16 September 2010
EMA/HMPC/246764/2009
Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Arctium lappa* L., radix

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)	*Arctium lappa* L., radix
Herbal preparation(s)	a) Comminuted herbal substance b) Powdered herbal substance c) Liquid extract (DER 1:1), extraction solvent ethanol 25% V/V d) Soft extract[1], extraction solvent water e) Tincture (ratio of herbal substance to extraction solvent 1:10), extraction solvent ethanol 45% V/V f) Tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent ethanol 25% V/V
Pharmaceutical forms	Comminuted herbal substance as herbal tea for oral use. Herbal preparations in solid or liquid dosage forms for oral use.
Rapporteur	Gert Laekeman
Assessors	Kristien Fonteyne, Bénédicte Van Baelen

[1] Codex Français 1949

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

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1. Introduction

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

Botanical description

Arctium lappa L. is known under the synonyms:
Latin: *Arctium majus* BERNH., *Lappa communis* var. *major* COSSON et GERM., *Lappa major* GAERTN., *Lappa officinalis* ALL., *Lappa vulgaris* HILL., *Lappa vulgaris* var. *major* NEILR

English: beggars button, burdock, cockle-bur, cockle-button, common burdock, cuckold-dock, great but, great clotbur, greater burdock, hardock, hare burr, hurr-bur, stick-button, bat weed

French: bardane, bouillon noir, choux d'ânes, glouteron, gouteron, grande bardane, grateau, grateron, herbe aux pouilleux, herbe aux teigneux, oreille de géant, pignet, teigneux

German: große Klette, Dollenkraut, gemeine Klette

Italian: bardana, bardana maggiore, farfariaccio, lappa bardana, lappola

Dutch: grote klis, grote klit, dokke, kladden, klevers, Jan-plak-an

Japanese: gobo

(Blaschek 1998, Delfosse 1998, De Smet 1993, Leclerc 1966, Van Os 1980, Wichtl 1994).

Arctium lappa L. is a biennial member of the *Compositae* (*Asteraceae*) that can reach one meter and a half. It has large cordiform leaves. The purple flowers appear from July until September. The spherical flower head, three to four centimeters in diameter, has rough hairs (Delfosse 1998, Lambinon 1998). Native in Europe, Northern Asia and North America (Wichtl 1994).

- Herbal substance(s)

Folium

The leaves are collected from 1-year old plants and dried (Blaschek 1998).
The use of fresh leaves is described in literature (Leclerc 1966, Valnet 2001).

Constituents:

- Sesquiterpenes: The dried leaves contain essential oil, arctiol, dehydrofukinone, eremophilene, β-eudesmol, fukinanolide, fukinone and petasitolone. The fresh leaves contain onopordopicrin and the ground leaves arctiopicrin.

- Triterpenes: Free terpene alcohols, free sterols, triterpene esters.
  From the petrolether extract of dried leaves are isolated: free triterpene alcohols (α-amyrine, β-amyrine, lupeol, phytol, ω-taraxasterol, taraxasterol), triterpene alcohol acetates (taraxasterol acetate, α-amyrine acetate, β-amyrine acetate, lupeol acetate, ω-taraxasterol acetate) triterpene alcohol esters with long chain fatty acids (taraxasterolester, α-amyrine ester, β-amyrine ester, lupeolester, phytolester, ω-taraxasterolester).

- Fatty Acids: 94.7% saturated (C_{14} - C_{26}) and 5.3% unsaturated (C_{18}) fatty acids.

- Phenol Carbonic Acid: Caffeic acid.

- Ascorbic Acid, -Mucilage, Tannins.

(Blascheck 1998).

Semen (fructus)

The mature fruit is collected in autumn and dried. Thereafter, the dried fruit is purified and dried again in the sun (Blaschek 1998).

The dried, ripe fruit is collected in autumn (Chinese Pharmacopoeia 1995, Körfers 2009).

Constituents:

- Fatty Oils: The seeds contain about 16% fatty oils, namely linoleic acid, oleic acid, octadecatrienic acid, palmitic acid, stearic acid, eicosatrienic acid, arachidonic acid, myristinic acid, linolenic acid, heptadecanic acid, margarinic acid and pentadecanic acid.
- Lignans: The fruit contains a broad spectrum of lignans. Lignans with two phenylpropane units: arctiin, arctigenin, matairesinol. Lignans with three phenylpropane units ("sesquilignans"): lappaol A, lappaol B, lappaol C, lappaol D, lappaol E. Lignans with four phenylpropane units ("dilignans"): lappaol F, lappaol H, neoarctin A, neoarctin B and diarctigenin.
- Daucosterol (fruit).

Radix

The most recent official definition is included in DAC 2008: dried, total or cut roots of *Arctium lappa* L. (=*A. major* Gaertn.), *A. minus* (Hill) Bernh., *A. tomentosum* Mill. (*Asteraceae*) and from related species, hybrids or mixtures thereof. The root is collected in the autumn of the first year or in the spring of the second year.

Similar or identical definitions can be found in Barnes (2007), Blaschek (1998), De Smet (1993), Duke (1988), Uchiyama (2005) and Wichtl (1994).

Constituents:

- Volatile constituents, essential oil: There are only 0.06-0.18% of essential oil in the roots of *Arctium lappa* L., altough this fraction is well investigated. More than 60 subclasses are known.

Blaschek (1998) categorizes them as follows:
Aliphatic hydrocarbons: aplotaxen, dihydroaplotaxen, 1-heptadecen, 1-pentadecen

Aliphatic and aromatic aldehydes: phenylacetaldehyde, propionaldehyde, benzaldehyde, butyraldehyde, caproicaldehyde, isovaleraldehyde and others

Carbonic acids: carbonic acids from C_2 until C_{13} and also tiglic acid, isovaleric acid among others

Pyrazines: 2-methoxy-3-methylpyrazin and six other 2-alkyl (C_3-C_5)-3-methoxypyrazines

Sesquiterpenes: α-guajen, cyperen, costic acid, dehydrocostuslacton

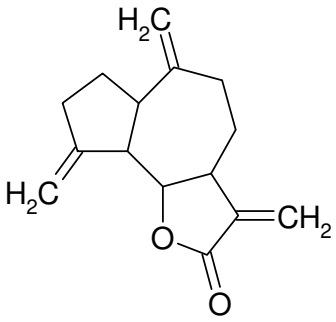

Figure 1: dehydrocostuslacton

- Lappaphenes: Lappaphen-a and lappaphen-b are isolated from the fresh root.

- Sulfur-free polyacetylenes: The polyacetylenes percentage is higher in a fresh root than in a dried root. More than ten different polyacetylenes can be identified. 1,11-tridecadiene-3,5,7,9-tetrayne is the most important one.

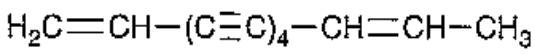

Figure 2: 1,11-tridecadiene-3,5,7,9-tetrayne

- Sulfur-containing polyacetylenes (thiophenes): arctinal, arctinol A, arctinol B, arctinon-A, arctinon-B, arctinon-A-acetaat, arctic acid B, arctic acid C and arctic acid-B-methylester have been isolated.

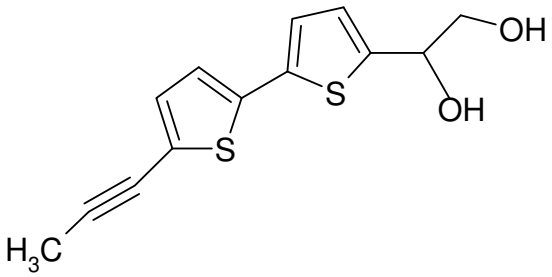

Figure 3: arctinol

- Phenolcarbonic acids and tannins: The fresh root contains 1.9 up to 3.65% polyphenols with chlorogenic acid, isochlorogenic acid and caffeic acid. More recent tests show the presence of derivatives of quinic acid. The root also contains a small amount of tannins.

- Lignans: neoarctin A and the lignanolide arctiin.

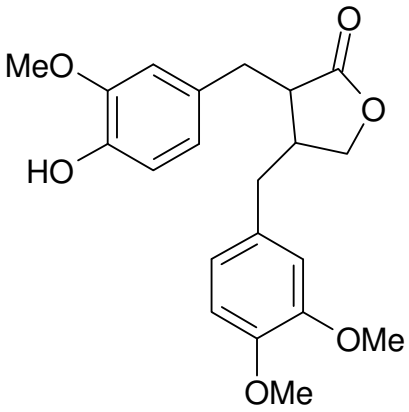

Figure 4: arctiin

- Triterpenes: 15.2% triterpenester, 12.8% free sterols (sitosterol, stigmasterol, a.o.), 10.7%, triterpenacetates, 2.9% triterpenacids and 2.4% triterpenalcohols (α-amyrine, β-amyrine, lupeol, ω-taraxasterol, phytol) are isolated from the petrolether extract of the dried root.
- Fatty acids: 0.4 until 0.8% fatty acids including linolenic acid, linoleic acid, myristic acid, palmitic- and stearic-acids
- Polysaccharides: The total carbohydrates may represent up to 70% of the dry mass and contain mainly inulin (about 45%).
- Other constituents: The aminoacid fraction contains γ-guanidino-n-butyric acid. Also vitamin C (23 mg/100 g) has been found.
- Baicalin

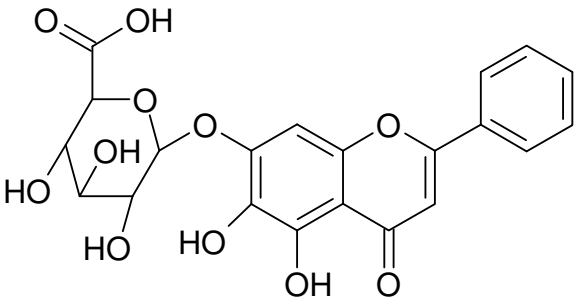

Figure 5: baicalin

- Aplotaxene

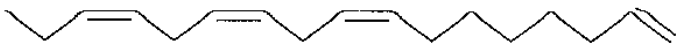

Figure 6: aplotaxene

- Herbal preparation(s)

Apart from the references cited, market information was included (Barnes 2007, Blaschek 1998, Delfosse 1998, Leclerc 1966, Valnet 2001, Van Hellemont 1985).

Hagers Handbuch der Pharmazeutischen Praxis (Blaschek 1998) mentions different fluid extracts of Radix Bardanae (Extractum Bardanae):

- Extractum Bardanae Portug.
- Extractum Bardanae Brasil.
- Extractum lappae fluidum
- Extractum lappae fluidum Brasil.
- Extractum lappae majoris stabilisatae

No further details could be retrieved for those preparations.

- 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.

'Essiac' is described as a formula that consists of four herbal substances: *Arctium lappa* L., *Rheum palmatum* L., *Rumex acetosella* L. and *Ulmus rubra* L. The preparation is only partially characterised.

Indication: cancer treatments but no convincing clinical evidence is available (Capasso 2003, Ulbricht 2009).

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

Regulatory status overview

Member State	**Regulatory Status**				**Comments**
Austria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorized or registered preparations
Belgium	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorized or registered preparations
Bulgaria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorized or registered preparations
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information
Czech Republic	☐ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify:	Only combination products
Denmark	☐ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify:	Only combination products
Estonia	☐ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify:	Only food supplements
Finland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information
France	☒MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Registered products on the market since 1980
Germany	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorized or registered products
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorized or registered products
Hungary	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorized or registered products

Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorized or registered preparations
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorized or registered preparations
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:	No information
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 registered preparations
Spain	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	Preparations authorized: see detailed information below
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.

Czech Republic

In the Czech Republic, a fixed combination (herbal tea) is used. This tea contains Phaseoli fructus sine semine, Myrtilli herba, Salviae officinalis herba, Galegae herba, Polygonii avicularis herba, Taraxaci radix cum herba, Rubi fruticosi folium, Foeniculi fructus, Bardanae radix and Liquiritiae radix.

Indication: adjuvant therapy in diabetes.

Denmark

An ayurvedic fixed combination is available in Denmark. It contains 40 mg *Arctium lappa* L. per tablet and 18 other ingredients. No information on details of the preparation is given.

Indication: claudicatio intermittens.

France

- Powdered herbal substance in hard capsules.

A preparation containing powdered herbal substance in capsules is on the market in France since 1980. It contains 350 mg powdered herbal substance per capsule.

Posology: 1 capsule 3 times daily (up to 5 capsules if necessary).

Indications:
- traditionally used in seborrhoeic skin conditions
- traditionally used to promote urinary and digestive elimination functions.

- Extract in hard capsules

A preparation with dry extract made with ethanol 70% V/V (DER 2.5-4.5:1), on the market in France since 1994.
It contains 200 mg dry extract per capsule.

Posology: 1 capsule 2 times daily.

Indications: Traditionally used in seborrhoeic skin conditions.

Spain

In Spain powdered or cut herbal substance is on the market as tea since 1973.

A daily dose of 3 g to 6 g can be taken.

Indication: facilitating the elimination of urine.

The herbal substance is also available in combination products.

There is partial information about other products on the Spanish market. The date of commercialising is not specified.

- Liquid extract (DER 1:1) 25-50 drops, 1 to 3 times daily
- Tincture (1:10) 50 drops 1 to 3 times daily
- Dry extract (DER 5:1) 1 g daily

The solvents for all these preparations are not specified.

These preparations are similar to the ones mentioned in the BHP (1983), cited by Barnes (2007) and Blaschek (1998).

Indication: similar uses as presented in registered products.

2. Historical data on medicinal use

2.1. Information on period of medicinal use in the Community

Arctium lappa L. has been widely used in folk medicine (Gentil 2006). Besides, the root and leaves are listed by the Council of Europe as a natural source of food flavouring (category N2) (Barnes 2007).

An herbal tea called 'Essiac plus' contains the same four substances as 'Essiac' (*Arctium lappa* L., *Rheum palmatum* L., *Rumex acetosella* L. and *Ulmus rubra* L.) plus four additional herbs: *Nasturtium officinale* L., *Cnicus benedictus* L., *Trifolium pratense* L. and *Laminaria digitata* (Huds.) Lamour. Indication: The tea is used by cancer patients during chemo- and radiation therapy. No further details about concentration and doses are given (Tai and Cheung 2005).

According to Tai and Cheung (2005), a product called 'Flor-Essence' at high concentrations has shown *in vitro* differential inhibitory effect on different human cancer cell lines.

In Spain, powdered or cut root is on the market as tea since 1973. The oral use of preparations with non specified root extract is reported by Leclerc (1966).

In some countries, mainly in Japan, a cultivated form of *Arctium lappa* L. is used as a vegetable (De Smet 1993).

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

Folium

Preparation	Single dose	Daily dose	References
Macerate: fresh leaves macerated during one night in salted vinegar (1:125) Or fresh leaves as such	External use as cataplasm: no dose specified	External use as cataplasm: no dose specified	Leclerc 1966, Valnet 2001

- Macerate: fresh leaves macerated during one night in salted vinegar (1:125)

Terray, cited by Leclerc (1966), reports good results when using the fresh macerated leaves wrapped around the painful body parts of patients with rheumatism. This can create an urticarial reaction which is considered to be even more beneficial (Leclerc 1966).

- Unknown way of administration and posology:

Tea infusions of leaves are used for stomach ulcer and gastritis. In case of infection of mouth and pharynx, a decoction is used to gargle. Topically it is used to treat skin diseases, insect bites (Bruneton 1999), itching and scratches (Blaschek 1998). Leaves may help to treat bruises, tumours and gouty swellings (Duke 1988).

Kloss, cited by Duke (1988), describes the leaves as 'excellent for cancer sores, gonorrhea, gout, leprosy, rheumatism, sciatica, scrofula and syphilis'. They have been used to treat bladder stones, eczema, gallstones, gout, and skin afflictions (Duke 1988).

Alcoholic extracts of the leaves are used for treating psoriasis and seborrhoeic eczema. Extracts would also promote hair growth and are used in the production of cosmetics (Blaschek 1998).

The crushed leaves of *Arctium lappa* L. were also applied on snake bites. Beneficial effects have been attributed to a modification of the main constituents in the venom. The oxidation that happens is thought to be similar to the one of potassium permanganate (Leclerc 1966, Valnet 2001).

As the traditional use is restricted to *ex-tempore* preparations of the fresh leafs, no monograph on *Arctium lappa* L., folium is proposed.

Semen

Preparation	Single dose	Daily dose	References
Dried seeds	4–6 g	6-12 g	Valnet 2001 Körfers 2009

The seeds of *Arctium lappa* are used in Korea for their supposed diuretic, anti-inflammatory and detoxifying effect. In TCM, the freshly crushed herbal substance is used to treat cough, flu, pharyngitis and infections of the respiratory tract (Chinese Pharmacopoeia 1995, Körfers 2009). It is also used for measles, mumps, rubella, erysipelas and carbuncles (Blaschek 1998) and in Urolithiasis (Valnet 2001).

In Asia, the seeds are used to treat constipation, flatulence, abscesses, dropsy, acne, scarlet fever, flu, snakebite, measles, scrofula and smallpox. Tinctures of the seeds are used for the treatment of kidney diseases, psoriasis, prurigo and acne (Duke 1988).

As only very limited information on the traditional use of the seeds within the Community is available (Blaschek 1998, Valnet 2001), no monograph on *A. lappa* L., fructus is proposed.

Radix

Use of different herbal preparations:

- Antibacterial and antimycotic use

Quoted from Bézanger-Beauquesnes (1980): *''... The fresh radix of Arctium lappa has antibacterial and antimycotic properties by the presence of polyenes and polyines, more particularly diene-tetraine ...".* No further reference is made to specific preparations. This use dates from 1960 or before that date.

- Rheumatism
  Root preparations have been used for rheumatism (Bradley 1992).

The root of *Arctium lappa* L. is described as a blood purifier, it is believed to clear toxins from the bloodstream (De Smet 1993).
In folk medicine, root infusions and plasters are often used for its anti-inflammatory activity (De Smet 1993).
The root has been used for gout (Valnet 2001).

- Choleretic and diuretic use
  Quoted from Bézanger-Beauquesnes (1980): *"... A choleretic and diuretic action is due to alcoholic acids related to hydromethacrylic acid. The components for its putative hypoglycemic activity are not known. All these properties lead to a purification-activity of the radix in certain nutritional and dermatological conditions and furunculosis ...".* No further reference is made to specific preparations. This use dates from 1960 or before that date.

Burdock root has been considered to have diuretic and diaphoretic actions to stimulate hepato-biliary function (Bradley 1992).
According to DAC 2008, the root is used in case of gout, rheumatism and to promote urinary

elimination and sweating.
The root can also be used as a diaphoretic and diuretic remedy. *Arctium lappa* L. promotes sweating, which helps to release toxins through the skin. It also promotes more urine production and gives further elimination of toxins via the kidneys and bladder (De Smet 1993, Duke 1988).
It is also used as a laxative for renal or urinary calculi, jaundice and furunculosis (De Smet 1993).

Treatment against urolithiasis has been mentioned by Valnet (2001).

- Skin disorders
  Root preparations have been used for skin disorders, seborrheic eczema and for stimulation of the hair growth. The hairy character of the plant might explain the belief of its hair growing characteristics (Bradley 1992).

Acording to DAC 2008, the root is externally used in seborrhoe of the skin, other skin diseases, wounds and acne.
It is also used against eczema (De Smet 1993).

Topical application can be used to treat poorly healing wounds, ichtyosis, psoriasis, acne and other skin diseases. The radix can also be added to bathwater. In the past, Oleum Bardanae was used topically for seborrheic eczema. Most of the sources are copying each other, referring to the BHP (1983), which is in fact a compilation of former BHP editions (BHP 1976). This preparation has to be considered as being traditionally used for more than 30 years.

- Gastro-intestinal complaints
  According to DAC (2008), the root is widely used in popular medicine: orally for treatment of gastro-intestinal complaints and loss of appetite.
- Coffee surrogate
  The roasted root can be consumed as a coffee surrogate (Blaschek 1998).
- Glandular tumors
  The root decoction alleviates ulcerated, glandular and white tumours (Duke 1988).

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

***Preparation* & Indication**	**Single dose**	**Daily dose**	**References**
Radix (= dried root) Skin disorders	2-6 g of cut root per cup water, let it rest during several hours and subsequently let it boil during 1 hour. Filter (decoction).	3 single doses	Barnes 2007, Delfosse 1998, Van Hellemont 1985
Radix (= dried root) (Uro-)lithiasis Measles	Decoction, 40 g per liter, cook for 10 minutes.	(Uro-) Lithiasis 2-3 cups per day measles: 1 coffee-spoon every 5 minutes for two hours	Valnet 2001

***Preparation* & Indication**	**Single dose**	**Daily dose**	**References**
Radix (= dried root) Gout	60 g/l, cook for 5 minutes.	2 l per day	Valnet 2001
Radix (= dried root) Seborrhoea, impetigo, acne	3 handful/l, cook for 20 minutes.	external use for washings	Valnet 2001
Powdered dried root Skin disorders Diuretic / diaphoretic Rheumatism	2-6 g per cup as an infusion. 2–4 g mixed with a suitable liquid.	3 single doses	Blaschek 1998 Valnet 2001 BHP 1976
Powdered dried root Traditionally used in seborrhoeic skin conditions; Traditionally used to promote urinary and digestive elimination functions	350 mg	350 mg 3 times daily (up to 5 capsules if necessary).	On the market in France since 1980
Liquid extract of root (DER 1:1), extraction solvent 25% ethanol V/V Liver crisis and liver congestion Diuretic Skin disorders and rheumatism	2-8 ml One small spoon (5 ml) 25 to 50 drops 2-6 ml	3 single doses 4 to 5 doses a day 3 doses 3 times daily	Barnes 2007 Blaschek 1998 BHP 1976 Delfosse 1998 Van Hellemont 1985 Market information from Spain Bradley 1992
Tincture of root (1:5) in 25% ethanol V/V Skin disorders and rheumatism Diuretic	8-12 ml	3 times daily	Bradley 1992 BHP 1976
Tincture of root (1:10) in 45% ethanol V/V Skin disorders and rheumatism Diuretic	8-12 ml 50 drops	3 single doses 3 doses	Barnes 2007 Blaschek 1998 BHP 1976 Market information from Spain
Decoction of root (1:20) or decoction of 30 g root/l Skin disorders and rheumatism	No information available	500 ml	Barnes 2007 Blaschek 1993 BHP 1976 Winter 1984
Dried root or decoction	2-6 g	3 times daily	Bradley 1992

***Preparation* & Indication**	**Single dose**	**Daily dose**	**References**
Skin disorders and rheumatism			BHP 1976
Radix nebulisate (1:4) *(No details on preparation available)* Liver function Diuretic Skin disorders	1 or 2 capsules of 50 mg	3 single doses	Delfosse 1998 Van Hellemont 1985 Van Hellemont 1986
Arctium lappa L. T.M. (Ø) Liver function Diuretic Skin disorders	50 drops	3 single doses	Delfosse 1998 Van Hellemont 1985
Syrup of root [(1)]*:* *Root soft stabilized extract Codex Francais (1949) 20 g* *Sirupus simplex ad 400 g* Liver function Diuretic Skin disorders	15 ml	9 doses	Garnier 1961
Pills: *Root soft stabilized extract Codex Francais (1949), extract 0.20 g* *Liquorice powder Q.s.* Liver function Diuretic Skin disorders	See daily dose	5-10 pills	Leclerc 1966 Garnier 1961
Elixir: *Root soft stabilized extract Codex Francais (1949) 8 g* *Garrus elixir 80 g* *Sirupus Simplex ad 200 g* Liver function Diuretic Skin disorders	See daily dose	Up to 9 spoons (15 ml)	Leclerc 1966 Garnier 1961

(1) Soft stabilised extract of the root:

A stabilised soft extract is described in the Codex Français (1949) and cited by Garnier (1961).

R/ *Arctium lappa,* powdered root 1000 g

Distilled water 8000 g

Macerate of the root in 5000 g distilled water during 12 hours under regular mixing and filter under pressure.

Macerate the residue in the remaining part of the water during 12 hours and filter under pressure.

Mix both filtrates and evaporate the water under reduced pressure until 3000 g remain. Let the fluid settle and filter after 24 hours. Evaporate under reduced pressure 'au bain-marie' until a soft consistency is obtained.

3. Non-Clinical Data

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

Activity of isolated compounds*:*

Antitumor properties

In 2008, a study investigated the anti-cancer properties of **arctiin**, a major lignan constituent of *Arctium lappa* L. 100-250 µM arctiin has a maximum growth inhibitory effect on several types of cancer cells, although it did not completely inhibit cell growth. There is a down-regulation of cyclin D1 protein expression. This induced suppression occurs in various types of human tumor cells, including osteosarcoma, lung, colorectal, cervical and breast cancer, melanoma, transformed renal cells and prostate cancer (Matsuzaki 2008).

A diet containing 0.1, 0.02 or 0.004% arctiin was administered for 18 weeks. Arctiin has been evaluated to exert no definite effects on prostate carcinogenesis in SV 40 T antigen transgenic rats at least in the experiment, although a weak inhibitory tendency was found in high dose groups (Zeng 2005).

Baicalin, a natural compound of *Arctium lappa* L. and genistin, a baicalin derivative, were found to be potent and selective inhibitors of terminal deoxyribonucleotidyltransferase (TdT), an eukaryotic DNA-polymerase. The IC50 of baicalin and genistin to TdT were respectively 18.6µM and 28.7µM. These inhibitors can be used as tools and molecular probes to distinguish DNA polymerases and to clarify their *in vivo* biological function (Uchiyama 2005).

Antioxidative effects and anti-inflammatory effects

Inhibitors of NO production in macrophages are important targets in the treatment of inflammatory diseases, such as rheumatoid arthritis. The **lignans isolappaol C, lappaol C, lappaol D, lappaol F** and **diarctigenin** were isolated from a methanolic extract of the seeds from *Arctium lappa* L. They were investigated in their inhibitory effects on the NO production in LPS-stimulated RAW264.7 cells. As a result, lappaol F and diarctigenin inhibited NO production with IC50 values of 9.5 and 9.6 µM, respectively. The other three compounds were inactive (Park 2007).

Kim (2008) describes the anti-inflammatory activity of *Arctium lappa* L. In Korea, the seeds of *Arctium lappa* L. are used for the treatment of inflammatory diseases. The study of Kim evaluates the pharmacological potential of *Arctium lappa* L. in NF-κB-associated inflammatory disorders. NF-κB is a transcription factor that plays an important role in the initiation and amplification of inflammatory responses. **Diarctigenin**, a lignan from *Arctium lappa* L. (0.6-30µM), was found to inhibit the production of many inflammatory mediators in macrophages such as PGE2, IL-6 and others. Diarctigenin down-regulated the expression of the inflammatory genes at the transcription level through suppression of NF-κB activation.

According to Knipping (2008), *Arctium lappa* L. might be a promising natural component for use in anti-allergic treatment. In their investigation, **arctiin** was able to significantly reduce the release of inflammatory mediators *in vitro* (through inhibition of degranulation and cys-leukotriene release). Arctiin was also able to inhibit acute skin response in mice *in vivo*.

Prebiotic effects

In 2008, Li studied the prebiotic potential of components of *Arctium lappa* L. They found that **inulin** of the root from *Arctium lappa* L. (1% w/v) promoted the specific growth rate of "beneficial bacteria" *in vitro* and *in vivo*. The final bacterial mass in the medium with inulin of *Arctium lappa* L. was greater

than that in the medium without inulin of *Arctium lappa* L. By stimulating the growth of these lactobacilli and bifidobacteria *in vitro,* the resistance to disease is thought to increase because these micro-organisms may retard the growth of pathogenic bacteria. There is also a production of inhibitory substances. Furthermore, these beneficial bacteria may have an immunomodulatory effect. The results of the *in vivo* study with mice confirmed the prebiotic effectiveness which was found in the *in vitro* study. However, studies on human subjects are needed to investigate whether *Arctium lappa* L. may have beneficial effects (Li 2008).

Other effects

Arctiin, a constituent of Fructus Bardanae, delays germination of other plant seeds. The anatomy of the stem is not influenced but in the root abnormal germination (= deformation of the root with root hairs that are shorter and twisted) is induced by *Arctium lappa* L. Due to short and twisted root hairs the nutrition intake is possibly heavily disturbed. An interaction with DNA is also observed. However, the kind of interaction is not yet clear (Blaschek 1998).

Activity of preparations from the leaves:

Hypoglycaemic effects

The possible anti-diabetic effect of *Arctium lappa* L. has been intensively examined.
Although the root of *Arctium lappa* L. has been found to cause hypoglycaemia in rats, newer studies have reported that oral administration of leaves to normal mice did not affect glucose homeostasis. Swanston-Flatt (1989) found that a treatment for 28 days with preparations of *Arctium lappa* L. gave an aggravation of hyperglycaemia, together with polydipsia and a loss of body weight in Streptozotocin-induced diabetic mice. They used a **decoction** prepared by addition of 1 g of dried leaves to 400 ml of cold water (Blaschek 1998, De Smet 1993, Swanston-Flatt 1989).

Antibacterial activity

Gentil (2006) examined the antibacterial activity of an **ethyl acetate fraction** extracted from the leaves of *Arctium lappa* L., solubilized in propylene glycol (concentration not known). Twenty-seven canine maxillaries were inoculated with a mixed bacterial suspension of *Pseudomonas aeruginosa, Escherichia coli, Lactobacillus acidophilus, Streptococcus mutans* and *Candida albicans*. The growth of all these microorganisms was inhibited by the medications prepared from an ethyl acetate fraction of *Arctium lappa* L. (on the 14^{th} and 30^{th} day). Gentil (2006) hypothesized that the antimicrobial activity can be attributed to the presence of flavonoids and tannins respectively.

Antioxidative effects and anti-inflammatory effects

Kardašová and Machová (2006) isolated eleven polysaccharides including from the leaves of *Arctium lappa* L. The polysaccharides were investigated for their ability to inhibit peroxidation of soybean lecithin liposomes by OH radicals. The antioxidant activity value of the **polysaccharide** from the leaves of *Arctium lappa* L. (31.3×10^{-3}mM) was 9.8%, while the activity of eight other polysaccharides ranged from 20 to 45%.

Activity of preparations from the seeds:

Platelet Activating Factor (PAF) antagonism

Platelet Activating Factor (PAF) induces platelet aggregation. In 1992, Iwakami tested the inhibitory effects of the extracts of different plants. **Lignans** in the seeds of *Arctium lappa* L. (**arctigenin, lappaol A and C**) have been found to inhibit the binding of platelet activating factor to rabbit platelets (74% inhibition at 200 µg/ml hot aqueous extract of the seeds) (Blaschek 1998, Iwakami 1992).

Hypoglycemic effect

In 2008, Xu studied the possible hypoglycaemic effect, effect on glucose tolerance and effect on serum insulin of **Fructus Arctii (8.0% w/w)** in diabetic and normal animal models. Experimental diabetes was induced in mice with a single injection of alloxan (90 mg/kg body weight), which is similar to diabetes type I. Hyperglycaemic-hyperlipidemia diabetes was induced in rats; this is similar to diabetes type II. The induction was accomplished by giving a fat emulsion which was prepared by dissolving and mixing lard (20 g), methylthiouracil (1 g), cholesterin (5 g), sodium glutamate (1 g), saccharose (5 g), fructose (5 g), propylene glycol (30 mg) and Tween 80 (20 ml) in 100 ml water; at 10 ml/kg each day for ten days. After fasting for at least 12 hours, they received alloxan 50 mg/kg. **Total lignan** was given to mice and rats daily for 10 days at doses of 2.0, 1.0, 0.5 g/kg and 1.38, 0.69, 0.35 g/kg respectively. A significant increase in the plasma insulin level was observed in the diabetic mice and rats. The blood glucose levels were reduced and glucose tolerance was improved. In type I mice, there was also an increase in serum cholesterol and triglycerides, which represents a risk of coronary heart disease. More research is needed to study the mechanism of action and the long-term effects.

Antimicrobial activity

An **ethanolic extract** from the fruit of *Arctium lappa* L. inhibited the growth of *Aspergillus parasiticus*. Two percent of *Arctium lappa* L. (part of the plant not specified) was used in an enriched medium, which was inoculated with spores and incubated at 28°C for 9 days. In the presence of *Arctium lappa* L., no sporulation of *Aspergillus parasiticus* occurred (Bahk and Marth 1983).

Antioxidative effects and anti-inflammatory effects

According to Knott (2008), natural ***Arctium lappa* L. fruit extract** (no specifications given) may improve clinical signs of ageing skin. *In vitro* studies on human dermal fibroblasts and monocyte-derived dendritic cells showed that pure **arctiin** stimulates collagen synthesis and decreases interleukin-6 and tumor necrosis factor-alpha concentration, respectively. Topical *in vivo* application of an *Arctium lappa* L. fruit extract-containing formulation stimulated procollagen synthesis and increased hyaluronan synthase-2 expression and hyaluronan levels. The formulation also reduced wrinkle volume in the crow's feet area.

Studies in tumor models

A **70% ethanol extract** from Fructus Bardanae showed potent antiproliferative activity against B cell hybridoma cells (MH60). The active ingredients were (-)-arctigenin with the most potent activity (IC_{50}:1.0 µM), (+)-7,8-didehydroarctigenin and (-)-matairesinol. The activity was associated with the induction of apoptosis (Matsumoto 2006).

According to Ishihara (2006), hyperthermia is an effective option for cancer therapy, complementary to chemotherapy or radiotherapy. However, cancer cells may develop thermotolerance. A specific inhibitor of HSP's (Heat Shock Proteins) in cancer cells would be useful, since it is critical to prevent the induction of thermotolerance, when hypertermia is used to treat cancer. Ishihara used mammalian cells and reported that **a methanolic extract** from the fruits of *Arctium lappa* L. (100 µg/ml) suppressed the expression of HSP, which was induced by heat shock. Further investigation identified **arctigenin** as the active component in the extract (100 µM). Further experiments showed that not only the 100 µg/ml extract and 100 µM arctigenin but also a 50 µg/ml extract and 50 µM arctigenin suppressed the synthesis of HSP70. Arctiin was not found to have an inhibitory effect.

According to Awale (2006), targeting nutrient-deprived cancer cells may be a new strategy in anticancer drug development. Antiangiogenic therapy is an attractive approach for cancer therapy. However, cancer cells can survive even under extreme conditions, such as that characterized by low nutrient and oxygen supply. A **CH_2Cl_2-soluble extract** of the dried seeds of *Arctium lappa* L. was found to exhibit 100% preferential cytotoxicity against nutrient-deprived cells at a concentration of 50

µg/ml. **Arctigenin** was identified as the primary compound responsible for such preferential cytotoxicity.

Activity of preparations from the root:

Anti-mutagenic activity

Arctium lappa L. root may contain a desmutagenic factor with a molecular weight >300 000, which might be a lignin-like compound containing about 10% sugar (De Smet 1993).

Arctium lappa L. reduced the mutagenicity to *Salmonella typhimurium* (TA98, TA100) of mutagens (not specified) both requiring and not requiring S9 metabolic activation. A lignan-like stucture is probably responsible for this desmutagenic activity. The addition of fibre (5%) of roots of *Arctium lappa* L. to the diet of rats apparently gave protection against toxicity of various artificial food colours (Barnes 2007).

Antioxidative effects and anti-inflammatory effects

Lin (2002) induced liver damage with ethanol and CCl_4. When administering *Arctium lappa* L. extract orally to rats, there was an improvement of the biochemical parameters. A normal saline solution of a **dry extract with water** of *Arctium lappa* L. roots was administered to the rats (300 mg/kg). The hepatoprotective mechanism of *Arctium lappa* L. may be linked to its antioxidant activity, which decreases the oxidative stress of hepatocytes.

Di Mambro (2005) has considered that topical use of antioxidants can protect and possibly correct oxidative skin damage by neutralizing free radicals. The antioxidant effect of an **extract of a mixture** of *Arctium lappa* L. root, *Glycyrrhiza glabra* L. and *Symphytum officinale* L. (at final concentrations of 0.125, 0.25, 0.50, 1.0, 2.0 and 4.0 µl/ml) was evaluated by Di Mambro (2005) as well as the inhibition of lipid peroxidation, induced by Fe^{2+}. The antioxidant effect was measured by evaluating their H-donor capabilities and their free radical scavenging effects by studying changes of the chemiluminescence intensity. The results suggest there is some antioxidative effect, although this activity is lower than the one of the *Glycyrrhiza glabra* L. and *Ginkgo biloba* L. extracts alone and the formulations containing these extracts.

Abdominal angiostrongyliasis in humans is caused by the parasite *Angiostrongylus costaricensis*. The effect of an **aqueous extract** of the root of *Arctium lappa* L. (1:10 m/v) on the evolution of intestinal lesions induced by this parasite was evaluated in mice (500 mg/kg) by Fante (2008). These researchers concluded *Arctium lappa* L. is not useful for humans affected by abdominal angiostrongyliasis, since the aqueous extract of *Arctium lappa* L. did not interfere with disease progression and did not protect against the lesions induced by *Angiostrongylus costaricensis* in mice.

Activity of *Arctium lappa* in general:

Antimicrobial activity

Arctium lappa L. (different parts of the plant) is used for the treatment of various infectious diseases. This antimicrobial activity has been associated with the positive effects of *Arctium lappa* L. on kidney diseases: nephritis and chronical glomerulonephritis (Blaschek 1998). Its antifurunculous effect may be explained the same way (Barnes 2007).

The antimicrobial activity is attributed to the polyacetylene constituents, although only traces have been found in the dried herb. Furthermore, arctiopicrin shows antibiotic activity against Gram-positive bacteria (concentrations not specified). The leaf, flower and root of *Arctium lappa* L. have antibiotic activity against Gram-negative bacteria (*Escherichia coli, Shigella flexneri, Shigella sonnei*). Gram-positive activity (e.g. *Staphylococcus aureus, Bacillus subtilis, Mycobacterium smegmatis*) has only been reported for the leaf and flower (Barnes 2007).

Activity of *Arctium lappa* in mixtures:

'Essiac'[2] (see II.3.1.) a formula that consists of four herbal substances (*Arctium lappa* L., *Rheum palmatum* L., *Rumex acetosella* L. and *Ulmus rubra* L.) was tested. The preparation is only partially characterised.
Indication: cancer treatments but no convincing clinical evidence is available (Capasso 2003, Ulbricht 2009).

'Essiac' has been reported to inhibit cell proliferation and to induce differentiation in human prostate cancer cell lines *in vitro*. Leonard (2006) has indicated that 'Essiac' has potent antioxidant and DNA-protective properties.

The results of their study demonstrate that 'Essiac' scavenges $^{\bullet}OH$ radicals, $O_2^{\bullet-}$ radicals and radicals produced by the RAW264.7 cellular reaction with Cr(VI). 'Essiac' also inhibited lipid peroxidation in cell membranes caused by exposure to $^{\bullet}OH$ radicals and inhibited DNA damage due to $^{\bullet}OH$ radicals produced by the Fenton reaction (Leonard 2006).

Kulp (2006) have reported that 'Essiac' can stimulate the *in vitro* growth of human breast cancer cells through estrogen receptor mediated as well as estrogen receptor independent mechanisms of action. No further details about concentration are given. Moreover, Essiac is a mixture.

According to Tai and Cheung (2005), Flor-Essence at high concentrations show *in vitro* differential inhibitory effect on different human cancer cell lines.

Bennett (2004), however, showed that Flor-Essence can promote DMBA-induced (dimethyl-benz[a]anthracene) mammary tumor initiation in Sprague-Dawley rats. This observation is in contrast with widely available anecdotal evidence that this commercially available herbal tonic will suppress or inhibit tumour growth.

Miscelaneous effects in general:

- Positive effects on nephrosis (fructus Bardanae) (Blaschek 1998).

- Effect against urolithiasis: This effect has been investigated by Grases (1994) using female Wistar rats. They concluded that beneficial effects of a.o. Arctium lappa L. on urolithiasis can be attributed to some disinfectant action.

- Diuretic effect (Blaschek 1998).

The above mentioned effects are described without further specification of the extracts or compounds used.

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

Arctiin

In vitro data:

To investigate the metabolism of arctiin, an experiment with gastric juice (pH 1.2–1.5) and intestinal flora of rats was performed in 1992. This experiment indicated that arctiin was not affected by gastric juice. In the intestinal tract a cleavage of the glycosidic binding (resulting in arctigenin) occurs rapidly,

[2] Essiac is a common name for complex plant mixtures. By the general us of the name, some confusion about the composition exists and the translation of pharmacological activities into practice remains difficult (Ulbricht 2009).

mainly followed by 3”-demethylation of the aglycons (to form 2-(3”, 4”-dihydroxybenzyl)-3-(3’, 4’-dimethoxybenzyl)-butyrolactone) (Blaschek 1998).

In 2003, another *in vitro* investigation demonstrated that after incubation of arctiin with a human fecal suspension, not only (2R,3R)-2-(3',4'-dihydroxybenzyl)-3-(3",4"-dimethoxybenzyl)butyrolactone was formed, but also five other metabolites: (-)-arctigenin, (2R,3R)-2-(3'-hydroxybenzyl)-3-(3",4"-dimethoxybenzyl)butyrolactone, (2R,3R)-2-(3'-hydroxybenzyl)-3-(3"-hydroxy-4"-methoxybenzyl)butyrolactone, (2R,3R)-2-(3'-hydroxybenzyl)-3-(3",4"-dihydroxybenzyl)butyrolactone, and (-)-enterolactone (Xie 2003).

In vivo data:

200 mg arctiin/kg was administered to rats. One hour after administration, arctigenin was detected in serum. Four hours after administration, arctigenin reached its maximal serum concentration, and four hours later arctigenin was not detectable anymore. Neither arctiin nor 2-(3”, 4”-dihydroxybenzyl)-3-(3’, 4’-dimethoxybenzyl)-butyrolactone, which was found to be the main metabolite, were present in the serum of the rats, not even the conjugated form of the metabolite. On the other hand, the concentration of conjugated arctigenin was thirty times higher than the concentration of free arctigenin. Investigation of the content of the intestinal tract of rats that were fed with arctiin, demonstrated that 2-(3”, 4”-dihydroxybenzyl)-3-(3’, 4’-dimethoxybenzyl)-butyrolactone was formed. Incubation of 2-(3”, 4”-dihydroxybenzyl)-3-(3’, 4’-dimethoxybenzyl)-butyrolactone with liver cytosol of rats, in the presence of S-adenosylmethionin, demonstrated that it was rapidly and completely 3”-methylated to arctigenin by COMT (in only three minutes) (Blaschek 1998).

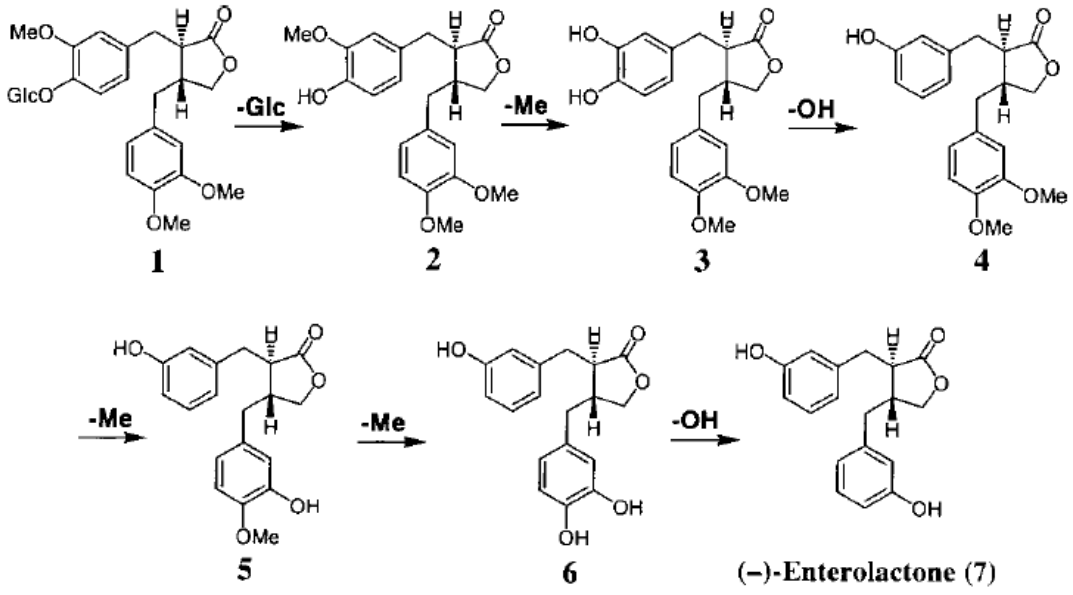

Figure 7: Possible pathway for the transformation of actiin (1) by human intestinal bacteria (Xie 2003).

Pharmacokinetic interactions with other medicinal products

In vitro data:

An ethanolic (55% v/v ethanol:water) extract of *Arctium lappa* L. root was tested for possible inhibition of CYP3A4, CYP19 and CYP2C19. Chlorogenic acid was used as a marker substance in the extracts.

Finally, the activity of an equivalent of 800 µg herbal substance was tested against 2 ng of ketoconazole.

Among 10 plant extracts tested, the extract from the root of *Arctium lappa* L. was only a weak inhibitor of CYP3A4 (10^{th} place on 10), CYP19 (9^{th} place on 10) and CYP2C19 (4^{th} place on 4). There were batch-to-batch differences with inhibition percentages varying between 11% and 33% (Scott 2006, Williamson 2009).

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

Carcinogenicity

Carcinogenicity data on the roots of *Arctium lappa* L. come from a study by Hirono (1977). Six male and six female rats were treated with a diet containing 33% of roots of *Arctium lappa* L. for 120 days. No tumors were detected in any animal (De Smet 1993).

Reproductive toxicity

Matsui reported no affection on fertility of female mice when injected twice a day for five days subcutaneously with an extract of *Arctium lappa* L. This extract was prepared by boiling unspecified plant parts in water (De Smet 1993).

Genotoxicity

No tests on preparations from *A. lappa*, root have been performed. Aqueous and methanolic extracts from fruits of *Arctium lappa* L. were screened for mutagenicity in *Salmonella typhimurium* strains TA 98 and TA 100 and *Bacillus subtilis* strains H17 Rec^+ and M45 Rec^-. The aqueous extract gave a positive response in *Salmonella typhimurium* TA 98 only in the presence of S9 mix, whereas the methanolic extract was positive in the *Bacillus subtilis* rec-assay (De Smet 1993).
Yamamoto (1982) tested an aqueous or methanolic extract from *Arctium* fruits in *Salmonella typhimuriu*m TA 98 and TA100 in the absence or presence of rat liver S-9 mix. No mutagenicity was observed (De Smet 1993).
In vivo studies have shown that fresh or boiled plant juice from *Arctium lappa* L. may cause a significant reduction in DMBA(7,12-dimethylbenz(a)anthracene)-induced chromosome aberrations (Barnes 2007).

The relevance of those studies for the assessment of preparations of the root is unclear.

3.4. Overall conclusions on non-clinical data

Pharmacology

Arctium lappa L. is recommended in various conditions, mostly based on long-term use and experience. A lot of *in vitro* studies in cell cultures, microbial strains and biochemical models and *in vivo* studies in rats and mice have already been performed. Despite these efforts, the pharmacodynamic profile of *Arctium lappa* L. is not fully established.

No safety concerns are originating from the available data on the pharmacological profile.

Pharmacokinetics

From *in vitro* and *in vivo* experiments in an intestinal environment there is evidence for phase II kinetic activity of actiin. From *in vivo* experiments (rats) Tmax for arctigenin and excretion parameters could be determined. These data have no relevance for the traditional use of *A. lappa*, radix. The reported actions on the Cytochrome-system do not present a reason for concern.

Toxicology

Very limited studies did not result in any signs of *in vivo* carcinogenicity (rats). Because studies did focus on other parts of the plant, the genotoxicity and toxicity on reproduction cannot be fully assessed for the root and root-derived preparations. However, the available data do not point to any serious concern with respect to safety.

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 data available.

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

No data available.

4.2. Clinical Efficacy

4.2.1. Dose response studies

No data available.

4.2.2. Clinical studies (case studies and clinical trials)

No data available.

'Essiac' (see section 1.1 and 1.2) has been used for breast-cancer treatment, secondary prevention, improving quality of life and controlling negative side-effects of conventional breast-cancer treatment. A retrospective cohort study in 510 women with a diagnosis of primary breast cancer demonstrated that 'Essiac', although it appears to be safe at the doses taken (total daily dose 43.6 ± 20.8 ml which correspond to the labelling of most 'Essiac' products), does not have a significant effect on HR-QOL (health-related quality of life) or mood states such as anxiety or vigor (Zick 2006).

'Essiac' may contain a lot of preparations, usually insufficiently specified, which provides additional confusion. Well-defined trials testing 'Essiac' or individual herbal components are necessary to derive any sound conclusions (Ulbricht 2009).

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

No data available.

4.3. Overall conclusions on clinical pharmacology and efficacy

There is a lack of clinical research assessing the effects of *Arctium lappa* L. in monopreparations and controlled clinical trials are absent. However, there is a long-standing, consistent traditional use in dermatological and urological complaints.

5. Clinical Safety/Pharmacovigilance

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

No data available.

5.2. Patient exposure

No exact data on patient exposure are available. However, the long-standing use and the inclusion in many standard handbooks of Phytotherapy and in official pharmacopoeias and compendia make a wide exposure plausible.

5.3. Adverse events and serious adverse events and deaths

Adverse events

- Dermatological reactions

The rough hairs of the above-earth parts of *Arctium lappa* L. can result in mechanical irritation of the skin (De Smet 1993).
Rodriguez (1995) reported three cases of contact dermatitis caused by *Arctium lappa* L. plasters applied for anti-inflammatory purposes. They describe two men in their thirties and one 14-year-old girl who had an erythematous exudative dermatitis after applying a plaster of *Arctium lappa* L.
There are no unambiguous reported cases of contact allergy to *Arctium lappa* L., though Rodriguez (1995) reports it as an irritant substance without further details; however, the root as well as aerial parts may be involved. It should be noted that urticaria has been reported after the topical use of the leaves (see 1.1), however this reaction has been attributed as a "beneficial effect" (Leclerc 1966).
Allergic reactions are likely to be associated with the presence of sesquiterpene-lactones such as arctiopicrin that is a weak sensitizer. Also dehydrocostuslactone, which is found in *Saussurea lappa* Clarke and Laurel oil, is well-known to cause allergic reactions (Hausen 1997). For this reason, a cross-reaction with other *Asteraceae* can be assumed.

- Ocular reactions

The rough hairs of *Arctium lappa* L. fruit may hook on clothing. Within the bur and attached to seed pods, *Arctium lappa* L. has thousands of tiny barbed needles. If these needles imbed in the conjunctiva, it may cause serious ocular reactions. Because they are very small, they are often missed by doctors who are not familiar with the plant. An *Arctium lappa* L. caused ophthalmic irritation can be recognised by the presence of linear scratch marks running in random directions on the cornea. The needle tip causes direct abrasion every time the eyelid moves, thus causing serious damage. The toxicity of a water soluble noxious agent may also play a role, which is suggested from animal tests. An aqueous extract caused severe reactions, which were not observed following the injection of an oily extract (De Smet 1993).

- Animal-data

For dogs (especially long-hair breeds) and occasionally cats who run free in areas with *Arctium lappa* L. the so called 'burr tongue' is commonly seen. The hair-like shafts of *Arctium lappa* L. have a little hook on the tip by which the bur sticks to the fur of the animals. When an animal wants to remove this bur, mostly by licking and chewing, some of the shafts may penetrate the membrane of the mouth and tongue. This causes fibrous granulation (De Smet 1993).

Serious adverse events and deaths

- Anaphylactic shock

Only one case of serious allergy to *Arctium lappa* L. is known. A 53-year-old Japanese man was diagnosed to be in anaphylactic shock after eating boiled burdock root. His symptoms were redness over his entire body, dyspnea and a low blood pressure of 64/29 mmHg. He recovered after subcutaneous injection of epinephrine (1 mg) and an intravenous drip of lactate Ringer's solution containing hydrocortisone (100 mg) and dexamethasone (8 mg). Sasaki (2003) warns of similar cases world-wide because burdock root is often used as an ingredient in tea or folk medicines in Western countries (Sasaki 2003).

Some remarks have to be made on this case. Apart from burdock, the patient consumed also carrot and curry with his rice. Skin prick tests revealed an allergic predisposition for burdock but also for carrot (not for curry). Boiled as well as raw plant materials were used for allergy testing (Sasaki 2003).

- Atropine like poisoning

De Smet (1993) mentions anticholinergic poisoning, due to adulteration or contamination with belladonna root. This is also reported by Barnes (2007). The patient exhibited symptoms of atropine-like poisoning after ingestion of *Arctium lappa* L. tea. Atropine is not a constituent of *Arctium lappa* L., but analysis showed that the tea was contaminated with an herbal source of solanaceous alkaloïds, possibly belladonna root.

Contamination with *Atropa belladonna* L. is reported in many handbooks. Older roots and roots that show a blue colour after treatment with iodine solutions (indicator for Radix Belladonnae) may not be used for this reason. According to Blaschek (1998), also substitution with *Symphytum officinale* L. or *Rumex obtusifolius* L. may also occur.

5.4. Laboratory findings

No data available.

5.5. Safety in special populations and situations

It has been reported that *Arctium lappa* L. may cause uterine stimulation and therefore the use of *Arctium lappa* L. should be avoided during pregnancy and lactation (Barnes 2007). However, no case reports or pharmacological studies that would support this assumption were found.

Intrinsic (including elderly and children) / extrinsic factors

None known.

Drug interactions

According to Barnes (2007), there are no documented interactions. Nevertheless, the authors warn with respect to the potential interactions with other medicines, particularly those with similar or opposing effects. Apart from this general statement, no clinical evidence is available; consequently, no warning should be included in the monograph.

Arctium lappa L. has also been associated with diuretic effects. Nothing is known about possible additive effects when *Arctium lappa* L. is taken concomitantly with diuretic drugs. No statement is needed in the monograph.

Tinctures of *Arctium lappa* L. may contain high concentrations of alcohol and may lead to vomiting if used with disulfiram. This aspect is covered in the monograph by a general warning on ethanol containing preparations.

Use in pregnancy and lactation

In vivo uterine stimulant action has been reported. In view of this and the lack of toxicity data, the use of burdock during pregnancy and lactation is not recommended (Barnes 2007). However, as neither case reports on toxicity nor pharmacological studies demonstrating an effect on the uterus have been found, the standard warning has been included in the monograph; i.e. that the use is not recommended due to insufficient data.

Overdose

No case of overdose has been reported.

Drug abuse

Drug abuse has not been reported.

Withdrawal and rebound

None reported.

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

No studies on the effect on the ability to drive and use machines have been performed.

5.6. Overall conclusions on clinical safety

Under the conditions of use mentioned in the monograph *A. lappa*, root can be considered as safe. There is evidence for local irritation, due to the barbed needles on the bur of the plant. These are not relevant for the root. Allergic reactions may occur; probably due to sesquiterpene-lactones. The quality of the herbal substance should be checked rigorously as contamination with *Atropa belladonna* may occur.

6. Overall conclusions

Some constituents of *Arctium lappa* L. are well investigated and documented. Many authors have described various pharmacological activities of *Arctium lappa* L. seed extracts or isolated constituents in animals or *in vitro*.

Despite their long tradition and their widespread use, there are no data available from controlled clinical studies using herbal preparations containing *Arctium lappa* L. root. In conclusion, *Arctium lappa* L. root preparations can only be considered for traditional use. More clinical research is needed to confirm the pharmacological properties.

The monograph on *Arctium lappa* L. is restricted to the root as there is no documented use of medicinal products from the leaves and there is insufficient evidence on the traditional use of the seeds.

Benefit-risk assessment

- Quality

There is no Arctii lappae radix monograph in the European Pharmacopoeia. The most recent official monograph comes from DAC 2008. Contamination with *Atropa belladonna* root has been mentioned, as well as exchanges with *Symphytum officinale* L. and *Rumex obtusifolius* L.

Conclusion: Contamination or adulteration of *Arctium lappa* root with serious health risks are possible and need to be excluded by adequate quality control in the framework of a registration procedure.

- Safety

There are very few side effects due to root preparations. The main risks are allergic reactions associated with sesquiterpene-lactones. There is one case of an anaphylactic reaction after eating boiled burdock. No overdoses with root preparations have been reported. Reproductive toxicity and genotoxicity were tested with non specified preparations or plant parts other than the root. No carcinogenicity was reported after feeding rats with root-enriched food; however this study does not comply with current standards. Other possible effects (e.g. interference with antidiabetic medicines) were seen in experimental conditions with plant parts other than root. There are no concerns about interactions with conventional medicines. *Arctium lappa* root has been repeatedly associated with antimutagenic activity *in vitro*. However, a list entry cannot be made as adequate tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed with Arctii lappae radix.

Conclusion: Preparations of *Arctium lappa* root can be considered as safe but no list entry can be prepared.

- Efficacy

Therapeutic indications for herbal preparations of *Arctium lappa* root as given in the monograph are based on more than 30 years traditional use in Europe but not supported by validated clinical experience. Even open clinical observations are missing. The use in seborrhoeic skin conditions (ICD L21, ATC D11AX) in urinary complaints and in stimulation of appetite is plausible on the basis of its long-standing, consistent use in those indications as well as inclusion in standard handbooks and official compendia. The diuretic use of herbal medicinal products with *Arctium lappa* root should not replace conventional diuretics with antihypertensive and heart protective therapeutic effects. The use in case of temporary loss of appetite must be considered as purely symptomatic, while it should not be continuously used without a clear diagnosis.

Conclusion: Traditional therapeutic use of *Arctium lappa* is safe under the conditions addressed in the monograph.

Annex

List of references