EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

6 May 2010
EMA/HMPC/142989/2009
Committee on Herbal Medicinal Products (HMPC)

This document was valid from 6 May 2010 until September 2017. It is now superseded by a new version adopted by the HMPC on 19 September 2017 and published on the EMA website.

Assessment report on *Ribes nigrum* L., folium

Based on Article 10a of Directive 2001/83/EC as amended (well-established use)

Based on Article 16d(1), Article 16f and Article 16h of Directive 2001/83/EC as amended (traditional use)

Final

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Ribes nigrum* L., folium; (blackcurrant leaf)
Herbal preparation(s)	a) Comminuted herbal substance b) Dry extract (DER 7:1), extraction solvent water
Pharmaceutical forms	Comminuted herbal substance as herbal tea for oral use. Herbal preparations in solid dosage forms. The pharmaceutical form should be described by the European Pharmacopoeia full standard term.
Rapporteur	Belgium
Assessor(s)	Gert Laekeman & Arnold Vlietinck

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7051
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

Table of contents

1. Introduction

Handbooks as well as publications (PubMed & local journals) were used as sources. Keywords: *Ribes nigrum*, blackcurrant, cassis.

1.1. Description of the herbal substance(s), herbal preparation(s) or combinations thereof

- Herbal substance(s)

Blackcurrant leaf consists of the dried leaves of *Ribes nigrum* L. (blackcurrant), belonging to the family of the *Grossulariaceae*. The genus *Ribes* contains between 140 and 150 species. The leaves are collected during or shortly after flowering (Pharm. Française 1996; Hänsel et al. 1994).

A dark green upper surface and a pale greyish green lower surface is characteristic for the slightly wrinkled leaf fragments. Furthermore a widely spaced reticulate venation is particularly distinct on the lower surface. Glands can be seen as scattering yellowish dots. In contrast with the fresh leaves, the dried leaves have no odour or taste. There are no falsifications as the herbal substance is harvested from cultivation (Wichtl 1994; Hänsel et al. 1994).

The dried *Ribes nigrum* leaf contains not less than 1.5% of **flavonoids**, expressed as rutin. The material complies with the monograph of the Pharmacopée Française (1996) (ESCOP, 2003).

- Phytochemistry

The most important secondary metabolites present in the herbal substance can be subdivided into several groups of phytochemical compounds.

Polyphenolic substances, more particularly **flavonoid glycosides**: kaempferol, quercetin.

Hydroxycinnamic acid derivatives: chlorogenic acid and chlorogenic acid derivatives (isochlorogenic acid, neochlorogenic acid), caffeic acid, gallic acid, ferulic acid, coumaric acid, gentisinic acid (Trajkovski, 1974a; Trajkovski 1974b).

Some substances can seasonally appear in the glands of leaves of *Ribes nigrum*. **Sakuranetin** is a methylated flavanone aglycone (4',5-diOH-7-methoxyflavanone). Its biosynthesis may be useful in the protection against parasites like *Botrytis cinerea* Pers. ex Fr. (Atkinson & Blakeman, 1982).

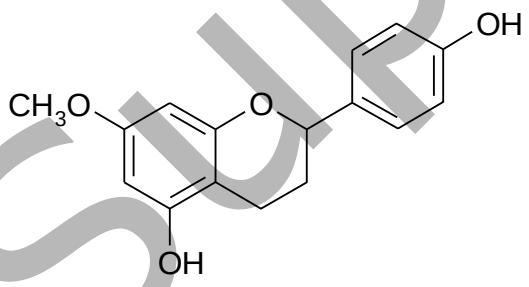

Figure 1: sakuranetin

Prodelphinidins (**proanthocyanidines)** were identified in a methanolic extract of the leaves. They may be responsible for the anti-inflammatory properties of the herbal preparations (Tits et al. 1992a; Tits et al. 1992b).

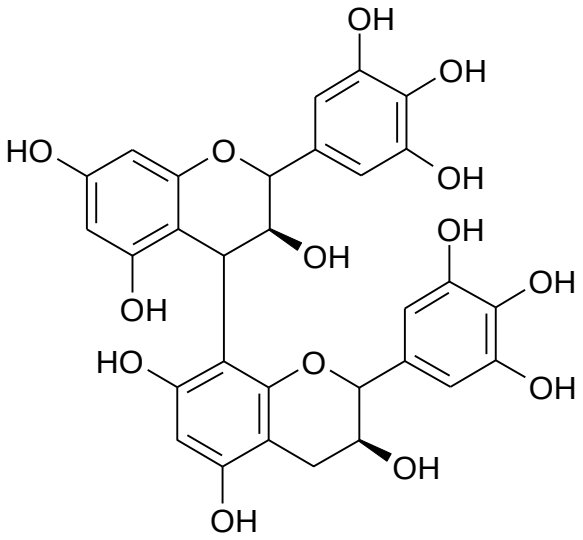

Figure 2: dimer prodelphinidin I

The presence of **glycerolipids** has been reported. The total fatty acid composition was unusual, because the following unsaturated fatty acids were identified: linolenic acid (alpha-18:3), together with cis-7, 10, 13-hexadecatrienoic acid (16:3) and lower amounts of stearidonic acid (18:4) and gamma-linolenic acid (gamma-18:3). This makes the lipid composition type mixed: typical of 16:3 plants but also partially typical for 18:4 plants (Dobson, 2000).

Ascorbic acid is present: between 100 and 270 mg per 100 g dried material (Hänsel et al. 1994).

- Herbal preparation(s)

The essential oil of the leaves of *Ribes nigrum* contains mainly monoterpenic substances like alpha-pinene, myrcene, p-cymene, limonene, beta-ocimene, beta-phellandrene, linalool, terpinen-4-ol, geraniol, citronellylacetate. Furthermore the sequiterpenes caryophyllene and humulene were identified, as well as methyl salicylate (Andersson et al. 1963).

The potassium-sodium ratios in the leaf of *Ribes nigrum* and decoctions of the leaves were 128:1 and 242:1 respectively. These ratios are considered as eventually contributing to the diuretic effect (Szentmihályi et al. 1998).

1.2. Information about products on the market in the Member States

Regulatory status overview

Member State	**Regulatory Status**				**Comments (not mandatory field)**
Austria	☐ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify:	No authorized or registered preparations. *Ribes nigri* folium only as an excipient or in mixed preparations
Belgium	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No preparations registered or authorized
Bulgaria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorized or registered preparations

Member State	Regulatory Status				Comments (not mandatory field)
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information
Czech Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorized or registered preparations
Denmark	☐ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify:	Only food supplements
Estonia	☐ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify:	Can be used in food supplements
Finland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorized or registered preparations
France	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	Registered preparations for oral use
Germany	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorized or registered preparations
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorized or registered preparations
Hungary	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Only combinations registered
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorized or registered preparations
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify:	Excipient in authorized medicines (berries and leaves)
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorized or registered preparations
Latvia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information
Lithuania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorized or registered preparations
Luxemburg	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information
Malta	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorized or registered preparations
The Netherlands	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorized or registered preparations
Norway	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorized or registered preparations
Poland	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	Herbal tea
Portugal	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorized or registered preparations
Romania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information
Slovak Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorized or registered preparations
Slovenia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorized or

Member State	Regulatory Status				Comments (not mandatory field)
					registered preparations
Spain	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	Comminuted herbal substance in capsules
Sweden	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorized or registered preparations
United Kingdom	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorized or registered preparations

MA: Marketing Authorisation
TRAD: Traditional Use Registration
Other TRAD: Other national Traditional systems of registration
Other: If known, it should be specified or otherwise add 'Not Known'
This regulatory overview is not legally binding and does not necessarily reflect the legal status of the products in the MSs concerned.

Marketing specifications

Country	Therapeutic indication	Details
Austria	One combination product is used as an adjuvant in case of liver and bile complaints.	The product is an oral solution containing *Ribes nigri folium*, apart from *Agrimonia eupatoria, Achillea millefolium, Mentha piperita, Rosa canina, Berberis vulgaris.* The content of ethanol is 20%.
France	Traditionally used to support renal and digestive elimination systems Traditionally used to treat minor articular pain.	Powdered herbal substance in hard capsules: 340 mg per capsule • on the market since 1988 • posology: 1 capsule 3x daily (maximally 5 capsules per day) Dry extract (DER 7:1; extraction solvent water) in hard capsules: 169 mg per capsule • on the market since 1990 • posology: 1 to 3 capsules daily
Ireland	Expectorant for the relief of chesty coughs, nasal congestion and catarrh	Listed as an excipient of a Chesty Cough and Decongestant Oral Solution
Poland	Herbal medicinal product traditionally used in minor rheumatic complaints. Topical use in minor skin inflammations.	Herbal tea: 2-4 g 3x daily There are 2 authorized products on the market. The herbal substance was described in the Polish Herbal Compendium from 1978.
Spain	Traditionally used as a diuretic and in minor rheumatic complaints Combination products are used for diuretic activity and as an adjuvant	(Powdered) herbal substance in hard capsules: 250 mg per capsule • on the market since 1991 • posology: 1-2 capsules, 2-3x daily Also in combination products: *Ribes nigrum*

Country	Therapeutic indication	Details
	in case of diets and for losing weight.	with *Camellia sinensis*.

1.3. Search and assessment methodology

2. Historical data on medicinal use

2.1. Information on period of medicinal use in the Community

Inflammatory conditions

Indications exclusively in folk medicine are: arthritis, rheumatic complaints, diarrhoea, spasmodic cough. Rarely preparations were locally applied on wounds (Wichtl, 1994). *Ribes* has been traditionally used as an infusion to cure joint complaints (traditionally classified as 'rheumatism') (Leclerc 1983; Rombi 1991). The only indication mentioned in the ESCOP monograph is 'adjuvant in the treatment of rheumatic conditions' (ESCOP, 2003).

Anti-inflammatory posology according to ESCOP (2003), Van Hellemont (1985) and Delfosse (1998):

- Dried leaves as an infusion: from 1.5 to 4 g per cup (= 150 ml; 3-4 cups daily) to 20-50g per litre (250 to 500 ml daily), infused during 15 minutes.
- Fluid extract (1:1): 5 ml 2x daily. The extraction solvent is not specified.

Other indications

Leaves of *Ribes nigrum* were mainly used in folk medicine as a diuretic, eliminating uric acid. The preparations mentioned are aqueous decoctions (Decaux, 1930; Hänsel et al. 1994).

Some authors mention the use of tea preparations containing *Ribes nigrum*, *Fraxinus excelsior* and *Ulmaria officinalis*.

The essential oil of *Ribes nigrum* should stimulate the renal epithelium and enhance diuresis (Garnier et al. 1961; Rombi 1991).

Leaves were applied on the head against migraine (Decaux, 1930).

Justification for acceptance of herbal preparations in the monograph

- Herbal tea (2-4 g up to 3 times daily) has been used since 1978 in Poland for minor rheumatic complaints and can be accepted according to the 30 years of use stipulated in Directive 2001/83/EC [article 16b paragraph (c)].
- Powdered herbal substance in capsules has been marketed in France (since 1988) and in Spain (since 1991) in different posologies (France: 340 mg up to 5 capsules per day; Spain: 250 mg up to 6 capsules per day). The period of use covers 15 years in Europe but is not fulfilling the 30 years of traditional use as stipulated in Directive 2001/83/EC [article 16b paragraph (c)]. The company provided evidence for a market introduction of a capsule containing 260 mg of 'cassis' powder in 1983. This would mean that the preparation could be included in the monograph from 2013 on.
- Dry extract (7:1; extraction solvent water) is marketed in France as capsules (169 mg per capsule; posology: up to 3 capsules daily) meets the 15 year tradition in Europe and does not comply with the 30 years of traditional use as stipulated in Directive 2001/83/EC [article 16b paragraph (c)]. Nevertheless during its meeting of 12 January 2010 the MLWP decided to accept this preparation based upon the following justification:
- - The extract is made with water, a procedure close to herbal tea preparations.
- - The drug-extract ratio is 7 to 1 and 169 mg is taken as a single dose up to 3 times a day. One capsule corresponds to 1183 mg of herbal substance. For herbal tea 2 to 4 g herbal substance is

infused; virtually, more material can be extracted by preparing the herbal tea. The number of daily doses is similar for the extract and the infusion.

- Topical use is not granted, because there are no preparations and posology specified (cf. Poland).

2.2. Information on traditional/current indications and specified substances/preparations

2.3. Specified strength/posology/route of administration/duration of use for relevant preparations and indications

3. Non-Clinical Data

3.1. Overview of available pharmacological data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

In vitro

- Biosynthesis and release of prostaglandins

Rabbit heart

The experimental model was the isolated heart of the rabbit with arachidonic acid as substrate (100 µg). The preparation consisted of purified flavonoid substances, but no further data about the exact composition are available.

The prostaglandins released in the heart effluent were detected by means of bioassay, using the rat stomach strip.

Total flavonoids extracted from the leaves of *Ribes nigrum*, **inhibited both biosynthesis and release of PG-like substances**. They were more active than rutin and isoquercitin. The IC_{30} were respectively 1.03 + 0.24 mg/ml, 3.76 + 0.24 mg/ml and 2.31 + 0.40 mg/ml (Chanh et al. 1986).

Chondrocytes and COX

The experimental model consisted of cultured human chondrocytes from cartilage isolated after surgery and cyclo-oxygenase-1 (COX-1) from ram seminal vesicles and cylco-oxygenase-2 (COX-2) from sheep placenta.

The herbal preparation consisted of leaf extract made with acetone (70% v/v in water). The resulting condensed tannins were purified using reversed phase and Sephadex LH20 column chromatography. The proanthocyanidines were purified to 95%. Purification yielded among others catechin, gallocatechin, gallocatechin-gallocatechin and gallocatechin-epigallocatechin.

Several effects of these purified fractions were evaluated on the cultivated chondrocytes:

- A positive effect on the production of proteoglycans with concentrations from 1 to 100 µg/ml.
- A positive effect on type II collagen production with concentration from 1 to 100 µg/ml.
- An **inhibitory effect on the prostaglandin E2 (PGE2) production** mainly with concentrations from 10 to 100 µg/ml.

Isolated prodelphinidines had an inhibitory effect on the biosynthesis of prostaglandins catalyzed by COX-1 and COX-2. A concentration of 10^{-4}M of gallocatechin and its dimer inhibited the formation of prostaglandins to the same extent as indomethacin 10-5M: 53%, 57% and 67% respectively (Garbacki et al. 2002).

Endothelial cells

The experimental model consisted of an LT2 cell line originating from human umbilical vein endothelium cells.

A proanthocyanidin-enriched fraction was obtained from leaves from *Ribes nigrum* with acetone extraction (70% v/v in water). Purification was done on reversed phase chromatography.

A significant inhibition of TNF-α (Tumor Necrosis Factor) stimulated ICAM-1 (Intercellular Adhesion Molecule 1) expression was obtained with proanthocyanidins in concentrations starting from 10 µg/ml on (Garbacki et al. 2005).

- Antilipoperoxidative effects

Methanolic crude extracts of fruits, leaves and buds of *Ribes nigrum* were tested in rat hepatic microsomes. The extracts contained between 818 to 997 mg polyphenols per 100g leaves. The oxidative mixture consisted of a Fe^{++} ($FeSO_4$) and ADP mixture in the presence of ascorbic acid. Antilipoperoxidative effects were measured by quantifiying the amount of malondialdehyde. The IC50 of the extracts varied between 9.31 and 6.44 µg/ml (Costantino et al. 1993).

In vivo

- Anti-inflammatory and analgesic effects

Reference	**Experimental model**	**Intervention**	**Outcome**
Declume (1989)	Rats Carrageenan paw oedema Extract of Rn in 14% ethanol PO 30 minutes prior to carrageenan	PO acute (1) Rn 1 and 10 ml/kg (2) Indo 2.5 and 5 mg/kg (3)Nifl 25 and 50 mg/kg PO subacute: 21 days (4) Rn 0.33, 1 and 10 ml/kg (5) Indo 1,66 mg/kg (6) Nifl 12.5 mg/kg	Reduction paw oedema (after 4 hours) (1) - 30% and - 54% (2) - 63% and - 66% (3) - 19% and - 70% Reduction paw oedema (4) - 30%, -42.5% and -46% (5) - 49% (6) - 53%
Mongold (1993)	Rats Maceration of Rn in 15% ethanol: lyophylizate Model 1 Carrageenan paw oedema Model 2 Cotton-pellet induced granuloma test: 2 cotton pellets intradorsally implanted Model 3 Freund's adjuvant-induced arthritis test: *Mycobacterium butyricum* injected in tail: paw oedema resulting	Model 1: IP acute: paw oedema (1) Rn 100 and 200 mg/kg (2) Indo 5 and 10 mg/kg Model 2 IP daily for 7 days (3) Rn 150 mg/kg (4) Indo 3 mg/kg Model 3 IP daily for 14 days (5) 100 and 200 mg/kg (6) Indo 3 mg/kg	Model 1 Paw oedema (after 3 hours) (1) - 70% (100 mg/kg) (2) - 77% (1) and (2) P<0.01 (vehicle) Model 2 Weight of granuloma (day 8) (3) - 18.6 % (4) - 24 % (3) and (4) P<0.001(vehicle) Model 3 Paw volume (5) - 18.7 and - 34.6% (6) - 37.7% (5) and (6) P<0.01 (vehicle)
Tits et al. (1991)	Rats Carrageenan paw	IP acute Prodelphinidins	Reduction paw oedema: (1) - 18%, - 40%, - 55% and

Reference	Experimental model	Intervention	Outcome
	oedema	(1) 5, 10, 40 and 60 mg/kg (2) Indo 4 mg/kg (3) ASA 200 mg/kg	- 57% (2) - 44% (3) - 47%
Mongold (1993)	Mice <u>Model 1</u> Acetic acid induced writhing test Maceration of Rn in 15% ethanol: lyophylizate: given 30 prior to acetic acid <u>Model 2</u> Hot-plate (55°C) response with Rn lyophilizate	<u>Model 1</u> IP acute (1) Rn lyophilizate (2) paracetamol <u>Model 2</u> IP acute (1) Rn lyophilizate: 200 mg/kg (2) Morphine 4 mg/kg	<u>Model 1</u> Reduction of writhing (1) ED_{50} = 61.5 mg/kg (2) ED_{50} = 132 mg/kg Therapeutic index = LD_{50}/ED_{50} (1) 17.7 (2) 3.8 <u>Model 2</u> Time to escape (1) not significant (vehicle) (2) > vehicle: P < 0.001
Garbacki (2004)	Male Wistar rats <u>Model 1</u> Carrageenin induced paw oedema: injection of of carrageenin 30 minutes after the test substances <u>Model 2</u> Carrageenin-induced pleurisy: injection of carrageenin in the right pleural cavity 30 minutes after the test substances Test substances = PACs of Rn by extraction in acetone 70% (v/v in water) + purification by RP	<u>Model 1</u> (1) IP injection: one dose PACs: 10, 30, 60 or 100 mg/kg (2) Saline <u>Model 2</u> IP injection: one dose of: (1) PACs: 10, 30, 60 or 100 mg/kg (2) Indomethacin 10 mg/kg Pleural cavity opened after 4 hours	Paw oedema evaluated after: 1 hour: PACs = saline 2 hours:,PACs (60 and 100 mg/kg) < saline (P<0.05) 4 hours: PACs (all doses) < saline (P<0.05) <u>Model 2</u> *Volume of exsudate* PACs (30, 60 and 100 mg/kg) and indo < saline (P<0.05) *Infiltration of PMNs* PAC (all doses) and indo < saline (P<0.05) *TNFα release* PACs (30 mg/kg) and indo < saline (P<0.05) *Release of IL-6 and IL-10* PACs: no influence Indo < saline (P<0.05) *Release of CINC-1* PACs (30 mg/kg) and indo < saline (P<0.05) *NOx formation* PACs (30 mg/kg) < saline (P<0.05) Indo ≈ saline
Garbacki (2005)	Male Wistar rats Carrageenin-induced pleurisy: injection of carrageenin in the right pleural cavity 30 minutes	IP injection: one dose (1) PACs: 10, 30 or 60 mg/kg (2) Saline Pleural cavity opened after	Production of cytokines by PMNs CD11a: no influence CD11b: stimulation with 60 mg/kg

Reference	Experimental model	Intervention	Outcome
	after the test substances PACs of Rn by extraction in acetone 70% (v/v in water) + purification by RP	4 hours	CD49d: inhibition with 10 mg/kg stimulation with 60 mg/kg

CINC-I = cytokine-induced neutrophil chemoattractant-I
ED_{50} = effective dose in 50% of animals
Indo = indomethacin
IP = intraperitoneal
LD_{50} = lethal dose in 50% of animals
Nifl = niflumic acid
PACs = proanthocyanidines
PMNs = polymorphonuclear leukocytes
PO = peroral
Rn = *Ribes nigrum*
RP = reversed phase (chromatography)

- Diuretic activity

The model used was a salidiuretic action. The intervention consisted of oral administration of a fluid extract (1:1) of blackcurrant leaf. The diuretic action of an equivalent of 1500 mg dried leaf/kg was **comparable to the effect of furosemide at 50 mg/kg** (Rácz-Kotilla & Rácz 1977).

- Antihypertensive effects

The model used was the antihypertensive effect on cats. Doses liquid extract (1:1) equivalent to of 400 mg dried blackcurrant leaf/kg were compared to tolazoline 0.75 mg/kg and 1.0 mg/kg. The **antihypertensive effects of both were comparable**, but the effect of the leaf extract lasted for 20 minutes as compared to 5 minutes for tolazoline (Rácz-Kotilla & Rácz 1977).

In another study normotensive rats were used. An infusion of blackcurrant leaf (20g/L) was administered intravenously at a dose equivalent to 360 mg dried leaf per kg. There was a **45% fall in blood pressure**, which after 30 minutes was still 30% (Laserre et al. 1983).

3.1.1. Assessor's overall conclusions on pharmacology

Most of the experimental in vivo pharmacology with *Ribes nigrum* herbal preparations was done on models of inflammation: carrageenin paw oedema, cotton pellet granuloma test and carrageenin induced pleurisy. Rats were the species used. The preparations consisted mainly of alcoholic liquid extracts which were mostly lyophilized. They were administered perorally as well as intraperitoneally. *Ribes nigrum* performed qualitatively and quantitatively well as compared to non steroidal anti-inflammatory substances like indomethacin, nifluminic acid and acetylsalicylic acid. Several inflammatory parameters were significantly reversed, especially the formation of oedema and the cellular components as illustrated by reduced exsudate, infiltration of polymorphonuclear leukocytes, release of interleukins and cytokines and the formation NO-components.

Apart from the anti-inflammatory activity there was also an analgesic activity demonstrated in the acetic acid induced writhing test and the hot-plate response with mice. Alcoholic extracts were intraperitoneally administered. The therapeutic index in the writhing test was about 5 times better than the one of paracetamol. On the contrary, *Ribes nigrum* was not effective in the hot plate response as compared to vehicle and morphine.

In vitro experiments confirmed the anti-inflammatory actions seen in vivo. Flavonoids extracted from *Ribes nigrum* inhibited the biosynthesis of prostaglandins in whole organs (rabbit heart) as did concentrated proanthocyanidines in COX-1 preparations (from ram seminal vesicles) and COX-2 preparations (sheep placenta). The effect was comparable to indomethacin.

Additional properties emerged from in vitro experiments with human chondrocytes. Purified proanthocyanidins stimulated the biosythesis of proteoglycans and collagen. This can be considered as an activity complementary to the treatment of inflammation. Furthermore proanthocyanidins inhibited the formation of tumor necrosis factor α and the intracellular adhesion molecule in human endothelial cells. Finally antilipoperoxydase effect can be added to this large scope of activities.

As a conclusion, an overview of the experimental pharmacology of *Ribes nigrum* preparations opens perspective for further clinical investigations in human subjects.

3.2. Overview of available pharmacokinetic data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

No data with regard to absorption, distribution, metabolism, elimination and pharmacokinetic interactions with other medicinal products are available.

3.2.1. Assessor's overall conclusions on pharmacokinetics

Not applicable.

3.3. Overview of available toxicological data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof

- Acute toxicity

Mice were used as animal species. *Ribes* nigrum leaf was administered intraperitoneally as liquid extract (1:1). The intraperitoneal LD_0 and LD_{50} were 22 and 49 g/kg respectively. The LD_{100} was estimated at 90 g/kg (ESCOP, 2003).

In another study with mice a lyophilizate obtained by maceration of 100 g leaf per litre 15% ethanol was administered. Intraperitoneal LD_{50} was 1.09 g/kg. Oral doses up to 3 g/kg did not show overt toxicity (ESCOP, 2003; Mongold 1993).

- Subacute toxicity

Rats were used as animal species. *Ribes nigrum* leaf was administered as a lyophilized 15% ethanolic extract (1 g of extract was equivalent to 1.8 g of leaf). The extract was administered orally in daily doses of 2 g/kg/day (21 days) and 1.34 g/kg/day (28 days) respectively. No signs of toxicity or gastric ulceration were observed (ESCOP, 2003).

Rats were used as animal species. *Ribes nigrum* leaf was administered as a lyophilizate obtained by maceration of 100 g leaf per liter 15% ethanol. The extract was administered orally during 10 days without specification of the dose. No change in feeding pattern, fluid consumption or body weight was seen. Blood analysis and histopathological evaluation of 14 organs did not reveal any abnormalities (ESCOP, 2003, Mongold 1993).

- Chronic toxicity

Feeding mice with a daily dose of 3 g/kg of dried leaves during 6 months did not reveal any toxicity (Hänsel et al. 1994).

3.3.1. Assessor's overall conclusions on toxicology

No signs of major toxicity can be seen. In contrast of what could be expected from preparations able to inhibit cyclo-oxygenase, no gastric damage could be detected.

3.4. Overall conclusions on non-clinical data

4. Clinical Data

4.1. Clinical Pharmacology

4.1.1. Overview of pharmacodynamic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents

No clinical data available.

4.1.1.1. Assessor's overall conclusions on pharmacodynamics

Not applicable.

4.1.2. Overview of pharmacokinetic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents

No data available.

4.1.2.1. Assessor's overall conclusions on pharmacokinetics

Not applicable.

4.2. Clinical Efficacy[1]

4.2.1. Dose response studies

No dose response studies available.

4.2.2. Clinical studies (case studies and clinical trials)

No clinical studies reported.

4.2.3. Clinical studies in special populations (e.g. elderly and children)

No clinical studies in special populations reported.

4.3. Overall conclusions on clinical pharmacology and efficacy

Not applicable.

[1] In case of traditional use the long-standing use and experience should be assessed.

5. Clinical Safety/Pharmacovigilance

5.1. Overview of toxicological/safety data from clinical trials in humans

No data collected.

5.2. Patient exposure

No data available.

5.3. Adverse events

No data available.

5.4. Serious adverse events and deaths

None reported.

5.5. Laboratory findings

None reported.

5.6. Safety in special populations and situations

Oedema due to heart failure or renal insufficiency is mentioned as a possible contra-indication without any further specification (Hänsel et al. 1994).

5.6.1. Intrinsic (including elderly and children) /extrinsic factors

No data available.

5.6.2. Drug interactions

No data available.

5.6.3. Use in pregnancy and lactation

No data available.

5.6.4. Overdose

No data available.

5.6.5. Drug abuse

No data available.

5.6.6. Withdrawal and rebound

No data available.

5.6.7. Effects on ability to drive or operate machinery or impairment of mental ability

No data available.

5.7. Overall conclusions on clinical safety

Not applicable.

6. Overall conclusions

There is a lot of interesting experimental work done in vitro as well in vivo with preparations of *Ribes nigrum*. The results of these studies substantiate the traditional use of blackcurrant leaves in inflammatory conditions. There is experimental evidence for an additional analgesic activity. No signs of general or gastro-intestinal toxicity are seen.
As a consequence the clinical perspective of *Ribes nigrum* leaves and its preparations may be promising. Up to now clinical data are totally absent which means that the herbal drug and herbal preparations thereof can only be considered as traditionally used.

6.1. Benefit-risk assessment

According to the ORGAM proposal[2] a benefit-risk assessment can be made of *Ribes nigri* folium.

- Quality issues

The herbal medicinal substance is not yet described in the European Pharmacopoeia, but there are other standard references as the quality of the raw material is concerned (French Pharmacopoeia, Hagers Handbuch and ESCOP). By these descriptions a clear definition of the raw material can be guaranteed. The herbal substance can be identified without too much difficulty. Moreover, there is a characteristic smell due to the essential oil content.

- Safety issues

There are no published reports on serious side effects when taking therapeutic doses or after (in)voluntary intoxications with the herbal substance or herbal preparations thereof. Secondary metabolites of *Ribes nigri* folium have a polyphenolic character and can be considered as antioxidants. Acute or chronic preclinical toxicity investigations are no subject to any major concerns. Nevertheless, polyphenols can be harmful in high concentrations and high daily intake in concentrated form. There is still a need for the investigation of genotoxic, mutagenic and cancerogenic properties in order to facilitate a list entry.

- Therapeutic issues

The pathological conditions for which *Ribes nigri* folium is used are mostly symptomatically approached. There are no conditions when they should be avoided. In inflammatory conditions a symptomatic approach is made. When comparing the herbal substance with the medicines actually in use, the effectiveness of the former is only preclinically documented. Nevertheless, the use of *Ribes nigri* folium and preparations thereof seems safer concerning side effects, more particularly gastro-intestinal side effects. Actually the possible therapeutic consequences of a hypothesized diuretic action of *Ribes nigri* folium cannot be compared with the clinical significance of the actual diuretics used in cardiovascular prevention and treatment. It is not recommendable to use the herbal substance or preparations thereof in this therapeutic context.

[2] Benefit-risk assessment. Annex to comment on concept paper benefit-risk: EMEA HMPC 2008.

There are no concerns of possible drug interactions. The use is not recommended in children and during pregnancy and lactation. This precaution is because safety data is lacking: there are no real indications for use in these groups at risk.
The herbal substance has been on the market for more than 30 years in some European countries. As the plant belongs to the European fauna of the mixed climate zone and the berries have been well known[3], traditional use of the leaves is much older and dates probably back for centuries.

Annex

List of references

[3] The use of leaves has already been mentioned by Rembertus Dodonaeus in his 'Herbarius ofte Cruydt-Boeck', Antwerpen 1608 p. 1264.