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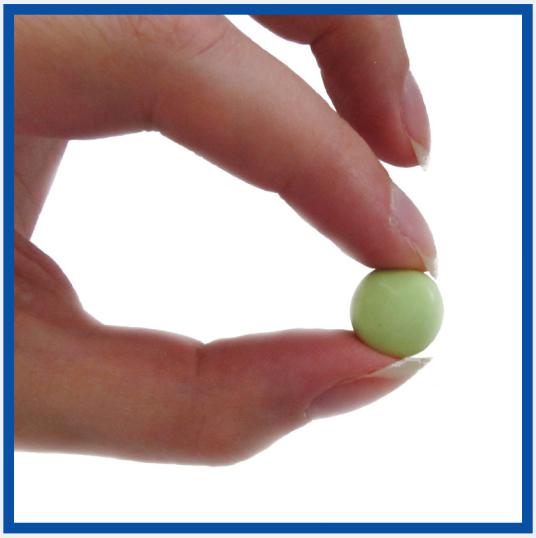
Online Series

The Scientific Foundation for Herbal Medicinal Products

Ballotae nigrae herba

Black Horehound

2015



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European Scientific Cooperative On Phytotherapy

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MONOGRAPHS

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

BALLOTAE NIGRAE HERBA
Black Horehound

2015

E/S/C/O/P
EUROPEAN SCIENTIFIC COOPERATIVE
ON PHYTOTHERAPY

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Edited by Simon Mills and Roberta Hutchins
Cover photographs by Prof Salvador Cañigueral Folcara (*Ballota nigra*) and Martin Willoughby
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Plant illustrated on the cover: *Ballota nigra*

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.

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Notes for the Reader
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The monograph text
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Board of Supervising Editors
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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

BALLOTAE NIGRAE HERBA 2015

Black Horehound

DEFINITION

Black horehound consists of the dried flowering tops of *Ballota nigra* L. It contains not less than 1.5 per cent of total *ortho*-dihydroxycinnamic acid derivatives, expressed as acteoside ($C_{29}H_{36}O_{15}$; M_r 624.6) and calculated with reference to the dried drug.

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

CONSTITUENTS

The main characteristic constituents are: phenylpropanoids (ca. 5.5%) including the *ortho*-dihydroxycinnamic acid glycosides acteoside (verbascoside), forsythoside B, arenarioside [Seidel 1996a], ballotetroside [Seidel 1997] and martynoside [Tóth 2007], and non-glycosidic (+)-*E*-caffeoyl-L-malic acid [Didry 1999]; flavonoids, mainly derivatives of luteolin and apigenin, e.g. luteolin 7-lactate and 7-glucosyl-lactate [Bertand 2000], apigenin 7-*O*-glucoside and apigenin 6,8-*C*-diglucoside (vicenin 2) [Darbour 1986]; and labdane diterpene lactones [Savona 1976; Savona 1977a; Savona 1977b; Seidel 1996b].

CLINICAL PARTICULARS

Therapeutic indications
Tenseness, restlessness and irritability with difficulty in falling asleep [Huriez 1991; Hänsel 1992].

Black horehound has also been documented for the relief of mild spasmodic gastric complaints [Hänsel 1992].

Posology and method of administration

Dosage

Adult single dose: 1.5-5 g of the drug (e.g. as a tea infusion) or equivalent preparations prepared with water or ethanol (maximum 45% V/V) [Huriez 1991; Ballota; Tisanes].

Elderly: as for adults.

Children from 3 to 12 years under medical supervision only: proportion of adult dose according to body weight, as non-alcoholic preparations.

Method of administration
For oral administration.

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

Contra-indications
None known.

Special warnings and special precautions for use
None required.

Interaction with other medicaments and other forms of interaction
None reported.

Pregnancy and lactation
No data available. In accordance with general medical practice, the product should not be used during pregnancy and lactation without medical advice.

Effects on ability to drive and use machines
Due to the sedative effects of black horehound, the ability to drive or use machines might be affected.

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Undesirable effects
None reported.

Overdose
No case of overdose reported.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

In vitro experiments

Receptor-binding activity
The competitive receptor binding activity of four phenylpropanoid glycosides, acteoside, forsythoside B, arenarioside and ballotetroside, and the non-glycosidic phenylpropanoid caffeoyl-L-malic acid, has been studied. Apart from ballotetroside, they showed affinity for benzodiazepine, dopaminergic and morphinic receptors isolated from rat brain with IC_{50} values between 0.4 mg/ml and 4.8 mg/ml [Daels-Rakotoarison 2000].

Antioxidant effects
A 75%-ethanolic extract from *Ballota nigra* subsp. *anatolica* inhibited the formation of superoxide anion with an IC_{50} of 0.74 mg/ml [Citoglu 2004].

An aqueous dry extract from black horehound showed a concentration-dependent activity in the DDPH assay (IC_{25} = 4.81 µg/ml), concentration-dependent superoxide radical scavenging activity using the xanthine/xanthine oxidase system (IC_{25} = 14.6 µg/ml) and NO radical scavenging activity (IC_{25} = 122 µg/ml) [Vrchovská, 2007].

The antioxidant activity of five phenylpropanoids (acteoside, forsythoside B, arenarioside, ballotetroside, and caffeoyl-L-malic acid) was investigated against the reactive oxygen species (ROS) superoxide anion, hydrogen peroxide, hypochlorous acid and hydroxyl radical. These phenylpropanoids exhibited ability to scavenge ROS with IC_{50} values comparable to that of *N*-acetylcysteine. Furthermore, they significantly and dose-dependently inhibited the release of ROS from isolated and stimulated polymorphonuclear neutrophils from human blood ($p<0.05$), with activity in the order acteoside > forsythoside B > caffeoyl-L-malic acid > arenarioside > ballotetroside. Proteine kinase C or phospholipase C pathways are involved in the mechanism of action [Daels-Rakotoarison 2000].

Five phenylpropanoids from black horehound were evaluated for their ability to inhibit Cu^{2+}-induced peroxidation of human LDL. They strongly inhibited peroxidation of LDL in a dose-dependent manner with ED_{50} values of 1 µM for acteoside and forsythoside B, 1.8 µM for arenarioside, 7.5 µM for ballotetroside and 9.5 µM for caffeoyl-L-malic acid, compared to 2.3 µM for quercetin. The capacity of phenylpropanoids to inhibit Cu^{2+}-induced LDL oxidation is linked to their free radical scavenging properties [Seidel 2000].

Antimicrobial activity
An aqueous dry extract from black horehound dose-dependently inhibited the formation of biofilm of MRSA with an IC_{50} of 8 µg/ml [Quave 2008].

Acteoside, forsythoside B and arenarioside, but not ballotetroside or caffeoyl-L-malic acid, exhibited moderate antibacterial activity against *Staphylococcus aureus* (Gram-positive) and *Proteus mirabilis* (Gram-negative) at a concentration of 128 µg/ml [Didry 1999].

In vivo experiments

Sedative and antidepressive effects
The psychotropic effects of a black horehound aqueous dry extract, intraperitoneally administered to rodents, were evaluated from a range of tests. A dose of 200 mg/kg b.w. significantly reduced mobility and, to a lesser extent, curiosity in mice; produced a significant tranquillizing effect in mice; significantly reduced anxiety but not locomotor activity in rats; and significantly prolonged barbiturate-induced sleeping time in rats. No muscle relaxant effects were evident in mice from doses of 200 or 400 mg/kg [Mongold 1991].

After i.p. administration to mice at 0.5 ml per animal a 10% aqueous extract from black horehound had a marked sedative effect on the central nervous system, reducing spontaneous motor activity by 60% after 1 hour and 65% after 3 hours [Rácz-Kotilla 1980].

After i.p. administration to rats an aqueous dry extract from black horehound showed significant antidepressant activity in the forced swimming test. Mean durations of immobility were 570 seconds for untreated control animals, 496 seconds after the extract at 240 mg/kg ($p<0.001$) and 379 seconds after amitriptyline at 5 mg/kg i.p. ($p<0.001$). This extract did not exert significant anxiolytic activity in the elevated plus-maze test [Vural 1996].

Hypoglycaemic effects
Oral administration of a 70%-ethanolic dry extract from black horehound to rats at 400 mg/kg b.w. daily for 7 days caused significant decreases in blood glucose and total serum cholesterol (both $p<0.01$). In the glucose tolerance test in rats, a single oral dose of the same extract at 400 mg/kg significantly reduced blood glucose levels ($p<0.001$) and increased serum insulin levels ($p<0.01$) within 15 minutes [Nusier 2007a].

In a further experiment with the same extract, a single oral dose at 400 mg/kg significantly reduced plasma glucose levels in healthy normoglycaemic rats by 32% and in alloxan-induced diabetic rats by 22% (both $p<0.001$) after 6 hours. At this dose level no significant changes were observed in spontaneous motor activity of the animals, nor noticeable changes in behaviour and intake of food and water [Nusier 2007b].

Clinical studies
In an open study, 28 patients with general anxiety disorder, diagnosed in accordance with the DSM (at least 6 of the 18 criteria comprising the DSM III R classification) and involving depression and sleep disorders, were treated daily for 90 days with 3 × 5 ml of a black horehound liquid preparation (14% ethanol, corresponding to 3 × 0.5 g of black horehound). Based on clinical examination and DSM III R assessment, responder rates after 60 and 90 days were 65 and 73% of patients respectively. Patients with sleep disorders showed particularly marked improvement. Out of 10 patients taking benzodiazepines prior to the study, 3 discontinued and 4 reduced their dose by half [Huriez 1991].

Pharmacokinetic properties
No data available.

Preclinical safety data

Acute toxicity
After administration of a single large dose of a black horehound aqueous dry extract to mice at 2 g/kg b.w. no mortality occurred and no signs of toxicity were evident over a period of 15 days or from post-mortem examination [Mongold 1991].

Clinical safety data

In an open clinical study, no major adverse effects were reported after treatment of 28 patients with 3 × 5 ml of a black horehound liquid preparation (14% ethanol, corresponding to 3 × 0.5 g black horehound) for 90 days. Feelings of fatigue, which diminished as the study progressed, and nausea, which was alleviated by taking the black horehound preparation after meals, were reported [Huriez 1991].

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MONOGRAPHS

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