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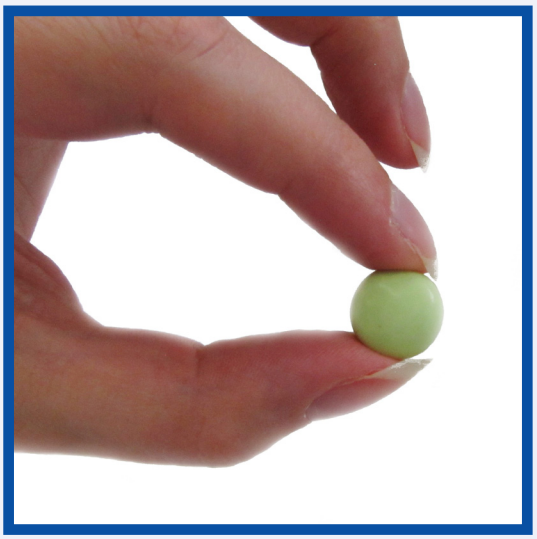
The Scientific Foundation for Herbal Medicinal Products

Marrubii herba
White horehound

2013



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

MARRUBII HERBA
White horehound

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

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Marrubii herba - White horehound

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Plant illustrated on the cover: *Marrubium vulgare*

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
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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

MARRUBII HERBA

2013

White horehound

DEFINITION

White horehound consists of the dried, entire or fragmented, flowering aerial parts of *Marrubium vulgare* L. It contains not less than 0.7 per cent of marrubiin ($C_{20}H_{28}O_4$; M_r 332.4) with reference to the dried drug.

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

CONSTITUENTS

The characteristic constituents are the labdane-type diterpenes marrubiin (0.12 to 1.0%) and marrubenol, metabolically derived from their precursors premarrubiin (0.13%) and premarrubenol during the growth period, as well as peregrinol or vulgarol; up to 7% tannins; up to 0.1% phenylethanoid esters, including acteoside, ballotetroside, forsythoside B, marruboside and arenarioside; essential oil (0.05 to 0.06%) consisting mainly of phenylpropanoids, mono- and sesquiterpenes; the hydroxycinnamic acids chlorogenic, caffeic, caffeoyl-L-malic acid and 1-caffeoylquinic acid; flavon- and flavonol glycosides, lactoylflavones; the methoxylated flavone ladanein; amines including choline (0.2%) and betonicine (0.3%) [Nawwar 1989; Sahpaz 2002a; Sahpaz 2002b; Martin-Nizard 2003; Belhattab 2006; Knöss 2006; Seitz 2007; Morteza-Semnani 2008; Blaschek 2009; Ahmed 2010; Alkhatib 2010; Zawislak 2011].

CLINICAL PARTICULARS

Therapeutic indications

Loss of appetite; dyspeptic complaints such as bloating and flatulence [Jänicke 2003; Schilcher 2007; Seitz 2007; Blaschek 2009].
Catarrh of the upper respiratory tract [Bradley 1992; Teuscher 2004; Schilcher 2007; Seitz 2007; Blaschek 2009].

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

Posology and method of administration

Dosage

Adults:
4.5 g of the drug daily, or 1 to 2 g as an infusion three times daily [Bradley 1992; Jänicke 2003; Teuscher 2004; Barnes 2007; Schilcher 2007; Seitz 2007; Blaschek 2009].

Fluid extract (1:1, 20% ethanol): 1 to 4 ml three times daily [Bradley 1992; Jänicke 2003; Barnes 2007; Seitz 2007].

Tincture (1:5; 25% ethanol): 3 to 6 ml daily [Bradley 1992].

Pressed juice: 2 to 6 tablespoons daily [Jänicke 2003; Schilcher 2007; Seitz 2007; Blaschek 2009].

Method of administration
For oral administration.

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

Contraindications
None known.

Special warnings and special precautions for use
None required.

Interaction with other medicaments and other forms of interaction
There are reports from a clinical trial with diabetic patients taking glibenclamide that consumption of aqueous white horehound extract was linked with minor symptoms of nausea, oral dryness or salivation, and dizziness. [Herrera-Arellano 2004].

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
See Interactions above.

Overdose
No toxic effects reported.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

In vitro studies

Antioxidant activity
Aqueous, and methanolic extracts and the essential oil of white horehound have been shown to have free radical scavenging and antioxidant activities in various assays, including on ABTS- or DPPH-radicals, determination of ferric reducing/antioxidant power (FRAP) and the inhibition of linoleic acid peroxidation. In some of the studies the effects were attributed to the polyphenol content of the drug [VanderJagt 2002; Berrougui 2006; Katalinic 2006; Matkowski 2006; Wojdylo 2007; Dall´Acqua 2008, Kadri 2011; Pukalskas 2012.].

A 40%-methanolic dry extract (DER 25:1) inhibited the formation of conjugated dienes (CD) in a dose-dependent manner after incubation of human-LDL with $CuSO_4$. The lag phase before CD formation was significantly increased ($p=0.014$) and the maximum rate of oxidation decreased significantly ($p= 0.004$). The degradation of α-tocopherol and the electrophoretic mobility of LDL (both induced by oxidation) were attenuated. HDL-mediated cholesterol efflux from THP-1 macrophages was potentiated in a dose-dependent manner from 50 µg/ml ($p<0.05$) to 100 µg/ml ($p<0.01$) [Berrougui 2006].

Acteoside, forsythoside B, arenarioside, ballotetroside and caffeoyl-malic acid isolated from white horehound inhibited copper-initiated LDL oxidation with ED_{50} values of 0.46, 0.68, 0.64, 1.82 and 2.07 µM, respectively. There were ED_{50} values of 0.39, 0.45, 0.50, 0.72 and 1.04 µM for the inhibition of oxidation induced by 2,2´-azobis(2-aminopropane)dihydrochloride. Extra- and intracellular peroxidation in endothelial cells after incubation with minimally oxidized LDL was measured by the accumulation of thiobarbituric acid reactive substances (TBARS). At a concentration of 10 µM each compound significantly decreased the accumulation of TBARS ($p<0.001$) [Martin-Nizard 2003].

Endothelin-1 secretion in bovine aortic endothelial cells was shown to be significantly increased by treatment with LDL ($p<0.01$) and copper-oxidised LDL ($p<0.001$). Acteoside, forsythoside B, arenarioside and ballotetroside previously isolated from white horehound completely eliminated this effect. The increase in endothelin-1 gene expression after treatment with copper oxidised LDL was also reversed by these compounds ($p<0.05$) [Martin-Nizard 2004].

Vasorelaxant effects
An aqueous extract of white horehound (DER approx 6:1) given to spontaneously hypertensive rats at an oral dose of 80 mg/kg b.w. for five days, reduced KCl-induced contractions in subsequently isolated aorta by 19% ($p<0.05$). Noradrenaline-induced contractions were also decreased.Preincubation of aortic rings with the extract resulted in a dose-dependent inhibition ofKCl-induced contractions. Maximum effects were reached with 0.7 mg/ml and led to an 87% decrease in contraction of aortic rings of spontaneously hypertensive rats (EC50 0.14 mg/ml) and a 73% decrease in those of normotensive rats (EC50 0.19 mg/ml) ($p<0.05$). Calcium-induced contractions in KCl-depolarized aortic rings were markedly decreased by the extract. Contractions induced by noradrenaline were inhibited by 73% and 37% respectively, in aortic rings of spontaneously hypertensive and normotensive rats. [El Bardai 2001].

The contractile tension induced by KCl in isolated rings of the aorta and the mesenteric artery of rats treated orally with an aqueous extract (80mg/kg/day for 10 weeks) was significantly lower when compared to those of untreated rats ($p<0.05$). The effect disappeared in the presence of the NO synthase inhibitor L-NOarginine. Acetylcholine-induced relaxation of the mesenteric artery following contraction induced by noradrenaline was shown to improve [El Bardai 2004].

A dose-dependent inhibition of KCl-induced contractions in isolated rat aorta was observed after preincubation with an aqueous extract of white horehound. After fractionation of the extract the effect was most pronounced in a cyclohexane fraction with 61.2% inhibition at a concentration of 16 µg/ml and 100% inhibition at a concentration of 64 µg/ml. From this fraction marrubiin and marrubenol were isolated, significantly reducing the contractions, with IC_{50} values of 24 µM and 7.7 µM respectively ($p<0.05$) [El Bardai 2003a].

In aortic rings, after removal of the endothelium, a similar relaxant effect was observed for marrubenol with an IC_{50} of 11.8 µM and maximum inhibition of KCl-induced contractions of 93.4%. Marrubenol inhibited contractions induced by noradrenaline to a lesser extent, and was ineffective in the same experiment in the presence of the Ca^{2+} channel blocker nimodipine. In fura-2 loaded aorta, both the cytosolic Ca^{2+} concentration and the contractions were decreased by marrubenol in a dose-dependent manner. The decrease of the quenching rate of the fluorescence of the fluorescent marker fura-2 in the presence of Mn^{2+} suggested that the activity of marrubenol was caused by an inhibition of Ca^{2+} influx. The study demonstrated that marrubenol decreased Ca^{2+} influx in aortic smooth muscle cells and inhibited smooth muscle contraction by blocking L-type calcium channels [El Bardai 2003b].

Other effects
A methanolic dry extract from white horehound leaf significantly suppressed cell growth in the human colon adenocarcinoma cell line HCT-116 by induction of apoptosis at a concentration of 250 µg/ml ($p<0.05$). At 100 µg/ml the extract increased the expression of the pro-apoptotic protein NAG-1 [Yamaguchi 2006].

An ethanolic extract (not further specified) exhibited moderate activity on the viability of a murine neuroblastoma cell line as assessed with resazurin-almar blue indicator dye (LC_{50} 3.64 mg/ml) [Mazzio 2009].

An ethanolic dry extract of white horehound exhibited anti-

microbial activity against *Bacillus subtilis* in the XTT colorimetric assay [Al-Bakri 2007].

A dry acetone extract (yield 6.6%) led to 67.5% inhibition of acetylcholinesterase from the electric eel and 83.5% inhibition of butyrylcholinesterase from horse serum at dosages of 50 µg/mL [Orhan 2010].

A methanolic extract exhibited antibacterial activity against *Bacillus subtilis* and *Staphylococcus aureus* (MIC 100 mg/ml) as well as *Staphylococcus epidermidis* (MIC 200 mg/ml) [Masoodi 2008].

In an immunomodulation assay an extract prepared with phosphate-buffered saline (10 g drug/100 mL) increased the proliferation of mice splenocytes ($p<0.05$) as compared with concanavalin-A. The protein fraction of this extract reduced the mitogenic effect of concanavalin-A [Daoudi 2012].

Acteoside, forsythoside B and arenarioside isolated from white horehound showed COX-2 inhibition of 63.9%, 72.5% and 67.8% respectively, at a concentration of 1 mM. The IC_{50} values were 0.69, 0.49 and 0.61 mM. The compounds did not inhibit COX-1 [Sahpaz 2002a].

In endothelial cells, acteoside, forsythoside B, arenorioside, ballotetroside and caffeoylmalic acid (10 µM) significantly decreased the cytotoxicity of minimally oxidized LDL ($p<0.001$) [Martin-Nizard 2003].

Ladanein, isolated from white horehound, showed moderate cytotoxicity against the murine leukemia cell line DA1-3b/M2$^{BCR-ABL}$ and the human leukaemia cell lines K562, K562R and 697 with IC_{50} values of 10.4, 25.1, 38.0 and 38.0 µM, respectively. It remained without effect on human acute myeloid leukaemia cells MOLM13 and on human peripheral blood mononuclear cells from healthy volunteers [Alkhatib 2010].

In vivo studies

Gastroprotective effects
A methanolic leaf extract from white horehound (not further specified) and isolated marrubiin were tested in different models of gastric ulcer. Swiss mice received a single oral dose of 25, 50 or 100 mg/kg b.w. of the extract or 25 mg/kg marrubiin. In ulcers induced by ethanol/HCl, the extract at 50 and 100 mg/kg and marrubiin significantly reduced the ulcer lesion index ($p<0.01$). A significant decrease in the total area of lesions and the percentage of lesion area was observed but only at the highest dose of the extract and marrubiin ($p< 0.01$). In indomethacin/bethanecol-induced ulcers all doses of the extract and marrubiin led to a significant reduction of the total area of lesions, the percentage of lesion area and the ulcer lesion index ($p<0.01$). The total area of lesions and the percentage of lesion area were significantly improved by 50 and 100 mg/kg of the extract and marrubiin ($p<0.05$) as compared to the positive control cimetidin. The two higher concentrations of the extract and marrubiin significantly raised gastric pH and decreased the concentration of H^+ ions ($p<0.01$). Free gastric mucus in the tissue was enhanced in all treated groups ($p<0.01$). After pre-treatment with L-NAME it was concluded that the protective effects of the extract and marrubiin were related to NO synthesis [Paula de Oliveira 2011].

Analgesic effects
Marrubiin isolated from white horehound exhibited pronounced antinociceptive effects in different mouse models [De Jesus 1999]:

- Acetic acid-induced writhing was reduced by pretreatment with marrubiin administered intraperitoneally 30 minutes before the challenge in a range of doses. The effect was significant for up to five hours ($p<0.01$ up to four hours, $p<0.05$ at five hours). Co-treatment with naloxone did not affect the activity of marrubiin. The ID_{50} was 2.2 µmol/kg; for aspirin it was 133 µmol/kg and for diclofenac 38 µmol/kg.
- In the formalin-induced pain test, first phase nociception after 5 minutes (representing neurogenic pain) and second phase effects after 15 to 30 minutes (representing inflammatory pain) were registered. Both pain phases were significantly inhibited ($p<0.05$) in a dose-dependent manner following pretreatment of the animals with marrubiin (3 to 90 µmol/kg intraperitoneally or 90 to 900 µmol/kg orally) 60 minutes before the formalin injection.
- Capsaicin-induced neurogenic nociception was inhibited by pretreatment with marrubiin at intraperitoneal doses of 3 to 90 µmol/kg (ID_{50} 28.8 µmol/kg; maximum inhibition 76 %).
- Marrubiin administered intraperitoneally at 180 µmol/kg had no effect in the hot plate test.

Anti-oedematous effects
In a model of microvascular leakage in mouse ears, marrubiin administered intraperitoneally at 1-100 mg/kg exhibited a significant dose-dependent antioedematous effect as determined by extravasated Evans blue. The ID_{50} and maximal inhibition of oedema induced by carrageenan were 13.6 mg/kg and 63% ($p<0.01$) respectively; in histamine-induced oedema 13.8 and 73.7% ($p<0.01$); and in bradykinin-induced oedema 15.8 mg/kg and 70% ($p<0.01$). Oedema after treatment with compound 4880, serotonin or dextran was reduced by up to 46.9%, 49.3% and 32% ($p<0.01$), respectively. To determine the activity in neurogenic inflammation, microvascular extravasation of Evans blue was induced with capsaicin or substance P. For these agents maximal inhibition was 28% and 27.6%. In mice sensitized to ovoalbumin, the allergic oedema after rechallenge was reduced by 67.6% for marrubiin (100 mg/kg i.p.; $p<0.01$) as compared to a 69.8% reduction by dexamethasone (0.5 mg/kg i.p.) [Stulzer 2006].

Antihypertensive effects
An aqueous extract from white horehound (DER appr. 6:1) administered at an oral daily dose of 80 mg/kg b.w. for five days, significantly lowered the systolic blood pressure in spontaneously hypertensive rats ($p<0.05$) but not in normotensive rats. Urine output, as well as the excretion of electrolytes, creatinine and urea, remained almost unchanged in hypertensive and normotensive rats [El Bardai 2001].

Oral treatment of spontaneously hypertensive rats with an aqueous white horehound extract at 80 mg/kg b.w./day for 10 weeks resulted in a significant decrease in systolic blood pressure ($p<0.05$), similar to amlodipine at 10 mg/kg b.w./day. The extract reduced aortic but not mesenteric artery weight ($p<0.05$). [El Bardai 2004].

Hypoglycaemic effects
Oral administration of 300 mg/kg b.w. of an ethanolic extract of white horehound (not further specified) to alloxan-induced diabetic rats led to a significant decrease of the blood glucose level ($p<0.01$) [Novaes 2001].

A methanolic extract (DER approximately 8.3:1) was administered at a daily dose of 500 mg/kg b.w. for 28 days to male Wistar rats. Treatment started 11 days after induction of diabetes with streptozotocin. Blood glucose levels were significantly reduced on treatment days 14, 21 and 28 as compared to diabetic control and baseline (all $p<0.05$), and even slightly better than in the group treated with glibenclamide. Plasma insulin, muscle

glycogen and liver glycogen were significantly increased on day 28 as compared to diabetic control ($p<0.05$). Positive effects on plasma lipid profile after treament with the extract were observed: a 24% decrease in total cholesterol, a 27% reduction in LDL cholesterol and a 27% increase of HDL cholesterol ($p<0.05$ as compared to diabetic control). The treatment improved hepatic enzyme activity and nearly normalized glutathione peroxidase, glutathione reductase, glutathione-S-transferase, reduced glutathione and malondialdehyde levels (all $p<0.05$). In an oral glucose tolerance test the effect of the extract on the total AUC was similar to glibenclamide [Elberry 2011].

Alloxan-induced diabetic Wistar rats were treated with an aqueous extract of white horehound (6 g/25 ml, containing 5.1 mg flavonoids and 14.1 mg cinnamic acid derivatives per 100 mg dry weight; DER 8.3:1). Oral doses of 100, 200 and 300 mg/kg b.w.were administered twice daily for 15 days. From day 5 a significant decrease of blood glucose was observed at all doses as compared to diabetic control ($p<0.001$). The dose-dependent decrease in glycaemia was 50.75%, 61.06% and 62.55% respectively. No significant changes in body weight were observed for the animals treated with white horehound as compared to normal control. The increase in serum glucose, total lipids, triglycerides and total cholesterol in the diabetic rats was significantly reduced by the extract ($p<0.001$) at the end of the experiment. The effects were comparable to the positive control glibenclamide (5 mg/kg b.w.) [Boudjelal 2012].

A slight but not significant hypoglycaemic effect was observed in rats pretreated with an ethanolic dry extract from white horehound leaves (not further specified) at a single oral dose of 100 mg/kg b.w. received 30 min. after a glucose load of 2g/kg [Vergara-Galicia 2012].

Hepatoprotective effects
A terpenoid isolated from white horehound, *p*-menthane-5,6-dihydroxy-3-carboxylic acid, was administered orally to male Wistar rats at a dose of 50 mg/kg b.w. for 7 days after hepatotoxic challenge with CCl_4. The increase in SGOT, SGPT and ALP after intoxication was significantly reduced by the treatment ($p<0.01$, 0.01 and 0.05, respectively). The decreased level in total proteins was significantly increased ($p<0.05$). A recovery of histopathological changes to almost normal architecture of the hepatocytes after treatment with the compound was observed [Ahmed 2010].

Pharmacokinetic properties
No data available.

Preclinical safety data

Acute toxicity
After oral treatment of female rats with 2 g/kg b.w. of a methanolic extract from white horehound no signs of toxicity were observed after 30 minutes, during the first 4 hours after administration and over a follow-up period of 14 days [Paula de Oliveira 2011].

Repeated dose toxicity
Rats treated orally with an aqueous extract of white horehound at a dose of 80 mg/kg/day over a period of 10 weeks did not show any sign of adverse effects [El Bardai 2004].

Male Wistar rats receiving oral doses of 100, 250, 500 and 1000 mg/kg b.w. of a methanolic extract (DER approximately 8.3:1) for 3 weeks did not show any physical signs of toxicity during the experimental period [Elberry 2011].

Mutagenicity
A tincture of white horehound did not cause any mutagenic effect in *Salmonella typhimurium* strain TA98 in the Ames test [Schimmer 1994].

Clinical safety data

In a study with 21 diabetic patients treated with glibenclamide, an infusion of 1g white horehound three times daily was given for 21 days. Only minor side effects such as nausea, oral dryness, hypersalivation or dizziness were observed in five patients [Herrera-Arellano 2004].

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