# E/S/C/O/P Monographs

Online Series

*The* Scientific Foundation for Herbal Medicinal Products

## Cimicifugae rhizoma

**Black Cohosh**

**2011**

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**

# CIMICIFUGAE RHIZOMA
## Black Cohosh

# 2011

**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**

# Cimicifugae rhizoma - Black Cohosh



Published by the European Scientific Cooperative on Phytotherapy (ESCOP)
Argyle House, Gandy Street, Exeter EX4 3LS, 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. The authors of the material herein have consulted sources believed to be reliable in their efforts to provide information that is complete and in accordance with standards accepted at the time of publication. 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 sheet 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 Peter Bradley
Cover photographs by Johannes Saukel (*Actaea racemosa*) and Martin Willoughby
Cover and text design by Martin Willoughby
Typeset in Optima by Roberta Hutchins

Plant illustrated on the cover: *Actaea racemosa* (*Cimicifuga racemosa*)

# 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 |
| 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 |
| CVI | chronic venous insufficiency |
| CYP | cytochrome P450 |
| 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 B4 |
| M | molar (concentration) |
| MAO | monoamine oxidase |
| MBC | minimum bactericidal concentration |
| MDA | malondialdehyde |
| MFC | minimum fungicidal concentration |
| MIC | minimum inhibitory concentration |
| 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 | necrosis factor |
| NO | nitric oxide |
| NOS | nitric oxide synthase |
| n.s. | not significant |
| NSAID | non-steroidal anti-inflammatory drug |
| ovx | ovariectomy or ovariectomized |
| PA | pyrrolizidine alkaloid |
| PAF | platelet activating factor |
| PCR | polymerase chain reaction |
| PEG | polyethylene glycol |
| PGE | prostaglandine 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 |
| 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 |

# CIMICIFUGAE RHIZOMA 2011

## Black Cohosh

### DEFINITION

Black cohosh consists of the dried rhizomes and roots of *Actaea racemosa* L. [*Cimicifuga racemosa* (L.) Nutt.] harvested in summer or autumn.

To comply with the monograph of the United States Pharmacopeia [Black Cohosh USP] the material should contain not less that 0.4 per cent of triterpene glycosides, expressed as 23-*epi*-26-deoxyactein ($C_{37}H_{56}O_{10}$; $M_r$ 660.8) and calculated with reference to the dried drug.

A draft monograph intended for inclusion in the European Pharmacopoeia has been published [Black Cohosh]; it requires not less that 1.0 per cent of triterpene glycosides, expressed as monoammonium glycyrrhizate ($C_{42}H_{65}NO_{16}$; $M_r$ 840) and calculated with reference to the dried drug.

### CONSTITUENTS

Triterpene glycosides with a highly oxidized cycloartane-type skeleton, glycosylated at the C-3 position. Acetylacteol, cimigenol and shengmanol represent the major aglycones, and arabinose and xylose the dominant sugar moieties [Bedir 2000, Bedir 2001, Chen 2002a, Chen 2002b, Chen 2007, He 2000, He 2006, Li 2006, Mimaki 2006, Nuntanakorn 2006, Shao 2000, Watanabe 2002, Wende 2001].

The major glycosides have been identified as actein [Chen 2002b, Ganzera 2000, He 2000, He 2006, Li 2002], cimicifugoside[1] [He 2000, He 2006, Piancatelli 1971, Shao 2000], cimiracemoside A[2] [Bedir 2000, Ganzera 2000, He 2006] and 23-*epi*-26-deoxyactein [Chen 2002b, He 2006], formerly known as 27-deoxyactein [Berger 1988, He 2000, Shao 2000]. Cimigenol-3-*O*-α-L-arabinoside has been proposed as a species-specific marker glycoside for *C. racemosa* [He 2006]. A chlorine-containing triterpene glycoside might be an artefact [Chen 2007].

Phenylpropanoids (min. 0.5% expressed as caffeic acid), principally derivatives of hydroxycinnamic acids:

- Caffeic, ferulic and isoferulic acids [He 2006, Kruse 1999].
- Hydroxycinnamic acid esters of fukiic acid, e.g. fukinolic acid, cimicifugic acid A, cimicifugic acid B and cimicifugic acid G [He 2006, Kruse 1999, Nuntanakorn 2006].
- Hydroxycinnamic acid esters of piscidic acid, e.g. cimicifugic acid D, cimicifugic acid E and cimicifugic acid F [He 2006, Kruse 1999, Stromeier 2005].
- Other phenylpropanoid esters such as methyl caffeate [Chen 2002c], caffeoylglycolic acid, cimiciphenol, cimiciphenone [Stromeier 2005], petasiphenone [Jarry 2007, Stromeier 2005] and cimiracemates A-D (phenylpropanoid ester dimers) [Chen 2002c].

Other constituents include a cyclic guanidine alkaloid, cimipronidine (also proposed as a potential marker for *C. racemosa*) [Fabricant 2005], $N_\omega$-methylserotonin [Powell 2008], starch, fatty acids, resin and tannins [Beuscher 1995].

[1] Cimicifugoside (cimigenol 3-O-β-D-xyloside) as isolated by He et al. [He 2000], Shao et al. [Shao 2000] and earlier by Piancatelli and coworkers [Piancatelli 1971] from *Cimicifuga racemosa*; in some literature it is called cimigoside or cimifugoside. A different 'cimicifugoside' has been isolated from the rhizoma of *Cimicifuga simplex* by Kusano et al. [Kusano 1998]; it is the 3-*O*-xyloside of an aglycone with a cyclolanost-7-ene structure.

[2] Cimiracemoside A (cyclolanost-7-ene 3-*O*-β-D-xyloside) as isolated by Bedir and Khan [Bedir 2000] and mentioned later by Ganzera et al. [Ganzera 2000] and He et al. [He 2006]. At almost the same time a different 'cimiracemoside A', identified as 21-hydroxycimigenol-3-*O*-α-arabinoside, was isolated from black cohosh by Shao et al. [Shao 2000].