EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 November 2010
EMA/HMPC/3206/2009
Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Quercus robur* L., *Quercus petraea* (Matt.) Liebl., *Quercus pubescens* Willd., cortex

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)	Quercus robur L. Quercus petraea (Matt.) Liebl. Quercus pubescens Willd. Cortex
Herbal preparation(s)	i) Herbal substance *Quercus robur* L., *Quercus petraea*.(Matt.) Liebl., *Quercus pubescens* Willd., oak bark. Cut and dried bark from the fresh young branches. ii) Herbal preparations - Comminuted herbal substance - Powdered herbal substance Dry extract (5.0-6.5:1), extraction solvent: ethanol 50% V/V
Pharmaceutical forms	Herbal substance or herbal preparations in solid or liquid dosage forms for oral use or as herbal tea for oral use. Herbal substance or comminuted herbal substance for decoction preparation for oromucosal cutaneous or anorectal use.
Rapporteur	Dr Ewa Widy-Tyszkiewicz
Assessor(s)	Dr Ewa Widy-Tyszkiewicz

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

Table of contents

1. Introduction

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

Herbal substance(s)

The herbal substance is mentioned in several well known handbooks such as Madaus (1938), Martindale (2007), Bisset and Wichtl (1994), PDR for Herbal Medicines (2000; 2004), German Comission E Monograph and European Pharmacopoeia 6.0, Duke's Handbook of Medicinal Herbs (2002), Mills and Bone (2000), Schulz et al. 1998, Wagner and Wiesenauer 1995; Weiss and Fintelman (1999).

In the European Pharmacopoeia, it is described as the cut and dried bark of young branches and the lateral shoots of *Quercus robur*, *Quercus petraea* and/or *Quercus pubescens.* It contains a minimal amount of 3% of tannins, expressed as pyrogallol, calculated with reference to the dried herbal substance.

The plant belongs to the family *Fagacae*, subfamily *Quercoideae*, genus *Quercus.*

Oak bark is harvested in spring from March to April.

The oak bark contains highly variable amount of tannins (8-20%). The tannin content depends on the time of the harvest, age of the branches and on the method of assay used. Tannins are polyphenolic secondary metabolites of higher plants. They comprise either: galloyl esters and their derivatives (gallotannins, ellagitannins and complex tannins) or they are oligomeric and polymeric proanthocyanidins and can possess different interflavanyl coupling and substitution patterns (condensed tannins) (Okuda et al. 1993; 2005). The oak bark contains both hydrolyzable and condensed tannins (Ahn and Gstirner 1971; 1973; Bate-Smith 1972; Bruneton 1995; Chen 1970; Evans 2009; Glasl 1983; Grundhöfer et al. 2001; Haddock et al. 1982; Haslam 2007; Haslam and Cai 1994; Herve du Penhoat et al. 1991a, 1991b; Ikram and Nowshad 1977; Ishimaru et al. 1987; Khanbabaee and van Ree 2001; König et al. 1994; Mämmelä et al. 2000; Niemetz and Gross 2005; Pallenbach et al. 1991, 1993; Roux and Evelyn 1958; Salminen et al. 2004; Scalbert et al. 1988; 1989, 1990; Schofield et al. 2001; Vivas et al. 1995; Vovk et al. 2003; Yoshida 1984).

- Hydrolysable tannins

They are previously known as pyrogallol tannins. Principal types of hydrolysable tannins are gallotannins and elagitannins. They are polyesters of glucose and can be hydrolysed by acids or enzymes sych as tannase. They release sugar upon hydrolysis and either gallic acid or hexahydroxydiphenic acid. Phenolic acids: gallic acid is present in gallotannins or hexahydroxydiphenic acid in ellagitannins. The latter undergoes lactonization to produce ellagic acid (Okuda et al. 1989).

Gallotannins are the simplest hydrolysable tannins, containing a polyphenolic and a polyol residue (mostly derived from D-glucose). Tannic acid is a polymer of about eight monomers of gallic acid and glucose.

  - Ellagitannins (formed from the gallotannins by the oxidative coupling of at least two galloyl units, yielding an axially chiral hexahydroxydiphenoyl (HHDP) unit) grandinin, castalagin, pedmolagin, pedunculagin, roburin A-E, vescalin, vescalagin, 2,3-(S)-hexahydroxy diphenoyl glucose (Bate-Smith 1972; Feldman 2005; Herve du Penhoat et al. 1991a; 1991b; Mämmelä et al. 2000; Peng et al. 1991; Vivas et al. 1995).

- Flavano-ellagitannins: acutissimins A an B, eugenigrandin A, guajavin B, stenophyllanin C (Khanbabaee and van Ree 2001).
- Procyanidinoellagitannin: mongolicanin.

Ellagitannins are instable and hydrolysed over time with formation of free ellagic acid and decrease of their solubility (Charrier et al. 1992; Klumpers et al. 1994; König and Scholz 1994; Mämmelä et al. 2000; Simon et al. 1999).

Present data suggest, that the pyrogallol phenols (+)-gallocatechin and leucodelphinidin, which are formed in oak leves, are oxidated by polyphenoloxidases in the heartwood and leaves to phlobatannin and are translocated to the bark. The increase in tannin concentration suggests a downward movement of phenolic metabolites from the leaves to the phloem (Hathway 1958; 1959).

- Condensed tannins (proanthocyanidins)

More than 20 compounds (catechins and low-molecular-mass, oligomeric, and polymeric proanthocyanidins) have been isolated from the bark of *Quercus robur*.

- Monomers: (−)-epicatechin, (−)-epicatechin gallate, (+)-catechin, (+)-catechin gallate, (+)-gallocatechin, (−)-epigalloatechin, and (−)-epigallocatechin gallate; dimeric proanthocyanidins: (+)-catechin-(4α-8)-(+)-catechin, 3-galloyl-(+)-catechin-(4α-8)-3-0-galloyl-(+)catechin, 3-)-galloyl-(+)-gallocatechin-(4β-8)-(+)-gallocatechin, (−)-epicatechin-(4β-8)-3-0-galloyl-(−)-epigallocatechin, 3-)-galloyl-(−)-epigallocatechin-(4β-8)-(+)-catechin.
- Oligomeric proanthocyanidins: D14-D19 (Kuliev et al. 1997; Matthews et al. 1997; Thompson et al. 1972).

Condensed tannins are not very stable; they can be oxidized into soluble phlobaphens, which have no tanning properties anymore.

- Triterpenes: friedelin, friedelinol, 3-friedelanol (Castola et al. 2002, Coquet et al. 2008; Kohlmünzer 2000; Scalbert and Haslam 1987, Sousa et al. 2006)
- Insoluble lipid polyesters: suberins (Graça and Santos 2007; Holloway 1983)
- Volatile acids: acetic and formic acid (Balaban and Uçar 2003)

Herbal preparation(s)

(Hänsel et al. 1994, PDR for Herbal Medicines 2000, 2004, Matindale 2007)

- Comminuted herbal substance (12 – 16% tannins)
- Decoctions: 20 g/L of water
- Infusions: 5 g/L of water
- Extracts: dry extract (5.0-6.5:1), extraction solvent: ethanol 50% V/V

Combinations of herbal substance(s) and/or herbal preparation(s) including a description of vitamin(s) and/or mineral(s) as ingredients of traditional combination herbal medicinal products assessed, where applicable

The herbal substance is also available in combination products. Main plants used in combination are: *Glycyrrhiza glabra*, *Triticum repens*, *Juglans regia*, *Potentilla erecta*, *Bistorta polygonum*, *Fucus*

vesiculosus, Althea officinalis, Foeniculum vulgare, Mentha piperita, Achillea millefolium, Salvia officinalis and *Thymus vulgaris*.

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

According to the information provided by the National Competent Authorities.

Regulatory status overview

Member State	**Regulatory Status**				**Comments (not mandatory field)**
Austria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Belgium	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	The herbal substance is present in combination products and in food supplements
Bulgaria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Czech Republic	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Denmark	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not present
Estonia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Finland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
France	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Germany	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not present
Hungary	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Latvia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Lithuania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Luxemburg	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Malta	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
The Netherlands	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Norway	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Poland	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	The herbal substance is present also in combination products
Portugal	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Romania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Slovak Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	

Member State	Regulatory Status				Comments (not mandatory field)
Slovenia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Spain	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Sweden	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
United Kingdom	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	

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.

1.3. Search and assessment methodology

Databases assessed until July 2010:

Science Direct, PubMed, Embase, Medline, Proquest, Academic Search Complete, Agricola, Toxnet.

Search terms: Quercus, Oak, cortex, bark and robur, petraea, pubescens.

2. Historical data on medicinal use

2.1. Information on period of medicinal use in the Community

The *Quercus* genus comprises many species widespread in Europe, Asia and America. The genus contains about 400 species. The most popular are, in central and northern Europe: *Quercus robur*, *Quercus pedunculata* and *Quercus petraea;* in southern Europe and in the Middle East: *Quercus infectoria*, *Quercus ilex*, *Quercus pubescens* and *Quercus brantii;* in the Mediterranean region: *Quercus cerris* and *Quercus coccifera;* in North America: *Quercus alba*, *Quercus havardii*, *Quercus breviloba*, *Quercus gambelli* and *Quercus douglassi*, in the Far East (China, Japan and Korea): *Quercus acuta*, *Quercus acutissima*, *Quercus aliena*, *Quercus ogilva*, *Quercus glauca*, *Quercus salicina*, *Quercus serrata* and *Quercus dentate*. Several Quercus species were tested as described in non-clinical part. Further data derive from accidental animal poisoning. Furthermore, *Quercus infectoria* and *Quercus ilex species* were examined due to their common therapeutical use in southern Europe.

Oak bark has been traditionally used as a tanning material in Europe since medieval times (Smout 2007). For commercial purposes, the timber and bark of *Quercus pedunculata* Ehrh. and *Quercus sessiflora* Salisb. are not differentiated.

Quercus was mentioned in the writings of Dioskurides, Hieronimus Bock 1565, Matthiolus (1626), Haller (1755), Hecker (1814), Clarus (1860), Rademacher (1851), Kissel (1863), (according to Madaus" Lehrbuch der Biologischen Heilmittel", 1938), Spencer (1832) and Schimpfky (1900). Its cultivation in Europe dates back to ancient and medieval times. The oak tree was held sacred by the ancient Greeks and Romans and in the rest of Europe. The origin of its name is said to be derived from the Celtic *quer* (fine) and *cuez* (tree).

The astringent effects of oak bark or nutgalls are known for centuries. Oak bark was applied topically to burns and wounds, or applied orally in gastritis or diarrhoea. After precipitation of superficial proteins, a protective coat is formed to protect healing of the damaged tissues.

Especially valuable oak bark was used to tan leather. An infusion formed a dye, which was used in rural regions to dye wool. Records of the bark use in folk medicine are found in many countries to counter diarrhoea, infusions for gargle for sore throat and for adding to a hot bath for sore or excessively perspiring feet or sprained ankle.

The infusions were also used for treatment of ulcers, toothache, neuralgia and rheumatism (Allen and Hatfield, 2004). Oak bark powder of *Quercus robur* is used for prophylaxis of diarrhoea in cattle, horses, pigs, sheep and chicken (EMEA Committee for Veterinary Medicinal Products 1997).

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

Belgium

Well-Established Use:

Is the Herbal Substance on the market?: ☒ Yes ☐ No

Status: ☒ Authorised products ☒ Food supplements

Combination products: ☒ The herbal substance is only available in combination products. Herbal teas (authorised since 1962).

Average number of combination substances: ☐ 2-3 ☐ 3-5 ☒ >5.

What are the main combination substances?: Glycyrhizae radix, Triticum repens, Galium luteum, Juglans regia, Potentilla erecta, Bistorta polygonum, Fucus vesiculosus, Althea officinalis.

Czech Republic

Traditional Use:

Preparations (kind of extract, extraction solvent, DER): comminuted herbal substance.

Since when are the preparations on the market?: 1998.

Pharmaceutical form (Standard Terms): comminuted herbal substance for infusion preparation or decoction for bath preparation.

Posology (Route of administration in Standard Terms + daily dosage): for infusion - -100g/1.5 L of hot water/25 minutes for bath - decoction from 1 spoon of herbal drug/1 L of water several times daily.

Indications: dermatitis, stomatitis, pharyngitis, inflammations of external genitals, haemorrhoids.

Risks (adverse drug effects, literature), contraindications: extensive necrosis of mucosa and skin, third-degree burns, alkali burns, in case of bath weepy eczema.

Special warning: hot bath should not be used in case of febrile or infectious illnesses, in heart insufficiency (III. and IV. stage NYHA) and hypertension (IV. stage WHO).

Undesirable effects: allergic reactions are reported. The frequency is not known.

Is the Herbal Substance on the market?: ☒ Yes ☐ No

Status: ☐ Authorised products ☒ Registered products* ☐ Food supplements

Were pharmacovigilance actions taken on medicinal products containing the herbal substance?: ☐ Yes ☒ No

* Registration was granted in the old legislative frame, not the 2004/24/EC Directive

Additional comments:

Quercus cortex has been a subject of Czechoslovak/Czech Pharmacopoeia since 1947; recommended dosage in the last version of the Czech Pharmacopoeia: single dose for oral use 1 – 1.5 g and for topical use 5.0 g/L, daily dose for oral use 3.0 g and for topical use 20.0 g/L.

Czech name of the herbal substance: dubová kůra.

Denmark

Well-Established Use:

Preparations (kind of extract, extraction solvent, DER): Quercus cortex and calcium carbonate ana partes.

Since when are the preparations on the market?: Old product. Withdrawn from the market in 1989.

Pharmaceutical form (Standard Terms): powder (pulvis).

Posology (Route of administration in Standard Terms + daily dosage): no information.

Indications: no information.

Is the Herbal Substance on the market?: ☐ Yes ☒ No

Germany

Traditional Use:

Preparations (kind of extract, extraction solvent, DER): none.

Is the Herbal Substance on the market?: ☒ Yes No

Well-Established Use:

Dry extract (5.0-6.5:1), extraction solvent: ethanol 50% V/V.

German Standard Marketing Authorisation: see below under additional comments.

Since when are the preparations on the market?: At least since 1976.

Pharmaceutical form (Standard Terms): coated tablet.

Posology (Route of administration in Standard Terms + daily dosage): For oral use in adults and adolescents over 12 years 4 x daily 1 coated tablet containing 140 mg dry extract.

Indications: Auxiliary treatment in unspecific acute diarrhoea.

Risks (adverse drug effects, literature): Interaction: enteral absorption of concomitantly administered medicine may be delayed. For this reason the product should be taken 1 hour and more before or after intake of other medicinal products.

Is the Herbal Substance on the market?: ☒ Yes ☐ No

Status: ☒ Authorised products ☐ Registered products ☐ Food supplements

Were pharmacovigilance actions taken on medicinal products containing the herbal substance?: ☐ Yes ☒ No

Combination products: In DE there are no authorized combination products.

Additional comments:

German Standard Marketing Authorisations:

Single active ingredient: 1 (herbal tea).

Combinations products: 0.

**For completeness, all preparations for which marketing authorisations for traditional use have been granted (with reference to former national regulations) are mentioned, regardless of the fact that some of them are not in accordance with current community law (as defined in directive 2004/24/EC). Traditional preparations were authorised in 10-50% of well-established use doses when in parallel the same preparations were authorised under well-established use.*

Greece

In Greece there no any product containing Quercus cortex as a single active ingredient primarily, as well as in combination product.

Poland

Traditional Use:

Preparations (kind of extract, extraction solvent, DER): comminuted herbal substance.

Since when are the preparations on the market?: 1967.

Pharmaceutical form (Standard Terms):

1) powdered herbal substance, 350-375 mg in 1 tablet, standarized to 20 mg of tannins/1 tablet.

2) comminuted herbal substance for infusion preparation or decoction for bath preparation.

Posology (Route of administration in Standard Terms + daily dosage):

1) 1 g of comminuted herbal substance for oral use 3 times daily; 1 teaspoon (3g) of the comminuted herbal substance in 1 cup (250 ml) of cold water and bring to a short boil, take 1 cup, 3 times daily.

2) for infusion - 20g/1 L of hot water/25 minutes; for bath - decoction from 5 g of herbal drug/1 L of water several times daily.

Indications:

1) Diarrhoea

2) Stomatitis, pharyngitis, dermatitis, inflammations of skin.

Risks (adverse drug effects, literature), contraindications: extensive necrosis of mucosa and skin, third-degree burns, alkali burns, in case of bath weeping eczema.

Special warning: hot bath should not be used in case of febrile or infectious illnesses, in heart insufficiency and hypertension. Undesirable effects: allergic reactions are reported. The frequency is not known.

Is the Herbal Substance on the market?: ☒ Yes ☐ No

Status: ☐ Authorised products ☒ Registered products* ☐ Food supplements

Combination products:

☒ The herbal substance is also available in combination products.

Average number of combination substances: ☐ 2-3 ☐ 3-5 ☒ >5.

What are the main combination substances?: Foeniculum vulgare, Mentha piperita, Millefolii herba, Salviae herba, Thymi herba, Potentilla erecta.

Registration was granted in the old legislative frame, not according to the 2004/24/EC Directive.

Were pharmacovigilance actions taken on medicinal products containing the herbal substance?: ☐ Yes ☒ No

Additional comments:

Quercus cortex has been a subject of Polish Pharmacopoeia since 1947; recommended dosage in the last version of the Polish Pharmacopoeia: single dose of comminuted herbal substance for oral use 1 – 1.5 g and for topical use 5.0 g/L, daily dose for oral use 3.0 g and for topical use 20.0 g/L.

Polish name of the herbal substance: kora dębu.

Additional comments:

Polish Standard Marketing Authorisations:

Single active ingredient: 3 (oak bark in tablets), 7 (herbal teas).

Combinations products: 2.

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

PDR for Herbal Medicines (2000, 2004)

Comminuted herbal substance: 3 g/day.

Tea: 1 g of comminuted oak bark is put to cold water, rapidly boiled and strained after some time (1 teaspoon corresponds to 3 g of drug).

Daily dosage: internally 3 g of oak bark, tea: 1 cup (250 ml) 3 times daily.

Externally: rinses/gargles: boil 2 dessert spoons finely cut drug with 3 cups water.

Bath additive: 5 g of oak bark is boiled with 1 L water and added to the full or hip bath.

Bath additive – duration: 20 minutes at 32 – 37 ^{0}C.

Hänsel et al. (1994)

Internal use:

Comminuted oak bark:

Tea: 1 g comminuted oak bark is put to cold water, rapidly boiled and strained after some time. Daily dose: 3 g of oak bark. Duration of use: 3 – 4 days.

External use:

For external use: 0.1 g of tannins/liter of water.

Rinses/gargles: boil 20 g of finely cut oak bark in 1 L of water.

Bath: 5g of oak bark is boiled with 1 L of water and added to the full or hip bath. Bath temperature: 32 – 37 ^{0}C, duration: 20 minutes, 2 – 3 times per week, no longer than 2 – weeks.

(Bundesanzeiger No 22a. 01.02.1990) Quercus cortex

Internal use: Comminuted oak bark, 3g daily. Preparations adequately.

External use: Rinses/gargles: 20 g of finely cut oak bark in 1 L of boiled water.

Baths: complete and partial: 5g of oak bark in 1 L of water.

Duration of use: If diarrhoea lasts longer than 3-4 days, qualified advice is required.

External use: no longer than 2 – 3 weeks.

Italian Monograph.Quercia (Quercus cortex)

Internal use: Comminuted oak bark, 3g daily. Preparations adequately.

External use: Rinses/gargles: 20 g of finely cut oak bark in 1 L of boiled water.

Baths: complete and partial: 5g of oak bark in 1 L of water.

Duration of use: If diarrhoea last longer than 3-4 days, qualified advice is required.

External use: No longer than 2 – 3 weeks.

3. Non-Clinical Data

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

Pharmacodynamics

Tannins are supposed to contribute to the therapeutic effect. Oak bark is used against chillblains, mouth sores, haemorrhoids and indigestion.

Tannins occurring in oak bark are reported to have various activities: antisecretolytic, antiirritant, antimicrobial and antiparasitic. Traditionally oak bark was used to treat nonspecific diarrhoea, inflammation of mouth and throat and slightly injured skin (Madaus (1938), Martindale (2007), Bisset and Wichtl (1994), Mills and Bone (2000) and Weiss and Fintelman (1999).

Astringent actions

The astringency of the extracts of Quercus bark is mainly due to its content of oligomeric proanthocyanidins. By hydrogen binding the available polyhydroxyphenolic groups are crosslinking with proteins. This effect is also involved in the process of leather tanning.

The phenolic groups of tannins may interact with proteins of saliva, mucus, gastric contents and epithelial cells of the gastrointestinal tract.

The presence of tannins in food may limit digestion and is recognized as a feeling of dryness in the palate, a feeling of roughness, dryness, constriction and loss of lubrication. Tannins are reported to repel predators by their strongly astringent taste (Prinz and Lucas 2000).

Salivary proteins in saliva (proline-rich proteins and histatins) are precipitators of tannins (Bacon and Rhodes 2000; Bennick 2002; Charlton et al. 1996; Fickel et al. 1999; Hu et al. 2007; Luck et al. 1994; Murray et al. 1994; Schenkels et al. 1995).

The astringency – characteristics of wine, tea etc. is associated specifically with the interaction polyphenols with proline rich proteins. They have high affinity for tannins and can act as postingestive countermeasures against dietary tannins. Proteins secreted in saliva can bind to dietary tannins in oral

cavity in the first stage of digestion. Proline rich proteins form approximately 70% of the protein content of saliva (Helmerhorst and Oppenheim 2007; Henson et al. 2004; Lawless et al. 1994; Lu and Bennick 1998; Luck et al. 1994). Polyphenols inhibit digestive enzymes, stabilize collagen, block several receptors and channels and reduce bioavailability of iron as potential metal chelators (Baxter et al. 1997; Kim and Miller 2005; Madhan et al. 2005; Zhu et al. 1997). Multivalent cross-linking leads to astringency – reduction of the lubricating power of saliva by precipitating salivary proteins and dewetting of the mucosal surface. Astringency increases with repeated use (Cai et al. 2006, Cai and Bennick 2006; Charlton et al. 1996, 2002; He et al. 2006; Jöbstl et al. 2006; Shimada 2006; Skopec et al. 2004).

It was shown, that the affinity for tannins is inversely related to the size of the polymer, and peptides with less than six residues interact very weakly with tannin. The specificity of interaction depends on size, conformation and charge of the protein molecules. Tightly coiled globular proteins like ribonuclease A, cytochrome C, lysozyme and myoglobin have much lower affinities for tannin than conformationally loose proteins like bovine serum albumine and histone F1. Proanthocyanidins may precipitate one protein in the presence of a large excess of another protein. The high affinity interactions between proanthocyanidins and some proteins may protect the plant from pathogens or predators (Dawra et al. 1988; Hagerman and Butler 1981).

Kandra et al. (2004) have shown that tannin (gallotannin) inhibited human salivary α-amylase. For this reason, tannin is suggested to be tested for the prevention of dental caries as some reports suggested that tea consumption reduces dental caries in experimental animals and humans.

The antidiarrhoeal effect of tannins: tri-*0*-galloyl-β-D-glucopyranose and penta-*0*-galloyl βD-glucopyranose was tested on isolated colon of guinea pigs in a model of experimental diarrhoea with water secretion stimulated by rhein perfusion (Verhaeren and Lemli 1986). Both tested tannins in a concentration of 0.1% completely inhibited the secretory effect of rhein. The antidiarrhoeal activity of gallotannins is attributed to the astringent action on mucosal proteins resulting in the formation of a protective layer (Verhaeren and Lemli 1986).

Comparison of astringency of ellegitannins and complex tannins from *Quercus petrea* bark has shown that relative potency of the oak bark ellagitannins (pedunculagin, vescalagin, stenophyllanin C, acutissimin A, eugenigrandin A, guajavin B) is rather low in the range of 0.45 % of the astringency of the bark (König et al. 1994). This weak activity can be explained by their rigid and inflexible structures and limited ability to complex with proteins. The astringency of the crude herbal substance is mainly due to its content of oligomeric proanthocyanidins (Pallenbach et al. 1993).

Gastroprotective activity

The mucosal cells are able to resist damage against exogenous and endogenous factors and epithelium acts as a barrier to the passive diffusion of harmful substances (Martin and Wallace 2006). Tannic and phenolic acids are reported to protect the stomach mucosa against toxicants and can prevent gastrointestinal inflammation.

Using an experimental model of ethanol induced gastric damage in rats Gharzouli et al. (1999) have shown that an aqueous extract of *Quercus ilex* root bark or tannic acid may be gastroprotective. When given orally to rats (3.62 mg/ml total polyphenols, n=9-10) *Quercus ilex* root bark extract induced a reduction on lesion number compared to water (n=9-10) control (7.3 ± 1.4 vs. 16.3 ±1.7, $p<0.05$) and ulcer index (35.3 ± 9.4 vs. 67.7 ±7.3, $p<0.05$). Plant extracts (5 ml/kg) were given orally 60 min before administration of 50% ethanol and rats were killed 15 min after ethanol treatment. Lesions were photographed at about 2.3 magnifications and the ulcer index was determined according to a 6 grade scoring scale.

Khennouf et al. (2003) reported gastroprotective effects of 25, 50 and 100 mg/kg of 70% acetone extracts of *Quercus suber* and *Quercus coccifera* leaves and of tannins (50 mg/kg of pedunculagin, castalgin, phillyraeoidin A and acutissimin B) given orally in the mouse ethanol-induced gastric ulcer model (n=8-10). Extracts and tannins were suspended in 5% carboxymethyl cellulose (CMC) and administered by gavage 1 h before 40% of ethanol. The control group (n=8-10) received CMC only. Lesions were delimited manually using an image tool program and the number and total area of the lesions were determined. The average number of lesions in the control group was 45.0 ± 13.9 on area of 12.1 ± 3.0 mm^2 of mucosa. Both extracts tested diminished the number of lesions (pooled mean: 11.7 ± 3.6 and reduced area of lesions (pooled mean areas of the lesions were 3.1 ± 1.5 mm^2 for the Q. coccifera and 2.5 ± 1.6 mm^2 for Q suber extract ($p<0.05$). The protection varied between 68 -91% and neither extract produced dose-dependent protection. Purified tannins (50 mg/kg) were also protective and the percent protection varied between 66 to 83%. Castalgin was most potent, but there were no significant differences between tannins tested ($p>0.05$). Authors conclude, that the gastroprotective properties of Quercus extracts and isolated tannins might be related to their strong antiperoxidant activity. However, a dose-response relationship was not investigated.

Antiulcer activity of ethanolic extracts of several Jordanian plants was tested by Alkofahi and Atta (1999) on a gastric ulcer ethanol model in rats. All extracts were given orally in a dose of 400 mg/kg, twice in a day preceding the experiment and a third time 90 min before induction of gastric ulceration with ethanol 50% (10 ml/kg). The control rats received distilled water. The strongest antiulcer activity was found with use of *Quercus coccifera* L. (curative ratio 99.5%) and with *Quercus aegilops* L. (curative ratio of 97.4%).

Antiviral activity

The antiviral effect of octyl gallate against influenza and other RNA viruses were studied *in vitro* by Yamasaki et al. (2007). They tested three different types of viruses: vesicular stomatitis virus VSV (*Rhabdoviridiae* family), influenza virus (*Orthomyxoviridiae* family) and poliovirus (*Picornoviridiae* family). The infected cells were incubated overnight in medium containing varying concentrations of octyl gallate. At the end of infection, the amounts of infectious progeny viruses were counted and were normalized to the virus yield in the absence of the octyl gallate. Octyl gallate inhibited multiplication of all tested viruses and in addition exhibited virucidal activity against enveloped viruses. The VSV virus yield was less than one hundredth of that in the absence of octyl gallate at concentration 4 μg/ml, for this effect 20 μg/ml concentration was required for influenza virus and poliovirus. The addition of octyl gallate at 2 h post infection almost completely abolished the formation. of the progeny viruses of influenza.

Octyl gallate also suppressed the multiplication of HSV-1 at early stages within 6 h p.i. in the infected Hep-2 or Vero cells. Moreover it induced inhibition of the multiplication of RNA viruses, such as VSV and poliovirus (Uozaki et al. 2007).

Several tannins exhibit significant HIV-reversal transcriptase inhibition *in vitro*. It is suggested, that their antiviral activity is rather due to interference with virus-cell adhesion. However comprehensive study on HIV and reverse transcriptase inhibition showed that activity of tannins in cell cultures is due to their toxic features. It was concluded, that relevance of tannins as anti HIV prospective treatment is greatly limited by their toxicity (Matthée et al. 1999).

Plausibility of several plants, *Quercus infectoria* included, was tested *in vitro* against HCV protease and significant inhibiting activity was reported (Jassim and Naji 2003).

Antibacterial activity

Tannins have been traditionally used as antimicrobial agents and their antibacterial activity and antiseptic treatment has long been recognized (Cowan 1999; Haslam 2007). Their mode of antimicrobial action may depend on inactivation of microbial adhesins, enzymes and cell envelope transport proteins. They may also form complexes with polysaccharide molecules. According to comprehensive review (Scalbert 1991) tannins can be toxic also to fungi and yeasts.

Tannic acid was proposed as a protein precipitating agent in genomic and plasmid DNA bacterial preparations. Tannic acid as the prototypical gallotannin was chosen as a model system. It is environmentally friendly and biodegradable (Van Huynh 2008).

Antimicrobial and oxidative activity of a methanol extract of Quercus robur bark (80% (v/v) methanol solution in water) were tested using agar diffusion method on *Staphylococcus aureus*, *Enterobacter aerogenes* and *Candida albicans* (Andrenšek et al. 2004). Extracts were prepared using a stepwise-gradient for preparative separation. Extracts of the oak bark were prepared by performing the extraction three times with each extraction solvent successively before the extraction solvent of higher polarity was applied. The total extractable dry matter from the bark was 8%. The substance related to the activity of the fractions was screened simultaneously by thin layer chromatography (TLC) and estimation of antioxidant activity. Extracts 10 and 12 [50% (v/v) MeOH in ethyl acetate] and extracts 16 and 18 [75% (v/v) MeOH in water] were bactericidal for *Staphylococcus aureus*. The less polar extracts (75% ethyl acetate in *n*-hexane, 100% ethyl acetate and 5% MeOH in ethyl acetate; extracts 1-9) and 5% were bacteriostatic against Gram negative *Enterobacter aerogenes* and the yeast *Candida albicans.* Extract 10 (95%MeOH in ethyl acetate) was bacteriostatic against *Enterobacter aerogenes.* The active substances against *Staphylococcus aureus* and against *Enterobacter aerogenes* and *Candida albicans* were in lipophilic extracts.

Kolodziej et al. (1999) studied *in vitro* antimicrobial potency of 27 pure tannins and related compounds. The chemotherapeutic activity was evaluated against *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Psedomonas aeruginosa*, *Proteus mirabilis* and yeasts: *Candida albicans* and *Cryptococcus neoformans*. Only weak to moderate antibacterial activity of tested tannins was detected, but the activity against *Cryptococcus neoformans* was found quite potent for gallic acid: MIC (minimal inhibitory concentration) = 250 μg/ml) and hydrolyzable tannins: corilagin (MIC = 250 μg/ml) and phyllantusiin C (MIC = 125 μg/ml).

The antimicrobial activities of *Quercus ilex* L. extracts were tested *in vitro* (Güllüce et al. 2004). *Quercus ilex* is an evergreen Mediterranean plant species used as a folk remedy to treat haemorrhages, chronic diarhoea and dysentery. A total of 55 human and plant bacteria, one yeast and four fungi were used in this study. The dried plant extracts were dissolved in methanol to a final concentration of 30 μg/ml. The extracts of *Quercus ilex* showed antibacterial effects against 35 bacterial strains tested on disc diffusion method: *Brucella*, *Enterobacter*, *Escherichia*, *Neisseria*, *Pseudomonas* and *Bacillus* and *Candida albicans.* Quite potent antibacterial effects were shown against *Escherichia coli* (MIC – 16 μg/ml). Negative control with methanol did not show any influence on diameter of inhibition zone.

Molochko et al. (1990) examined antistaphylococcal properties of plant extracts against several strains of *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Staphylococcus saprophyticus.* The most active was a water/alcohol extract of oak bark.

Berahou et al. (2007) examined antibacterial activity of extracts of *Quercus ilex* L. bark. Plant material was extracted with methanol (35.97%, w/w), dissolved in hot distilled water and successively extracted with n-hexane, dichloromethane, ethyl acetate and n-butanol. Each extract was dried under sodium sulphate and reduced to give: hexane extract (1.74%, w/w), ethyl acetate extract (1.5%,

w/w), butanol extract (16.05%, w/w) and final aqueous layer (16.36%, w/w). Evident antibacterial activity was reported against all tested strains for ethyl acetate, *n*-butanol, and final aqueous extracts with MIC ranging from 128 to 512 µg/ml. The tested reference bacteria strains were: *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Proteus mirabilis*, *Klebsiella pneumoniae*, *Bacillus subtilis*, *Salmonella typhimurium*, *Vibrio cholerae*, *Streptococcus pyogenes* and *Streptococcus agalactiae.*

Akiyama et al. (2001) performed studies on the antibacterial action of several tannins against *Staphylococcus aureus*. They examined influence of tannins on plasma coagulation by *Staphylococcus aureus* and the effect of conventional chemotherapy combined with tannic acid below the MIC. All tannins inhibited coagulation below the MIC. Coagulation was significantly inhibited in plasma containing tannic acid (100 mg/l, gallic acid (5000 mg/l), ellagic acid (5000 mg/l), (-)-epicatechin (1500 mg/l), (-)-epicatechin gallate (500 mg/l) or (-)-epigallocatechin gallate (200 mg/l) after incubation for 24 h. Also the MICs of oxacillin and cefdinir for *Staphylococcus aureus* were reduced to ≤ 0.06 mg/l with tannic acid (100 mg/l) at a concentration below MIC. These results indicate the possibility of treatment of *Staphylococcus aureus* skin infections with tannic acid as adjuvant agent in addition to beta-lactam antibiotics. Tannic acid at a sub-MIC concentration presents useful topical application in *in vivo* conditions.

Voravuthikunchai and Kitpit (2005a; 2005b) investigated antibacterial effects of aqueous and ethanolic extracts of several plants including *Quercus infectoria* against hospital isolates of methicillin-resistant *Staphylococcus aureus* (MRSA ATCC 25923). Aqueous and ethanolic extracts of *Quercus infectoria* showed activity against all MRSA isolates, with MICs of 0.2 – 0.4 mg/ml. It should be investigated if *Quercus infectoria* extracts might provide a new treatment effective against multiresistant *Staphylococcus aureus* infections.

Voravuthikunchai et al. (2006) tested the effects of ethanolic extracts of *Punica granatum* and *Quercus infectoria* on 10 clinically isolated *Helicobacter pylori* strains. Both extracts were strongly effective against *Helicobacter pylori* in the range of MIC from 0.78 to 6.25 and 3.12 to 6.25 mg/ml respectively. There was no resistance to these extracts found in any isolates, irrespective of their antibiotic resistance.

Aqueous and ethanolic extracts of 38 medicinal plants were used against enterohaemorrhagic *Escherichia coli* 0157:H7 (Voravuthikunchai et al. 2004). The greatest inhibition zone was produced from the ethanolic extract of *Quercus infectoria* with the MIC values of 0.09 mg/ml and MBC (minimal bactericidal concentration) values of 0.78 mg/ml.

Limsuvan et al. (2005) tested an ethanolic extract of *Quercus infectoria* with E. coli 0157:H7 strain with MIC values of 0.09 to 0.78 ng/ml. However no correlation was found between MIC and cell aggregation.

Park et al. (2006) examined extracts from nine types of Korean oak trees (*Castanopsis cuspidata var. sieboldii*, *Quercus acuta*, *Quercus acutissima*, *Quercus aliena*, *Quercus dentata*, *Quercus ogilva*, *Quercus glauca*, *Quercus salicina* and *Quercus serrata*) to determine their antibacterial activity against *Microcystis aeruginosa*. The most potent extracts of *Quercus*: *salicina*, *acuta*, *gilva* and *acutissima*, inhibited the growth of M. aeruginosa by approximately 50% at 20 mg/l.

Antiprotozoan activity

Gallic acid was shown to have trypanocidal effects *in vitro* both against the bloodstream forms and procyclic forms of *Trypanosoma brucei* (Koide et al. 1998). LD_{50} values of gallic acid are 46.96 ± 1.28 µM for bloodstream forms and 30.02 ± 3.49 for procyclic forms. The authors suggest that the pyrogallol moiety could be responsible for this activity.

Antifungal activity

Hwang et al. (2001) reported the inhibitory activity for chitin synthase II from *Saccharomyces cerevisiae* by tannins and related compounds. Seven tannins and related compounds identified as gallic acid, methyl gallate and others inhibited chitin synthase II, with most potent activity of 3-*O*-galloyl-(-)-shikimic acid (IC_{50} value of 18 μM). Gallic acid, methyl gallate and ellagic acid have had IC_{50} values 206, 87 and 149 μM, respectively.

Fungicidal activity of oils obtained by oak bark pyrolysis at temperature 400 – 450 ^{o}C were tested against brown rot fungus (*Gleophyllum trabeum*) and white-rot fungus (*Trametes versicolor*) (Mohan et al. 2008). The pyrolytic lignin-rich fractions consisted mainly of phenols and neutrals. The lignin-rich fractions showed stronger fungal inhibition (45 – 58 kg/m^3) than whole bio-oils for an impregnation solution of 10% concentration level.

Antiparasitic activity

Extracts of several plants including *Quercus robur* were tested *in vivo* by Paolini et al. (2004) against nematodes living in small ruminants: *Teladorsagia circumcinta*, *Haemonchus contortu*s and *Trichostrongylus colubriformis*. Crushed oak bark (5 g) was extracted by 100 ml of water at 90^0 C for 2 h. The filtrate was concentrated to obtain dried powdered sample. Powders were dissolved in phosphate-buffered saline and serially diluted immediately prior to incubation. *T. circumcinta* and *T. colubriformis* extracts of oak bark significantly reduced migration of the larvae (1200 μg/ml, $p<0.01$). After incubation with oak bark extract (1200 μg/ml) significant reduction of motility was only noted for adult worms of *T. colubriformis* ($p<0.01$). Results confirmed that tannins were the source of inhibition of motility of the 3rd-stage larvae and adult worms and could represent an alternative choice to chemotherapy.

Antioxidant activity

Chen et al. (2007) showed protective activity of tannic acid, gallic acid, ellagic acid and propyl gallate against reactive oxygen species (ROS) using human lung fibroblast IMR-90 cells model. All compounds were incubated at concentration of 10 μg/ml and alleviated H_2O_2-induced lipid peroxidation. Compounds were also tested against the depletion of intracellular glutathione. When IMR-90 cells were pretreated with 10 μg/ml propyl gallate, it was demonstrated to be the only compound successfully preventing depletion of GSH. Results of the study suggested, that tested compounds can protect cells from oxidative stress.

Anticancer activity

Pan et al. (1999) showed induction of apoptosis by penta-*O*-galloyl-β-D-glucose through activation of caspase-3 in human leukemia HL-60 cells. Penta-*O*-galloyl-β-D-glucose induced apoptosis in a concentration and time dependent manner. HL-60 cells were incubated with different doses (5, 10, 20, 30, 40, 50 and 100 μM) of penta-*O*-galloyl-β-D-glucose. The percentage of apoptotic HL-60 cells was 2.89%, 2.47%, 2.86%, 8.25%, 46.99% and 64.08% after 0, 3, 6, 12, 18 and 24 h of incubation with penta-*O*-galloyl-β-D-glucose (50 μM), respectively. The apoptosis potency of penta-*O*-galloyl-β-D-glucose is correlated to its cancer chemopreventive efficacy in animal models.

Sehrawat et al. (2006) reported preventive effects of tannic acid on 2-acetylaminofluorene (2-AAF) mediated hepatic oxidative stress and cell proliferation in rats. Treatment of rats with tannic acid (125 and 250 mg/kg bw) resulted in significant increase of glutathione hepatic levels, increase of antioxidant activity and phase-II metabolizing enzymes as compared to saline treated control. Inhibition of electrophilic species – significant decrease in lipid peroxidation, xanthine oxidase and hydrogen peroxide generation was also reported. The tumor promotor markers parameters (ornithine decarboxylase activity and DNA synthesis) were dose-dependently decreased.

Influence on Angiotensin Converting Enzyme Activity (ACE)

Uchida et al. (1987) examined the effects of condensed tannins on angiotensin converting enzyme activity. Procyanidin B-5 3.3'-di-*O*-gallate and procyanidin C-1 3.3'- di-*O*-gallate strongly inhibited activity of the ACE enzyme. The IC_{50} values for procyanidin B-5 3.3'-di-*O*-gallate and procyanidin C-1 3.3'- di-*O*-gallate were 1.3 and 1.7 x 10^{-6} respectively. For inhibition of other proteases: trypsin, chymotrypsin, leucine aminopeptidase, carboxypeptidase A and urinary kallikrein over one hundred times the concentration was required.

Influence on the nervous system

The effects on central nervous activity of extracts of galls of *Quercus infectoria* were studied by Dar et al. (1976) and Dar and Ikram (1979). The methanolic fraction of galls which has been identified as syringic acid exhibited significant local anaesthetic (1 2% solution), analgesic and central depressive activity in mice (doses of 250 and 500 mg/kg). Galls of *Quercus infectoria* are reported to contain also ellagic acid and gallotannins.

The effects of tannic acid were shown by Takahashi et al. (1986). Tannic acid dose dependently (10 - 100 mg/kg) reduced abdominal constrictions in mice (writhing analgesic model induced by i.p. injection of 0.6% acetic acid), increased nociceptive threshold measures by the hot-plate test and potentiated pentobarbital sleeping time. Tannic acid (100 mg/kg) significantly inhibited locomotor activity in mice.

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

No data are available concerning oak bark pharmacokinetics due to its complex phytochemical composition.

The metabolism of polymeric proanthocyanidins by human colonic microflora has been investigated *in vitro* in anoxic conditions using ^{14}C-labelled purified proanthocyanidin (Déprez et al. 2000). Polymers were degraded after 48 h of incubation. As metabolites, low-molecular-weight aromatic compounds: phenylacetic, phenylpropionic and phenylvaleric acids were recognized by gas chromatography. The results show, that proanthocyanidins can be metabolized by the colonic microflora into low-molecular-weight aromatic acids.

Evaluation of polyphenol bioavailability was tested *in vitro* in isolated segments of the rat small intestine (Carbonaro et al. 2001). As model compounds, tannic acid and catechin were used. The results indicated a significant, concentration-dependent uptake of both compounds by the small intestinal wall. Higher uptake (50%) was recorded for tannic acid compared with catechin (30%). However, only catechin demonstrated a complete transfer through the gut wall, whereas tannic acid remained in the gut wall via interaction with wall proteins. Both polyphenols were bound significantly by proteins in the intestinal lumen.

Interactions

Incubation of isolated human serum proteoglycans, which play an important role in cell adhesion and communication, with tannic acid and tannins, caused a dose dependent decrease in glycan content. Tannic acid was more active than oak tannins (Savolainen 1997).

Oak bark (*Quercus petrea*) aqueous methanol extracts enhanced stability of casein micelles: increased the heat stability of skim milk (at 140 ^{0}C) and concentrated milk (at 120 ^{0}C) and retarded rennet coagulation *in vitro* (O'Connell and Fox 1999).

Overview of pharmacokinetics

Due to lack of data on pharmacokinetics of oak bark no conclusions can be drawn. Tannic acid seems to be retained in the gut lumen and wall after peroral administration, whereas for catechin a partial absorption could be demonstrated.

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

Genotoxicity

No published data could be found on the genotoxicity of oak bark and on the oak bark preparations.

In the Ames test, Weissmann and al. (1989) did not observe any mutagenic activity of lipophilic extracts of oak heartwood (*Quercus robur*) prepared step by step by petroleum/ether, aceton/water, ethanol/water and water extraction. Extracts consisted of wax-like esters and free acids: gallic acid, ellagic acid, ω-hydroxy fatty acids, cis- and trans-ferulic acid.

Oak tannins are genotoxic in cultured human embryonic MRC-5 lung cells (Zhou et al. 1995). Authors evaluated the ability of solvent extracts of natural woods to induce chromosome aberrations. In experiments three concentrations per extract with or without metabolic activation and 100 metaphase cells were examined. No dose dependent activity was found with tested extracts in the presence of S9, but dose-dependent chromosomal and chromatid breaks were caused by oak wood. No metabolic activation was required for their effect.

Labieniec and Gabryelak (2003) showed that tannic, ellagic and gallic acids have genotoxic and cytotoxic properties in Chinese hamster cell line B14 when using the Comet assay for detection of DNA damage. Tannic, ellagic and gallic acids were exposed at concentration range of 15 – 240 μM. Tannins decreased viability of the cells, with highest cytotoxicity at the concentration of 60 μM. The formation of DNA single-strand breaks was observed.

Carcinogenicity

No published data could be found on the carcinogenicity of the oak bark and the oak bark preparations.

The International Agency for Research on Cancer (IARC) has evaluated the potential carcinogenicity risk of wood dust exposures. It was observed, that wood dust exposure (mixture of oak, beech and pine wood) significantly enhanced the incidence of neoplasia. Occupational sinonasal cancer risk is associated with inhalation exposure to hardwood dust, although constituents responsible for carcinogenicity are not known. Components of bark and sapwood in comparison with heartwood may display both qualitative and quantitative differences. Moreover the studies of wood dust and cancer lack quantitative exposure data. Due to the complex nature of the exposure it has not been possible to prove the causal relationship.

Acute toxicity

No studies on acute toxicity have been performed with oak bark or oak bark preparations.

Acute toxicity (LD_{50}) of tannic acid given intragastrically to rats was found to be 2.26±0.083 g/kg body weight. Death was associated with hepatic necrosis and nephritis and acute gastroenteritis (Boyd et al. 1965).

In humans fatal liver damage after barium enemas containing 0.25% tannic acid were described in 5 adult patients. They died with symptoms of fulminating acute liver failure. Autopsy findings showed hemorrhagic central necrosis of liver lobules (Anonymus 1964; Lucke et al. 1963).

Oak leave toxicosis in ruminants

As hydrolysable tannins are considered to present greater risk to health, several cases of acute poisonings of ruminants were noted due to ingestion of fresh leaves of several oak species.

Severe toxicosis in cattle was observed in Europe (*Quercus robur*), in China (6 different Quercus species) and in USA (*Quercus havardii*, *Q. breviloba*, *Q. gambelli*). Oak poisoning occurred in cattle due to consuming for 2 days immature oak leaves of *Quercus incana* in India (Garg et al. 1992; Reed 1995). Mortality was 70%. The cattle exhibited anorexia, constipation, depression and respiratory distress. Significant decreases of blood hemoglobin and elevations in serum bilirubin were seen. Symptoms of renal and hepatic damage were observed. There was bilirubinuria, proteinuria, and increased activities of serum aspartate aminotransferase, lactate dehydrogenase and alkaline phosphatase. The poisoning may be due to hydrolysable tannins and simple phenols. The levels of tannins and condensed tannins were 97.7 mg tannic acid equivalent and 5.8 mg catechin equivalent/g of dry leaves.

Toxicity of oak leaves (*Quercus robur*) was studied in 2 moose which were given oak leaves harvested in June intraruminally by stomach tube for ten days. The daily dose was 58 g (30% dry matter) of oak leaves per kg. This dose was above the maximum daily intake. There were no signs of disease in post-dosing periods (Flaoyen et al. 1999).

Oak toxicosis cases in cattle were also registered in northern California. In April 1985 2700 cattle in northern California died of oak toxicosis. After snow and freezing weather the cattle ingested toxic amounts of oak buds (*Quercus douglassi*). Acute toxicosis was charcterized by diffuse renal damage, gastrointestinal ulceration ascites, hydrothorax and hepatic necrosis. The toxicity was attributed to the high concentration of gallotannins hydrolyzed in the rumen to gallic acid, pyrogallol, resorcinol and several small phenolic molecules. Absorbed tannins bind to plasma proteins and to the endothelium of blood vessels. This results in hemorrhages, edema and renal tubular necrosis (Spier et al. 1987).

Experimental toxicosis in two calves given immature blue oak (*Quercus douglassi*) leaves in spring tested for gallic acid content (Plumlee et al. 1998). The oak leaves contained 1,542 ppm of gallic acid. They consumed voluntarily oak leaves for 7 days (approximately 1.9, 2.7, 0.9, 1.4, 1.6, 0.7 and 0.2 kg respectively). They refused to eat the oak leaves after day 7. Necropsy findings revealed perirenal oedema, ascites and severe nephrosis with secondary nephritis. Commercial tannic acid (45% gallic acid) was given orally for seven days (67, 94, 31, 49, 55, 24, and 7 mg/kg respectively on days 1 – 7). Neither calf developed any abnormalities throughout the experiment.

Oak toxicosis in sheep was presented by Derakhshanfar et al. (2008) after experimental consumption in sheep oak acorns of *Quercus brantii* (2.2 kg/day for 20 days). After the end of the experiment, autopsy revealed mild hepatic fibrosis, lymphocytic hepatitis and interstitial nephritis as symptoms of oak poisoning.

Repeated dose toxicity

No studies on repeated dose toxicity have been performed with oak bark or oak bark preparations.

To investigate the response of pancreas to tannins and changes in activities of enzymes in the lumen of the small intestine, broiled cockerels were fed on increasing levels of tannin-containing diet (Ahmed et al. 1991). The birds were fed with a diet consisted mainly of hydrolysable gallotannins for 4 weeks at levels of 13.5, 25 and 50 g/kg. Weight of pancreas was significantly increased with increasing dose of tannins. Activity of trypsin and α-amylase was also dose-dependently increased. Activities of dipeptidase and sucrose α-glucosidase (disaccharidase) in the intestinal mucosa were inhibited. Growth of the birds fed on tannins diet was adversely affected.

Assessor's overall conclusions on toxicology

Practically no toxicity studies on oak bark or oak bark preparations are available in the literature.

Tannins, which are considered as major therapeutically active compounds, are detectable in the bark of oak species, in immature fruits and also in tea, coffee, cocoa and wine. The ability of tannins to form strong complexes with proteins is considered as their most important activity for both therapeutic and toxicological effects. Hydrolysable tannins are potentially toxic to ruminants. The acute cases of sheep and cattle poisonings are associated with the consumption of oak leaves.

In Europe the toxicity occurs mainly due to *Quercus robur*, in America due to *Quercus havardii*, *Quercus breviloba* and *Quercus gambelli* ingestion. In China many lethal cases in animals are registered due to ingestion of several different oak species.

Bacterial tannases hydrolyze galloyl esters to release gallic acid which is further metabolized by bacteria to pyrogallol and other low-molecular-weight phenols.These substances are absorbed and could cause necrosis of the liver and proximal tubular damage in the kidney. The toxic compound is suggested to be tannic acid, pyrogallol or resorcinol.

Nasal cancer risk associated with occupational exposure to wood dusts via inhalation cannot be applied to the oral use of oak bark preparations.

Due to the lack of data on acute and chronic toxicity, repeated dose toxicity, mutagenicity, carcinogenicity, reproductive and developmental toxicity, a list entry for *Quercus cortex* cannot be recommended.

3.4. Overall conclusions on non-clinical data

Experimental preclinical data presenting astringent, gastroprotective, antibacterial and antiviral activity of oak bark confirm long tradition and support plausibility of its therapeutic use.

Antifungal, antiprotozoan, antiparasitic, anticancer and other effects could be demonstrated when single active constituents of oak bark were assayed. A general conclusion for oak bark cannot be drawn.

The published data on pharmacological activities support the traditional use of preparations containing oak bark in the proposed indications.

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

There are no data on human pharmacodynamics.

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

There are no data on human pharmacokinetics.

4.2. Clinical Efficacy

4.2.1. Dose response studies

There are no specific data available on dose-response studies.

4.2.2. Clinical studies (case studies and clinical trials)

Observational studies.

In dermatological therapy oak bark is recommended for topical treatment of wounds as astringent, helping to dry oozing and bleeding (Grimme and Augustin 1999). It is also used in treating dermatitis by coagulating surface proteins of cells and reducing permeability and increased secretion in inflammatory conditions. The precipitated proteins form a protective layer on the skin and have antimicrobial properties (Bedi and Shenefelt 2002).

For the same purpose synthetic tannins are used in dermatology, frequently in neonates and children (Fölster-Holst et al. 2007).

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

No information available.

4.3. Overall conclusions on clinical pharmacology and efficacy

There are no data available from controlled clinical studies; therefore the medicinal use of oak bark has to be regarded as traditional.

Administration of preparations of oak bark can be regarded as safe and justified, especially at therapeutic doses, concentrations and short time of use.

5. Clinical Safety/Pharmacovigilance

There are no adverse effects reported from the Member States, however allergic reactions to *Fagaceae* family should be considered.

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

There are no data from clinical trials available.

5.2. Patient exposure

None reported.

5.3. Adverse events and serious adverse events and deaths

Allergy

Sensitisation to pollen of *Quercus ilex* and *Quercus robur* was found in two patients suffering from rhinoconiunctivitis and seasonal bronchial asthma between April and June. Specific IgE to *Quercus ilex* and *Quercus robur* and coniunctival challenge test to *Quercus robur* pollen was positive in two patients (Bartra et al. 2004).

Akhapkina and Zheltikova (2004) reported cross reactivity to pollen allergens from birch (*Betula pendula*), hazel (*Corylus avelana*), alder (*Alnus glutinosa*), wormwood (*Arthemisia absintium*), ash tree (*Fraxinus excelsior*) and oak (*Quercus robur*).

Bronchial hyperresponsiveness and symptomps of asthma were associated with exposure of workers at wooden furniture factories on beech (*Fagus* sp.) and oak (*Quercus* sp.) (Bohadana et al. 2000). Cumulative exposure to dust was calculated for each worker by multiplying the duration of the work by the intensity of exposure (years.mg/m^3). The median cumulative exposure to dust was 110 years.mg/m^3. Dose-response relationship was found between intensity of exposure, sore throat and increased prevalence of positive metacholine bronchial challenge tests.

A single case of anaphylactic reaction to *Quercus ilex* acorn nut was investigated by Vega et al. (1998). The acorn is edible, but is more used in animal feed than in human diet. The patient with previous history of allergy (urticaria) to peanuts ingestion presented generalized urticaria, vomiting, diarrhoea, angioedema, dizziness and hypotension. Skin-prick tests were positive for acorn and peanut, but also for oaks (*Quercus robur* and *Quercus alba*).

Anaphylaxis by fruits of the *Fagaceae* family: acorn and chestnut were presented by Zapatero et al. (2005). A 4 year old boy developed immediately after peeling and eating an acorn of *Quercus ilex* the ocular itching, lip angioedema, unproductive cough, wheezing and dyspnea. Prick results were positive for *Quercus ilex* and *Castanea sativa.*

5.4. Laboratory findings

No data available.

5.5. Safety in special populations and situations

Intrinsic (including elderly and children)/extrinsic factors

There are no reports of use of oak bark in children. The use of oak bark is not recommended in children younger than 12 years of age.

Use in pregnancy and lactation

The oak bark should not be used during pregnancy and lactation.

Overdose

None reported.

Drug interactions

None reported for oak bark preparations. However, it is reported in literature that oak bark ingestion causes reduction or inhibition of absorption of some alkaloids or alkaline drugs (Hänsel et al 1994; (BAZ) No 22. 01.02.1990; Mills and Bone 2000; PDR for Herbal Medicines 2000, 2004; Poppenga 2002). Some authors mention that tannins may also interfere with iron absorption. Detailed studies are necessary to clarify if this is a concern. For safety reasons it seems reasonable to avoid taking iron and herbal preparations of oak bark together (Miller 1998, Mills and Bone 2000). However it is not clear, whether these findings have definitely consequences on the medical use of oak bark.

Effect on ability to drive or operate machinery or impairment of mental ability

None reported.

5.6. Overall conclusions on clinical safety

There are no reports of adverse effects of oak bark from Member States.

The allergic reactions in patients allergic to Fagaceae should be considered.

6. Overall conclusions

The available data are sufficient to include the traditional use of specified preparations of oak bark in a Community herbal monograph. Oak bark fullfils the requirement of therapeutic use for at least 30 years (15 years within the European Union, Directive 2004/24/EC).

Indications for treatment: 1) Traditional herbal medicinal product for symptomatic treatment of mild diarrhoea, 2) Traditional herbal medicinal product for symptomatic treatment of minor inflammation of the oral mucosa or skin. 3) Traditional herbal medicinal product for symptomatic relief of itching and burning associated with haemorrhoids after serious conditions have been excluded by a medical doctor.

The HMPC concluded that prior to using oak bark in symptomatic self-medication by haemorrhoid patients, serious conditions should be excluded by a medical doctor.

Hemorrhoids are a common chronic condition with symptoms that include rectal bleeding, protrusion, and itching. Because other conditions (diverticulitis, vascular ectasias, colorectal cancer, colitis and megacolon) can lead to identical symptoms, a professional careful rectal examination and proctosigmoidoscopy is justified for any patient who reports hemorrhoids. Only medical doctors, gastroenterologists and surgeons are qualified to accurately diagnose hemorrhoids and offer a consequent, competent treatment plan.

Due to the lack of data on acute and chronic toxicity, repeated dose toxicity, mutagenicity, carcinogenicity, reproductive and developmental toxicity, a list entry for *Quercus cortex* can not be recommended.

Benefit/risk assessment

Oak bark is a subject of a European Pharmacopoeia monograph.

There are no concerns about serious side effects or interactions with oak bark preparations.

There are reported side effects concerning gastrointestinal reactions and allergic reactions due to the oak bark preparations used. No serious adverse events with a therapeutic posology of the herbal preparations are reported.

Despite limited toxicological data, levels of exposure associated with the use of oak bark, either by oral or topical route of administration for limited times; most probably do not result in any significant risk to human health.

It can be concluded that the benefit/risk assessment for oak bark preparations is positive for use in therapeutical dosages in specific conditions of mild diarrhoea, in minor inflammatory conditions of the oral mucosa or skin and in conditions of medically diagnosed haemorrhoids before anorectal use.

Annex

List of references