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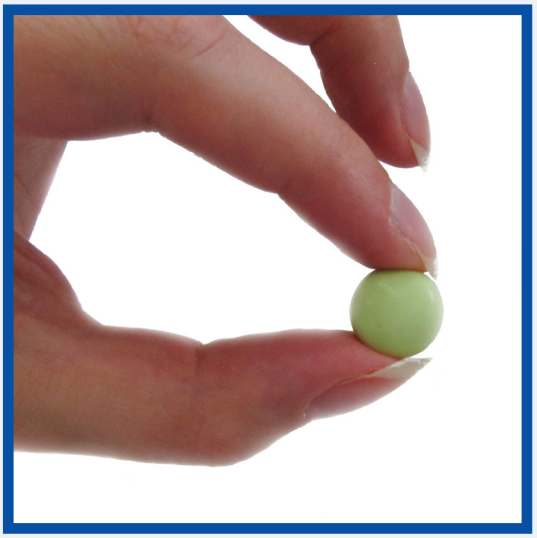
The Scientific Foundation for Herbal Medicinal Products

Hamamelidis cortex

Hamamelis Bark

2012



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E/S/C/O/P
MONOGRAPHS

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

HAMAMELIDIS CORTEX
Hamamelis Bark

2012

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

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Hamamelidis cortex - Hamamelis Bark

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Edited by Simon Mills and Roberta Hutchins
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Typeset in Optima by Roberta Hutchins

Plant illustrated on the cover: *Hamamelis virginiana*

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
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Foreword and Preface
Notes for the Reader
Abbreviations
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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

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Hamamelis Bark

DEFINITION

Hamamelis bark consists of the dried bark from stems and branches of *Hamamelis virginiana* L., collected in spring. It contains not less than 4.0% of hide powder-precipitable tannins, expressed as pyrogallol ($C_6H_6O_3$; M_r 126.1) and calculated with reference to the dried drug.

The material complies with the monograph of the Deutscher Arzneimittel-Codex [Hamamelisrinde] or the British Herbal Pharmacopoeia [Hamamelis Bark].

CONSTITUENTS

The main characteristic constituent is hamamelitannin, a mixture of the α- and β-forms of 2',5-di-*O*-galloylhamamelose [Mayer 1965; Friedrich 1974; Vennat 1988; Hoffmann-Bohm 1993; Haberland 1994; Hartisch 1996; Wang 2003; Bradley 2006]. Proanthocyanidins are also present including: procyanidin dimers such as catechin-(4α→8)-catechin, 3-*O*-galloyl-epicatechin-(4β→8)-catechin and epicatechin-(4β→8)-catechin-3-*O*-(4-hydroxy)benzoate [Friedrich 1974; Vennat 1988; Hartisch 1996a,b]; prodelphinidins such as epigallocatechin-(4β→8)-catechin, 3-*O*-galloyl epigallocatechin-(4β→8)-catechin and 3-*O*-galloyl epigallocatechin-(4β→8)-gallocatechin [Hartisch 1996a,b; Bradley 2006]; and proanthocyanidin oligomers consisting of 4-9 catechin/gallocatechin units, some of which are 3-*O*-galloylated [Hartisch 1996b; Hartisch 1997; Dauer 1998; Dauer 2003b; Bradley 2006].

Other constituents include flavan-3-ols such as (+)-catechin, (+)-gallocatechin, (–)-epicatechin-3-*O*-gallate, and (–)-epigallocatechin-3-*O*-gallate [Friedrich 1974; Hartisch 1996a; Wang 2003; Bradley 2006]; di-and tri-*O*-galloyl-hamameloses and related 4-hydroxybenzoates [Haberland 1994; Hartisch 1996a,b], pentagalloyl glucose [Friedrich 1974], gallic acid [Friedrich 1974; Vennat 1988; Wang 2003; Bradley 2006] and about 0.1% of volatile oil [Hoffmann-Bohm 1993; Bradley 2006].

CLINICAL PARTICULARS

Therapeutic indications

Internal use
Inflammation of mucous membranes of the oral cavity [Hoffmann-Bohm 1993; Laux 1993; Hiller 2009].
Short-term symptomatic treatment of diarrhoea [Hamamelis Bark; Laux 1993; Bradley 2006].

External use
Haemorrhoids [Reynolds 1982; Van Hellemont 1988; Hoffmann-Bohm 1993; Laux 1993; Bradley 2006, Schilcher 2007; Hiller 2009], minor injuries and local inflammations of the skin [Reynolds 1982; Hoffmann-Bohm 1993; Laux 1993; Hörmann 1994; Millikan 2003; Bradley 2006; Bühring 2008; Hiller 2009; Schilcher 2010].
Symptomatic treatment of problems related to varicose veins, such as painful and heavy legs [Van Hellemont 1988; Hoffmann-Bohm 1993; Bradley 2006; Hiller 2009; Schilcher 2010].

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

Posology and method of administration

Dosage

Internal use
2-10 g of the drug daily as a decoction, used as a mouthwash [Van Hellemont 1988; Hoffmann-Bohm 1993; Bradley 2006; Hiller 2009; Schilcher 2010], or

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2-3 g daily as a tea [Bradley 2006; Hiller 2009].
2-4 ml of tincture, used diluted as a mouthwash 3 times daily [Hamameils Bark; Bradley 2006].
Other preparations: the equivalent of 0.1-1 g of the drug, 1-3 times daily [Hoffmann-Bohm 1993; Bradley 2006; Hiller 2009; Schilcher 2010].

External use
5-10 g of the drug as a decoction in 250 ml of water [Hoffmann-Bohm 1993; Bradley 2006; Bühring 2008].
Use of the decoction (e.g. for compresses and baths) is also recommended in children [Bühring 2008].
Extracts in semi-solid or liquid preparations corresponding to 20-30% of the drug [Hoffmann-Bohm 1993].

Method of administration
For oral administration or local application.

Duration of administration
No restriction. Medical advice should be sought if diarrhoea persists for more than 3 days.

Contraindications
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 internally during pregnancy and lactation without medical advice.

Effects on ability to drive and use machines
None known.

Undesirable effects
In sensitive persons, stomach irritation may occasionally occur after intake of hamamelis bark preparations [Hoffmann-Bohm 1993]. Chamomile-sensitive persons might also react to hamamelis preparations after topical application [Paulsen 2008].

Overdose
No toxic effects reported.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

In vitro studies

Astringent effect
The astringent effect of a tincture (1:3; 62% ethanol) prepared from fresh hamamelis bark was demonstrated with hide powder [Gracza 1987].

Antibacterial activity
Hamamelitannin did not affect growth of *Staphylococcus aureus* and *Staphylococcus epidermidis* even at high concentrations, but significantly ($p<0.05$) down-regulated RNAIII production in reporter cells at a dose of 50 µg in both strains. Furthermore, it inhibited bacterial cell attachment of both strains in a concentration-dependent manner and reduced delta-haemolysin production in a Western blotting test. [Kiran 2008].

Cytotoxic activity
After 4 days of incubation, polyphenols isolated from hamamelis bark showed moderate cytotoxicity to GLC_4 lung carcinoma and COLO 320 cells. The 3-*O*-galloyl compounds were more effective than other compounds. IC_{50} values of galloyl compounds were between 38 µM and 110 µM for GLC_4 and between 18.3 µM and 90.8 µM for COLO 320 cells; almost complete inhibition of growth was observed at 200 µM [Hartisch 1996a].

Polymeric proanthocyanidins from Hamamelis bark, in contrast to polysaccharides thereof, significantly ($p<0.1$, $p<0.05$) increased proliferation of human keratinocytes after 9 days of incubation at doses of 1 and 10µg/ml, respectively. There was no influence on the differentiation towards cornified cells [Deters 2001].

Polyphenolic fractions from Hamamelis bark (containing catechins, proanthocyanidins and gallotannins) inhibited cell proliferation in HT29 and HCT116 human colon cancer cell lines with average IC_{50} values of 28 and 29 µg/ml, respectively; the highly galloylated fractions being the most effective. In the same way, these fractions were able to arrest different phases of the cell cycle and to induce early apoptosis in HT29 cancer cells [Lizzárraga 2008].

Fractions rich in pyrogallol-containing polyphenols (proanthocyanidins, gallotannins, gallates) protected red blood cells from free radical-induced haemolysis in a dose-dependent manner with IC_{50} values between 21.5 and 24.5 µg/ml. They were mildly cytotoxic to HaCat keratinocytes (IC_{50} between 38 and 68 µg/ml) and 3T3 fibroblasts (IC_{50} between 33 and 51 µg/ml), and also inhibited the proliferation of tumoural SK-Mel 28 melanoma cells (IC_{50} between 26 and 39 µg/ml) [Touriño 2008].

Cell and DNA-protective effects
Catechin, hamamelitannin and two proanthocyanidin fractions prepared from Hamamelis bark were investigated in human Hep G2 cell lines using single cell gel electrophoresis (SCGE) for the detection of DNA-damage. Catechin and a low-molecular weight proanthocyandin fraction (W_M) caused only slight increases in DNA-migration up to concentrations of 166 µg/ml whereas hamamelitannin and the proanthocyandin fraction with higher molecular weight (W_A) dose-independently led to a two-fold enhancement of DNA-migration at the same concentrations. Treatment of the cells with the test compounds in a dose-range of 2–166 µg/ml prior to the exposure to 10 µM (2.5 µg/ml) benzo(a)pyrene (B(a)P) led to a significant reduction of induced DNA damage. The inhibitory effects of proanthocyanidins were stronger than those of catechin and hamamelitannin; the lowest effective concentrations were about 2 µg/ml [Dauer 2003a].

Hamamelitannin at concentrations of 1 to 100 µM inhibited TNF-mediated cell death and DNA fragmentation in a dose-dependent manner with a 100% protection at concentrations higher than 10µM. The protective effect was comparable to that of epigallocatechin gallate, and higher than gallic acid with less than 40% protection. However, hamamelitannin at concentrations of 1 to 100 µM did not alter the TNF-induced upregulation of endothelial adhesiveness [Habtemariam 2002].

Anti-inflammatory effects
In the lyso-PAF:acetyl-CoA acetyltransferase assay, hamamelitannin proved to be ineffective [Hartisch 1997], but in the same assay a proanthocyanidin oligomer isolated from hamamelis bark showed inhibitory potential [Hartisch 1996a, 1997]. A range of compounds from hamamelis bark had an inhibitory effect on 5-lipoxygenase (from a cytosol fraction of RBL-1 cells), galloyl compounds showing greater potency than

other substances; hamamelitannin had the strongest effect with an IC_{50} of 1.0 µM [Hartisch 1996a, 1997].

Anti-inflammatory effects of polyphenols isolated from hamamelis stem and twig bark were evaluated in human polymorphonucleocytes (PMNs) and human macrophages. With the exception of hamamelitannin, all the tested substances inhibited the synthesis of platelet activating factor (PAF) in human PMNs. Dimeric galloylated proanthocyanidins showed the strongest effects with IC_{50} values of 7.8 and 6.4 µM. The synthesis of leukotriene B_4 (LTB_4) in PMNs was inhibited by the tested substances. Oligomeric proanthocyanidins had stronger activity (IC_{50}: 1.5 µM) than hamamelitannin, which had the weakest effect (IC_{50}: 12.5 µM). The polyphenols were shown to inhibit zymosan-induced luminol-dependent chemiluminescence in human macrophages, with galloylated proanthocyanidins having stronger effects (IC_{50}: 2.3 and 2.0 µM) than hamamelitannin (IC_{50}: 10.5 µM) [Hartisch 1996a].

Antiviral activity
Hamamelitannin and fractions obtained by ultrafiltration from a hydroethanolic extract of hamamelis bark exhibited antiviral activity against *Herpes simplex* virus type 1 in monkey kidney cells. After 2-3 days the ED_{50} of hamamelitannin for antiviral activity was 26 µg/ml, compared to 6.3 µg/ml for a fraction consisting mainly of oligomeric to polymeric proanthocyanidins and 0.42 µmol/ml for acyclovir as a positive control [Erdelmeier 1996].

Radical-scavenging effects
A dry 50%-ethanolic extract from hamamelis bark exhibited active-oxygen scavenging activity, determined by an electron spin resonance (ESR) spin-trapping technique, with IC_{50} values of 0.17 µg/ml for superoxide anions, 7.79 µg/ml for hydroxyl radicals and 44.08 µg/ml for singlet oxygens, compared to 4.10, 3.30 and 21.18 µg/ml respectively for ascorbic acid. The extract at 50 µg/ml also protected murine dermal fibroblasts from cell damage induced by active-oxygen, increasing the survival rate to 69.0% ($p<0.01$) compared to about 15% for the control [Masaki 1995].

A suppressive effect of hamamelitannin against depolymerization of hyaluronic acid (induced by a xanthine/xanthine oxidase system) was demonstrated by measuring the viscosity of a 0.9 mg/ml solution; the inhibitory rate was 73.8% for hamamelitannin compared to 24.7% for ascorbic acid and 84.4% for superoxide dismutase [Masaki 1993].

Polyphenolic fractions from Hamamelis bark induced a dose-dependent protection against DNA damage in the hydroxyl radical system at doses from 10-100 µM, and showed oxygen radical scavenging activity as detected by (ESR) spectroscopy, being most effective at a dose of 50µM [Lizzárraga 2008].

The radical scavenging properties of hamamelitannin and gallic acid were evaluated in further experiments using ESR spin-trapping. For superoxide anion scavenging, the IC_{50} values were 1.31 µM for hamamelitannin and 1.01 µM for gallic acid, compared to 23.31 µM for ascorbic acid [Masaki 1993, 1994, 1995]. In hydroxyl radical scavenging, hamamelitannin gave the lowest IC_{50} of 5.46 µM, compared to 78.04 µM for gallic acid and 86.46 µM for propyl gallate (a well-known antioxidant). In singlet oxygen scavenging, the IC_{50} values of hamamelitannin and gallic acid were 45.51 µM and 69.81 µM respectively, compared to 66.66 µM for propyl gallate [Masaki 1994].

Fractions rich in pyrogallol-containing polyphenols (proanthocyanidins, gallotannins, gallates) were strong free radical scavengers against ABTS (6mmol Trolox equiv/g), DPPH (ED_{50} between 26.1 and 58.8 µg fraction/µmol radical) and tris-(2,4,6-trichloro-3,5-dinitrophenyl)-methyl HNTTM radical (ED_{50} between 38.2 and 86.2 µg/µmol) [Touriño 2008]. In a similar experiment, fractions of polyphenols with different degrees of galloylation and polymerization demonstrated protection against erythrocyte lipid peroxidation, haemolysis and 3T3 cytotoxicity caused by H_2O_2 at concentrations of 25, 50 and 75 µg/mL [Mitjans 2011].

The ability of polyphenolic fractions from Hamamelis bark to reduce the α-tocopheroxyl radical was investigated in a homogenous hexane system and a phospholipid-like system based on sodium dodecyl sulfate (SDS) micelles. Tocopheroxyl radicals were monitored and quantified by ESR spectroscopy in the absence and presence of phenolic substances. Polyphenolic fractions from hamamelis reduced 80% of α-tocopheroxyl radicals in the hexane system and approximately 90% in SDS micelles [Pazos 2009].

Hamamelitannin was also found to have antioxidative and scavenging activities against organic radicals such as 1,1-diphenyl-2-picrylhydrazyl (DPPH). Expressed as an index number (the number of mol required to scavenge one mol of DPPH), hamamelitannin and gallic acid gave results of 9.4 and 8.8 respectively, compared to 2.2 for DL-α-tocopherol and 2.0 for ascorbic acid [Masaki 1994].

The protective activities of hamamelitannin and gallic acid on cell damage induced by superoxide anion radicals were evaluated in a cell-culture system using murine fibroblasts. Hamamelitannin and gallic acid showed significant protective activity against superoxide radicals at minimum concentrations of 50 µM and 100 µM respectively ($p<0.01$) [Masaki 1994, 1995]; at 50 µM, hamamelitannin enhanced the survival of fibroblasts to 52.4% compared to 36.9% for the control [Masaki 1995]. Pre-treatment of fibroblasts with hamamelitannin at 200 µM for 24 hours at 37°C before exposure to superoxide anions increased cell survival to 63.8%, compared to 25.4% for gallic acid and 19.0% for the control. Further observations confirmed that hamamelitannin is superior to gallic acid in protecting against cell damage induced by superoxide anions and suggested that the high affinity of hamamelitannin for cells or membranes may be an important factor for protecting cells against active oxygen species [Masaki 1995].

In contrast, against cell damage induced in murine fibroblasts by hydroxyl radicals, hamamelitannin showed protective activity at a minimum concentration of 500 µM whereas gallic acid was effective at 50 µM. Against cell damage induced by singlet oxygens hamamelitannin at 100 µM enhanced survival to 80.6% ($p<0.01$), while gallic acid had no significant effect at 100 µM and required 500 µM to enhance survival to 98.6% ($p<0.01$) compared to 60.4% survival for controls [Masaki 1994].

Hamamelitannin and a fraction of molecular weight < 3 kDa obtained by ultrafiltration from a hydroethanolic hamamelis bark extract were found to have greater radical scavenging activity (ED_{50} values of 29 and 80 ng/ml respectively) than a higher molecular weight procyanidin fraction (≥ 3 kDa; ED_{50} 160 ng/ml) as quantified by the emission of chemiluminescence during autoxidation of mouse brain lipids [Erdelmeier 1996].

An extract from Hamamelis leaf and bark (ethanol 60%) showed antioxidant activity in the ABTS assay in a dilution of 1:10000 with an activity equivalent to 40 µM of trolox [Pereira da Silva A 2000].

Hamamelitannin showed strong peroxynitrite (ONOO-)-scavenging properties at a concentration of 5.0 µg/ml in an

experiment using dihydrorhodamine 123 as a substrate for oxidation [Choi 2002].

Antimutagenic activity
In the Ames mutagenicity test, a tincture (1:5) and a methanolic extract (1:5) of hamamelis bark dose-dependently inhibited 2-nitrofluorene-induced mutagenicity in *Salmonella typhimurium* TA98, by 60% and 54% respectively at 100 µl/plate. It was demonstrated that the antimutagenic effect increased with increasing degree of polymerisation of proanthocyanidins, the most active fraction consisting of catechin and gallocatechin oligomers with an average degree of polymerization of 9.2 [Dauer 1998].

In vivo studies

Anti-inflammatory effect
A hydroethanolic extract of hamamelis bark showed a significant anti-inflammatory effect (43% inhibition of oedema; $p<0.05$) in the croton oil ear oedema test in mice when applied topically at 250 µg per ear. After ultrafiltration of the crude extract, this effect was shown to be mainly due to proanthocyanidins of molecular weight ≥ 3 kDa (69% inhibition at 250 µg per ear; $p<0.05$); proanthocyanidins of lower molecular weight had no effect and hamamelitannin produced only 7% inhibition [Erdelmeier 1996].

Anti-bacterial effect
Preincubating grafts contaminated with *Staphylococcus aureus* and *Staphylococcus epidermidis* with hamamelitannin for 7 days prevented infections in male Wistar rats (n=10). No bacteria were found after preincubation with >20µg oh hamamelitannin, while the bacterial load in the untreated control group was 10^7 CFU/ml. In a parallel experiment, grafts soaked with increasing hamamelitannin concentrations were implanted into the animals and bacteria injected onto the graft. Hamamelitannin caused a significant ($p<0.05$) decrease in bacterial load, whereas in the untreated control group 10^7 CFU/ml were found. No bacterial load was found in grafts soaked with 30 mg/l hamamelitannin [Kiran 2008].

Pharmacological studies in humans
The irritant sodium lauryl sulphate was applied at 0.5% twice daily for 3 days under patch occlusion to seven healthy volunteers who also received a semi-solid preparation containing 1 % of hamamelis procyanidin or placebo. Treatment with the preparation reduced increased transepidermal water loss by 53% as compared to placebo (45%). The treatment also increased the clinical scoring of dermal inflammation better than placebo and reduced erythema formation [Deters 2001].

Pharmacokinetic properties
No data available.

Preclinical safety data
No data available.

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