 0.0015 mL/kg, resulted in a 28% increase of respiratory tract fluid without influencing chloride concentration or density [Boyd 1954]. Administration of the oil vapour to anaesthetised rabbits by inhalation (in steam) dose-dependently increased the volume of respiratory secretion by 19-82%; doses added to the vaporizer were 0.7-6.5 g/kg b.w. (the amount to which the animals were exposed being considerably less). However, at the highest dose level there were signs of tissue damage and a mortality rate of 20% [Boyd 1968].

Sedative effect
The pentobarbital-induced sleeping time of mice was prolonged by 93.5% ($p<0.01$) after simultaneous intraperitoneal administration of essential oil at 50 mg/kg b.w.; *trans*-anethole gave similar results [Marcus 1982].

Anticonvulsant effect
The anticonvulsant effect of intraperitoneally administered aniseed oil in mice with seizures induced by pentylenetetrazole (PTZ) and maximal electroshock (MES) was investigated. Pretreatment with the oil significantly ($p< 0.001$) suppressed PTZ-induced hind limb tonic extensions (HLTE) and mortality with an ED_{50} value of 0.52 mL/kg b.w., and MES-induced HLTE and mortality with an ED_{50} value of 0.20 mL/kg b.w. ($p<0.001$). The essential oil dose-dependently increased the dose of i.v. administered PTZ needed to induce seizures in the mice ($p<0.01$ for 1 mL oil/kg b.w.) [Pourgholami 1999].

Oestrogenic activity
Trans-anethole administered orally to immature female rats at 80 mg/kg b.w. for 3 days significantly increased uterine weight, to 2 g/kg compared to 0.5 g/kg in controls and 3 g/kg in animals given oestradiol valerate subcutaneously at 0.1 µg/rat/day ($p<0.001$). The results confirmed that *trans*-anethole had oestrogenic activity; other experiments showed that it has no anti-oestrogenic, progestational, anti-progestational, androgenic or anti-androgenic activity [Dhar 1995].

Local anaesthetic activity
In the rabbit conjunctival reflex test, solutions of *trans*-anethole administered into the conjunctival sac concentration-dependently increased the number of stimuli required to evoke the conjunctival reflex ($p<0.01$): 9.7 stimuli at 10 µg/mL, 31.8 stimuli at 30 µg/mL and 65.2 stimuli at 100 µg/mL, compared to about 3 stimuli for vehicle controls. The effect was comparable to that of procaine [Ghelardini 2001].

Anti-tumour activity
In Swiss albino mice with Ehrlich ascites tumour (EAT) in the paw, anethole administered orally at 500 or 1000 mg/kg on alternate days for 60 days significantly and dose-dependently reduced tumour weight ($p<0.05$ at 500 mg/kg, $p<0.01$ at 1000 mg/kg), tumour volume ($p<0.01$ at 500 mg/kg, $p<0.001$ at 1000 mg/kg) and body weight ($p<0.05$ to 0.01) compared to EAT-bearing controls. Mean survival time increased from 54.6 days to 62.2 days (500 mg/kg) and 71.2 days (1000 mg/kg). Histopathological changes were comparable to those after treatment with cyclophosphamide (a standard cytotoxic drug). These and other results demonstrated the anticarcinogenic, cytotoxic and non-clastogenic nature of anethole [Al-Harbi 1995].

Anti-ulcer activity
An aqueous suspension of aniseed, administered to rats intragastrically at a dose equivalent to 250 and 500 mg crude drug/kg b.w., significantly ($p<0.001$) prevented gastric mucosal lesions induced by 80% ethanol, 0.2M NaOH or 25%NaCl [Al Mofleh 2007].

Enzyme induction
Subcutaneous administration of the essential oil to partially (two-thirds) hepatectomized rats at 100 mg/animal/day for 7 days stimulated liver regeneration ($p<0.01$) [Gershbein 1977].

Experiments in which rats were injected intraperitoneally with a mixture of *trans*-anethole (100 mg/kg b.w.) and [14C] parathion (1.5 mg/kg) showed no significant effect of *trans*-anethole on metabolism and excretion of the insecticide. However, when rats were fed a diet containing 1% of *trans*-anethole for 7 days and subsequently cell fractions from the livers of these rats were incubated for 2 hours with [14C] parathion, significantly less unchanged parathion (1.6%) was recovered compared to controls (12.5%). The data were interpreted as suggesting that feeding *trans*-anethole to rats for 7 days induced the synthesis of parathion-degrading liver enzymes [Marcus 1982].

Anti-diuretic activity
Aniseed oil, added to drinking water at a 0.05% concentration, exerted a significant ($p<0.027$) anti-diuretic effect in rats, as expressed by the urine to water intake ratio [Kreydiyyeh 2003].

Pharmacokinetic properties

Pharmacokinetics in animals
No data available for aniseed.

In mice and rats *trans*-anethole is reported to be metabolized by O-demethylation and by oxidative transformation of the C3-side chain. After low doses (0.05 and 5 mg/kg b.w.) O-demethylation occurs predominantly, whereas higher doses (up to 1500 mg/kg b.w.) give rise to higher yields of oxygenated metabolites [Sangster 1984a; Sangster 1984b].

Pharmacokinetics in humans
No data available for aniseed.

After oral administration of radioactively-labelled *trans*-anethole (as the *methoxy*-^{14}C compound) to 5 healthy volunteers at dose levels of 1, 50 and 250 mg on separate occasions, it was rapidly absorbed. 54-69% of the dose (detected as ^{14}C) was eliminated in the urine and 13-17% in exhaled carbon dioxide; none was detected in the faeces. The bulk of elimination occurred within 8 hours and, irrespective of the dose level, the principal metabolite (more than 90% of urinary ^{14}C) was 4-methoxyhippuric acid [Caldwell 1988]. An earlier study with 2 healthy subjects taking 1 mg of *trans*-anethole gave similar results [Sangster 1987].

Preclinical safety data
Most toxicity studies relevant to aniseed have been conducted on *trans*-anethole, the major constituent of the essential oil.

Acute toxicity
Oral LD_{50} values per kg b.w. have been determined for the

essential oil as 2.7 g in rats [Sangster 1987] and for *trans*-anethole as 1.82-5.0 g in mice, 2.1-3.2 g in rats and 2.16 g in guinea pigs [Lin 1991].

Intraperitoneal LD_{50} value for the essential oil from aniseed was determined as 0.93 (1.11-0.79) mL/kg bw. for mice [Pourgholami 1999].

Intraperitoneal LD_{50} values for *trans*-anethole have been determined as 0.65-1.41 g/kg in mice and 0.9-2.67 g/kg in rats [Lin 1991].

Repeated-dose toxicity
No data available for aniseed.

In 90-day experiments in rats, 0.1% of *trans*-anethole in their diet caused no toxic effects. However, dose-related oedema of the liver was reported at higher levels of 0.3%, 1% and 3%, which have no therapeutic value [Lin 1991]. Male rats receiving 0.25% of anethole in their diet for 1 year showed no toxic effects, while others receiving 1% for 15 weeks had slight oedematous changes in liver cells [Hagan 1967]. Rats given *trans*-anethole as 0.2, 0.5, 1 or 2% of their diet for 12-22 months showed no effects at any level on clinical chemistry, haematology, histopathology or mortality. Slower weight gain and reduced fat storage were noted at the 1% and 2% levels [Lin 1991, LeBourhis 1973].

Reproductive toxicity
Trans-anethole exerted dose-dependent anti-implantation activity after oral administration to adult female rats on days 1-10 of pregnancy. Compared to control animals (all of which delivered normal offspring on completion of term), *trans*-anethole administered at 50, 70 and 80 mg/kg b.w. inhibited implantation by 33%, 66% and 100% respectively. Further experiments at the 80 mg/kg dose level showed that in rats given *trans*-anethole only on days 1-2 of pregnancy normal implantation and delivery occurred; in those given *trans*-anethole only on days 3-5 implantation was completely inhibited; and in those given *trans*-anethole only on days 6-10 three out of five rats failed to deliver at term. No gross malformations of offspring were observed in any of the groups. The results demonstrated that *trans*-anethole has antifertility activity. From comparison with the days 1-2 group (lack of antizygotic activity), the lower level of delivery in the days 6-10 group was interpreted as a sign of early abortifacient activity [Dhar 1995].

Mutagenicity
A dry ethanolic aniseed extract was mutagenic at high concentrations (5 mg/plate) to streptomycin-dependent strains of *Salmonella typhimurium* TA 98 [Shashikanth 1986]. An ethanolic aniseed extract gave negative results at the maximum non-toxic concentration of 0.1 mg/mL in chromosomal aberration tests using a Chinese hamster 1984 cell line [Ishidate].

The essential oil and *trans*-anethole were mutagenic at 2 mg/plate in the Ames test using *Salmonella typhimurium* strains TA 98 and TA 100, and mutagenicity was potentiated by S13 activation [Marcus 1982]. In another study, *trans*-anethole was mutagenic to *Salmonella typhimurium* TA 100 in the Ames test with S9 activation, doses of 30-120 µg/plate showing a dose-dependent increase in revertants, which did not exceed twice the number of the control [Sekizawa 1982]. Other investigations with metabolic activation have confirmed that *trans*-anethole is weakly mutagenic [Lin 1991].

Estragole, a minor constituent of anise oil, has also shown mutagenic potential in various Ames tests, demonstrating the need for carcinogenicity studies [DeVincenzi 2000; European commission 2001].

Anti-genotoxic activity of trans-anethole
In the mouse bone marrow micronucleus test, oral pre-treatment of mice with trans-anethole at 40-400 mg/kg b.w., 2 and 20 hours before intraperitoneal injection of genotoxins, led to moderate, dose-dependent protective effects against known genotoxins such as cyclophosphamide, procarbazine, N-methyl-N'-nitrosoguanidine, urethane and ethyl methane sulfonate ($p<0.05$ to $p<0.01$ at various dose levels). No significant increase in genotoxicity was observed when *trans*-anethole (40-400 mg/kg b.w.) was administered alone [Abraham 2001].

Carcinogenicity
A 1-year experiment in which mice received *trans*-anethole in their diet gave no evidence of carcinogenic potential: low levels of DNA adducts were observed in liver tissue [Lin 1991]. In another chronic study of *trans*-anethole in mice there were no histological differences between treated and control animals [Miller 1983]. In a study in rats, the highest dose feeding group (1% *trans*-anethole for 117 weeks) presented with hyperplastic and partially neoplastic changes in the livers of female (but not male) rats; a review of these results confirmed that the observed neoplastic changes in the liver were not due to a direct genotoxic effect induced by *trans*-anethole [Lin 1991].

Genotoxicity studies performed with aniseed extracts, the essential oil, *trans*-anethole and estragole do not provide adequate data to fully evaluate the carcinogenic risk. However, the carcinogenic risk from aniseed in man is assumed to be low [Aniseed].

Clinical safety data
A severe case of poisoning with anise oil after intake of 10-15 ml oil is reported. The symptoms were convulsions, unconsciousness and vomiting [Bang 2008].

REFERENCES

Abraham SK. Anti-genotoxicity of *trans*-anethole and eugenol in mice. Food Chem Toxicol 2001;39:493-8. http://dx.doi.org/10.1016/S0278-6915(00)00156-3

Aburjai T, Darwish RM, Al-Khalil S, Mahafzah A, Al-Abbadi A. Screening of antibiotic resistant inhibitors from local plant materials against two different strains of *Pseudomonas aeruginosa*. J Ethnopharmacol 2001;76:39-44. http://dx.doi.org/10.1016/S0378-8741(01)00206-9

Al-Harbi MM, Qureshi S, Raza M, Ahmed MM, Giangreco AB, Shah AH. Influence of anethole treatment on the tumour induced by Ehrlich ascites carcinoma cells in paw of Swiss albino mice. Eur J Cancer Prev 1995;4:307-18. http://dx.doi.org/10.1097/00008469-199508000-00006

Al-Mofleh IA, Alhaider AA, Mossa JS Al-Soohaibani MO, Rafatullah S. Aqueous suspension of anise "*Pimpinella anisum*" protects rats against chemically induced gastric ulcers. World j gastroenterol 2007; 13:1112-8.

Andersen KE. Contact allergy to toothpaste flavours. Contact Dermatitis 1978;4:195-8. http://dx.doi.org/10.1111/j.1600-0536.1978.tb03788.x

Aniseed - Anisi fructus. European Pharmacopoeia, Council of Europe.

Baerheim Svendsen A. Über das Vorkommen der Chlorogen- und Kaffeesäure in der Pflanzenfamilie der Umbelliferen. Pharm Acta Helv 1951;26:253-8

Bang J, Mortensen OS, Ebbehøj N. Forgiftning med anisolie. Ugeskr. Læger 2008;170:461.

Barnes J, Anderson LA, Phillipson JD. Aniseed. In: Herbal Medicines - A guide for healthcare professionals, 3rd ed. London-Chicago: Pharmaceutical Press, 2007:57-60

Blaschek W, Ebel S, Hackenthal E, Holzgrabe U, Keller K, Reichling J, SchulzV, editors. Pimpinella in: Hagers Handbuch der Pharmazeutischen Praxis 6th ed. Band 12. WVG Stuttgart 2007:681-97

Boskabady MH, Ramazani-Assari M. Relaxant effect of *Pimpinella anisum* on isolated guinea pig tracheal chains and its possible mechanism(s). J Ethnopharmacol 2001;74:83-8. http://dx.doi.org/10.1016/S0378-8741(00)00314-7

Boyd EM, Pearson GL. On the expectorant action of volatile oils. Am J Med Sci 1946;211:602-10. http://dx.doi.org/10.1097/00000441-194621150-00013

Boyd EM. Expectorants and respiratory tract fluid. Pharmacol Rev 1954;6:521-42.

Boyd EM, Sheppard EP. The effect of steam inhalation of volatile oils on the output and composition of respiratory tract fluid. J Pharmacol Exp Therap 1968;163:250-6.

Caldwell J, Sutton JD. Influence of dose size on the disposition of *trans*-[*methoxy*-^{14}C]anethole in human volunteers. Food Chem Toxicol 1988;26:87-91. http://dx.doi.org/10.1016/0278-6915(88)90103-2

Ceska O, Chaudhary SK, Warrington PJ, Ashwood-Smith MJ. Photo-active furocoumarins in fruits of some umbellifers. Phytochemistry 1987;26:165-9. http://dx.doi.org/10.1016/S0031-9422(00)81503-4

Chainy GBN, Manna SK, Chaturvedi MM, Aggarwal BB. Anethole blocks both early and late cellular responses transduced by tumor necrosis factor: effect on NF-κB, AP-1, JNK, MAPKK and apoptosis. Oncogene 2000;19:2943-50. http://dx.doi.org/10.1038/sj.onc.1203614

Czygan F-C, Hiller K. Anisi fructus - Anis. In: Wichtl M, editor. Teedrogen und Phytopharmaka. Ein Handbuch für die Praxis auf wissenschaftlicher Grundlage, 4th ed. Stuttgart: Wissenschaftliche Verlagsgesellschaft, 2002:42-4.

Czygan F-C. Anis (Anisi fructus DAB 10) - *Pimpinella anisum* L. Z Phytotherapie 1992;13:101-6.

De Vincenzi M, Silano M, Maialetti F, Scazzocchio B. Constituents of aromatic plants: II. Estragole. Fitoterapia 2000;71:725-9. http://dx.doi.org/10.1016/S0367-326X(00)00153-2

Dhar SK. Anti-fertility activity and hormonal profile of *trans*-anethole in rats. Indian J Physiol Pharmacol 1995;39:63-7.

Dirks U, Herrmann K. 4-(β-D-glucopyranosyloxy)benzoic acid, a characteristic phenolic constituent of the Apiaceae. Phytochemistry 1984a;23:1811-2. http://dx.doi.org/10.1016/S0031-9422(00)83504-9

Dirks U, Herrmann K. Hochleistungsflüssigkeitschromatographie der Hydroxycinnamoylchinasäuren und der 4-(β-D-glucopyranosyloxy)-benzoesäure in Gewürzen. Z Lebensm Unters Forsch 1984b;179:12-6. http://dx.doi.org/10.1007/BF01042847

Dorsch W, Loew D, Meyer-Buchtela E, Schilcher H. In: Kooperation Phytopharmaka, editor. Kinderdosierung von Phytopharmaka, 3rd ed. Teil I. Empfehlungen zur Anwendung und Dosierung von Phytopharmaka, monographierte Arzneidrogen und ihren Zubereitungen in der Pädiatrie: Foeniculi fructus (Fenchelfrüchte). Bonn: Kooperation Phytopharmaka, 2002:70-1.

El-Moghazi AM, Ali AA, Ross SA, Mottaleb MA. Flavonoids of *Pimpinella anisum* L. growing in Egypt. Fitoterapia 1979;50:267-8.

El-Wakeil F, Khairy M, Morsi S, Farag RS, Shihata AA, Badel AZMA. Biochemical studies on the essential oils of some fruits of Umbelliferae family. Seifen-Öle-Fette-Wachse 1986;112:77-80.

European Commission: Scientific Committee on Food. Opinion of the scientific committee on food on estragole (1-allyl-4-methoxybenzene). 26 September 2001.

Franks A. Contact allergy to anethole in toothpaste associated with loss of taste. Contact Dermatitis 1998;38:354. http://dx.doi.org/10.1111/j.1600-0536.1998.tb05786.x

Fujimatu E, Ishikawa T, Kitajami J. Aromatic compound glucosides, alkyl glucoside and glucide from the fruit of anise. Phytochemistry 2003;63:609-16. http://dx.doi.org/10.1016/S0031-9422(03)00179-1

Garcia VG, Jané PG, Zavala BB. Aniseed-induced nocturnal tongue angioedema. J investig allergol clin immunolol 2007;17.406-8.

Garcia-Gonzales JJ, Bartolomé-Zavala B, Fernandez-Melendez S, Barcelo-MunõsJM, Paez AM, Carmona-Bueno MJ, VegaChicote JM, Carrasco MAN, Godoy AA, Espinosa RP. Occupational rhinoconjunctivitis and food allergy because of aniseed sensitization. Ann allergy asthma immunol 2002;88:518-22.

Gershbein LL. Regeneration of rat liver in the presence of essential oils and their components. Food Cosmet Toxicol 1977;15:173-81. http://dx.doi.org/10.1016/S0015-6264(77)80386-6

Ghelardini C, Galeotti N, Mazzanti G. Local anaesthetic activity of monoterpenes and phenylpropanes of essential oils. Planta Med 2001;67:564-6. http://dx.doi.org/10.1055/s-2001-16475

Gülcin I, Oktay M, Kirecci E, Küfrevioglu. Screening of antioxidant and antimicrobial activities of anise (*Pimpinella anisum* L.) seed extract. Food chem. 2003;83:371-82. http://dx.doi.org/10.1016/S0308-8146(03)00098-0

Hagan EC, Hansen WH, Fitzhugh OG, Jenner PM, Jones WI, Taylor JM et al. Food flavourings and compounds of related structure. II. Subacute and chronic toxicity. Food Cosmet Toxicol 1967;5:141-57. http://dx.doi.org/10.1016/S0015-6264(67)82961-4

Hammer KA, Carson CF, Riley TV. Antimicrobial activity of essential oils and other plant extracts. J Applied Microbiol 1999;86:985-90. http://dx.doi.org/10.1046/j.1365-2672.1999.00780.x

Hänsel R, Sticher O, Steinegger E. Anis und Anisöl. In: Pharmakognosie-Phytopharmazie, 6th ed. Berlin-Heidelberg-NewYork-London: Springer-Verlag, 1999:692-5.

Hausen BM. The sensitizing capacity of sulfuretin. In: Allergiepflanzen - Pflanzenallergene. Part 1. Landsberg/München: ecomed, 1988:300.

Hinneburg I, Dorman HJD, Hiltunen R. Antioxidant activities from selected culinary herbs and spices. Food chem. 2006;97:122-9. http://dx.doi.org/10.1016/j.foodchem.2005.03.028

Howes M-J R, Houghton PJ, Barlow DJ, Pocock VJ, Milligan SR. Assessment of estrogenic activity in some common essential oil constituents. J Pharm Pharmacol 2002;54:1521-8. http://dx.doi.org/10.1211/002235702216

Ibrahim YKE, Ogunmodede MS. Growth and survival of *Pseudomonas aeruginosa* in some aromatic waters. Pharm Acta Helv 1991;66:286-8.

Ishidate M, Sofuni T, Yoshikawa K, Hayashi M, Nohmi T, Sawada M, Matsuoka A. Primary mutagenicity screening of food additives currently used in Japan. Food Chem Toxicol 1984;22:623-36. http://dx.doi.org/10.1016/0278-6915(84)90271-0

Kartnig T, Scholz G. Über einige Lipoid-Inhaltsstoffe aus den Früchten von *Pimpinella anisum* L. und *Carum carvi* L. Fette Seifen Anstrichmittel

1969;71:276-80. http://dx.doi.org/10.1002/lipi.19690710406

Kassi E, Paroutsi Z, Fokialakis N, Messari I, Mitakou S, Moutsatsou P. Greek plant extracts exhibit selective estrogen receptor modulator (SERM)-like properties. Agric food chem. 2004;52:6956-61.

Kreydiyyeh SI, Usta J, Knio K, Markossian S, Dagher S. Aniseed oil increases glucose absorption and reduces urine output in the rat. Life sci 2003;74:663-73. http://dx.doi.org/10.1016/j.lfs.2003.07.013

Kubeczka K-H, von Massow F, Formacek V, Smith MAR. A new type of phenylpropane from the essential fruit oil of *Pimpinella anisum* L. Z Naturforsch 1976;31b:283-4.

Kubeczka K-H. Grundlagen der Qualitätsbeurteilung arzneilich verwendeter ätherischer Öle. Acta Horticulturae 1978;73:85-93.

Kunzemann J, Herrmann K. Isolierung und Identifizierung der Flavon(ol)-O-glykoside in Kümmel (*Carum carvi* L.), Fenchel (*Foeniculum vulgare* Mill.), Anis (*Pimpinella anisum* L.) und Koriander (*Coriandrum sativum* L.) und von Flavon-C-Glykosiden im Anis. Z Lebensm Unters-Forsch 1977;164:194-200. http://dx.doi.org/10.1007/BF01263030

Le Bourhis B. Propriétés biologiques du *trans*-anéthole. Essai de détermination de la dose journalière acceptable. Parfums Cosmet Sav Fr 1973;3:450-6.

Lin FSD. Trans-anethole. In: Joint FAO/WHO Expert Committee on Food Additives. Toxicological evaluation of certain food additives and contaminants. WHO Food Additives Series 28. Geneva: World Health Organization 1991:135-52.

Marcus C, Lichtenstein EP. Interactions of naturally occurring food plant components with insecticides and pentobarbital in rats and mice. J Agric Food Chem 1982;30:563-8. http://dx.doi.org/10.1021/jf00111a038

Maruzzella JC, Freundlich M. Antimicrobial substances from seeds. J Am Pharm Assoc 1959;48:356-8.

Miller EC, Swanson AB, Phillips DH, Fletcher L, Liem A, Miller JA. Structure-activity studies of the carcinogenicities in the mouse and rat of some naturally occurring and synthetic alkenylbenzene derivatives related to safrole and estragole. Cancer Res 1983;43:1124-34.

Müller-Limmroth W, Fröhlich H-H. Wirkungsnachweis einiger phytotherapeutischer Expektorantien auf den mukoziliaren Transport. Fortschr Med 1980;98:95-101.

Orav A, Raal A, Arak E. Essential oil composition of *Pimpinella anisum* L. fruits from various European countries. Nat prod res 2008;22:227-32. http://dx.doi.org/10.1080/14786410701424667

Pimpinella. In: British Herbal Pharmacopoeia 1983. Bournemouth: British Herbal Medicine Association, 1983:160-1.

Pourgholami MH, Majzoob S, Javadi M, Kamelinejad M, Fanaee GHR, Sayyah M. The fruit essential oil of *Pimpinella anisum* exerts anticonvulsant effects in mice. J ethnopharmacol 1999;66:211-5. http://dx.doi.org/10.1016/S0378-8741(98)00161-5

Ramadan FM, El-Zanfaly RT, El-Wakeil FA, Alian AM. On the antibacterial effects of some essential oils. I. Use of agar diffusion method. Chem Mikrobiol Technol Lebensm 1972;2:51-5.

Reiter M, Brandt W. Relaxant effects on tracheal and ileal smooth muscles of the guinea pig. Arzneim-Forsch/Drug Res 1985;35:408-14.

Sangster SA, Caldwell J, Smith RL, Farmer PB. Metabolism of anethole. I. Pathways of metabolism in the rat and mouse. Food Chem Toxicol 1984a;22:695-706. http://dx.doi.org/10.1016/0278-6915(84)90196-0

Sangster SA, Caldwell J, Smith RL. Metabolism of anethole. II. Influence of dose size on the route of metabolism of *trans*-anethole in the rat and mouse. Food Chem Toxicol 1984b;22:707-13. http://dx.doi.org/10.1016/0278-6915(84)90197-2

Sangster SA, Caldwell J, Hutt AJ, Anthony A, Smith RL. The metabolic disposition of [*methoxy*-^{14}C]-labelled *trans*-anethole, estragole and *p*-propylanisole in human volunteers. Xenobiotica 1987;17:1223-32. http://dx.doi.org/10.3109/00498258709167414

Sekizawa J, Shibamoto T. Genotoxicity of safrole-related chemicals in microbial test systems. Mutat Res 1982;101:127-40. http://dx.doi.org/10.1016/0165-1218(82)90003-9

Shashikanth KN, Hosono A. *In vitro* mutagenicity of tropical spices to streptomycin-dependent strains of *Salmonella typhimurium* TA 98. Agric Biol Chem 1986;50:2947-8. http://dx.doi.org/10.1271/bbb1961.50.2947

Shukla HS, Tripathi SC. Antifungal substance in the essential oil of anise (*Pimpinella anisum* L.). Agric Biol Chem 1987;51:1991-3. http://dx.doi.org/10.1271/bbb1961.51.1991

Schultze W, Lange G, Kubeczka K-H. Direkte massenspektrometrische Analyse von *Pimpinella anisum* L. - Anispulver und Anisöl. Dtsch Apoth Ztg 1987;127:372-8.

Schulz JM, Herrmann K. Analysis of hydroxybenzoic and hydroxycinnamic acids in plant material. II. Determination by gas-liquid chromatography. J Chromatogr 1980;195:95-104. http://dx.doi.org/10.1016/S0021-9673(00)81546-0

Soliman KM, Badeaa RI. Effect of oil extracted from some medicinal plants on different mycotoxigenic fungi. Food chem tox 2002;40:1669-75. http://dx.doi.org/10.1016/S0278-6915(02)00120-5

Sweetmann SE, editor. Aniseed, Anise oil. In: Martindale - The complete drug reference, 37rd ed. London: Pharmaceutical Press, 2011:1580.

Tabanca N, Khan SI, Bedir E, Annavarapu S, Willett K, Khan IA, Kirimer N, Baser KHC. Estrogenic activity of isolated compounds and essential oils of *Pimpinella* species from Turkey, evaluated using a recombinant yeast screen. Planta med 2004;70:728-35. http://dx.doi.org/10.1055/s-2004-827203

Teissedre PL, Waterhouse AL. Inhibition of oxidation of human low density lipoproteins by phenolic substances in different essential oil varieties. J agric food chem. 2000;48:3801-5. http://dx.doi.org/10.1021/jf990921x

Tisserand R, Balacs T. Anise. In: Essential Oil Safety - A Guide for Health Care Professionals. Edinburgh: Churchill Livingstone, 1995:117.

Van Dongen K, Leusink H. The action of opium-alkaloids and expectorants on the ciliary movements in the air passages. Arch Int Pharmacodyn 1953;93:261-76

Von Skramlik E. Über die Giftigkeit und Verträglichkeit von äterischen Ölen. Pharmazie 1959;14:435-45

Weiss RF. Lehrbuch der Phytotherapie. 8th ed Stuttgart. Hippocrates 1997:83,443

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	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 978-1-901964-19-6