EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

This document was valid from 13 September 2011 until March 2018. It is now superseded by a new version adopted by the HMPC on 27 March 2018 and published on the EMA website.

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)	*Cynara scolymus* L., Cynarae folium
Herbal preparation(s)	a) Comminuted or powdered dried leaves for herbal tea b) Powdered leaves c) Dry extract (DER 2.5-7.5:1), extraction solvent water d) Dry extract of fresh leaves (DER 15-35:1), extraction solvent water e) Soft extract of fresh leaves (DER 15-30:1), extraction solvent water f) Soft extract (DER 2.5-3.5:1), extraction solvent ethanol 20% (v/v)
Pharmaceutical forms	Comminuted herbal substance as herbal tea for oral use. Herbal preparations in solid or liquid form for oral use
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1. Introduction

Latin Name: *Cynara scolymus* L., *Asteraceae* family (*Compositae*)
In a recent botanical taxonomic revision of the genus *Cynara* [ESCOP 2009] it has been accepted that the leafy cardoon (*Cynara cardunculus* L.) and the globe artichoke (*Cynara scolymus* L.) are two cultivars of a new subspecies *Cynara cardunculus* L. subsp. *flavescens* Wiklund [ESCOP 2009]. Nevertheless, the botanical name, *Cynara scolymus* has been kept for the monograph, in accordance with the European Pharmacopoeia (*Cynara scolymus)* not distinguishing morphologically the two types of the plant cultivars (globe artichoke and leafy cardoon).

Pharmacopoeial Name: Cynarae folium
Other Names: The name has originated from ardi shauki, which is Arabic for ground-thorn, through the Italian: articiocco, English: globe artichoke, French: artichaut, German: Artischocke, Hungarian: articsóka level, Latvian: artišoka lapas, Greek: Κινάρα, Swedish: kronärtskocka, Dutch: artisjok, Portuguese: alcachofra, Croatian: artičoka, Turkish: enginar, Russian: артишок, Spanish: alcachofa, alcachofera.

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

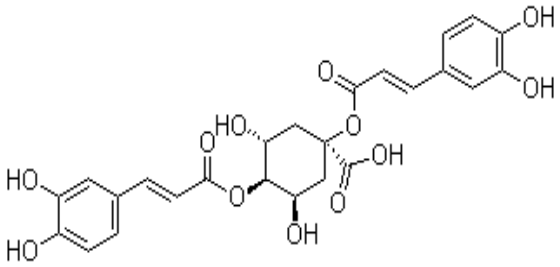
- Herbal substance(s)

Pharmacopoeial grade artichoke leaf consists of the dried basal leaves of *Cynara scolymus* L. containing a minimum 0.8% of chlorogenic acid ($C_{16}H_{18}O_9$; M_r 354.3) (dried drug). Botanical identification is carried out by thin-layer chromatography, macroscopic and microscopic evaluations, and organoleptic tests. The dried leaf must contain not less than 25% water-soluble extractive [BHP 1996; Pharmacopeé Francaise 1987; Blumenthal *et al.* 2000; Bruneton 1999].

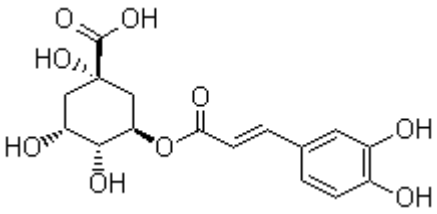
Globe Artichoke (*Cynara scolymus* L.) is a perennial thistle originating in southern Europe around the Mediterranean (northern Africa and the Canary Islands) [Leung & Foster, 1996]. It grows to 1.5-2 m tall, with arching, deeply lobed, silvery glaucous-green leaves 50–80 cm long. The flowers develop in a large head from an edible bud about 8–15 cm diameter with numerous triangular scales; the individual florets are purple. The edible portion of the buds consists primarily of the fleshy lower portions of the involucral bracts and the base, known as the "heart"; the mass of inedible immature florets in the center of the bud are called the "choke".

Its cultivation in Europe dates back to ancient Greece and Rome [Grieve 1971]. It is cultivated in North Africa as well as in other subtropical regions [Iwu 1993]. The material of commerce comes as whole or cut dried leaves obtained mainly from southern Europe and northern Africa [BHP 1996].
Artichoke leaf contains up to 2% phenolic acids, mainly 3-caffeoylquinic acid (chlorogenic acid), plus 1.3-di-O-caffeoylquinic acid (cynarin), and caffeic acid; 0.4% bitter sesquiterpene lactones of which 47-83% is cynaropicrin; 0.1^{-1}% flavonoids including the glycosides luteolin-7-β-rutinoside (scolymoside), luteolin-7-β-D-glucoside and luteolin-4-β-D-glucoside; phytosterols (taraxasterol); sugars; inulin; enzymes; and a volatile oil consisting mainly of the sesquiterpenes β-selinene and caryophyllene [Hänsel *et al.* 1992, 1994; Leung & Foster 1996; Meyer-Buchtela 1999; Newall *et al.* 1996].
Analytically, artichoke's main plant chemicals are caffeic acid, caffeoylquinic acids, chlorogenic acid, cyanidol glucosides, cynaragenin, cynarapicrin, cynaratriol, cynarin, cynarolide, decanal, eugenol, ferulic acid, flavonoids, folacin, glyceric acid, glycolic acid, heteroside-B, inulin, isoamerboin, lauric acid, linoleic acid, linolenic acid, luteolin glucosides, myristic acid, neochlorogenic acid, oleic acid, palmitic acid, phenylacetaldehyde, pseudotaraxasterol, scolymoside, silymarin, sitosterol, stearic acid,

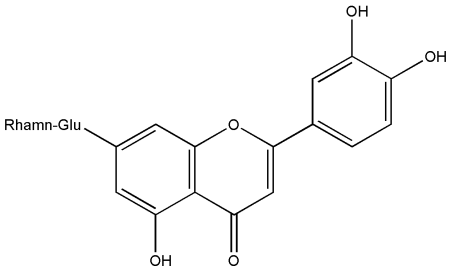
stigmasterol, and taraxasterol [Dorne 1995; Maros *et al.* 1966, 1968; Montini *et al.* 1975; Samochowiec *et al.* 1971].



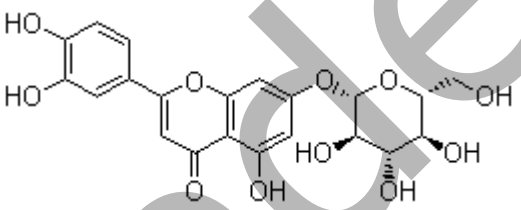
Cynarin



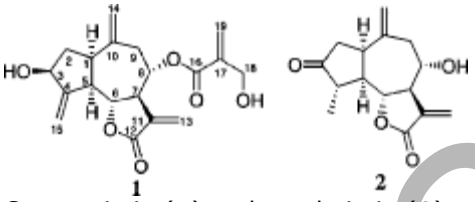
Chlorogenic acid



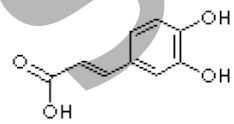
Scolymoside



Cynaroside



Cynaropicrin (**1**) and grosheimin (**2**)



Caffeic acid

The artichoke is popular for its pleasant bitter taste, which is attributed mostly to a plant chemical called cynarin found in the green parts of the plant. Cynarin is considered one of artichoke's main biologically active chemicals. It occurs in the highest concentration in the leaves of the plant, which is why leaf extracts are most commonly employed in herbal medicine. Other documented "active" chemicals include flavonoids, sesquiterpene lactones, polyphenols and caffeoylquinic acids.

- Herbal preparation(s)

Concerning the information provided by the Member States the intended use of the following preparations is:

Traditional use

- Comminuted or powdered leaves for herbal tea (Belgium, Germany, Spain and Poland)

- Powdered leaves (France)

- Dry aqueous extract (DER 2.5-3.5:1), dried leaf (France 1976)

- Dry extract (DER 4-6:1), extraction solvent water (Germany 1978 WEU)

- Dry extract (DER 5.8-7.5:1), extraction solvent water (Germany 1978)

- Dry aqueous extract from fresh leaf (DER 15-30:1), (France 1976, Germany 1978 WEU)

- Dry extract from fresh leaves (DER 25-35:1), extraction solvent water (Germany 1978 WEU)

- Soft extract fresh leaves (DER 15-30:1), extraction solvent water (France)

- Soft extract (DER 2.5-3.5:1), extraction solvent ethanol 20% (v/v) (Germany 1978 WEU)

- 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.

For combination products there is the following information in European market:

  - Spain: Combinations products: Artichoke extract with laxative products or with Boldo extract
  - Sweden: There is one combination product, a so called natural remedy, containing *Cynara scolymus* together with *Gentiana lutea* and *Curcuma longa*
  - Germany: Seven authorised combination products with Matricariae flos, Taraxaci herba cum radix, Menthae piperitae folium, Millefolii herba, Foeniculi amari fructus, Helichrysi flos

Combinations containing artichoke are not subject of this assessment.

- Vitamins and Minerals

Not applicable.

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:	
Belgium	☒ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Bulgaria	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Czech Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Only combinations
Denmark	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Estonia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Finland	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	No marketed product
France	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Germany	☒ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	Also in combinations
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No marketed product
Hungary	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No marketed product
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Latvia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No marketed product

Member State	Regulatory Status				Comments
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Lithuania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No marketed product
Luxemburg	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Malta	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
The Netherlands	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Norway	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Poland	☒ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Portugal	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No marketed product
Romania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Slovak Republic	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Slovenia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Spain	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	Also combinations
Sweden	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Only in combination
United Kingdom	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	TU: Dry extract(4-6:1), extraction solvent: water Since: 2009

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.

Member State	**Regulatory Status - products, indications**
Austria	**Traditional use** **Preparations:** 1) dry extract, DER 4-6:1, solvent water 350 mg 2) dry extract (no further details) 300 mg 3) dry extract, DER 4-6:1, solvent water 320 mg 4) dry extract, DER 4-6:1, solvent water 600 mg 5) dry extract, solvent water (no further details) 400 mg **Since:** 1) 2000; 2) 1999; 3) 1998; 4) 2000; 5) 1999 **Pharmaceutical form:** 1), 2), 4), 5) coated tablet 3) capsules **Posology** for oral use in adults: 1) 3 times daily 1-2 coated tablets 2), 4), 5) 3 times daily 1 coated tablet 3) 3 times daily 1-2 capsules **Indications** : 1), 2), 4), 5) Digestive complaints

Member State	Regulatory Status - products, indications
	3) Dyspepsia **Risks:** No adverse effects known. There are also products in the market as a combination with Menthae pip. folium, Taraxaci radix, Curcumae rhizoma and Silybi marianae fructus as well as combinations containing Cynarae folium, Silybi marianae fructus and Taraxaci radix. **Well established use** **Preparations:** 1) dry extract, DER 25-35:1, solvent water 300 mg 2) dry extract, DER 25-35:1, solvent water 450 mg 3) dry expressed juice from 12000 mg fresh leaves 400 mg 4) dry extract, DER 4-6:1, standardised to >1.25% caffeoylquinic acids 5) soft extract, DER 4-6:1, standardised to >0.5% caffeoylquinic acids 5 ml contain 200 mg 6) dry extract, DER 3.8-5.5:1, solvent water 400 mg 7) dry expressed juice from 12000 mg fresh leaves 400 mg **Since:** 1), 2), 6), 7) 2002; 3) 2004; 4), 5) 1992 **Pharmaceutical form:** 1), 2), 3), 4), 7) coated tablet 5) solution for oral intake 6) capsules **Posology** for oral use in adults: 1) oral, 3 times daily 300 mg 2) oral, 3 times daily 450 mg 3) oral, 1 times daily 1-2 coated tablets 4) oral, 3 times daily 1-2 coated tablets 5) oral, 3 times daily 5-10 ml 6) oral, 3 times daily 1 capsule 7) oral, 3 times daily 1-2 coated tablets **Indications:** 1), 2), 6) Digestive complaints, regulation and improvement of lipid metabolism 3) Improvement of digestion 4), 5), 7) dyspeptic disorders, post-treatment after hepatitis, chronic hepatopathies, subacute or chronic diseases of the biliary tract, after-care of cholecystectomy **Risks:** 4), 5), 7) None known 1), 2) Rarely mild laxative effects 6) hypersensitivity reactions
Belgium	**Well established use** **Preparations:** 1) powdered leaves 2), 3) dry "purified" extract, equiv. 1.875% chlorogenic acid (no further details) 4) dry extract (no further details) **Since:** 1) 2006; 2), 3) 2000; 4) 1999

Member State	Regulatory Status - products, indications
	Pharmaceutical form: 1) capsules, hard; 200 mg powder per capsule 2) coated tablets; 200 mg extract/tablets 3) oral solution; 240 ml extract/ml 4) coated tablets; 200 mg extract/tablets **Posology** for oral use in adults and adolescents: 1) 2 times 3-4 capsules daily 2) 2 times 3 tablets daily 3) 2-4 times 2.5 ml daily 4) 2-4 times 3 tablets daily **Indications:** 1) enhances bile excretion, after exclusion of serious pathologies 2) cholagogue, after exclusion of serious pathologies. Minor increase in renal water excretion. Marketing Authorisations for the teas date from 1962 50-200 mg *Cynara* herb per gram tea **Combinations products**: Artichoke leaf extract with Boldo folium, herba hepaticae, Centaurii herba, Cardui benedicti herba, Fraxini folium
Bulgaria	**Well established use** **Preparations**: 1) dry extract, (DER 4-6:1), tablets 2) soft extract (DER 4-6:1), liquid **Since:** 1) 2001; 2) 2006 **Pharmaceutical form:** 1) coated tablet 5) solution for oral intake **Posology** for oral use in adults (children over 12 years): 1) adults 1-2 tablets 3 times daily 2) adults 1-2 teaspoon 3 times daily **Indications:** 1), 2) dyspeptic symptoms and meteorism following fatty meals and meals which are difficult to digest, follow-up treatment by liver and biliary dysfunction **Risks**: 1), 2) hypersensibility, diarrhoea, flatulence, nausea
Cyprus	Not known.
Czech Republic	No authorised herbal medicinal products containing Cynarae folium as a single drug preparation are on the market.
Denmark	No authorised herbal medicinal products containing Cynarae folium as a single drug preparation are on the market.
Estonia	Not known.
Finland	No authorised herbal medicinal products containing Cynarae folium as a single drug preparation are on the market.

Member State	Regulatory Status - products, indications
France	**Traditional use** **Preparations:** 1), 2) powdered dried leaves 3) aqueous extract 4) dry aqueous extract 5) dry aqueous extract , DER 2-3.5:1 6), 7) dry aqueous extract; DER 2.5-3.5:1 dried leaf or DER 15-30:1 fresh leaf 8) soft aqueous extract **Since:** 1) 1988; 2) 1994; 3) 1988; 4) 1990; 5) 1986; 6-7) 1976; 8) 1966 **Pharmaceutical form:** 1), 4), 5) Hard capsules 6) coated tablet 2), 3), 7), 8) solution for oral intake **Posology** for oral use in adults: 1) hard capsule 3 times daily 200 mg of powdered drug/capsule 2) 1 ampoule (5 ml) 2 times daily (0.5 g of powdered drug/ ampoule) 3) 3-6 ampoules (15 ml) daily (0.3 g of extract/ampoule) 4) 1-2 hard capsules 2 times daily (192.5 mg of extract/capsule) 5) 1 hard capsule 2 times daily (200 mg of extract/capsule) 6) 1-2 coated tablets 3 times daily (200 mg of extract/tablet) 7) 1 coffee spoon 3 times daily (20 g of extract/100 ml) 8) 1 ampoule (10 ml) 3 times daily (2 g of extract/ampoule) **Indications:** 1-5) Traditionally used to promote urinary and digestive elimination functions. Traditionally used as a choleretic and cholagogue 6-8) Traditionally used to promote urinary and digestive elimination functions **Risks:** None reported
Germany	**Traditional use** **Preparations:** dry extract (DER 5.8-7.5:1), extraction solvent water **Since:** 1978 **Pharmaceutical form:** coated tablet **Posology** for oral use in adults: 1 coated tablet contains 300 mg dry extract 1-2 times daily 1 coated tablet **Indications**: traditional used to promote the digestion **Risks:** Adverse reactions: slight diarrhoea with abdominal spasm, epigastric complaints like nausea and heartburn, reactions of hypersensitivity like exanthema. Interactions: concomitant use may decrease the efficacy of anticoagulants (coumarin derivates like Phenprocoumon, Warfarin). Tight monitoring is necessary. **Seven authorised combination products** with Matricariae flos, Taraxaci herba cum radix, Menthae piperitae folium, Millefolii herba, Foeniculi amari fructus, Helichrysi flos Moreover the following authorised products for **traditional use**: **Cynarae flos**: 3 expressed juices from fresh artichoke flower buds (1:0.6-0.9) on the

Member State	Regulatory Status - products, indications
	market since 1978, expr. juice, for traditional use **Cynarae herba:** 1 fluid extract from artichoke herb (1:2.4-5.2), extraction solvent: ethanol on the market since 1978, liquid, for traditional use **Well established use** **Preparations:** 1), 3-11), 14-16), 18-19), 21-23), 27-34), 36), 38), 43) dry extract (DER 4-6:1), extraction solvent water 2, 26) dried expressed juice from fresh artichoke leaves (DER 25-35:1), extraction solvent water 12, 39-40) dry extract from fresh artichoke leaves (DER 25-35:1), extraction solvent water 13, 41, 42) dry extract (DER 5.8-7.5:1), extraction solvent water 17) fluid extract (DER 1:0.9-1.1), extraction solvent ethanol 35% (v/v) 20) dry extract (DER 3.8-5.5:1), extraction solvent water 25, 35) dry extract from fresh artichoke leaves (DER 15-30:1), extraction solvent water 37) soft extract (DER 2.5-3.5:1), extraction solvent ethanol 20% (v/v) **Since:** 1, 14, 16) 2000; 2) 2005; 3, 6, 9, 15, 18, 21-24) 1998; 4, 7, 10, 12, 13, 17, 19, 20, 35-42) 1978; 5, 11) 1999; 8, 28-31, 43) 2003; 25, 27, 32) 2002; 26) 2006; 33, 34) 2004 **Pharmaceutical form:** 1, 3, 5, 6, 9-11, 14-16, 18, 20-24, 38) hard capsule 2, 4, 8, 12, 13, 26-36, 39-43) coated tablet 7, 25) film tablet 17, 19, 37) oral liquid **Posology** for oral use: Adults and adolescents over 12 years 1, 3, 6, 9, 14-16, 18, 21-24) 1 hard capsule contains 400 mg dry extract; 1 times 3 times daily 2, 26) 1 coated tablet contains 400 mg dried expressed juice; 2 times daily 1 coated tablet 4) 1 coated tablet contains 232 mg dry extract; 5 coated tablets per day in the following order: 2 coated tablets in the morning, 2 coated tablets at noon and 1 coated tablet in the evening 5) 1 hard capsule contains 400 mg dry extract; 2-3 times daily 1 hard capsule 7) 1 film tablet contains 200 mg dry extract; 3 times daily 2 film tablets 8, 27-34, 43) 1 coated tablet contains 600 mg dry extract; 2 times daily 1 coated tablet 10) 1 hard capsule contains 200 mg dry extract; 3 times daily 2 hard capsules 11) 1 hard capsule contains 400 mg dry extract; 3 times daily 1 hard capsule 12) 1 coated tablet contains 450 mg dried expressed juice; 1-2 coated tablets 13, 41, 42) 1 coated tablet contains 300 mg dry extract 17) 1 ml liquid contains 1 ml fluid extract; 4 times daily 45 drops fluid extract 19) 10 ml liquid contains 400 mg dry extract; 3 times daily 2 teaspoons (=10 ml) of liquid 20) 1 hard capsule contains 200 mg dry extract; 3 times daily 1 hard capsule, if

Member State	Regulatory Status - products, indications
	necessary 4 times daily 25) 1 film tablet contains 320 mg dry extract; 4 times daily 1 film tablet 35) 1 coated tablet contains 160 mg dry extract; 4 times daily 2 coated tablets 36) 1 coated tablet contains 220 mg dry extract; 3 times daily 2 coated tablets 37) 100 g (=94.8 ml) liquid contains 33.333 mg soft extract; 3 times daily 40 drops 38) 1 hard capsule contains 320 mg dry extract; 2 times daily 2 hard capsules 39) 1 coated tablet contains 300 mg dry extract; Adults: 3-4 times daily 2 coated tablets 40) 1 coated tablet contains 150 mg dry extract; Adults: 3-4 times daily 2-4 coated tablets **Indications :** 1, 3, 6, 7, 9, 11-16, 18-25, 39-42) dyspeptic complaints, particularly based on functional affections of the biliary tract 2, 4, 5, 8, 17, 26-38, 43) dyspeptic complaints, particularly based on functional affections of the biliary tract 10) dyspeptic complaints based on insufficient bile secretion like sense of fullness, flatulence, minor gastrointestinal spasms **Risks:** 1–43) Adverse reactions: slight diarrhoea with abdominal spasm, epigastric complaints like nausea and heartburn, reactions of hypersensitivity like exanthema. Interactions: concomitant use may decrease the efficacy of anticoagulants (coumarin derivates like Phenprocoumon, Warfarin). Tight monitoring is necessary.
Hungary	**Traditional use** **Preparations:** 400 mg Cynarae scol. folium extr. sicc (3-6:1, extraction solvent water) **Since:** 2001 **Pharmaceutical form:** Dragée, coated tablet **Posology:** for oral use in adults 3 times 1 dragée: The use is not recommended in children under 12 years of age because of the lack of available experience. Duration treatment: Until the existence of the complaints but not more 2-3 months. If the complaints reoccur the cure can be restarted but at least one month's break should be kept. **Indications:** For digestive complaints, feeling of fullness, nausea, flatulence, gallbladder disease, to promote bile secretion (as cholagogue) , to promote fat digestion **Risks:** Contraindication: Obstruction of bile duct, cholangitis, hepatitis, hypersensitivity to artichoke or other species of the *Compositae*. Warnings: Patients with cholelithiasis should take artichoke leaf only after consulting a health care professional. Interactions: There are no data on concomitant use of Artichoke leaf with other preparations. Pregnancy, lactation: Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not

Member State	Regulatory Status - products, indications
	recommended. Adverse effects: mild digestive system disturbances may occur in rare cases; allergic reactions might occur in sensitised patients.
Poland	**Traditional use** **Preparations:** 1) Cynarae herbae extractum sicuum (3-6:1), extraction solvent water 2) Cynarae herbae tinctura (1:5), extraction solvent ethanol 70% (v/v) 3) Cynarae folii extractum siccum (25-35:1), extraction solvent water 4) Cynarae herbae extractum siccum (4:1), extraction solvent ethanol 50% (v/v) 5) Cynarae herba –herbal tea **Since:** 1, 3) 1967; 2, 4) 1997; 5) since many years **Pharmaceutical form:** 1) capsule, hard 2) oral liquid 3) capsule, hard 4) tablets 5) herbal tea **Posology** 1) oral use, 3-4 capsules daily 2) oral use, 10 ml 3 times daily 3) oral use, 1 capsule daily 4) oral use, 2 tablets once a day (digestive disorders) or 2 tablets 3 times daily (hyperlipidaemia) 5) oral use: 3 g (of the dried Cynarae herba in one glass of bolding water–as infusion) 1-3 times daily or in hyperlipidaemia 1.5 g (of the dried Cynarae herba in one glass of bolding water – as infusion) 4 times daily **Indications :** 1, 3) digestive complaints (e.g. stomach ache, feeling of fullness, flatulence) 2) digestive complaints and hepatobiliary disturbances 4) digestive complaints and hepatobiliary disturbances. Adjuvant to a low fat diet in the treatment of mild to moderate hyperlipidaemia, 5) digestive complaints (feeling of fullness, nausea, flatulence). Adjuvant to a low fat diet in the treatment of mild to moderate hyperlipidaemia. **Risks:** Mild gastro-intestinal disturbances reactions may occur in rare cases; allergic reactions might occur in sensitised patients. **Well established use** **Preparations**: Cynarae folii extractum aq siccum (4-6:1), extraction solvent: water **Since:** 1997 **Pharmaceutical form**: capsule, hard **Posology:** for oral use, 1-2 capsules once a day (digestive disorders) or 3-5 capsules daily (mild hyperlipidemia) **Indications:**

Member State	Regulatory Status - products, indications
	digestive complaints (feeling of fullness, nausea, flatulence, heartburn)- Adjuvant to a low fat diet in the treatment of mild to moderate hyperlipidaemia **Risks**: Mild gastro-intestinal disturbances reactions may occur in rare cases; allergic reactions might occur in sensitised patients
Slovakia	**Well established use** **Preparations:** extractum fluidum **Since:** 1996 **Pharmaceutical form**: oral solution **Posology** for oral use: (tea spoon for 3 times a day) **Indications:** Indicated in light forms of hyperlipidaemia as additional treatment. Indicated for adults, adolescents and children **Risks:** None reported
Spain	**Traditional use** **Preparations:** 1) Dried leaves for oral use as herbal tea or 2) Powdered leaves in pharmaceutical forms for oral use, at least since 1973 **Pharmaceutical form:** 1) Herbal tea 2) Tablets/Capsules **Posology** for oral use in adults: 1) up to 3 g a day (1-3 capsules of tea a day) 2) 600-1500 mg a day (Capsules of 150; 175; 300; 500 mg) **Indications:** Dyspepsia **Risks**: None reported **Combinations products:** Combination of Artichoke with laxative products and with Boldo extract
Sweden	There is one combination product, a so called natural remedy, containing *Cynara scolymus* together with *Gentiana lutea* and *Curcuma longa*.
United Kingdom	**Traditional use** **Preparations**: Dry extract (4-6:1), extraction solvent: water **Since:** 2009 **Pharmaceutical form**: capsule, hard **Posology:** Adults elderly for oral use, 1-capsule twice par day **Indications:** digestive complaints such as digestion, upset stomach, nausea, feeling of fullness, flatulence, particularly caused by over indulgence of food and drink, based on traditional use only

1.3. Search and assessment methodology

Not specified by the Rapporteur.

2. Historical data on medicinal use

2.1. Information on period of medicinal use in the Community

The artichoke was used as a food and medicine by the ancient Egyptians, Greeks, and Romans. Artichoke leaf has been used as a choleretic and diuretic in traditional European medicine since Roman times [Bianchini & Corbetta 1977]. Artichoke is widely cultivated in Mediterranean countries, particularly in Italy, the sprout being consumed as a vegetable. Globe artichokes were first cultivated at Naples around the middle of the 15th century, and are said to have been introduced to France by Catherine de "Medici". The Dutch introduced artichokes to England, where they were growing in Henry VIII's garden at Newhall in 1530. They were introduced to the United States in the 19th century, to Louisiana by French immigrants and to California by Spanish immigrants.

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

Type of tradition, where relevant

European tradition.

Evidence regarding the indication/traditional use

The alcoholic extract of the leaves, currently used for the production of bitter liqueurs (about 10 g of dried leaves per litre), has been documented as a traditional folk remedy for dyspeptic disorders. Especially artichoke is the primary flavour of an Italian liquor.
The *Commission E* reported choleretic activity [Blumenthal *et al.* 2000; ESCOP 2009].
The *British Herbal Pharmacopoeia* reported hepatic action [BHP 1996].
The *Merck Index* reported the therapeutic category of cynarin, an active principle of artichoke, as choleretic [Budavari 1996].

The *African Pharmacopoeia* indicates its use for the treatment of liver dysfunction as well for its diuretic and anti-atherosclerotic actions [Iwu 1993].

Traditional medicinal uses of artichoke pertain to liver function as its leaves are considered choleretic (bile increasing), hepatoprotective, cholesterol-reducing, and diuretic [Kirchhoff *et al.* 1994]. Artichoke has been used in traditional medicine for centuries all over Europe as a specific liver and gallbladder remedy and several herbal drugs based on the plant are used as well for high cholesterol and digestive and liver disorders. Other uses around the world include treatment for dyspepsia and chronic albuminuria. Artichoke is also often used to mobilise fatty stores in the liver and detoxify it, and as a natural aid to lower cholesterol. In Brazilian herbal medicine systems, leaf preparations are used for liver and gallbladder problems, diabetes, high cholesterol, hypertension, anaemia, diarrhoea (and elimination in general), fevers, ulcers, and gout. Artichoke leaf has shown cholesterol-lowering and lipid-lowering activity in rats and humans [Lietti 1977]. Human studies have validated carminative, spasmolytic, antiemetic and choleretic actions [Kraft 1997].

In vivo, artichoke leaf has demonstrated hepatoprotective and hepatostimulating properties [Adzet *et al.* 1987i; 1987ii; Maros *et al.* 1966].

In Germany, artichoke leaf is used widely as a choleretic [Commission E Monographs 1998; Meyer-Buchtela 1999] for its lipid-lowering, hepato-stimulating, and appetite-stimulating actions since at least thirty years [Hänsel *et al.* 1992, 1994; Meyer-Buchtela 1999]. Moreover, in German paediatric medicine, herbs with a relatively low bitter value such as artichoke leaf are considered suitable for the treatment of appetite disorders [Schilcher 1997].

Preparations of artichoke have been used for bloating, nausea, and impairment of digestion [Bruneton 1999]. It is specifically indicated for "dyspeptic syndrome" though its proven lipid-lowering actions suggest that it may also be useful as a prophylactic against atherosclerosis [Kraft 1997]. Artichoke leaf has shown cholesterol-lowering and lipid-lowering activity in rats and humans [Lietti 1977]. Human studies have validated carminative, spasmolytic, antiemetic, and choleretic actions [Kraft 1997].

In France, several pharmaceutical forms of artichoke leaf extracts are in use for the last 30 years [Pharmacopeé Francaise 1987; Martindale 1993; WHO Monographs 2009; ESCOP monographs supp. 2009].

Worldwide ethnomedical uses

Europe	**for bile insufficiency, cancer, detoxification, dyspepsia, gallbladder disorders, high cholesterol, hyperglycaemia, jaundice, liver disorders, nausea**
Brazil	for acne, anaemia, arthritis, arteriosclerosis, asthma, bile insufficiency, blood cleansing, bronchitis, diabetes, diarrhoea, dyspepsia, digestive disorders, dandruff, fever, flatulence, gallbladder disorders, gallstones, gout, heart function, haemorrhage, haemorrhoids, high cholesterol, hypertension, hyperglycaemia, inflammation, kidney insufficiency, liver disorders, nephritis, obesity, prostatitis, rheumatism, seborriasis, ulcers, urethritis, urinary disorders, and as an astringent and vasoconstrictor
Dominican Republic	for bile insufficiency, digestive problems, gallbladder disorders
Haiti	for oedema, hypertension, kidney disorders, liver problems, urinary insufficiency
Mexico	for cystitis, gallstones, hypertension, liver disorders

The following herbal substances and herbal preparations are for more than 30 years on the European market and are proposed for the monograph on traditional use.

a) Comminuted or powdered leaves for herbal tea (Belgium, Germany, Spain, Poland)

b) Powdered leaves (Spain)

c) Dry extract (DER 2.5-7.5:1), extraction solvent water from preparations:
dry aqueous extract; (DER 2.5-3.5:1) dried leaf (France 1976)
dry extract (DER 4-6:1), extraction solvent water (Germany 1978 WEU)
dry extract (DER 5.8-7.5:1), extraction solvent water (Germany 1978)

d) Dry extract from fresh leaves (DER 15-35:1), extraction solvent water from preparations:
dry aqueous extract from fresh leaf; (DER 15-30:1) (France 1976, Germany 1978 WEU)
Dry extract from fresh leaves (DER 25-35:1), extraction solvent water (Germany 1978 WEU)

e) Soft extract from fresh leaves (DER 15-30:1), extraction solvent water (France)

f) Soft extract (DER 2.5-3.5:1), extraction solvent ethanol 20% (v/v) (Germany 1978 WEU)

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

Posology and indications of the traditional herbal substance and preparations of artichoke

Indications: traditionally used

a) Traditional herbal medicinal product to promote digestion (against dyspepsia, digestive complaints) (Germany)

b) Traditional herbal medicinal product against digestive complaints (e.g. stomach ache, feeling of fullness, flatulence) and/or adjuvant to a low fat diet in the treatment of mild to moderate hyperlipidaemia (Poland)

c) Traditional herbal medicinal product against biliar disturbances, biliar colic

d) Adjuvant to allow fat diet in the treatment of mild to moderate hyperlipidaemia (for reducing cholesterol (Spain)

e) Traditionally used to promote urinary and digestive elimination functions. Traditionally used as a choleretic and cholagogue (France)

The therapeutic indication which has been accepted by the MLWP/HMPC is:

Traditional herbal medicinal product for the symptomatic relief of digestive disorders such as dyspepsia with a sensation of fullness, bloating and flatulence.

The product is a traditional herbal medicinal product for use in the specified indication exclusively based upon long-standing use.

Posology:

Generally it has been proposed an average oral daily dose: for hypercholesterolaemia and dyspepsia, 1–2 g of a dried aqueous extract [Englisch *et al.* 2000; Petrowicz *et al.* 1997; Holtmann 2003]. While for adults daily dose: 5–10 g of crude drug; or equivalent galenical preparations for oral use [Blumenthal *et al.* 2000; Blaschek *et al.* 2002, WHO monographs, Vol. 4 2009]

In Germany exist also the following authorised products for traditional use:

a) Comminuted or powdered dried leaves for herbal tea
Daily dose of 6 g (3 g times 1-2 times per day or 1.5 g times 4 times per day)

b) Powdered dried leaves
Daily dose of 600-1500 mg (in doses of 150, 175, 300, 500 mg)

c) Dry extract (DER 2.5-7.5:1) extraction solvent water
Daily dose 600- 1320 mg (in doses of 200, 300, 400, 440, 600 mg or 640 mg)

d) Dry extract from fresh leaves (15-35:1), extraction solvent water
Daily dose of 900 mg-2400 mg (in doses of 300, 320 mg, 600mg)

e) Soft extract of fresh leaves (DER 15-30:1), extraction solvent water
Daily dose of 600-1200 mg (in doses of 200 mg) or in liquid form daily 9 ml (20 g of extract/100 ml)

f) Soft extract (DER 2.5-3.5:1), extraction solvent ethanol 20% (v/v)
Daily dose 2.1 g (in doses of 0.7 g)

Cynarae flos
Three expressed juices from fresh artichoke flower buds (1:0.6-0.9) have been on the market since 1978, expressed juice, for traditional use.

Cynarae herba
One fluid extract from artichoke herb (1:2.4-5.2), extraction solvent ethanol has been on the market since 1978, liquid, for traditional use.
Cynarae herbae extractum siccum (3-5:1) extraction solvent – ethanol 50% (v/v) has been on the market since 1981 (Poland).

3. Non-Clinical Data

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

Primary pharmacodynamics

Antioxidative, hepatoprotective and choleretic effects of artichoke leaf extracts as well as lipid-lowering and anti-atherogenic activity with increased elimination of cholesterol and inhibition of hepatocellular de novo cholesterol biosynthesis have been demonstrated in various *in vitro* and *in vivo* test systems. Antidyspeptic effects are mainly attributed to increased choleresis [Kraft 1997; ESCOP 2003].

Choleretic effect

The following information was retrieved from ESCOP (2003), while similar results are reviewed by Hager in 1992 [Hänsel 1992; Blaschek 2002].

- ***In vitro* experiments**

Antioxidant and cytoprotective effects

Antioxidant and cytoprotective effects of an artichoke leaf aqueous dry extract (4.5:1) were demonstrated in primary cultures of rat hepatocytes exposed to t-butyl hydroperoxide (t-BHP). When added simultaneously or prior to t-BHP, the extract inhibited lipid peroxidation in a concentration-dependent manner down to 0.001 mg/ml [Gebhardt 1997i; 1997ii]. Several characteristic polyphenolic constituents of artichoke leaf were effective in reducing t-BHP- induced melondialdehyde production. EC_{50} values were 7, 8.1, 12.5, 15.2 and 28 µg/ml for luteolin caffeic acid, chlorogenic acid, cynarin and luteolin-7-glucoside respectively. The extract also prevented loss of intracellular glutathione by t-BHP [Gebhardt 1995i, 1995ii, 1997i, 1997ii; Gebhardt *et al.* 1998].
The effect of an artichoke leaf aqueous dry extract (4.5:1) on free radical production was also studied in human polymorphonuclear cells by flow cytometry using phorbol 12-myristate-13-acetate as the stimulant. The extract strongly inhibited the generation of reactive oxygen species with an EC_{50} of 0.23 µg/ml [Perez-Garcia *et al.* 2000].
Cynarin and caffeic acid showed significant cytoprotective activity ($p<0.01$ at 1 mg/ml) against carbon tetrachloride in isolated rat hepatocytes, reducing leakage of the liver enzymes glutamine oxaloacetic transaminase and glutamic pyrovic transaminase [Adzet *et al.* 1987].
Artichoke leaf aqueous dry extract at t-20 µg/ml retarded Cu^{2+}-mediated oxidation of human low density lipoproteine (LDL) in a dose –depended manner: the effect was attributed in part to luteolin 7-glucoside (as well as caffeoylquinic acids) [Brown & Rice-Evans 1990].
An aqueous dried extract (9:2) of the leaves was studied in human leukocytes to assess activity against oxidative stress. The extract (median effective concentration 0.23 µg/ml) produced a

concentration-dependent inhibition of oxidative stress when cells were stimulated with agents that generate reactive oxygen species: hydrogen peroxide, phorbol- 12-myristate-13-acetate and *N*-formyl-methionyl-leucyl-phenylalanine. Cynarin, caffeic acid, chlorogenic acid and luteolin, constituents of artichoke leaf extracts, also showed a concentration-dependent inhibitory activity in the above models, contributing to the antioxidant activity of the extract in human neutrophils [Pérez- García *et al.*2000].

A study measured the effects of aqueous and ethanol extracts of the leaves on intracellular oxidative stress stimulated by inflammatory mediators, tumour necrosis factor alpha and oxidized low-density lipoprotein (ox-LDL) in endothelial cells and monocytes. Both extracts inhibited basal and stimulated reactive oxygen species production in endothelial cells and monocytes, in a dose-dependent manner. In endothelial cells, the ethanol extract (50 µg/ml) significantly reduced ox-LDL-induced intracellular reactive oxygen species production by 60% (p<0.001) and the aqueous extract (50 µg/ml) reduced ox-LDL-induced intracellular reactive oxygen species production by 43% (p<0.01). The ethanol extract (50 µg/ml) reduced ox- LDL-induced intracellular reactive oxygen species production in monocytes by 76% (p<0.01). Effective concentrations of 25–100 µg/ml were well below the cytotoxic levels of the extracts which started at 1 mg/ml as assessed by lactate dehydrogenase leakage and tryptan blue exclusion [Zapolska-Downar *et al.* 2002].

The flavonoids from artichoke (*Cynara scolymus* L.) have been shown for their up-regulate endothelial-type nitric-oxide synthetase gene expression in human endothelial cells [Li *et al.* 2004]. The phenolic compounds of the plant have been studied for antioxidative activities [Wang *et al.* 2003] and several products from artichoke extracts showed similar activities [Llorach *et al.* 2002]. A study by Cervellati *et al.* (2002) focused on the antioxidant effects of artichoke extract in cultured blood vessel cells and reported that the extract demonstrated "marked protective properties against oxidative stress induced by inflammatory mediators". Artichoke's antioxidant properties were also confirmed in others studies that focused on human cells under various induced oxidative stresses [Jimenez-Escrig *et al.* 2003; Sarawek *et al.* 2008]. The water leaf extract of the plant has been assayed and reported to possess strong antioxidative, anti-inflammatory and antiproliferative properties [Trouillas *et al.* 2003]. Antioxidative activities have been reported for *Cynara* extracts in several publications [Li *et al.* 2004; Stoev SD *et al.* 2004; Jimenez-Escrig *et al.* 2003; Wang *et al.* 2003; Llorach *et al.* 2002; and Cervellati *et al.* 2002].

Anti-atherosclerotic and antihypercholesterolaemic activities

Artichoke leaf aqueous dry extract (4.5:1) inhibited the biosynthesis of cholesterol from ^{14}C-acetate in primary cultured rat hepatocytes. Concentrations of 0.007-0.1 mg/ml produced moderate inhibition of about 20%; at 1 mg/ml the inhibition was about 80% [Gebhardt 1995ii, 1998]. At 50-100 µg/ml, caffeic acid and cynarin produced negligible inhibition, chlorogenic acid 10-15% and cynaroside (luteolin 7-glucoside) 19-22% but luteolin 51-63% [Gebhardt 1998]. When cynaroside was incubated with β-glucosidase, maximum inhibition of 50-60% was observed with an EC_{50} of approximately 30 µM. In human hepatic (HepG2) cells the maximum response of luteolin was more than 80% and the EC_{50} value was slightly higher. It was concluded that luteolin (a minor constituent) and indirectly its glucoside, cynaroside, seem to be mainly responsible for the inhibition of hepatic biosynthesis of cholesterol by artichoke leaf extracts [Gebhardt 1997i; 1997ii; 1998]. Subsequently it was demonstrated that artichoke extracts inhibit cholesterol biosynthesis from ^{14}C-acetate in primary cultured rat hepatocytes. The inhibition in human hepatic (HepG2) cells was weak unless they have been pre-treated with β-glucosidase. This was explained by the fact the rat hepatocytes contain more endogenous β-glucosidase, enabling release of luteolin from its glucoside, cynaroside. Since β-glucosidase is present in the intestinal tract and in the liver, release of luteolin fron cynaroside may occur in the human body [Gebhardt 1998; Gebhardt 2001, 2002i, 2002ii; Brown & Rice Evans *et al.* 1990; Fritsche *et al.* 2002].

Cynara scolymus is suggested to be among the herbs responsible for serum cholesterol reduction [Thomson Coon *et al.* 2002, 2003]. It has been reported that artichoke juice improves the endothelial function in hyperlipidaemia [Lupattelli *et al.* 2004].

Hepatobiliary effects

In vitro an artichoke leaf aqueous dry extract enhanced the secretion of biliary substances in bile canaliculi reformed in primary cultures of hepatocytes. A cholestatic effect induced in the cultures by lithocholate was inhibited by the extract [Gebhardt 1996]. The choleretic effect of pressed juice (sap) from fresh artichoke was investigated in isolated perfuse rat liver. Pressed juice, undiluted and diluted 1:3 and 1:5, produced dose-dependent increase in bile flow of up to 150%, 125% and 112% respectively, detectable 20 minutes after addition and reaching maximum value 10 minutes later. Bile acid production remained almost unchanged [Matuschowski *et al.* 2005]. By testing fractions of present juice, it was shown that phenolic constituents were mainly responsible for the choleric action the strongest effects on both choleresis and bile acid production being exerted by mono-and dicaffeoylquinic acids. In further experiments with isolated perfuse rat liver a different pressed juice (from fresh artichoke flower buds) produced a comparable increase in bile flow and increased bile acid excretion by up to 128%. In contrast, dried pressed juice (16:1 from flower buds) and dry aqueous extract (4:1) from artichoke leaf increase bile flow without significantly increasing bile acid secretion and no correlation with the content of caffeoylquinic acids was evident.

Antihepatotoxic activity

The effects of an aqueous extract of the leaves on taurolithocholate-induced cholestatic bile canalicular membrane distortions were studied in primary cultured rat hepatocytes using electron microscopy. Artichoke extracts at concentrations between 0.08 and 0.5 mg/ml were able to prevent the formation of canalicular membrane transformations in a dose-dependent manner when added simultaneously with the bile acid. However prevention also occurred when the hepatocytes were pre-incubated with the extracts, indicating that absorption of the bile acid to components of the extracts was not involved [Gebhardt 2002]. The hepatoprotective activity of cynarin against carbon tetrachloride (CCl4)-induced toxicity in isolated rat hepatocytes was compared with other phenolic compounds. Only cynarin and, to a lesser extent, caffeic acid showed a cytoprotective effect [Adzet 1987i; 1987ii]. Treatment of rats with three consecutive doses of 500 mg/kg body weight of an extract of the crude drug, administered by gavage 48, 24 and 1 hour before CCl4 intoxication, produced a significant decrease in glutamic-oxaloacetic transaminase, glutamic-pyruvic transaminase (also known as alanine aminotransferase or ALT), direct bilirubin and glutathione levels, thus indicating a reduction in the potential for hepatotoxicity [Adzet *et al.* 1987i].

Primary cultures of rat hepatocytes exposed to *tert*-butyl hydroperoxide were used for characterising the antioxidative and hepatoprotective potential of an aqueous extract of the crude drug and some selected constituents. Addition of *tert*-butyl hydroperoxide to the culture media resulted in enhanced lipid peroxidation as measured by the production of malondialdehyde and enhanced cytotoxicity detected by leakage of lactate dehydrogenase. The extract added prior to or simultaneously with *tert*-butyl hydroperoxide reduced both phenomena with a median effective concentration (EC50) of 95 and 12 µg leaf powder/ml respectively. Furthermore, the aqueous extract prevented the loss of intracellular glutathione caused by *tert*-butyl hydroperoxide. Several polyphenolic and flavonoid constituents of the extract were found to reduce malondialdehyde production. The median effective concentration values were 8.1, 12.5, 15.2 and 28 µg/ml for caffeic acid, chlorogenic acid, cynarin and cynaroside, respectively [Gebhardt and Fausel 1997ii].

Primary rat hepatocyte cultures exposed to *tert*-butyl hydroperoxide or cumene hydroperoxide were used to assess the antioxidative and protective potential of aqueous extracts of the leaves. Both hydroperoxides stimulated the production of malondialdehyde, particularly when the cells were pretreated with diethylmaleate in order to diminish the level of cellular glutathione. Addition of the extract did not affect basal malondialdehyde production, but prevented the hydroperoxide-induced increase of malondialdehyde formation in a concentration-dependent manner when presented simultaneously with or prior to the peroxides. The effective concentrations were as low as 0.001 mg/ml [Gebhardt 1997i]. The liver protective actions of artichoke have also been reported by other authors [Maros T *et al.* 1966; Aktay G *et al.* 2000; Speroni E *et al.* 2003].

Gastrointestinal effects

The antispasmodic activity of several fractions from artichoke and of cynaropicrin as well as other Brazilian traditionally used medicinal plants, on guinea-pig ileum has been demonstrated [Emendorfer *et al.* 2005i, 2005ii].

Antimicrobial effects

The antibacterial and antifungal activities of artichoke extracts and their phenolic compounds have been assayed [Zhu XF *et al.* 2004, 2005; Yang B *et al.* 2005; Stoev SD *et al.* 2004].

- ***In vivo* experiments**

Hepatobiliary and hepatoprotective affects

Chlorogenic acid administered orally to rats at 5-40 mg/kg body weight significantly stimulated choleresis (70%) and peristaltic activity (40%) in a concentration depended manner. A dose-depended increase in bile flow of up to 95% and an increase in biliary-excreted cholesterol were observed following a single intravenous administration of cynarin (7-166 mg/kg body weight) in the bile fistula rat model. Choleresis was still observed 4 hours after administration of 100 or 166 mg/kg body weight [Preziosi 1956, 1958, 1959, 1960].

A deproteinized aqueous extract of artichoke leaf, administrated orally to partially hepatectomized rats at 0.5 ml/animal daily for 21 days, significantly increased liver tissues regeneration as measured by residual liver weight, mitotic index and percentage of dinucleated liver cells [Maros *et al.* 1966]. In further experiments using the same methodology, the deproteinized extract accelerated the increase in liver weight, induced pronounced hypereamia and increased the percentage of binuclear hepatocytes and the content of ribonucleic acid in liver cells [Maros *et al.* 1968].

Intraperitoneal administration of a purified acid-rich, butanolic extract of artichoke leaf at 10 mg/kg protects mice against toxicity induced by ethanol: the LD_{50} for treated mice was 6.8 g ethanol/kg compared to 5.6 g ethanol/kg for the control group. The effect of the artichoke extract could be reproduced by administration of a mixture of citric, malic, succinic and hydroxymethylecrylic acids (2.5 mg/kg: LD_{50} of 7.1 g ethanol/kg) [Mortier *et al.* 1976].

Two hydroethanolic extracts of fresh artichoke [Bombardelli *et al.* 1977] were administered i.p. to groups of rats: a total extract (19% caffeoylquinic acids, 200 mg/kg body weight) and a purified extract enriched in phenolic compounds (46% caffeoylquinicacids, 25 mg/kg body weight). Through bile duct cannulation it was shown that both extracts stimulated choleresis significantly increasing the bile dry residue and the total cholate secretion ($p<0.05$) [Lietti 1977]. The same extracts administered

orally (400 mg/kg body weight of total extract or 200 mg/kg of purified extract) increased gastrointestinal propulsion in rats by 11% and 14% respectively ($p<0.05$).

An aqueous extract of artichoke leaf (2.2% caffeoylquinic acids, 0.9% luteolin 7-glucoside) administered orally to rats at 500 mg/kg body weight 48 hours, 24 hours and 1 hours before inducing liver intoxication with carbon tetrachloride , improved liver function as measured by decreased levels of bilirubin glutathione and liver enzymes [Adzet *et al.* 1987i].

In bile duct cannulated rats an undefined artichoke leaf fluid extract (0.45 mg/kg body weight) administered *intraperitoneal* produced increases of 32% in bile flow and 49% in bile acid concentration respectively [Saenz Rodriguez *et al.* 2002].

Two aqueous alcoholic extracts of the fresh leaves (total extract containing 19% caffeoylquinic acids, at a dose of 200 mg/kg body weight and a semi purified extract containing 46% caffeoylquinic acids, at a dose of 25 mg/kg body weight) were assessed in rats. Intraperitoneal administration stimulated choleresis, and significantly increased bile dry residue and total cholate secretion ($p<0.05$). Intragastric administration of the same extracts (400 mg/kg body weight, total extract and 200 mg/kg body weight of the semi purified extract) also increased gastrointestinal motility by 11% and 14%, respectively ($p<0.05$) [Lietti 1977].

The effects of an extract of the crude drug on bile flow and the formation of bile compounds in anaesthetised rats after acute administration and repeated oral administration (twice a day for 7 consecutive days) were studied. A significant increase in bile flow was observed after acute treatment with the extract as well as after repeated administration. The choleretic effects of the extract were similar to those of the reference compound dehydrocholic acid. Total bile acids, cholesterol and phospholipid were determined by enzymatic assays. At the highest dose (400 mg/kg body weight), a significant increase was observed after single and repeated administration ($p<0.01$) [Saınz Rodriguez *et al.* 2002].

The choleretic effects of four extracts of the leaves (not described) were assessed *in vivo* in a study in rats. Extracts 1, 2 and 4 did not show significant choleretic activity at a dose of 1 and 2 g/kg body weight. Extract 3, however, was found to induce an increase of bile flow, which was gradual and sustained. Cynarin and chlorogenic acid, administered as pure compounds, did not show choleretic activity at any of the doses tested and neither of them decreased the malondialdehyde content in liver [Speroni *et al.* 2003].

Treatment of rats with three consecutive doses of 500 mg/kg body weight of an extract of the crude drug, administered by gavage 48, 24 and 1 hour before CCl4 intoxication, produced a significant decrease in glutamic-oxaloacetic transaminase, glutamic-pyruvic transaminase (also known as alanine aminotransferase or ALT), direct bilirubin and glutathione levels, thus indicating a reduction in the potential for hepatotoxicity [Adzet *et al.* 1987i].

Lipid-lowering and anti-atherogenic effects

Powdered artichoke aerial parts, administered orally at 110 mg/kg body weight for 120 days to rats fed on an atherogenic diet, lowered increases in serum and liver cholesterol and prevented the formation of atherosclerotic plaques [Samochowiec 1959, 1962i, 1962ii]. After 60 days on an atherogenic diet, 110 mg/kg body weight of powdered artichoke aerial parts, administered orally to rats daily for 10 weeks, lowered serum cholesterol by 36% compared to 25% in the control group [Samochowiec 1962iii].
Two hydroethanolic extracts of fresh artichoke a total extract (19% caffeoylquinic acids 100 mg/kg body weight) and a purified extract (46% caffeoylquinic acids 25 mg/kg body weight), administered intraperitoneally to rats four times over a 28-hours period after inducing hyperlipidaemia with Triton

WR1339, decreased total cholesterol by 14% and 45% and triglycerides by 18% and 33% respectively [Saenz Rodriguez 2002].

Cynarin (100 and 200 mg/kg body weight) administered intravenously to rabbits, lowered serum cholesterol by about 20% Triton WR 1339-induced hypercholesterolaemia. In rats it was significantly lowered (p=0.05-0.02) by cynarin after intraperitoneal administration (2*200 mg/kg body weight) [Preziosi 1958]. Cynarin injected at 30 mg/kg /day significantly lowered the increases in total serum lipids ($p<0.05$) and esterified serum fatty acids ($p<0.001$) induced in rats by giving them 15% ethanol instead of drinking water for 20 days [Samochowiec 1971].

Other effects

The preventive effect of a hydroalcoholic *Cynara scolymus* extract on appearance of type 1 diabetes mellitus in male rats has been studied [Mahmoodabadi *et al.* 2007].

3.1.1. Conclusions on traditional use

Based on information obtained from Member states and data retrieved from handbooks it can be concluded that the following extracts and uses of artichoke leaves fulfil the criteria for traditional use:

- Comminuted or powdered dried leaves for herbal tea
- Powdered leaves
- Dry extract (DER 2.5-7.5:1) extraction solvent water
- Dry extract from fresh leaves (DER 15-35:1), extraction solvent water
- Soft extract from fresh leave (DER 15-30:1), extraction solvent water
- Soft extract (DER 2.5-3.5:1), extraction solvent ethanol 20% (v/v)

Safety pharmacology

No information available except toxicity data presented under section 3.2 below.

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

After two days of a low-polyphenol diet to 10 healthy volunteers, they have been treated with 3 x 320 mg of an artichoke leaf aquaeus dry extract (4-6:1; caffeoylquinic acids 34.3 mg/g, flavonoids 5.6 mg/g) every 4 hours (at 0.4 and 8 hours). Phenolic derivatives present in the artichoke extract were not detected in the urine either as conjugates or aglycons; however b-glucuronidase treatment of urine revealed the presence of ferulic, isoferulic, dihydroferulic and vanillic acids as major metabolites of caffeoylquinic acids [Rechner *et al.* 2001].

In order to investigate potential inhibition or activation of cytochrome P450 (CYP) isoforms by extracts of popular herbal drugs a series of studies were made in a screening approach to predict impending interactions [Hilgendorf & Döppenschmidt 2003]. Methods: Human liver microsomes were employed for screening, using 8 standard subtype-specific CYP substrates. The testing included ethanolic extracts of *Serenoa repens* (*Sabal serrulata*, SR), *Hypericum perforatum*, *Harpagophytum procumbens*, *Piper methysticum* (Kava, KA) and *Cynara scolymus*. Organic solvent was removed for testing. At extract concentrations derived from dose recommendations provided by German Authorities (Commission E),

differential effects of the various plants were observed. The effects ranged from strong activation of enzymatic turnover, i.e. *Harpagophytum procumbens*: 272 ± 12% ($p<0.001$) of control (mean ± SD, n=3) for CYP2E1 to almost complete abolition of activity, e.g. for *Hypericum perforatum*: 3 ± 0.7% ($p<0.0001$) for 3A4 and 0% ($p<0.0001$) for 2C8. Overall, most pronounced inhibitory effects were observed for *Hypericum perforatum* (0% ($p<0.0001$) to 73 ± 2% ($p<0.001$)) and KA (5 ± 4% ($p<0.001$) to 92 ± 9% (not significant)), while *Harpagophytum procumbens* exhibited inhibitory (2C19:59 ± 1% ($p<0.0001$)) as well as stimulatory effects (2E1: see above). The extracts of herbal drugs broadly used in Germany accomplish inhibition as well as activation of human CYP activity *in vitro*. Detailed results concerning *Cynara* are not presented.

[Wittemer *et al.* 2002, 2005]. A variety of mono- and dicaffeoylquinic acids and flavonoids have been described as the main constituents of artichoke (*Cynara scolymus*) extract. Among them chlorogenic acid, cynarine and the flavonoid luteolin-7-O-glucoside (cynaroside) are the most prominent. A wide range of *in vitro* activities of artichoke have been established, e.g. antioxidative and choleretic actions and lipid reduction. Here, the metabolism and disposition of 2 different leaf extracts (extract A: dicaffeoylquinic acids 28.9%, flavonoids 8.8%; extract B: dicaffeoylquinic acids A 6.2%, flavonoids 0.9%) were investigated in healthy volunteers enrolled in a 2-way crossover study. Neither the mono- and dicaffeoylquinic acids nor the flavonoids present in the extracts were detected in human plasma as their original moieties. No safety relevant information is provided.

[Wittemer & Veit 2003]. Artichoke leaf extract (water>80°C, DER 4-6:1). A validated method was developed for the simultaneous determination of the hydroxycinnamates caffeic, dihydrocaffeic, ferulic, dihydroferulic, and isoferulic acid and the flavonoid luteolin in human plasma as metabolites derived from artichoke leaf extract. Selectivity and sensitivity towards the target compounds were achieved by using the HPLC method with electrochemical array detection. Calibration curves were constructed in the ranges 2.1-51.7 ng/ml hydroxycinnamates caffeic, 2.0-76.7 ng/ml dihydrocaffeic, 2.2-53.7 ng/ml ferulic, 2.1-79.2 ng/ml dihydroferulic, 1.1-52.6 ng/ml isoferulic acid and 2.1-258.6 ng/ml flavonoid luteolin. Values for within-day and between-day precision and accuracy were in accordance with the international guidelines for validation of bioanalytical methods. It is concluded that this newly developed method is appropriate for analysing samples from bioavailability and pharmacokinetic studies after oral administration of artichoke leaf extract. The authors describe a validated HPLC method for the determination of prominent artichoke leaf extract metabolites in human plasma. The availability of this method may stimulate further systematic investigation into the metabolic fate of artichoke leaf constituents.

[Wittemer *et al.* 2005]. Artichoke leaf extract (water>80°C, DER 4-6:1). In order to get more detailed information about absorption, metabolism and disposition of Artichoke leaf extract, two different extracts were administered to 14 healthy volunteers in a crossover study. Each subject received doses of both extracts. Extract A) administered dose: caffeoylquinic acids equivalent to 107 mg caffeic acid and luteolin glycosides equivalent to 14.4 mg luteolin. Extract B) administered dose: caffeoylquinic acids equivalent to 153.8 mg caffeic acid and luteolin glycosides equivalent to 35.2 mg luteolin. Urine and plasma analysis were performed by a validated HPLC method using 12-channel coulometric array detection. In human plasma or urine none of the genuine target extract constituents could be detected. However, caffeic acid, its methylated derivates ferulic acid and isoferulic acid and the hydrogenation products dihydrocaffeic acid and dihydroferulic acid were identified as metabolites derived from caffeoylquinic acids. Except of dihydroferulic acid all of these compounds were present as sulfates or glucuronides. Peak plasma concentrations of total caffeic acid, ferulic acid and isoferulic acid were reached within 1 hour and declined over 24 hours showing almost biphasic profiles. In contrast maximum concentrations for total dihydrocaffeic acid and dihydroferulic acid were observed only after 6-7 hours, indicating two different metabolic pathways for caffeoylquinic acids. Luteolin administered as glucoside was recovered only from plasma and urine as sulfate or

glucuronide but neither in form of genuine glucosides nor as free luteolin. Peak plasma concentrations were reached rapidly within 0.5 hour. The elimination showed a biphasic profile. This well designed pharmacokinetic study reveals interesting insights into the fact of *Cynara* leaf extract constituents after oral administration. However, at the presence status these data are of no relevance for the risk benefit ratio and the safety profile of artichoke leaf preparations.

After oral consumption of cooked edible heads of *Cynara scolymus* L. (cultivar Violetto di Provenza) a pilot study **[Azzini *et al.* 2007]** investigated the absorption and metabolism of bioactive molecules in human subjects.
Results showed a plasma maximum concentration of 6.4 (standard deviation=sd 1.8) ng/ml for chlorogenic acid after 1 hour and its disappearance within 2 hours ($P<0.05$). Peak plasma concentrations of 19.5 (sd 6.9) ng/ml for total caffeic acid were reached within 1 hour, while ferulic acid plasma concentrations showed a biphasic profile with 6.4 (sd 1.5) ng/ml and 8.4 (sd 4.6) ng/ml within 1 hour and after 8 hours respectively. The authors observed a significant increase of dihydrocaffeic acid and dihydroferulic acid total levels after 8 hours ($p<0.05$). No circulating plasma levels of luteolin and apigenin were present. The study confirms the bioavailability of metabolites of hydroxycinnamic acids after ingestion of cooked edible *Cynara scolymus* L. The study shows the absorption pathways of hydroxycinnamic acids after consumption of edible cooked artichoke in human subjects. No safety relevant information is given.

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

Acute toxicity

Herbal preparations
The oral LD_{30} and intraperitoneal LD_{10} in male rats of hydroalcoholic total extract of artichoke leaf (19% caffeoylquinic acids) were determined as >2000 mg/kg and >1000 mg/kg body weight respectively. With a purified extract (46% caffeoylquinic acids) the oral LD_{40} and intraperitoneal LD_{50} were 2000 mg/kg and 265 mg/kg respectively [Bombardelli *et al.* 1977].

In primary cultures of rat hepatocytes no cytotoxic effects from an artichoke leaf aqueous dry extract (4.5:1) were observed at concentrations of up to 1 mg per ml of culture medium [Gebhardt 1997i, 1995i, 1995ii, 1997i; 1997ii].

Cynarin
The LD_{50} of cynarin in mice was determined as 1900 mg/kg body weight. Upon administration intraperitoneally to rats at 800 mg/kg or intravenously to rabbits at 1000 mg/kg/hour, cynarin produced no apparent side effects or signs or toxicity [Preziosi 1958].

Sub-acute toxicity

Cynarin
Cynarin administered intraperitoneally to adult rats for 15 days at doses of 50-400 mg/kg/day produced no macroscopic or histological abnormalities or changes in blood parameters [Preziosi 1958].

The oral and intraperitoneal median lethal doses of a hydroalcoholic extract of the leaves in rats were 2 g/kg and 1 g/kg body weight, respectively [Lietti 1977]. External application of a leaf extract to the skin of white rats, at doses of 1-3 g/kg body weight for 21 days, did not produce any toxic effects or have any cumulative effects on haematological parameters or the biochemistry of rats. No skin-irritating or eye-irritating effects were observed in guinea-pigs [Holtmann *et al.* 2003; WHO monographs 2009].

Chronic oral toxicity

Cynarin
Cynarin administered intraperitoneally to rats daily for 40 days at 50-400 mg/kg/day caused no changes in overall condition or blood parameters. Increased body weight and significantly increased kidney weight ($p<0.01$) were observed only in animals treated with 400 mg/kg and significantly increased liver weight ($p<0.01$) in animals treated with 100-400 mg/kg. Some rats treated with cynarin at 100,200 and 400 mg/kg showed irrigative- degenerative changes in liver and kidneys most evident in rats receiving 400 mg. Young rabbits treated intravenously with cynarin at 50 mg/kg/day for 30 days remained in good condition with no evidence of toxicity from extensive haematological and histological investigation [Preziosi 1958].

Carcinogenicity

Caffeic acid (and chlorogenic acid)
The International Agency for Research on Cancer (IARC) has evaluated caffeic acid for its potential carcinogenicity (Anonymous 1993). After dietary administration of high doses of caffeic acid (intakes 2-3 g/kg body weight), there were high incidences of forestomach hyperplasia and renal tubular-cell hyperplasia in mice of both sexes and an increase in forestomach squamous-cell papillomas and carcinomas in male mice and renal-cell adenomas in female mice. In rats, a high dietary intake (about 0.7-0.8 g/kg) of caffeic acid produced squamous-cell papillomas and carcinomas of the forestomach in animals of each sex and a few renal-cell adenomas in males.
Oral administration of caffeic acid in combination with known carcinogens resulted in enhancing or inhibiting effects depending upon the carcinogen and the time of administration. The IARC (1993) working group decided that caffeic acid is possibly carcinogenic to humans (Group 2B), because there is sufficient evidence in experimental animals for the carcinogenicity of caffeic acid. No data were available on the carcinogenicity of caffeic acid to humans (it should be noted that the recent review on coffee carcinogenicity came to the conclusion, that caffeine drinking is generally protective as regards to cancer [Nkondjock 2009]). The Working Group noted that humans and experimental animals metabolise caffeic acid to the same metabolites and hydrolyse chlorogenic acid to caffeic acid. *In vitro* and *in vivo* genotoxicity tests were generally negative, except increased gene mutations and chromosomal aberrations in cultured rodent cells at high exposures; no evaluation was made regarding these positive findings.

Genotoxicity

Several studies on mutagenicity/genotoxicity of *Cynara scolymus* are available.

Antimutagenic potential of *Cynara scolymus*:

[Križková *et al.* 2004]. Three different triterpenoid saponins (cynarasaponins) from involucral bracts of artichoke were isolated and their antimutagenic effect was assessed. Using spectrophotometric method it was shown that all three substances possess very good absorptive capability. The antimutagenic effect of these substances was estimated against acridine orange (AO)- and ofloxacin-induced damage of chloroplast DNA in Euglena gracilis assay. These cynarasaponins were experimentally confirmed to exhibit different, statistically significant activity in reducing damage of chloroplast DNA of the flagellate Euglena gracilis induced by AO and ofloxacin ($p_t<0.05$-0.01). These findings suggest that the antimutagenic effect of these compounds against AO-induced chloroplast DNA impairment could be a result of their absorptive capacity. As far as ofloxacin is concerned, a possible mechanism of the reduction of the chloroplast DNA lesion was not elucidated so far.

[Miadokova *et al.* 2006]. The potential antimutagenic activity of an extract from artichoke was assayed by a test on sex-linked recessive lethal mutations detection in *Drosophila melanogaster* males treated with ethylmethane sulfonate (EMS). The possible enhancement of cytostatic/cytotoxic effect of cisplatin by extract from artichoke was evaluated in the cell revitalisation assay by measuring cell viability via Trypan blue exclusive assay using mouse leukemia cells L1210. Results: EMS was both toxic and genotoxic in *D. melanogaster* males. It statistically significantly increased the frequency of sex-linked recessive lethal mutations in comparison to the negative control. Furthermore, the extract from artichoke statistically significantly reduced the genotoxic effect of EMS. It acted in a desmutagenic manner via EMS inactivation. In the cell revitalisation assay, extract from artichoke enhanced the cytotoxic/cytostatic effect of cis-Pt. The therapeutic potential of the extract from artichoke was established on the basis of statistically significantly lowered recovery of cisplatin pre-treated mouse leukemia cells in the presence of extract from artichoke. Conclusions: The results imply that the extract isolated from artichoke *Cynara cardunculus* L. has marked beneficial activities (antimutagenic and therapeutic effect enhancing) and its potential biomedical application in the combination therapy of cancer and some neurodegenerative diseases may be suggested.

[Miadokova *et al.* 2008]. An extract of artichoke (*Cynara cardunculus* L.) was investigated for its potential antigenotoxic and antioxidant effects using four experimental model systems. In the *Saccharomyces cerevisiae* mutagenicity/antimutagenicity assay, *Cynara cardunculus* L. significantly reduced the frequency of 4-nitroquinoline-N-oxide- induced revertants at the ilv1 locus and mitotic gene convertants at the trp5 locus in the diploid *Saccharomyces cerevisiae* tester strain D7. In the simultaneous toxicity and clastogenicity/anticlastogenicity assay, it exerted an anticlastogenic effect against N-nitroso-N'-methylurea-induced clastogenicity in the plant species *Vicia sativa* L. On the contrary, despite *Cynara cardunculus* L. not being mutagenic itself, in the preincubation Ames assay with metabolic activation, it significantly increased the mutagenic effect of 2-aminofluorene in the bacterial strain *Salmonella typhimurium* TA98. In the 1.1-diphenyl-2- picrylhydrazyl free radical scavenging assay, *Cynara cardunculus* L. exhibited considerable antioxidant activity. The SC_{50} value representing 0.0054% *Cynara cardunculus* L. corresponds to an antioxidant activity of 216.8 µM ascorbic acid which was used as a reference compound. Although the mechanism of *Cynara cardunculus* L. action still remains to be elucidated, different possible mechanisms are probably involved in the *Cynara cardunculus* L. antigenotoxic effects. The authors concluded that *Cynara cardunculus* L. is of particular interest as a suitable candidate for an effective chemopreventive agent.

[Edenharder *et al.* 2003]. After *in vivo* mouse bone marrow micronucleus assay, homogenates of artichoke among other vegetables and fruits reduced induction of micronuclei by benzo[a]pyrene (BaP) by 43-50%. The flavonoids quercetin and its glucoside isoquercitrin, administered orally in doses of 0.03 mmol/kg body weight simultaneously with intraperitoneally given BaP, reduced the number of micronuclei in polychromatic erythrocytes of the bone marrow of mice by 73 and 33%. Ten-fold higher concentrations, however, reversed the effects with a particular strong increase observed with isoquercitrin (+109%; quercetin: +16%).

The genotoxic effects of flavonoid constituents present in the crude drug (quercetin and luteolin) were assessed in two short-term bacterial assays. In *Salmonella typhimurium* (strains TA1538 uvrB- and TA1978 uvrB+) the flavonoids did not induce damage in the DNA as recognised by UvrABC nuclease. Results of the SOS-chromotest in *Escherichia coli* K-12 strains PQ37 and PQ243 indicated that the flavonoids only weakly induced the SOS system [Czeczot and Kusztelak 1993].

Teratogenicity

No data available.

3.4. Overall conclusions on non-clinical data

Pharmacokinetics

Six different studies provide information on pharmacokinetic properties after the administration of water extracts of leaf artichoke to healthy volunteers. In all cases none of the constituents of the extracts have been detected in human plasma or urine. Caffeic acid its methylated derivatives ferulic and isoferulic acids and the hydrogenated products dihydrocaffeic and dihydroferulic acid were identified as metabolites from caffeoylquinic acids; except for dihydroferulic acid all of the other compounds were found as sulfates or glucuronides. The luteolin administered as glucosides was recovered from plasma and urine only as sulfate or glucuronide.

Toxicology

Various extracts of *Cynara scolymus* seemed to be of low acute or subchronic toxicity potential. It should be also noted that all carcinogenicity (and other associated) studies available are not up to current standards. The current consensus is that forestomach tumours in rodents after high irritating exposures are less relevant for human risk assessment [Proctor *et al.* 2007]. The same opinion applies also to rodent renal adenomas. No mutagenicity or genotoxicity studies were available. There are no data on teratogenicity or carcinogenicity. Antimutagenic potential of artichoke has been reported but they seem incomplete.

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

Primary pharmacodynamics

Antioxidative, hepatoprotective and choleretic effects of artichoke leaf extracts as well as lipid-lowering and anti-atherogenicactivity with increased elimination of cholesterol and inhibition of hepatocellular de novo cholesterol biosynthesis have been demonstrated in various *in vitro* and *in vivo* test systems. Antidyspeptic effects are mainly attributed to increased choleresis [Kraft 1997; ESCOP 2003].

Assessor's overall conclusions on pharmacodynamics

At present, the mechanism of action of artichoke and its main compounds cannot be considered clarified.

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

Data on the pharmacokinetics of artichoke's constituents are not available.

4.2. Clinical Efficacy

4.2.1. Dose response studies

Not specified by the Rapporteur.

4.2.2. Clinical studies (case studies and clinical trials)

Blood lipid and cholesterol lowering effects

[Petrowicz *et al.* 1997]. In a randomised double-blind, placebo-controlled study, the lipid-lowering effects of an artichoke leaf standardised dry aqueous extract (4.5-5:1) were investigated in 44 healthy volunteers over 12 weeks. The mean initial concentrations were very low in both the verum (204.2 mg/dl, n=22) and placebo (203 mg/dl, n=22) groups in volunteers with initial cholesterol>230 mg/dl(n_v-n_p=3). 640 mg of extract three times daily significantly decreased concentration of total cholesterol (p=0.015) and triglycerides (p=0.01) compared to placebo in volunteers with initial cholesterol >220 mg/dl (n_v-n_p=5). Serum cholesterol was not significantly different (p=0.14) after treatment with the extract compared to placebo: however a significant difference (p=0.012) could be detected for triglycerides. In volunteers with initial cholesterol >210 mg/dl (n_v=10,n_p=7), treatment with the extract led to a significant difference (p=0.022) for triglycerides compared to placebo.

[Wojcicki & Winter 1975]. Daily administration of 900 mg of an artichoke aerial parts ethanolic extract (maximum polyphenolic acids content of 5.5%) to 10 industrial workers with long term occupational exposure to carbon disulfide for 30 days significantly lowered blood levels of cholesterol (p<0.02) free fatty acids , phospholipids and total lipids (p<0.05).

[Wojcicki *et al.* 1981]. Decreases in cholesterol, triglycerides, three fatty acids, phospholipids and β-lipoproteins were observed in 30 healthy elderly subjects after daily administration for 6 weeks of 0.45 or 0.9 g of an undefined artichoke extract (defined as ethanolic extract from the aerial parts of artichoke) containing 0.09% or polyphenols.

[Wojcicki *et al.* 1982; Wojcicki *et al.* 1980 upubl. data]. In a comparative study, 73 patients with primary hyper-triglyceridaemia resistant to treatment with clofibrate were treated daily for 1 month with 9 tablets containing an undefined artichoke extract (this extract was defined as ethanolic extract of the aerial parts of artichoke, Cynarae herba), each tablet containing 5 mg of polyphenolic acids, n=25) or with cynarin (0.75 g, n=28 or 1.5 g, n=20). The artichoke extract exerted significant total lipid-, triglyceride-, and phospholipids-lowering, effects in about 56% of the patients , whereas 0.75 g or 1.5 g of cynarin improved lipid parameters in 61% or 40% of the patients, respectively.

[Held 1991]. In an open study, 403 patients with functional gall bladder disorders were treated with an undefined artichoke extract (2 tablets twice daily, each containing 375 mg of extract standardised to 1% caffeoylquinic acids). After 4 weeks of treatment, complains such as nausea, stomach pains or loss of appetite had disappeared in more than 52% of patients and symptoms had improved in more than 80% of patients [ESCOP 2009].

[Englisch *et al.* 2000]. In a multicentre, randomised, placebo-controlled, double- blind study, the effect of a fresh artichoke leaf aqueous dry extract (25-35:1) was investigated in 143 patients with hyperlipoproteinaemia (cholesterol >280 mg/dl) . Patients received either 1800 mg of artichoke extract (n=71) or placebo (n=72) daily as coated tablets for 6 weeks. In the verum group reductions of total cholesterol (18.5%) and LDL- cholesterol (22.9%) from baseline to end of treatment were significantly superior (p=0.0001) to those in the placebo group (8.6% and 6.3% respectively). The LDL/HDL ratio decreased by 20.2% in the artichoke extract group and 7.2% in the placebo group.

[Schmidel 2002]. Lowering of the cholesterol level by artichoke and fibre. In this study with 54 test patients at an average duration of about 24 days the effect of a standardised preparation (aqueous artichoke leaf extract 3.8-5.5:1) was measured in comparison with placebo or fibre. The average lowering of cholesterol in all test patients with verum was 16.8% compared to 10% in all patients with placebo. This difference was statistically significant. An even stronger cholesterol lowering effect could

be found tendentious with a simultaneous dose of fibre. The lowering of LDL is similar to that of total cholesterol. The LDL/HDL-quotient could be lowered in the verum and fibre groups while it rose slightly in the placebo group. Patients with flatulence obtained under verum a significant improvement on their troubles while the troubles remained unchanged under placebo. Under verum, no more dropouts or side effects than under placebo were found. The investigated extract was found to be effective in lipid lowering treatment. Adverse events/side effects: verum: hypersensitivity reactions [SOC: immune system disorders] n=1; placebo: flatulence [SOC: gastrointestinal disorders] n=1; further adverse events reported were nausea, headache, sleep disturbances and stomachache without any information whether they occurred in the verum or in the placebo group.

[Lupatteli *et al.* 2004]. Artichoke juice improves endothelial function in hyperlipaemia. Artichoke extracts have been shown to produce various pharmacological effects, such as the inhibition of cholesterol biosynthesis and of LDL oxidation. Endothelial dysfunction represents the first stage of atherosclerotic disease; it is usually evaluated in humans by a non-invasive ultrasound method as brachial flow-mediated vasodilation (FMV) and by the determination of several humoral markers such as vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and E-selectin. Aim of the study was to investigate the effects of dietary supplementation with artichoke leaf pressed juice on brachial FMV of hyperlipemics. The authors studied 18 moderately hyperlipemic patients (LDL cholesterol > 130 <200 mg/dl and/or triglycerides >150 <250 mg/dl) of both genders and 10 hyperlipemic patients, matched for age, sex and lipid parameters. All subjects were under isocaloric hypolipidic diet. A basal determination of serum lipids, soluble VCAM-1, ICAM-1, E-selectin and brachial FMV was performed. Thereafter patients were given 20 ml/die of frozen artichoke juice. The same parameters were repeated after 6 weeks. After artichoke treatment there was an increase of triglycerides (156 +/- 54 vs 165 +/- 76 mg/dl, p <0.05) and a reduction of total cholesterol (261 +/- 37 vs 244 +/- 38 mg/dl, p <0.05) and LDL cholesterol (174 +/- 31 vs 160 +/- 34 mg/dl, p <0.05). Controls showed a significant decrease in total and LDL cholesterol (respectively: 267 +/- 22 vs 249 +/- 20 mg/dl and 180 +/- 24 vs 164 +/- 23 mg/dl, both p <0.001). After artichoke there was a decrease in VCAM-1(1633 +/- 1293 vs 1139 +/- 883 ng/ml, p <0.05) and ICAM-1(477 +/- 123 vs 397 +/- 102 ng/ml, p <0.05), brachial FMV increased (3.3 +/- 2.7 vs 4.5 +/- 2.4%, p <0.01), while controls did not exhibit significant changes in VCAM-1, ICAM-1, E-selectin and brachial FMV. Univariate analysis showed that, in artichoke patients, changes of VCAM-1 and ICAM-1 were significantly related to changes in brachial FMV (respectively: r=-0.66 and r=-0.62; both p <0.05). The authors concluded that artichoke dietary supplementation seems to positively modulate endothelial function in hypercholesterolemia.

[Bundy *et al.* 2008]. The objective of this trial was to assess the effect of artichoke leaf extract on plasma lipid levels and general well-being in otherwise healthy adults with mild to moderate hypercholesterolemia. One hundred and thirty one adults were screened for total plasma cholesterol in the range 6-8 mmol/l, with 75 suitable volunteers randomised onto the trial. Volunteers consumed 1280 mg of a standardised artichoke leaf extract or matched placebo, daily for 12 weeks. Plasma total cholesterol decreased in the treatment group by an average of 4.2% (from 7.16 (SD 0.62) mmol/l to 6.86 (SD 0.68) mmol/l) and increased in the control group by an average of 1.9% (6.90 (SD 0.49) mmol/l to 7.03 (0.61) mmol/l), the difference between groups being statistically significant (p=0.025). No significant differences between groups were observed for LDL cholesterol, HDL cholesterol or triglyceride levels. General well-being improved significantly in both the treatment (11%) and control groups (9%) with no significant differences between groups.

Assessor's comment: In conclusion, artichoke leaf extract consumption resulted in a modest but favourable statistically significant difference in total cholesterol after 12 weeks. In comparison with a previous trial, it is suggested that the apparent positive health status of the study population may have contributed to the modesty of the observed response.

Hepatobiliary effects including influence on choleresis

[Kirschhoff *et al.* 1994]. In one double-blind placebo-controlled cross-over study, clinical trial, **20** male volunteers with acute or chronic metabolic disorders, the choleretic effect of a single dose of an artichoke product was investigated. The group was separated in two randomised subgroups of 10, either 1.92 g of the extract (the contents of 6 proprietary capsules each containing 320 mg of extract plus excipients of a standardised dry aqueous extract (4.5-5:1) of artichoke leaf extract in 50 ml water or a placebo of similar appearance was administered via an intraduodenal probe, the subject having empty stomach on test days. The monitored bile secretion was significantly higher ($p<0.01$) in the verum group: 127% higher at 30 minutes after administration, 151% after 60 minutes (the maximum effect) and 94% after 90 minutes. Results after 120 minutes and 150 minutes were also significantly higher ($p<0.05$). Placebo treatment stimulated bile secretion to a lesser extent, with a maximum increase of 39% after 30 minutes. No adverse or relevant changes in laboratory safety parameters were observed.

[Kraft 1997]. An article by Kraft summarised various post-marketing surveillance studies conducted on patients with dyspepsia and/or diseases of the liver or bile duct. The studies included anywhere from **417 to 557** patients and treatment duration ranged from 4 to 6 weeks. Statistically significant reduction of symptoms (e.g., abdominal pain, bloating, flatulence, and nausea) was reported for the surveillance studies referred to in this paper. Artichoke preparations were well tolerated (up to 95% of cases) with a low rate of side-effects.

- **Antidyspeptic and Gastrointestinal effects**

[Fintelmann 1996]. A multicentre open study with average treatment duration of 43.5 days was conducted in **553** patients with dyspeptic complaints. The daily dose was generally 3-6 capsules of artichoke leaf aqueous dry extract (3.8-5.5:1, 320 mg per capsule). Digestive complains declined in a clinically relevant and statistically significant manner within 6 weeks of treatment, the overall symptoms improved by about 71%. Compared to initial values, the subjective score reduction was approximately 66% for meteorism, 76% for abdominal pain, 82% for nausea and 88% for emesis. In subgroup of 302 patients, total cholesterol decreased by 11.5% and triglycerides by 12.5% while HDL-cholesterol showed a minimal rise of 2.3%. The global efficacy assessed by the physicians was excellent or good in 87% of cases.

[Fintelmann & Petrowicz 1998]. The same extract at a daily dosage of 3-6 capsules (320 mg per capsule) was evaluated in a 6-month open study of **203** patients with dyspeptic complains. After 21 weeks of treatment, the overall improvement of symptoms was 66% compared to initial values, e.g. vomiting by 84%, abdominal pain by 78%, nausea by 76%, flatulence by 70% and meteorism by 69%. Concentration of total blood cholesterol and triglycerides, determined tin 171 and 170 patients decreased by 10.9% and 11%, respectively. From determinations in **159** patients, LDL-cholesterol decreased by 15.8% and HDL- cholesterol increased by 6.3%. The global efficacy assessed by the physicians was excellent or good in 85.7% of cases. No adverse reactions were reported.

[Marakis *et al.* 2002, 2003]. A recent post-marketing study indicated that high doses of standardised artichoke leaf extract (water >80°C, DER 4-6:1, minimum 0.3% flavonoids) may reduce symptoms of dyspepsia. To substantial these findings, this study investigated the efficacy of a low-dose artichoke leaf extract on amelioration of dyspeptic symptoms and improvement of quality of life. The study was an open, dose-ranging postal study. Healthy patients with self-reported dyspepsia were recruited through the media. The Nepean Dyspepsia Index (NDI) and the State-Trait Anxiety Inventory were completed at baseline and after 2 months of treatment with artichoke leaf extract, which was randomly allocated to volunteers as 320 or 640 mg daily. Of the **516** participants, 454 completed the study. In both dosage groups, compared with baseline, there was a significant reduction of all dyspeptic symptoms, with an average reduction of 40% in global dyspepsia score. However, there

were no differences in the primary outcome measures between the two groups, although relief of state anxiety, a secondary outcome, was greater with the higher dosage (P=0.03). Health-related quality of life was significantly improved in both groups compared with baseline. The authors conclude that artichoke leaf extract shows promise to ameliorate upper gastro-intestinal symptoms and improve quality of life in otherwise healthy subjects suffering from dyspepsia.

Assessor's comment: The results of this open study add some evidence to the traditional use of artichoke leaf extract in functional dyspepsia. The relatively low doses which were found effective in this study are worth mentioning. However, as the study was uncontrolled the effectiveness of these low doses remains in question. Adverse event/side effects: constipation: n=2; loose stool: n=2; flatulence: n=1 [SOC: gastrointestinal disorders]. No change of the safety profile.

[Holtmann *et al.* 2003]. This study aimed to assess the efficacy of artichoke leaf extract [(water > 80°C DER 4-6:1), capsules, 2 x 320 mg three times daily], in the treatment of patients with functional dyspepsia and irritable bowel syndrome (IBS). In a double-blind, randomised placebo controlled, multicenter trial (RCT), of 6 weeks treatment, **247** patients with functional dyspepsia (ROME II criteria, but concomitant IBS symptoms, not dominating the clinical picture were allowed) were recruited and treated with either a commercial artichoke leaf extract LI 120 preparation or a placebo. Patients with predominant reflux- or IBS-symptoms were excluded. The primary efficacy variable was the sum score of the patient's weekly rating of the overall change in dyspeptic symptoms (four-point scale). Secondary variables were the scores of each dyspeptic symptom and the quality of life as assessed by the Nepean Dyspepsia Index (NDI). Two hundred and forty-seven patients were enrolled, and data from 244 patients (129 active treatments, 115 placebos) were suitable for inclusion in the statistical analysis (intention-to-treat). The overall symptom improvement over the 6 weeks of treatment was significantly greater with artichoke leaf extract than with the placebo (8.3 +/- 4.6, vs. 6.7 +/- 4.8, P < 0.01). Similarly, patients treated with artichoke leaf extract showed significantly greater improvement in the global quality-of-life scores NDI compared with the placebo-treated patients (41.1 +/- 47.6 vs. -24.8 +/- 35.6, P < 0.01). Safety parameters were comparable between both groups.

Assessor's comment: In accordance with the commonly accepted monographs of the Commission E and ESCOP and earlier published clinical studies the artichoke leaf preparation was superior to placebo in the treatment of patients with functional dyspepsia. The safety profile was very good, adverse events [sense of coherence (SOC): gastrointestinal disorders] mostly classified as mild or moderate and self-resolving. One serious reaction (moderate bilateral adnexitis; [SOC: infections and infestations]) occurred in the placebo group. No change of the safety profile but additional evidence for the indication of functional dyspepsia is concluded.

Other effects

[Wone *et al.* 1986]. In a placebo-controlled, double- blind study in malaria patients, a purified aqueous dry extract from fresh artichoke leaf juice administration intramuscularly (100 mg/day) and orally (1600 mg/day) for 3 days continuing the oral treatment on day 4 to 7 (n=46) or placebo (n=46) was given as additional treatment to standard quinine therapy. More rapid improvement in clinical symptoms of malaria observed in patients given artichoke therapy in addition to quinine was attributed to hepatoprotective effects of the artichoke extract.

Irritable bowel syndrome

Irritable bowel syndrome (IBS), characterised by abdominal pain and altered bowel habit, has symptoms that overlap with those of dyspepsia. Since the crude drug is used for the treatment of dyspepsia, a postmarketing surveillance study was performed to assess its effects on IBS. A subgroup of patients (*n*=279) with symptoms of IBS was identified from a sample of individuals (*n*=553) with dyspeptic syndrome who were being monitored in a post marketing surveillance study of the extract

for 6 weeks. Analysis of the data from the subgroup with IBS revealed significant reductions in the severity of symptoms including abdominal pain, bloating, flatulence and constipation, and favourable evaluations of overall effectiveness by both physicians and patients [Walker *et al.* 2001].

[Bundy *et al.* 2004]. A subset analysis of a previous dose-ranging, open, postal study, in adults suffering dyspepsia. Two hundred and eight (208) adults were identified post hoc as suffering with IBS. IBS incidence, self-reported usual bowel pattern, and the NDI were compared before and after a 2-month intervention period. There was a significant fall in IBS incidence of 26.4% ($p < 0.001$) after treatment. A significant shift in self-reported usual bowel pattern away from "alternating constipation/diarrhoea" toward "normal" ($p < 0.001$) was observed. NDI total symptom score significantly decreased by 41% ($p < 0.001$) after treatment. Similarly, there was a significant 20% improvement in the NDI total quality-of-life score in the subset after treatment. This report supports previous findings that artichoke leaf extract ameliorates symptoms of IBS, plus improves health-related quality-of-life. Artichoke leaf extract (extraction solvent: water; 5:1) 320 or 640 mg/per day was used for the study.

Assessor's comment: This study evaluates the therapeutic value of artichoke leaf extract in those patients with dyspepsia who suffer from IBS. The analysis was performed on a subset of patients from a previously performed study in patients with dyspepsia and indicates that artichoke leaf extract may be of therapeutic value in IBS patients not only for the symptoms assigned to dyspepsia but also for other symptoms. Especially the condition of alternating constipation/diarrhoea responded very good to the artichoke extract treatment. Although not placebo controlled, this study/subset analysis yields evidence for a possible therapeutic value of artichoke leaf extract in the treatment of IBS, which is currently not an approved indication of artichoke products. Adverse events/side effects were not reported. No change of the safety profile.

Overview of clinical studies with artichoke

Study ID	Study Dates Persons	Design Control type Study objective	Study & Ctrl Drugs Dose, Route,	Duration	Gender M/F	Diagnosis Inclusion Criteria	Primary Efficacy Endpoint
Wojcicki & Winter 1975	10 industrial workers	Efficacy, tolerability	Daily administration of 900 mg artichoke extract (max. polyphenolic acids content 5.5%)	30 days	10 industrial workers long term occupational exposure to carbon disulfide	Cholesterol lowering effects	Significantly lowered blood levels of cholesterol ($p<0.02$) free fatty acids , phospholipids and total lipids (p, 0.05)
Wojcicki *et al.* 1982	73	Comparative study	Undefined artichoke leaf extract (9 tablets, of 5 mg of polyphenolic acids , n=25) or 0.75 g or 1.5 g cynarin *per os* 1	1 month	73 patients with primary hyper-triglyceridaemia resistant to treatment with clofibrate	Lipid lowering effects	The artichoke leaf extract exerted significant total lipid-, triglyceride-,and phospholipids-lowering, effects in 56% of patients , whereas 0.75 g or 1.5 g of cynarin improved lipid parameters in 61% or 45% of patients
Kirschhoff *et al.* 1994	20	Double-blind, placebo-controlled , cross-over study Efficacy, tolerability, safety	1.92 g (320 x 6) of stand dry water extract (4.5-5:1) of artichoke leaf (6 capsules -320 mg) in 50 ml water or placebo admnistr. via an intraduodenal probe		20 males in two subgroups	Acute or chronic metabolic disorders	Bile secretion higher ($p<0.01$) in verum group: 127% higher 30 min after admin., 151% after 60 min. (the maximum effect) and 94% after 90 min result a after 120 min and 150 min were also significantly higher ($p<0.05$). Placebo treatm. max. increase 39% after 30 min
Fintelmann 1996	553	Multicentre open study, safety, efficacy,	Daily dose 3-6 caps. artichoke leaf extract aqueous dry extract (3.8-5.5:1, 320 mg per capsule) *per os*	43.5 days	553 patients with dyspeptic complaints	Dyspepsia digestive complaints	Digestive complains declined within 6 weeks of treatm. All symptoms improved 71%. Meteorism reduction approx 66%, 76% for abdominal pain, 82% for nausea 88% for emesis. In subgroup of 302 patients, total cholesterol decreased 11.5% triglycerides 12.5%. Global efficacy by physicians excellent as good in 87% of cases. No AEs
Kraft 1997	417 to 557 patients	Post-marketing surveillance studies		4 to 6 weeks	417 to 557 patients	Dyspepsia and/or diseases of the liver or bile duct	Statistically significant reduction of symptoms (e.g., abdominal pain, bloating, flatulence, and nausea) was reported for the surveillance studies referred to in this paper. Artichoke

Study ID	Study Dates Persons	Design Control type Study objective	Study & Ctrl Drugs Dose, Route,	Duration	Gender M/F	Diagnosis Inclusion Criteria	Primary Efficacy Endpoint
							preparations were well tolerated (up to 95% of cases) with a low rate of side-effects
Petrowicz *et al.* 1997	44 health-volunteers	Randomised double-blind , placebo-controlled study Efficacy, tolerability	640 mg of dry water extr), 640 mg x 3 daily *per os* Placebo	12 weeks	44 groups in volunteers with initial cholesterol >230 mg/dl(n_v-n_p=3)	Lipid lowering effects	Decreased concentration of total cholesterol (p=0.015) and triglycerides (p=0.01) to placebo in volunt. cholesterol >220 mg/dl (n_v-n_p=5), significant differ. (p=0.012) for triglycerides compared to placebo
Fintelmann & Petrowicz 1998	203	Multicentre open study, safety, efficacy, tolerability, safety	Daily dose 3-6 capsules artichoke leaf extract aqueous dry extract (3.8-5.5:1, 320 mg per capsule) *per os*	6 months	203 patients with dyspeptic complains	Dyspepsia digestive complaints	After 21 weeks treatm. improvement of symptoms 66% e.g. vomit by 84%, abdominal pain 78%, nausea 76%, flatulence 70% and meteorism 69%. Total blood cholesterol - triglycrds, in 171 among patients decreas. 10.9% and in 159 determ. patients, LDL-cholesterol decreas. by 15.8% and HDL-cholesterol by 6.3%. Global efficacy by the physicians excellent or good in 85.7% of cases. No AEs
Englisch *et al.* 2000	143	Multicentre randomised, placebo-controlled, double- blind study efficacy, tolerability	Fresh artichoke leaf water extr. (25-35:1) Daily 1800 mg (n=71) or placebo (n=72) as coated tabs *per os* 1	6 weeks	143 patients with hyperlipoproteinaemia (cholesterol >280 mg/dl)	Lipid lowering effects	In verum group reduction total cholesterol (18.5%) and LDL- (22.9%) from baseline to end of treatment signif. superior (p=0.0001) `to those in placebo group (8.6% and 6.3% respectively) LDL/HDL ratio decreased by 20.2% in verum group and 7.2% in the placebo group
Schmidel 2002	54 test patients		Stand. preparation (aqueous artichoke leaf extract 3,8-5,5:1) (comparison with	24 days	54 patients with hyperlipoproteinaemia	Lipid lowering effects	The average lowering of cholesterol in all test patients with verum was 16.8% compared to 10% in all patients with placebo. This difference was statistically significant side

Study ID	Study Dates Persons	Design Control type Study objective	Study & Ctrl Drugs Dose, Route,	Duration	Gender M/F	Diagnosis Inclusion Criteria	Primary Efficacy Endpoint
			placebo)				effects: verum: hypersensitivity reactions [SOC: immune system disorders] n=1; placebo: flatulence [SOC: gastrointestinal disorders] n=1; ad. effects nausea, headache, sleep disturbances and stomach ache without information whether they occurred in the verum or in placebo group
Lupatteli *et al.* 2004	28		20 ml/day of frozen artichoke juice	6 weeks	18 moderately hyperlipemic patients (LDL cholesterol > 130 <200 mg/dl and/or triglycerides >150 <250 mg/dl) 10 hyperlipemic patients males and women	Lipid lowering effects	Controls showed signif. decrease in total and LDL cholesterol (267 +/- 22 vs 249 +/- 20 mg/dl and 180 +/- 24 vs 164 +/- 23 mg/dl, both p <0.001). Also decrease in VCAM-1(1633 +/- 1293 vs 1139 +/- 883 ng/ml, p <0.05) and ICAM-1(477 +/- 123 vs 397 +/- 102 ng/ml, p <0.05), brachial FMV increased (3.3 +/- 2.7 vs 4.5 +/- 2.4%, p <0.01).
Bundy *et al.* 2008	131	Randomised, double blind placebo controlled trial	1280 mg (320 x 4) of a standardised artichoke leaf extract, or matched placebo, daily	12 weeks	131 adults	Lipid lowering effects	Plasma total cholesterol decreased in the treatment group by average of 4.2% (from 7.16 (SD 0.62) mmol/l to 6.86 (SD 0.68) mmol/l) and increased in the control group by an average of 1.9% (6.90 (SD 0.49) mmol/l to 7.03 (0.61) mmol/l), difference between groups statistically significant (p=0.025). No significant differences between groups were observed for LDL cholesterol, HDL cholesterol or triglyceride levels.
Kirschhoff *et al.* 1994	20	Double-blind, placebo-controlled , cross-over study	1.92 g (320x6) of stand.dry water extr.(4.5-5:1) of artichoke leaf (6 capsules - 320 mg) in 50		20 males in two subgroups	Acute or chronic metabolic disorders	Bile secretion higher (p<0.01) in verum group: 127% higher 30 min after admin., 151% after 60min. (the maximum effect) and 94% after 90 min result a after 120 min and 150 min

Study ID	Study Dates Persons	Design Control type Study objective	Study & Ctrl Drugs Dose, Route,	Duration	Gender M/F	Diagnosis Inclusion Criteria	Primary Efficacy Endpoint
		Efficacy, tolerability, safety	ml water or placebo admnistr via an intraduodenal probe				were also significantly higher (p<0.05). Placebo treatm max. increase 39% after 30 min.
Marakis *et al.* 2003	516 454 completed the study	320 or 640 mg of artichoke leaf extract daily	Open, dose-ranging postal study	2 months	516 participants 454 completed the study self-reported dyspepsia. NDI and State-Trait Anxiety Inventory were completed at baseline	Dyspepsia digestive complaints	Significant reduction of all dyspeptic symptoms, with an average reduction of 40% in global dyspepsia score. Health-related quality of life signif. improved compared with baseline. Artichoke leaf extract ameliorates upper gastro-intestinal symptoms and improves quality of life in healthy suffering from dyspepsia. side effects: constipation: n=2; loose stool: n=2; flatulence: n=1 [SOC: gastrointestinal disorders]
Holtmann *et al.* 2003	247 patients	Artichoke leaf extract [(water > 80° C DER 4-6:1), capsules, 2 x 320 mg t.i.d.],	Double-blind, randomised controlled trial (RCT)	6 weeks	Treatment of 247 patients with functional dyspepsia quality of life as assessed by the NDI	Functional dyspepsia	Data from 244 patients (129 active treatments, 115 placebos) were suitable statistical analysis. All symptom improvement was signif. higher with verum than with the placebo (8.3 +/- 4.6, vs. 6.7 +/- 4.8, P < 0.01). Artichoke leaf extract showed signif. greater improvement in global quality-of-life scores (NDI) compared with placebo-treated patients (41.1 +/- 47.6 vs. - 24.8 +/- 35.6, P<0.01).
Bundy *et al.* 2004	208 patients	Artichoke leaf extract (extraction solvent: water; DER 1:5) 5:1) 320 or 640 mg/per day	Subset analysis of a previous dose-ranging, open, postal study	2 months	IBS self-reported usual bowel pattern, and the NDI	Dyspepsia dealing with IBS	Significant fall in IBS incidence of 26.4% (p<0.001) after Artichoke leaf extract NDI total symptom score signif. decreased by 41% (p<0.001) after Artichoke leaf extract. Signif. Improvement 20% in NDI total quality-of-life.

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

In a multicentre, randomised , placebo-controlled , double- blind study by [Englisch *et al.* 2000], the effect of a fresh artichoke leaf aqueous dry extract (25-35:1) was investigated in 143 patents for its lipid lowering effects without obtaining convincing results: In the verum group, the reduction of total cholesterol was 18.5% and of LDL 22.9%. In another randomised double-blind, placebo-controlled study by [Petrowicz *et al.* 1997] the same lipid lowering effects were studied with water extract of *Cynara* in 44 healthy volunteers. After 12 weeks, a decreased concentration of total cholesterol ($p=0.015$) and triglycerides ($p=0.01$) to placebo (volunt. cholesterol >220 mg/dl (n_v-n_p=5), significant difference ($p=0.012$) for triglycerides compared to placebo) was reported. The groups were too small to adequately evaluate the final results.

Finally, in the study of [Holtmann *et al.* 2003] it was aimed to assess the efficacy of artichoke leaf extract (water > 80°C, DER 4-6:1, 2 x 320 mg three times daily), in the treatment of patients with functional dyspepsia and irritable bowel syndrome. In the double-blind, randomised placebo controlled, multicenter trial, 247 patients with functional dyspepsia (ROME II criteria; concomitant IBS symptoms, not dominating the clinical picture were allowed) were recruited and treated with either a commercial preparation (2 x 320 mg plant extract three times daily) or a placebo. The overall symptom improvement over 6 weeks of treatment was higher with *Cynara* extract than with placebo (8.3 +/- 4.6, vs. 6.7 +/- 4.8, $P<0.01$) with higher improvement in the global quality-of-life scores. However, a sufficiently detailed and accepted definition of functional dyspepsia is missing.

Throughout all existing clinical trials, the efficacy was not supported sufficiently but the determined safety of the use of *Cynara* extracts was evaluated adequately.

5. Clinical Safety / Pharmacovigilance

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

Not specified by the Rapporteur.

5.2. Patient exposure

Not specified by the Rapporteur.

5.3. Adverse events and serious adverse events and deaths

No major adverse events have been reported from clinical human pharmacological studies with preparations containing extracts of artichoke leaf involving over 1600 subjects and study duration of up to 2 years. Overall, 19 minor adverse events were reported; mainly gastrointestinal complaints [Fintelmann 1996; Fintelmann & Petrowicz 1998; Kirschhoff *et al.* 1993; Englisch *et al.* 2000; Petrowicz *et al.* 1997; Wojcicki *et al.* 1975, 1981; Palacz *et al.* 1981; Woyke *et al.* 1981; Wone *et al.* 1986]. A systematic review of published human studies concluded that safety data for artichoke leaf extract indicate only mild and infrequent adverse effects [Pittler & Ernst 1998].

The following groups of adverse events/side effects are mentioned by the review authors:

- *Immune system disorders*

- allergic reactions

- *Metabolism and nutrition disorders*

- decreased appetite

- *Gastrointestinal disorders*

- flatulence

- *General disorders and administration site conditions*

- weakness
- hunger

Known allergies to artichokes and related species (*Asteraceae* or *Compositae*).

Obstruction of bile ducts. In case of gallstones, use only after consulting a physician.

5.3.1. Serious adverse events and deaths

One (serious) case was related to the treatment with a medicinal product containing artichoke leaf dry extract. The other 4 cases are related to allergic reactions following ingestion of artichoke or are connected to occupational situations, however, not transferable to the use of herbal medicinal products containing *Cynara*.

A 24-year–old woman was hospitalised on 30th of November 2005 because of asthenia and urticaria. She had neither any medical history nor any risks of virus infection or acute or chronic alcoholic intoxication. She had started consumption of Hepanephrol (2 ampoules/day) for slimming on 6 November 2005. Liver tests were normal in September 2005 on the occasion of a routine check. On 30 November 2005 she developed asthenia and urticaria requiring medical consultation. Clinical examination revealed no fever, no icterus, no signs of hepatocellular insufficiency and no signs of hepatic encephalopathy. Abdominal palpation revealed a painless abdomen without signs of hepatomegaly. There were no signs of thrombosis, and auscultation of the heart was normal. Hepatic enzymes were elevated as follows: ALAT 40 times higher than normal (N), ASAT 48 x N; GGT 1.3 x N, ALP 1.3 x N. Bilirubin and prothrombin were in normal range. Tests for hepatitis A, B, C, herpes, cytomegaly, Epstein-Barr, or toxoplasmosis were negative. Further tests were without findings. The ECG was normal. Ultrasound testing of the liver and the bile ducts didn't show any abnormal findings; no gallstones or signs of dilatation of the bile ducts or signs of chronic hepatopathy were found. The administration of Hepanephrol was stopped on day of admission. Liver parameters improved within 3 weeks. A liver biopsy was not performed [Sinayoko *et al.* 2007].

Assessor's comment: As stated by the authors, a causal relationship is formally possible in this case because of a plausible temporal relationship and because of an improvement of the reaction following the discontinuation of the product. Thus, an intolerability or hypersensitivity reaction cannot completely be excluded. However, the used product is insufficiently described including the relevance of the used dosage. In addition, the product was not used in the recommended indication (off label use). In summary, based on the available information it is assessed that this case report may not be directly transferred to other artichoke preparations as used in Germany. If a general advice not to use a product in case of known hypersensitivity is given in the SPC, no change of the safety profile is concluded; no other measures have to be taken.

[Franck *et al.* 2005]. Anaphylactic reaction to inulin: first identification of specific IgEs to an inulin protein compound. This case of an immediate allergic reaction resulting in an anaphylactic shock was not caused by an artichoke leaf preparation but two food products containing added inulin (Raftilose). However, differential diagnosis of this case led to the assumption of a cross-allergy with artichoke. Given the extremely rare occurrence of inulin allergy the probability of an allergic cross reaction after the intake of medicinal artichoke products in patients previously sensitised against inulin by consumption of other inulin containing food is considered to be extremely low. No change of the safety profile.

[Gabdan *et al.* 2003]. Acute oedema of the tongue: a life-threatening condition. This paper focuses on a number of life-threatening cases of acute tongue oedema. In one of ten cases reported in this paper the patient had consumed an "artichoke" prior to the event. The authors assess this case as being directly related to the artichoke consumption. However, as the artichoke was consumed as a food, it may have been that it was prepared with a spice dressing, or was otherwise prepared or concomitantly consumed with other, not mentioned food. Thus, the causality of artichoke for the adverse reaction is not assessable. However, the reaction must be assessed as possible in relation to artichoke which belongs to the family of *Asteraceae*. The - generally low - possibility of such reactions against any *Asteraceae* is well known and adequately addressed in most products with a warning label for patients with known allergy against any *Asteraceae* plant. No change of the safety profile.

[Miralles *et al.* 2003]. Occupational rhinitis and bronchial asthma due to artichoke (*Cynara scolymus*): Two cases of contact allergy are reported. Both cases involved vegetable warehouse workers who developed occupational rhinitis and bronchial asthma following expose to artichokes. While the symptoms described in these cases are relatively severe the article also stresses that only two additional case reports of artichoke allergy were found in a Medline and Embase data base search. Both cases fit into the well known picture of rarely occurring allergy against *Cynara*. No change of the benefit risk ratio.

Assessor's comment: A total of 5 cases with adverse reactions during treatment with *Cynara* have been identified in the literature, which did not change the benefit risk ratio.

5.4. Laboratory findings

None reported.

5.5. Safety in special populations and situations

None reported.

Drug interactions

Concomitant use with *Cynara* containing medicinal products may decrease the efficacy of anticoagulants (coumarin derivates like Phenprocoumon, Warfarin) [ESCOP 2009].

Use in pregnancy and lactation

One publication reviews herbal infusions used for induced abortion [Ciganda & Laborde 2003]. In this paper, *Cynara* is only briefly mentioned in a table without any clinical proof.

However, due to the lack of any data and in accordance with general medical practice, *Cynara*-containing herbal medicinal products should not be used during pregnancy and lactation.

Overdose

No information.

Drug abuse

No information.

Withdrawal and rebound

No information.

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

No information.

5.6. Overall conclusions on clinical safety

Only mild adverse events were reported in all published clinical trials. The pharmaceutical forms are therefore acceptable with respect to clinical safety.

6. Overall conclusions

Artichoke is characterised by the phenolic acid constituents, in particular cynarin. Experimental studies (*in vitro* and *in vivo*) support some of the uses of artichoke. Traditionally, the choleretic and cholesterol-lowering activities of globe artichoke have been attributed to cynarin [Lietti 1977]. Studies in animals and humans have suggested that these effects may in fact be due to the monocaffeoylquinic acids and cynarin present in artichoke (e.g. chlorogenic and neochlorogenic acids). Clinical trials investigating the use artichoke and cynarin in the treatment of hyperlipidaemia generally report positive results. However, further rigorous clinical trials are required to establish the benefit of globe artichoke leaf extract as a lipid – and cholesterol-lowering agent. Hepatoprotective and hepatoregenerating activities have been documented for cynarin *in vitro* and in animals (rats). However, these effects have not yet been documented in clinical studies.

The existing clinical trials indicate that the artichoke leaf extracts (water dry extract of dried and fresh leaves) is somehow effective against functional dyspepsia and also for its lipid lowering effects. Because it is not adequately documented, the well-establish use cannot be supported.

Moreover, the following herbal preparations are for more than 30 years on the European market and are proposed to be included in the monograph for Traditional Use:

a) Comminuted or powdered dried leaves for herbal tea
b) Powdered leaves
c) Dry extract (2.5-7.5:1), extraction solvent water
d) Dry extract from fresh leaves (15-35:1), extraction solvent water
e) Soft extract fresh leaves (15-30:1), extraction solvent water
f) Soft extract (DER 2.5-3.5:1), extraction solvent ethanol 20% (v/v)

These herbal preparations are indicated for the symptomatic relief of digestive disorders such as dyspepsia with a sensation of fullness, bloating and flatulence, based on long standing use.

A total of 5 cases with adverse reactions during treatment with *Cynara* have been identified in the literature, which did not alter the benefit risk ratio.

Due to the lack of data and in accordance with general medical practice, *Cynara*-containing herbal medicinal products should not be used during pregnancy and lactation.

Only mild adverse events were reported in all published clinical trials. The pharmaceutical forms are therefore acceptable with respect to clinical safety.

As there is no adequate data on genotoxicity, carcinogenicity and reproducibility, the establishment of a Community List Entry is not supported.

Annex

List of references