E/S/C/O/P Monographs

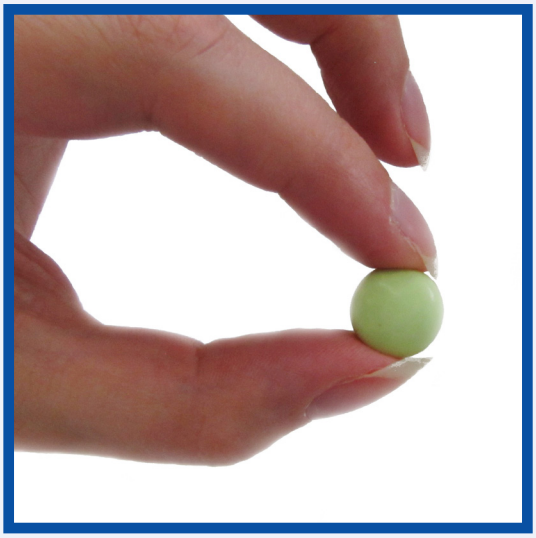
Online Series

The Scientific Foundation for Herbal Medicinal Products

Urticae folium/herba

Nettle Leaf/Herb

2018



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

URTICAE FOLIUM/HERBA
Nettle Leaf/Herb

2018

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

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Plant illustrated on the cover: *Urtica dioica*

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.

Dr. Tankred Wegener
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
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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
CCl_4	carbon tetrachloride
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
DMSO	dimethyl sulfoxide
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
Pgp	P-glycoprotein
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
TC	total cholesterol
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

URTICAE FOLIUM/HERBA 2018

Nettle Leaf/Herb

DEFINITION

Nettle Leaf/herb consists of the whole or cut dried leaves of *Urtica dioica* L., *Urtica urens* L., or a mixture of the 2 species. It contains minimum 0.3 % for the sum of caffeoylmalic acid and chlorogenic acid expressed as chlorogenic acid (dried drug).

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

CONSTITUENTS

Caffeic acid esters, principally caffeoylmalic acid in *Urtica dioica* (up to 1.6%) but none in *Urtica urens*; chlorogenic acid (up to 0.5%) and small amounts of neochlorogenic acid and free caffeic acid in both species.
Flavonoids, principally kaempferol, isorhamnetin, quercetin and their 3-rutinosides and 3-glucosides. Anthocyanins, such as peonidin 3-*O*-rutinoside, peonidin 3-*O*-(6''-*O*-p-coumaroyl glucoside), rosinidin 3-*O*-rutinoside. 13-hydroxyoctadecatrienoic acid, diastereoisomeric 3-hydroxy-α-ionol glucosides, scopoletin, sitosterol and its 3-glucoside, glycoprotein, free amino acids (30 mg/kg).
Minerals (ca. 18% expressed as ash) including potassium (1.8-2.0%) and silicon (0.9-1.8%). The potassium-sodium ratio has been determined as 63:1 in the unprocessed drug.
Stinging hairs on the leaves contain acetylcholine, histamine, 5-hydroxytryptamine (serotonin) and small amounts of leukotrienes.
[Collier 1956; Piekos 1976; Lutomski 1983; Chaurasia 1987; Ellnain-Wojtaszek 1988; Czarnetzki 1990; Bauer 1997; Budzianowski 1991; Lapke 1993; Neugebauer 1995; Schomakers 1995; Szentmihalyi 1998; Schulze-Tanzil 2002].

CLINICAL PARTICULARS

Therapeutic indications

Adjuvant in the symptomatic treatment of arthritis, arthroses and/or rheumatic conditions [Ramm 1995,1996,1997; Hansen 1996; Enderlein 1997; Wolf 1998; Randall 2000].

Nettle leaf or herb is also used as to enhance renal elimination of water in inflammatory complaints of the lower urinary tract [Schilcher 1988,1992; Jaspersen-Schib 1989; Czygan 2002].

Posology and method of administration

Dosage

Internal use

Adults: Hydroalcoholic extracts corresponding to 8-12 g of nettle leaf daily, divided into 2-3 doses [Ramm 1995,1996,1997; Hansen 1996; Wolf 1998]; 3-5 g of the drug as an infusion up to three times daily [Urtica BHP 1983; Van Hellemont 1988 Jaspersen-Schib 1989; Schilcher 1992]; tincture 1:5 (25% ethanol) 2-6 ml three times daily [Urtica BHP 1983]; 15 mL of fresh juice up to three times daily [Kirchhoff 1983].

External use

Adults: Fresh nettle leaf applied to the skin in the area of pain for 30 seconds once daily [Randall 2000].

Method of administration

For oral or topical administration.

Duration of use

No restriction.

Contraindications
None known.

Special warnings and special precautions for use
None required.

Interaction with other medicinal products 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
None known.

Undesirable effects
Gastrointestinal upset or allergic response in a few individuals after oral use [Ramm 1995,1997; Hansen 1996; Enderlein 1997; Wolf 1998].

Overdose
No case of overdose reported.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

In vitro experiments

Anti-inflammatory activity
A hydroethanolic extract (6.4-8:1) and its main phenolic constituent, caffeoylmalic acid, were tested for inhibitory potential on the biosynthesis of arachidonic acid metabolites by rat leukaemic basophilic granulocytes (RBL-1 cells). The extract (0.1 mg/mL) and the isolated acid (1 mg/mL) showed partial inhibitory effects of 20.8% and 68.2% respectively on the 5-lipoxygenase-derived synthesis of leukotriene B_4; caffeoylmalic acid exhibited concentration-dependent activity with an IC_{50} of 85 µg/mL. Both the extract and the acid showed strong concentration-dependent inhibition of the synthesis of cyclooxygenase-derived prostaglandins (IC_{50} of 92 µg/mL for the extract and 38 µg/mL for the acid) [Obertreis 1996].

The same extract significantly and dose-dependently reduced LPS-stimulated release of two proinflammatory cytokines, TNF-α and IL-1β, in human whole blood from 6 healthy volunteers. After 24 hours, TNF-α concentration was reduced by 50.8% and IL-1β concentration by 99.7% using the highest tested extract concentration of 5 mg/mL ($p<0.001$); after 65 hours the inhibition was 38.9% and 99.9% respectively ($p<0.001$). The extract and LPS stimulated the release of IL-6 in human blood when used separately, but showed no additive effect when used simultaneously; IL-6 acts antagonistically to IL-1β, decreasing IL-1β-induced PGE_2 synthesis by fibroblasts and synovial cells. Selected constituents of nettle leaf (caffeoylmalic acid, chlorogenic acid, caffeic acid, quercetin and rutin), tested in the same way did not influence the release of TNF-α, IL-1β or IL-6 at concentrations up to 5×10^{-5} mol/litre [Obertreis 1996].

Th1 and Th2 cells (T helper cells) have cytokine patterns which regulate cell-mediated and humoral immune responses. Th1 cells produce IL-2 and IFN-γ, proinflammatory cytokines that induce a cascade of inflammatory responses. Th2 cells produce IL-4, IL-5 and IL-10. The cytokine patterns of these Th effector cells are antagonistic and cross-regulated; thus agents that promote Th1 cytokine expression inhibit Th2 cytokine production and vice versa. The water-soluble fraction from a nettle leaf extract (6.4-8.1:1) significantly inhibited phytohaemagglutinin (PHA)-stimulated production of Th1-specific IL-2 ($p<0.01$) and IFN-γ ($p<0.02$) in human peripheral blood mononuclear cells (PBMC) in a dose-dependent manner, by 50 ± 32% and 77 ± 14% respectively at the highest concentration tested (equivalent to 400 µg/mLexpressed as the total extract). The dose-dependent inhibiting effect on IL-2 and IFN-γ expression was also detected by reverse transcriptase-polymerase chain reaction in PHA-stimulated PBMC. In contrast, the extract fraction enhanced the secretion of Th2-specific IL-4 by PHA-stimulated PBMC, but dose-dependently decreased IL-10 secretion [Klingelhoefer 1999].

Incubation of HeLa cells with various concentrations of an extract (6.4-8.1:1) before stimulation with TNF demonstrated that the extract potently and dose-dependently inhibited the formation of an NF-κB DNA complex and inhibited NF-κB reporter gene activity; in both cases even stronger inhibition was observed with a water-soluble fraction of the extract. Pretreatment with the water-soluble fraction also inhibited NF-κB activation in stimulated Jurkat T, L929 fibrocarcinoma and MonoMac6 cells. Further experiments with stimulated HeLa and Jurkat T cells suggested that the water-soluble fraction of the extract inhibits NF-κB activation not by modification of DNA binding but by preventing the degradation of its inhibitory subunit IκB-α [Riehemann 1999].

In an *ex vivo/in vitro* study, 2 x 670 mg of an extract (6.4-8.1:1) was administered daily for 21 days to 18 healthy volunteers from whom blood samples were taken at 0, 7 and 21 days. Testing of the whole blood samples revealed, in comparison with day 0 values, significant reductions in LPS-stimulated release of two cytokines, TNF-α and IL-1β: at day 7 and day 21, release of TNF-α had decreased by 14.6% ($p<0.01$) and 24.0% ($p<0.001$), and IL-1β by 19.2% ($p<0.01$) and 39.3% ($p<0.001$), respectively. When a water-soluble fraction from the same batch of nettle leaf extract, at various concentrations, was incubated for 24 hours with 0-, 7- and 21-day whole blood samples from the volunteers, concentration-dependent (and time-dependent in the sense of 7- and 21-day samples from the volunteers) inhibition of LPS-induced release of the same cytokines was demonstrated; at the highest concentration of extract fraction (160 µg/mL) incubated with 21-day blood samples, release of TNF-α decreased by 79.5% ($p<0.001$) and IL-1β by 99.2% ($p<0.001$) compared to day 0 values of blood untreated with the extract fraction [Teucher 1996].

An extract, prepared as 0.25 mg/mL of a lyophilized aqueous extract in water, produced 93% inhibition of PAF-induced exocytosis of elastase from human neutrophils. The same extract (0.2 mg/mL) showed no activity in a test for inhibition of the biosynthesis of prostaglandins [Tunon 1995].

A dry 95%-isopropanolic extract (19-33:1) and 13-hydroxy-octadecatrienoic acid (a constituent present in the extract) at 10 µg/mL significantly suppressed IL-1β-induced expression of matrix MMP proteins on cultured human chondrocytes: relative expression of MMP-1, MMP-3 and MMP-9 decreased by 63-96% ($p = 0.0014$ to 0.0057) with the extract and 60-88% ($p = 0.0078$ to 0.054) with 13-hydroxyoctadecatrienoic acid [Schulze-Tanzil 2002].

A dry 95%-isopropanolic extract (19-33:1) exhibited an immunosuppressant effect in preventing the maturation of cultured human myeloid dendritic cells (without affecting their viability), leading to reduced induction of primary T cell responses [Broer 2002].

Other effects
Aqueous extracts (not further specified) produced slight contraction followed by relaxation in isolated uterine smooth muscle from the non-pregnant mouse. Application of the extracts to uterine muscle from the pregnant mouse produced a diametrically opposed effect, increase of muscular tone and contractions of considerable amplitude [Broncano 1987].

Inhbitory effects of various extracts (petroleum ether, ethyl acetate, methanol and water) and flavonoid aglycone and flavonoid glycoside fractions (1 mg/mL) from *Urtica dioica* leaves on rat platelet aggregation induced by thrombin 0.5 U/mL were analysed. Only the ethyl acetate extract (60-80%), flavonoid aglycones (86.5%) and flavonoid glycosides (82.8%) were significantly ($p< 0.001$) active [El Haouari 2006].

The results from perfusion of glucose-containing Islets of Langerhans by an aqueous extract (10 g/200 mL) showed an increase in insulin secretion both in 2.8 and 16.7 mM solutions [Farzami 2003].

The antiproliferative activity of an aqueous extract of *Urtica dioica* at 0, 0.375, 0.75, 1.5, 2 and 3 mg/mL concentrations on MCF-7 cell line was tested after 24, 48 and 72 hrs. After 72 hrs a dose-dependent manner antiproliferative activity was observed (IC_{50}: 2 mg/mL). There was a significant difference in cell viability between 0.375 mg/mL and 0.75 mg/mL $p< 0.05$) [Fattahi 2013].

The antioxidant activity of an aqueous extract of *Urtica dioica* was evaluated by MTT and showed significant activity ($p< 0.05$) at 3-12 mg/mL concentration [Fattahi 2013].

A hydroethanolic dry extract (not further specified) showed histamine receptor antagonist activity with an IC_{50} of 251 (±13) µg/mL and histamine receptor negative agonist activity with an IC_{50} of 193 (±71) µg/mL. It also showed inhibition of mast cell tryptase, COX-1, COX-2 and haematopoietic prostaglandin D2 synthase with IC_{50} values of 172 (±28), 160 (±47), 275 (±9) and 295 (±13) µg/mL respectively [Roschek 2009].

Ex vivo experiments
An ethanolic extract (5 g/100 mL) of *Urtica dioica* caused significant inhibition (25 µL, 50 µL ($p< 0.01$) and 100 µL ($p< 0.02$)) of adenosine deaminase activity in prostate tissue from patients with prostate cancer (Gleason scores 4-7) [Durak 2004].

In vivo experiments

Antidiabetic Activity
Normal and streptozotocin diabetic rats were injected i.p. with a fraction obtained from an aqueous extract of *Urtica dioica*. A significant ($p< 0.05$) rise in the level of serum insulin was observed after 60 min. Glucose level showed a decrease, initiated at 60 min and 120 min [Farzami 2003].

A hydroalcoholic extract (not further specified) of *Urtica dioica* was administered to Wistar rats at 100 mg/kg/day i.p. for five days and then hyperglycaemia was induced with streptozotocin. After five weeks, blood glucose concentrations were significantly ($p<0.05$) lower in the treatment group compared to an untreated diabetic group (303.6±100.6 and 454.7±34.5 respectively). The percentage of β-cells was significantly ($p<0.05$) higher in the treatment group compared to the untreated diabetic group (1.9 and 22.9 % respectively) [Golalipour 2007].

Hepatoprotective Activity
The effects of 14 days treatment with a hydroethanolic extract (80% ethanol; 50 and 100 mg/kg b.w. p.o.) of *Urtica dioica* were investigated in the liver of Swiss albino mice (8-9 weeks old). Significant increases were observed for the activities of cytochrome b5 (cyt b5), NADH-cytochrome b5 reductase (cytb5R; $p< 0.001$ at doses of 50 mg/kg and 100 mg/kg), glutathione S-transferase and DT-diaphorase ($p< 0.005$ at 50 mg/kg, $p< 0.05$ at 100 mg/kg), and glutathione peroxidase, glutathione reductase, superoxide dismutase and catalase ($p< 0.001$ at doses of 50 mg/kg and 100 mg/kg). Both treatment groups showed significantly lower activity of cytochrome P450, lactate dehydrogenase ($p< 0.001$), NADPH-cytochrome P450 reductase ($p< 0.005$, $p< 0.001$), total sulfhdryl groups ($p< 0.05$, $p< 0.005$) and protein bound sulfhydryl groups (100 mg/kg $p< 0.001$) [Özen 2003].

A study investigated the effects of 14 days treatment with a hydroethanolic extract (80% ethanol; 50 and 100 mg/kg b.w. p.o.) of *Urtica dioica* on hepatic aniline 4-hydroxylase (A4H), NADH and NADPH-NADH in Swiss albino mice (8-10 weeks old). Hepatic aniline 4-hydroxylase (A4H) cofactor requirements were significant at both doses for cofactors NADH ($p< 0.05$), NADPH-NADH at 50 mg/kg ($p< 0.01$) and at 100 mg/kg ($p< 0.005$), and not significant for NADPH at 50 mg/kg but significant at 100 mg/kg ($p< 0.01$). Also A4H activity on Mg^{2+} in mice was found to be significant at doses of 50 mg/kg ($p< 0.05$) and 100 mg/kg ($p< 0.005$), and on Ca^{2+} at 50 mg/kg ($p< 0.01$), but not significant at 100 mg/kg [Özen 2009].

Diuretic effects
The effects of continuous intravenous perfusion into anaesthetized rats for 1.25 hours of solutions (in isotonic 0.9% saline) of a dry aqueous extract at two dose levels, 4 mg/kg/hour or 24 mg/kg/hour, were compared with the effect of furosemide (as a control diuretic), similarly perfused at 2 mg/kg/hour. Compared to control periods (perfusion of saline only), the extract caused dose-dependent increases in diuresis (urine volume) of 11% and 84% (both $p<0.001$) and in natriuresis of 28% and 143% (both $p<0.001$) respectively, while furosemide increased diuresis by 85% and natriuresis by 155% (both $p<0.001$) [Tahri 2000].

No effect on diuresis or ion excretion could be demonstrated in rats after oral administration of an aqueous extract at a dose of 1 g/kg b.w. [Lasheras 1986].

Furthermore, no significant diuretic effect was observed during 2 hours after oral administration to rats of an unspecified ethanolic extract at 1 g/kg b.w., whereas urinary excretion increased significantly after intraperitoneal administration of 500 mg/kg [Tita 1993].

Although the potassium-sodium ratio of dried nettle leaf was determined as 63:1, the ratio in a decoction (2 g of dried leaf boiled in 200 ml of deionized water) was found to be much higher at 448:1 [Szentmihalyi 1998].

Spontaneous motility
An infusion and aqueous extract (3:1) produced dose-dependent reductions in spontaneous motility and body temperature in rats and mice when administered i.p. at doses of 1.739 and 3.748 g/kg b.w. for the infusion and 303 and 606 mg/kg for the extract [Broncano 1987]. An aqueous extract at a dose of 750 mg/kg led to a significant reduction in spontaneous activity in mice during the first 16 hours after administration [Lasheras 1986].

Hypotensive effects
In the perfusion experiments described above under *Diuretic effects*, the diuretic and natriuretic effects were accompanied by a dose-dependent hypotensive effect. Compared to control periods (perfusion of isotonic 0.9% saline only), perfusion of a dry aqueous extract (in isotonic saline) reduced arterial blood

pressure by 15% at 4 mg/kg/hour and 38% at 24 mg/kg/hour (both $p<0.001$); while furosemide at 2 mg/kg/hour reduced arterial blood pressure by 28% ($p<0.001$). The hypotensive effect was reversible within about 1 hour of recovery after the lower dose of extract or furosemide, but was persistent after the higher dose of extract, indicating a possible toxic effect at that dose level [Tahri 2000].

Nettle herb produced a rapid but only transient decrease of 31.7% on the blood pressure of anaesthetized rats after i.v. administration of an aqueous extract at a dose of 25 mg/kg b.w. [Lasheras 1986]. In cats, an aqueous extract (3.3:1) administered by cannula at a dose of 26.6 mg/kg b.w. produced a marked hypotensive effect and bradycardia, which was not compensated by subsequent administration of adrenaline [Broncano 1983].

Hyperglycaemic activity
Both an 80% ethanolic extract and an aqueous decoction, evaporated to dryness, resolubilized and administered to mice at the equivalent of 25 g drug/kg b.w. 2 hours prior to glucose load, produced hyperglycaemic effects in an oral glucose tolerance test [Neef 1995].

Analgesic activity
After administration of an aqueous extract at a dose of 1200 mg/kg, mice showed much greater resistance to thermal stimulation in the hot plate test at 55°C, taking 190% longer time to react than control animals [Lasheras 1986].

An ethanolic extract (not further specified) reduced the writhing response to phenylquinone in rats after oral (1 g/kg) and intraperitoneal (500 mg/kg) treatment but demonstrated no analgesic activity in the hot plate test [Tita 1993].

An *U. urens* extract (80% ethanol) showed significant anti-nociceptive activity in chemically induced mouse pain models; in the writhing test (96.5% inhibition at 250 mg/kg i.p., $p<0.01$), the formalin test (62.8% inhibition at 500 mg/kg p.o., $p<0.05$) and significant ($p<0.01$) antiinflammatory activity in the carrageenan-induced rat hind paw oedema test (41.5% inhibition at 300 mg/kg) [Marassini 2010].

Local anaesthetic activity
Local application to the rat tail of 0.05 mL of an aqueous extract (100 mg lyophilized extract per mL), in the same region as subsequent application of heat in the tail flick test, produced a local anaesthetic effect comparable to that of lignocaine [Lasheras 1986].

Clinical studies

Adjuvant treatment of arthritis, arthroses and/or rheumatic conditions
Five open, multicentric, post-marketing surveillance studies have been carried out on patients with arthritic or rheumatic complaints using a preparation containing a dry hydroethanolic extract (6.4-8:1) at a daily dosage of 2 x 670 mg (corresponding to 9.648 g of dried leaf per day). In each study a proportion of the patients also continued other therapies, primarily non-steroidal anti-inflammatory drugs (NSAIDs), while others received only the nettle leaf extract. Assessments were carried out through patient questionnaires and consultations with physicians. Overall, 80-95% of patients rated the efficacy of the extract, and 93-95% its tolerability, as good or very good [Ramm 1995,1996,1997; Hansen 1996; Wolf 1998]:

- 152 patients with rheumatic pains, of whom about 60% had degenerative disorders of joints, were treated in a 3-week study. Pain symptoms assessed by a visual analogue scale (VAS) improved in 70% of patients by at least one third: pain at rest by 50%, movement pain by 51%. In patients receiving only nettle leaf extract (n = 12) pain decreased by 43% [Ramm 1995].

- 219 patients, mainly with degenerative or inflammatory joint disorders, were treated in another 3-week study. Pain symptoms (VAS) improved by at least one-third in 70% of patients; in patients with pain of degenerative origin by about 50%. Patients taking only nettle leaf extract found it as effective as the extract + NSAIDs [Hansen 1996].

- 223 patients with arthritis (over 50% gonarthritis, 34% coxarthritis) were treated in a 6-week study. Pain intensity (VAS) decreased by 56% and objective assessment of all findings on joints (reddening, overheating, swelling, pressure pain and joint discharge) improved by 60-65% on average. A reduction in complaint symptoms of at least 33% from initial values was experienced by 75% of the patients and this was reflected in patients' responses to a Quality of Life questionnaire. Out of the 130 patients initially taking concomitant NSAIDs, 106 (81%) reduced or discontinued their NSAID dosage [Ramm 1997].

- 8955 patients suffering pain and impairment of mobility due to osteoarthritis or rheumatoid arthritis were treated in a 3-week study. The total symptom scores (1-5 point scales for pain at rest, exercise pain and restricted mobility) of 96% of patients decreased by 45% on average and no clinically relevant differences in efficacy were evident between the group taking only the extract compared to those continuing with NSAIDs or other therapy. 64% of those patients who initially continued NSAID treatment reduced (38%) or discontinued (26%) their NSAID dosage later in the study [Ramm 1996].

- 819 patients with gonarthritis were treated in a 12-month study. Symptoms such as pain, joint stiffness and impaired joint function, assessed by a quantitative gonarthritis-specific questionnaire, decreased by 61% on average. The frequency of each of 5 symptoms (swelling, pressure pain, reddening, joint discharge and overheating) decreased significantly ($p<0.001$) [Wolf 1998].

In an open, randomized 14-day study, patients with acute arthritis received daily either 2 × 100 mg of diclofenac (n = 17) or 50 mg of diclofenac and 50 g of a prepacked stewed nettle leaf purée (water content 95.5%, caffeoylmalic acid content 20 mg) (n = 19). Both groups also received the gastroprotective misoprostol (a prostaglandin analogue). The main criterion of the study was relative improvement in elevated serum levels of C-reactive protein, which decreased by about 70% in both groups. Assessments (verbal rating score 0-4) of physical impairment, subjective pain and pressure pain by patients, and stiffness by physicians, showed improvements in the range 52-77%, with no significant differences between the two groups [Enderlein 1997].

An exploratory study was carried out on the alleviation of pain by external application of fresh nettle leaves, which causes urtication. From analysis of recorded, semi-structured interviews between a doctor and 18 people who had tried this self-treatment for joint or muscle pains, 15 out of 18 claimed that nettle treatment worked on every application; 17 out of 18 reported pain relief after the first course of treatment and had found no other treatment as effective as nettle leaf. Onset of pain relief occurred in less than 24 hours in 11 out of 18 patients. The stinging sensation was reported by 14 out of 18 as 'not painful, with a not unpleasant warmth' and, other than

3 cases of localised numbness for 6-24 hours and a few rashes, no side effects were reported [Randall 1999].

Subsequently a randomized, double-blind, crossover study was carried out involving 27 patients with persistent osteoarthritic pain at the base of the thumb or index finger, none of whom had previously used nettle leaf as a treatment. Existing analgesic or anti-inflammatory treatments were continued during the study. A fresh leaf from pot-grown, non-flowering *Urtica dioica* or *Lamium album* (white deadnettle, as a placebo of similar appearance), handled through plastic, was applied to the affected area once daily for 30 seconds in a standard manner. One week of treatment was followed by a wash-out period of 5 weeks before one week of the alternative treatment. Compared to placebo, significantly greater reductions in scores were observed with nettle leaf on a visual analogue scale for pain ($p = 0.026$) and the Stanford health assessment questionnaire for disability ($p = 0.0027$). No serious side affects were reported and the localized rash and itching associated with nettle leaf was acceptable to 23 of the 27 patients [Randall 2000].

Diuretic effects
In an open 2-week study, 32 patients suffering from myocardial or chronic venous insufficiency were treated daily with 3 × 15 mL of nettle herb pressed juice. A significant increase in the daily volume of urine was observed throughout the treatment, the volume on day 2 being 9.2% higher ($p<0.0005$) than the baseline amount in patients with myocardial insufficiency and 23.9% higher ($p<0.05$) in those with chronic venous insufficiency. Minor decreases in body weights (about 1%) and systolic blood pressure were also observed. Serum parameters were unaffected [Kirchhoff 1983].

Antidiabetic effect
In a randomized, double-blind, placebo-controlled clinical trial, the effects of a dried hydroethanolic *Urtica dioica* extract (ethanol 70%, yield 20.24%) were examined in type 2 diabetic patients. Patients continued with their same dose of conventional oral antihyperglycaemic drugs during the trial. They received one capsule every 8 hours for 3 months, containing either 500 mg of the extract (n=46) or placebo (n=46). Effects on the blood levels of fasting glucose, postprandial glucose, glycosylated haemoglobin (HbA1c), creatinine and liver enzymes SGOT and SGPT, as well as on systolic and diastolic blood pressure were evaluated. Compared with placebo, the extract lowered the blood levels of fasting glucose, 2 hours postprandial glucose and HbA1c significantly ($p<0.001$, $p= 0.009$, and $p= 0.006$ respectively) without any significant effects on the other parameters ($p>0.05$) [Kianbakht 2013].

Antioxidant Effect
A randomized, double-blind, placebo-controlled trial involved 50 patients with type 2 diabetes, administered with either 100 mg/kg b.w. of a hydroethanolic extract (45% ethanol; 2.7 g dry matter per 1L extract) or placebo for 8 weeks. In blood samples collected after 8 weeks, *in vitro* Total Antioxidant Capacity (TAC) and Superoxide Dismutase (SOD) were significantly ($p<0.05$) increased in the intervention group compared to the control group [Namazi 2012].

Pharmacokinetic properties
No data available.

Preclinical safety data
The intraperitoneal LD_{50} of an aqueous extract of *Urtica dioica* herb in mice has been determined as 3.625 g/kg b.w. [Lasheras 1986].

An ethanolic extract of *Urtica dioica* herb showed low toxicity in both rats and mice after oral and intraperitoneal administration at the equivalent of up to 2 g of dried drug per kg b.w. [Tita 1993].

Clinical safety data
No serious adverse effects were reported from 5 clinical studies in which a total of 10,368 patients took 2 x 670 mg of a dry hydroethanolic extract (6.4-8:1), corresponding to about 9.7 g of dried leaf, daily for periods varying from 3 weeks to 12 months; the incidence of minor adverse effects (mainly gastrointestinal upsets or allergic reactions) was 1.2-2.7% [Ramm 1995-1997; Hansen 1996; Wolf 1998]. In a study where 19 patients received 50 g of a stewed nettle leaf purée daily for 14 days, 3 patients reported meteorism [Enderlein 1997].

A case of gynaecomastia in a man and a case of galactorrhoea in a woman were reported after consumption of 2-3 cups nettle tea daily for one month. However, the causal relationship was unclear [Şahin 2007].

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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	Online Series, 2018
ANGELICAE RADIX	Angelica Root	Supplement 2009
ANISI FRUCTUS	Aniseed	Online Series, 2014
ARNICAE FLOS	Arnica Flower	Second Edition, 2003
ARCTII RADIX	Burdock Root	Online Series, 2016
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BETULAE FOLIUM	Birch Leaf	Online Series, 2015
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
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COLAE SEMEN	Cola	Online Series, 2014
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CRATAEGI FRUCTUS	Hawthorn Berries	Supplement 2009
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CURCUMAE LONGAE RHIZOMA	Turmeric	Second Edition, 2003
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ECHINACEAE PALLIDAE RADIX	Pale Coneflower Root	Online Series, 2018
ECHINACEAE PURPUREAE HERBA	Purple Coneflower Herb	Supplement 2009
ECHINACEAE PURPUREAE RADIX	Purple Coneflower Root	Supplement 2009
ELEUTHEROCOCCI RADIX	Eleutherococcus	Supplement 2009
EQUISETI HERBA	Equisetum stem	Online Series, 2018
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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
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PASSIFLORAE HERBA	Passion Flower	Second Edition, 2003
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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	Online Series, 2016
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	Online Series, 2017
RATANHIAE RADIX	Rhatany Root	Online Series, 2017
RHAMNI PURSHIANI CORTEX	Cascara	Online Series, 2015
RHEI RADIX	Rhubarb	Online Series, 2018
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SALVIA TRILOBAE FOLIUM	Sage Leaf, Three-lobed	Online Series, 2014
SENNAE FOLIUM	Senna Leaf	Second Edition, 2003
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