EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

12 November 2009
EMA/HMPC/212897/2008
Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Taraxacum officinale* Weber ex Wigg., radix cum herba

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)	*Taraxacum officinale* Weber ex Wigg., radix cum herba
Herbal preparation(s)	Dried root with herb, comminuted Dry extract (DER 5.6-8.4:1), extraction solvent ethanol 60% V/V Liquid extract (DER 1:0.9-1.1) extraction solvent ethanol 30% V/V Liquid extract (DER 0.75:1) extraction solvent ethanol 30% m/m Expressed juice[1] from fresh flowering Taraxaci radix cum herba (DER 1 : 0.5-0.8)
Pharmaceutical forms	Herbal preparations in solid or liquid dosage forms for oral use. Comminuted herbal substance as herbal tea for oral use.
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[1] The material, when dried, complies with Ph. Eur. monograph on herbal drugs and DAC 2004.

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1. Introduction

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

- Herbal substance(s)

Taraxaci herba cum radice (DAC 2004):

Dried, in spring collected whole or comminuted aerial parts, roots and rhizome of *Taraxacum officinale* Weber (Cichoriaceae).

Note: Asteraceae family is mentioned in the current scientific literature

Radix cum Herba Taraxaci (WHO monographs, Vol.3, 2007):
Consists of entire plant of *Taraxacum officinale* Weber ex Wigg.

Radix taraxaci cum herba (Pharmacopoeia Bohemoslovaca, Ed.4, 1987):
Dried root, rhizome, leave and flower buds of *Taraxacum officinale* agg.

Constituents:

Root

Sesquiterpenes

1. eudesmanolides 4α,11β, 13,15-tetrahydroridentin B and taraxacolide-O-glucopyranoside (Hänsel R *et al.* 1980),
2. guaianolides 11β,13-dihydrolactucin and ixerin D (Kisiel W and Barszcz B 2000), and germacranolides taraxinic acid *D*-glucopyranoside, its 11β,13-dihydro-derivative and ainslioside (Hänsel R *et al.* 1980, Kuusi T *et al.* 1985, Kisiel W and Barszcz B 2000).

Sterols

Taraxasterol, β-taraxasterol, their acetates and their 16-hydroxy derivatives arnidol and faradiol, α- and β-amyrin, β-sitosterol, β-sitosterol-D-glucopyranoside and stigmasterol (Burrows S and Simpson J 1938, Hänsel R *et al.* 1980, Akashi T *et al.* 1994).
Triterpenic 3β-hydroxylup-18(19)-ene-21-one in fresh roots (Kisiel W and Barszcz B 2000).

Phenolics

Chicoric acid and its isomer, monocaffeoyltartaric, 4-caffeoylquinic, chlorogenic, caffeic, p-coumaric, ferulic, p-hydroxybenzoic, protocatechuic, vanillic, syringic and p-hydroxyphenylacetic acids, umbelliferone, esculetin, scopoletin, benzyl-O-β-glucopyranoside, dihydroconiferin and a mixture of syringin and dihydrosyringin (Clifford MN *et al.* 1987, Wolbis M *et al.* 1993, Williams CA *et al.* 1996, Kisiel W and Barszcz B 2000).

p-hydroxyphenylacetic acid (Kuusi T *et al.* 1985) and its derivative β-O-[4-O-(*p*-hydroxyphenylacetyl]-β-*D*-glucopyranosyl]-β-hydroxy-γ-butyrolactone (Rauwald HW and Huang JT 1985).

Inulin contents of roots range from 2% in spring to 40% in autumn (Bisset NG *et al.* 1994).

Root and herb

Phenolics

chlorogenic acid, cryptochlorogenic acid, 3,4-di-O-caffeoylquinic acid, 3,5-di-O-caffeoylquinic acid, 4,5-di-O-caffeoylquinic acid, cis-caftaric acid, trans-caftaric acid, trans-coutaric acid, caffeoyl-dihydroxy-phenyllactoyltartaric acid, caffeoyl hexoside, caffeic acid, quinic acid derivative, chicoric acid, quercetin triglycosides, quercetin diglycosides, luteolin triglycoside, luteolin diglycosides, luteolin 7-O-rutinoside, luteolin 7-O-glucoside, luteolin 4-O-glucoside, chrysoeriol diglycoside, quercetin pentoside, luteolin, luteolin 7-O-gentiobioside (Schütz K *et al.* 2005).

Leaves

Phenolics

Luteolin-7-glucoside, luteolin 7-O-rutinoside, isorhamnetin 3-O-glucoside, quercetin 7-O-glucoside, apigenin 7-O-glucoside, two different luteolin-7-diglucosides, chicoric acid, chlorogenic acid, monocaffeyltartaric acid, cichoriin and esculin were detected in leaves extract prepared from 80% methanol. The most abundant phenolic compounds in leaves and flowers are hydroxycinnamic acid derivatives, in particular caffeic acid esters such as chlorogenic, dicaffeoyltartaric (chicoric acid) and monocaffeoyltartaric acids extract (Wolbis M and Krolikowska M 1985; Wolbis M *et al.* 1993; Williams CA *et al.* 1996; Budzianowski J 1997; Kristó ST *et al.* 2002).

In ethanolic extract prepared in Soxhlet apparatus ca. 0.59% of β-amyrin and 0.12% of β-sitosterol were determined by densitometry (Simándi B *et al.* 2002). The common phytosterols stigmasterol, campesterol, cycloartenol and 24-methylene-cycloartanol (Westermann I and Roddick K 1981) and β-sitosterol (Kuusi T *et al.* 1985) also were found.

T. officinale leaves contain a high potassium concentration. In a three-year experiment values between 30.37 and 47.73 mg potassium/1 g of drug were determined (Tsialtas JT *et al.* 2002).

Trace metals, determined in wild growing plants from 29 sites in USA by inductively coupled plasma atomic emission spectrometry (ICP-AES) and flame atomic absorption spectrometry (FAAS), reached a wide range of mean concentrations (mg/kg): Cd 0.55-3.11, Cr 2.83-61.72, Cu 2.10-58.41, Fe 61-3916, Mn 21.70-276.95, Ni 2.15-38.02, Pb 0.50-45.00, and Zn 18.60-261.40 (Keane B *et al.* 2001).

In another study, in samples from 13 sites in Poland levels (mg/kg) of Cd 0.04-0.27, Cu 1.5-8.7, Pb 3.3-175.3, and Zn 7.9-103.6 were determined by FAAS (Królak E 2003).

519 mg/l of potassium were found in an infusion (prepared by using 5 g of dandelion leaves from Spain in 200 ml of water at 70°C during 2 hrs) by ICP-AES. In leaves 29.68 mg potassium/1 g were determined by a wavelength-dispersive x-ray fluorescence method. So, potassium exhibits a high degree of solubility in infusion, approximately 67% (Queralt I *et al.* 2005).

No statistical difference between potassium or sodium content in dandelion root with herb decoction and infusion samples (310.22 vs. 962.64 mg/g for decoction and 340.90 vs. 1059.61 mg/g for infusion, $p>0.05$) was established by flame emission photometry (Ertaş ÖS *et al.* 2005).

- Herbal preparation(s)

  a) Comminuted herbal substance for infusion. 3-4 g of cut or powdered drug per cup of water or 1 tablespoon of cut drug per cup of water. German Commission E (Blumenthal M *et al.* 1998)

  b) Dry extract (5.6-8.4:1), extraction solvent ethanol 60% (V/V) (Document for information exchange for the preparation of the assessment report for the development of community monographs and for inclusion of herbal substance(s), preparation(s) or combinations thereof in the list, Answer from Germany 12/2007)

  c) Liquid extract (1:0.9-1.1) extraction solvent ethanol 30% (V/V) (Document for information exchange for the preparation of the assessment report for the development of community monographs and for inclusion of herbal substance(s), preparation(s) or combinations thereof in the list, Answer from Germany 12/2007)

  d) Liquid extract (0.75:1) extraction solvent ethanol 30% (m/m) (Document for information exchange for the preparation of the assessment report for the development of community monographs and for inclusion of herbal substance(s), preparation(s) or combinations thereof in the list, Answer from Germany 12/2007)

  e) Expressed juice from fresh drug. (Rote Liste 2006)

- 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.

Taraxaci radix cum herba is used in many combinations with many other herbal substances/herbal preparations. The monograph EMA/HMPC/212895/2008 refers exclusively to Taraxaci radix cum herba.

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

See section 2.1

Regulatory status overview

Member State	Regulatory Status				Comments (not mandatory field)
Austria	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	In combination only
Belgium	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	In combination only
Bulgaria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No licensed products
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Czech Republic	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	In combination only
Denmark	☒ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	In combination only
Estonia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Finland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No licensed products
France	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Germany	☒ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No licensed products
Hungary	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No licensed products
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No licensed products
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No licensed products
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No licensed products
Latvia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	In combination only
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Lithuania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Luxemburg	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	In combination only
Malta	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No licensed products
The Netherlands	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No licensed products
Norway	☐ MA	☐ TRAD	☒ Other TRAD	☐ Other Specify:	Tea
Poland	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	In combination also TR
Portugal	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No licensed products
Romania	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	In combination teas only TRAD
Slovak Republic	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	In combination only
Slovenia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No licensed products
Spain	☒ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	MA in combination only
Sweden	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	In combination only
United Kingdom	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	

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

2. Historical data on medicinal use

2.1. Information on period of medicinal use in the Community

In German folk medicine since 16th century (Kroeber L 1950, Faber K 1958). In fact Taraxaci radix cum herba has been in medical use for many decades in Germany:

1. aar Löwenzahn Dragees, coated tablet: dry extract (5.6-8.4:1).
   Extraction solvent: Ethanol 60% V/V (since 1976)
2. Löwenzahn zur Verdauung, coated tablet: dry extract (5.6-8.4:1).
   Extraction solvent: Ethanol 60% V/V (since 1976)
3. Carvicum Tropfen, oral liquid: Liquid extract (1:0.9-1.1).
   Extraction solvent: Ethanol 30% V/V, disturbance of bile secretion with dyspeptic complaints like sense of fullness and flatulence (since 1976)
4. Paverysat L Bürger, oral liquid: Liquid extract (0.75:1).
   Extraction solvent: Ethanol 30% m/m, in appetence and disturbance of bile secretion with dyspeptic complaints like sense of fullness and flatulence (since 2007)
5. Bad Wörishofener Pflanzensaft Löwenzahn, oral liquid: squeezed sap from fresh flowering Taraxaci radix cum herba (1:0.6-0.8), Traditional used to promote the digestion (since 1976)
6. Pflanzenextrakt Löwenzahn, oral liquid: squeezed sap from fresh flowering Taraxaci radix cum herba (1:0.6-0.8), disturbance of bile secretion with dyspeptic complaints like sense of fullness and flatulence (since 2005)
7. Löwenzahn Pflanzensaft Kneipp, oral liquid: squeezed sap from fresh flowering Taraxaci herba (1.75:1), disturbance of gall-bladder and liver functions (since 1976)
8. Florabio naturreiner Heilpflanzensaft Löwenzahn (Schoenenberger), oral liquid: 100 ml contains squeezed sap from fresh dandelion herb and roots, cholagogum (since 2006)

Therefore Taraxaci radix cum herba as requested by Directive 2004/24 EC qualifies for use in traditional herbal medicinal products, as it has been in medical use for a period of at least 30 years including at least 15 years in the European Union.

Type of tradition, where relevant

European tradition.

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

Traditional use

The following indications have been reported for Taraxaci radix cum herba:
Treatment of diabetes, rheumatism, urinary tract infections, fever, insomnia, inflammation of the eye, sore throat, abscess, lung, jaundice. As a galactogogue, laxative and tonic. (WHO monographs Vol.3 2007, Bisset NG *et al.* 1994).

Wording for the traditional indications

a. Traditional herbal medicinal product to increase the amount of urine to achieve flushing of the urinary tract as an adjuvant in minor urinary complaints.

b. Traditional herbal medicinal product for the relief of symptoms related to mild digestive disorders such as feeling of abdominal fullness, flatulence, and slow digestion, and in temporary loss of appetite.

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

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

Evidence regarding the specified posology

Average daily dose:

3-4 g of cut or powdered drug three times (decoction in 150 ml of water) (Gehrmann B *et al.* 2005)

1 tablespoon full of drug (infusion in 150 ml of water)
0.75-1.0 g of native dry extract 4:1 m/m
3-4 ml fluid extract 1:1 (g/ml) (Blumenthal M *et al.* 1998).

5-10 ml of tincture (1:5 in 45% ethanol), three times (British Herbal Pharmacopoeia 1996).

Adults: 4-10 g of the drug or as an infusion, three times daily.
2-5 ml of tincture (1:5, ethanol 25% V/V), three times daily.
5-10 ml of juice from fresh leaf, twice daily (Bradley PR 1992).

Evidence regarding the route of administration

The oral administration is the only route for Taraxaci radix cum herba preparations in the recommended traditional indications.

Evidence regarding the duration of use

No restriction on the duration of use has been reported for Taraxaci radix cum herba. As clinical safety studies are lacking, it is proposed to limit the duration of use to 2 weeks.

Assessor's overall conclusion on the traditional medicinal use

Preparations from Taraxaci radix cum herba have been used for the relief of symptoms of mild digestive disorders that were, historically, associated with bile flow or for the stimulation of diuresis. The traditional medicinal use is made plausible by pharmacological data.

3. Non-Clinical Data

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

Diuretic action

No data available for Taraxaci radix cum herba.

According to the British Herbal Medicine Association (British Herbal Pharmacopoeia 1996), for the leaves a diuretic action is described.

The diuretic action of aqueous extracts obtained from dandelion herb was reported to be stronger than that from the root extracts (administered through a gastric tube to male rats at a dose of 50 ml/kg body weight). The highest diuretic and saluretic indices corresponded to 8 g dried herb/kg body weight. Comparable diuretic and saluretic indices were reached with furosemide at 80 mg/kg body weight. The very high saluretic index concerning potassium excretion may be due to the high (4.25%) potassium content (Rácz-Kotilla E *et al.* 1974).

Purified fractions isolated from dandelion roots collected in autumn were examined using saline-loaded mice. A petrol ether fraction and two methanol fractions in concentration of 50 ml/kg body weight slightly increased the final urine volume (Hook I *et al.* 1993).

Other authors could not confirm a diuretic activity: per os (p.o.) or intraperitoneal (i.p.) application of an ethanolic extract (Tita B *et al.* 1993) or of an aqueous root extract in female Wistar rats (Grases F *et al.* 1994).

Theoretically, patients on lithium therapy who use herbal preparations with a diuretic action (e.g. dandelion) may experience dehydration and resulting lithium toxicity (Harkness R and Bratman S 2003).

Choleretic action

After intraduodenal administration of water decoction from *Taraxacum* leaves in rats, the bile volume per hour increased up to 40% (Böhm K 1959).

A decoction from fresh leaves (or 5 g of dried ones), after intravenous administration to dogs, induced a twofold increase of the bile volume during a 30-minute period (Chabrol E *et al.* 1931).

Anti-inflammatory action

The effects of *Taraxacum officinale* on oxidative stress, inflammation, and lipid profile in C57BL/6 mice fed atherogenic diet were studied (Kim J *et al.* 2007). Five groups of C57BL/6 mice were given atherogenic diet (control) and containing 1.5%, 3% *Taraxacum officinale* whole plant water extract (TOWE) and alcohol extract (TOAE) for 6 weeks, respectively after 6 weeks of supplementation. Plasma and hepatic triglyceride and total cholesterol concentrations were decreased significantly in TOWE and TOAE groups compared to control group, while faecal total lipid, triglyceride and total cholesterol concentrations were also higher significantly in both treatment (TO) groups compared to control group (concentrations were lower in TOWE group than TOAE one). Superoxide dismutase activity was significantly lower in TO extract groups, but catalase activity and glutathione level were significantly higher in TO groups than control group. The authors conclude that *Taraxacum officinale* may reduce the risk of atherosclerosis via the attenuation of anti-inflammatory, antioxidative and hypolipidemic processes.

In the rat paw oedema induced by carrageenan test, a partial inhibition was observed after intraperitoneal treatment with 100 mg/kg (Tita B *et al.* 1993) or orally 100 mg of dried 80% ethanolic extract from root/kg body weight 1 h before oedema elicitation (Mascolo N *et al.* 1987).

Extracts of *Taraxacum officinale* methanol leaf or roots exhibited inhibition of 69 and 51%, respectively, in the TPA-induced paw oedema assay in mice, while indomethacin inhibition was 96 % (Yasukawa K *et al.* 1998).

Significant inhibitory activity toward the formation of leukotriene B4 from human neutrophils, activated with calcium ionophore, was found for the butanol fraction of the aqueous methanol extract of the root of *Taraxacum officinale*, while the ethyl acetate and water fractions displayed only weak inhibitory activity (Kashiwada Y *et al.* 2001).

Water decoction from aerial parts of *Taraxacum officinale* (10 mg/kg) was orally administered, followed by 75 µg/kg cholecystokinin (CCK) octapeptide injected subcutaneously three times after 1, 3 and 5 h for 5 days. This treatment significantly decreased the pancreatic weight/body weight ratio in CCK octapeptide-induced acute pancreatitis, also increased the pancreatic levels of HSP60 and HSP72, and decreased the secretion of IL-6 and tumour necrosis factor-α (TNF-α) (Seo S-W *et al.* 2005).

The 70% ethanolic extract from dried aerial parts showed a radical-scavenging activity in the DPPH assay, a diminishing effect on intracellular reactive oxygen species (ROS) level, an anti-angiogenic activity in the chicken chorioallantoic (CAM) assay, inhibited production of exudate, and significantly diminished nitric oxide (NO) and leukocyte levels in the exudate in a carrageenan-induced air pouch model. It also possessed an inhibitory effect on acetic acid-induced vascular permeability and caused a dose-dependent inhibition on acetic acid-induced abdominal writhing in mice. Suppressive effects of the extract on the production of NO and expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) in lipopolysaccharide (LPS)-stimulated macrophages were also assessed. The authors conclude that the aerial parts of *Taraxacum officinale* present anti-angiogenic, anti-inflammatory and anti-nociceptive activities through its inhibition of NO production and COX-2 expression and/or its antioxidative activity (Jeon HJ *et al.* 2008).

The opposite effect, an increase of NO production through an increased amount of iNOS protein was observed after stimulation of mouse peritoneal macrophages with water decoction from aerial parts of *Taraxacum officinale* after the treatment with recombinant interferon-γ (rIFN-γ). The increased production of NO from rIFN-γ plus decoction-stimulated cells was decreased by treatment with a protein kinase C inhibitor staurosporin. Synergy between rIFN-γ and decoction was mainly dependent on decoction-induced TNF-α secretion (Hyung M *et al.* 1999).

Antidiabetic action

No data available for Taraxaci radix cum herba.

Powdered whole dandelion plant was suspended in 2% tragacanth gum solution and administered to rabbits p.o. In a dose of 0.5 g/kg body weight of normoglycaemic animals no effect on blood glucose was observed. Doses 1-2 g/kg body weight produced a significant lowering of blood glucose. Similar doses given to alloxan-diabetic animals failed to show any significant results (Akhtar MS *et al.* 1985).

A 20-45% inhibition of α-amylase was described for water extract from aerial parts of *Taraxacum officinale*. This effect might be associated with a positive action on diabetes mellitus Type 2 (Funke I and Melzig MF 2005).

A water infusion from not specified plant part(s) of *Taraxacum officinale* inhibited also three types of α-glucosidase (from baker's yeast, rabbit liver and rabbit intestine) – IC_{50} (mg plant/ml): 2.3, 3.5 and 1.83, respectively. For comparison, IC_{50} values for acarbose were 0.5, 0.75, and 0.25 mg/ml. The studied infusion may be a weak *in vitro* α-glucosidase inhibitor (Őnal S *et al.* 2005).

Another possible activity – insulin release from INS-1 cells *in vitro* in the presence of 5.5 mM glucose – was found for an ethanol extract from aerial parts of this plant at 40 µg/ml. This dose was significantly higher than for other samples e.g. *Artemisia roxburghiana*, *Salvia coccinia* or *Monstera deliciosa* showed insulin secretagogue activity at 1 µg/ml (Hussain Z *et al.* 2004).

Hepatoprotective action

Park *et al.* (2007) investigated the protective effect of dandelion whole plant hot water extract (DWE) on liver injury induced by carbon tetrachloride (CCl_4) in Sprague-Dawley rats. The DWE supplement significantly decreased the serum alanine and aspartate aminotransferase (ALT and AST) activity. Comparing with the CCl_4 intoxicated group, the contents of GSH peroxidase, GSH reductase and superoxide dismutase (SOD) increased dose dependent manner, and mRNA and protein expression levels of cytochrome P450 2E1 significantly decreased in the dandelion administered group. These results indicate that DWE may have a protective effect on acute liver inflammation induced by CCl_4 in rats.

In the second study the protective effect of DWE on liver injury induced by D-galactosamine in Sprague-Dawley rats was observed. The DWE intake ameliorated reactions with respect to ALT and AST as well as alkaline phosphatase and TNF-α. Hepatic enzymes (catalase, GSH peroxidase, GSH reductase, and Mn-SOD were slightly elevated. Histological findings corresponded with biochemical results (Park JY *et al.* 2008).

Effects of different mixtures of *Taraxacum officinale* (T), *Vitis vinifera* (V), *Schizandra chinensis* (S), *Gardenia jasminoides* (G) on fatty liver and hepatotoxicity induced by an ethanol liquid diet were evaluated in the male Sprague-Dawley rats model. Treatment with V+S+T or V+G+T combination decreased the levels of triglycerides, free fatty acids, and total cholesterol in the serum and liver, with a concomitant reduction in the activity of serum ALT and ALP. No conclusions on possible effects of *Taraxacum*-preparations can be drawn from these data (Kim MK *et al.* 2006).

Antiplatelet action

Ethanolic extracts of dandelion root caused a dose-dependent inhibition of ADP-induced human platelet aggregation, with a maximal inhibition of 85% observed at a concentration corresponding to 0.04 g dried root/ml of human platelet-rich plasma (PRP). Arachidonic- and collagen-induced platelet aggregation was not affected. High molecular weight fraction (M_r > 10,000) enriched in low-molecular polysaccharides showed a 91% inhibition of platelet aggregation, while a lower one (M_r < 10,000) containing triterpenes and steroids caused an 80% inhibition, both at a concentration equivalent to 0.04 g crude material/ml PRP (Neef H *et al.* 1996).

No effect on ADP-induced platelet aggregation in PRP from healthy volunteers was found for a water infusion from dandelion leaves (Saulnier P *et al.* 2005).

Antioxidative action

No data available for Taraxaci radix cum herba.

Effects of dandelion water lyophilisates on Wistar rats liver microsomes were studied (Hagymási K *et al.* 2000a). The malondialdehyde products were decreased by both folium and root extracts, in a dose-dependent manner. The folium extract exerted more effective membrane protection, (IC_{50}=0.55 mg/ml), compared with the radix extract (IC_{50}=1 mg/ml). Root and folium extracts can stimulate the NADPH-cytochrome P-450 reductase activity even without NADPH cofactor, but at a smaller rate. The folium lyophilisate proved to be more effective in both systems.

The same authors described also the hydrogen-donating ability, reducing power property and radical scavenging capacity of lyophilisates. The higher hydrogen donor, reducing agent and hydrogen

peroxide scavenger capability of the leaf extract correlates with the approximately 3 times higher polyphenol content compared to radix extract (Hagymási K *et al.* 2000b,c).

Antioxidant effects of flower, leaf, stem and root were observed for all dandelion extracts investigated by measuring liposomal lipid peroxidation induced by Fe2+ and ascorbic acid with the exception of the ethyl acetate flower extract in combination with CCl_4, the chloroform and aqueous stem extract, either alone or in combination with CCl_4, and the aqueous root extract, either alone or in combination with CCl_4. Fullerenol exhibited an anti-oxidant effect in combination with all the extracts accompanied by a decreased lipid peroxidation (Popovic M *et al.* 2001).

The same authors studied also inhibition of hydroxyl radical production by different dandelion extracts. Ethyl acetate and water extracts of dandelion flowers and aqueous dandelion stem extract were most active. Inhibitory effects were also obtained using chloroform and ethyl acetate extracts of leaf and ether, or n-butanol extracts of roots (Kaurinovic B *et al.* 2003).

A relatively high scavenging activity of DPPH radical (compared to Trolox®) of dandelion root 80 % methanol extract among 32 herbs selected was found (Wojdylo A *et al.* 2007). Low activity in ABTS and FRAP assays (Trolox® equivalents) could not be correlated to high phenolics content (12.6 gallic acid equivalent/100 g dry weight).

Peroxynitrite (10 µM) scavenging activity (measured by fluorometric dihydrorhodamine 123 oxidation) below 20% for dandelion root methanolic extract (5 µg/ml) was the weakest from 28 tested herbs (Choi HR *et al.* 2002). CCl_4 in a single dose of 1.5 ml/kg, i.p. was administrated to Albino rats of Wistar strain to produce acute hepatotoxicity. Pretreatment with 100 mg/kg (p.o.) of a suspension of 70% ethanol dandelion root extract with acacia gum improved the SOD, catalase, glutathione, and peroxidase levels significantly (Sumanth M and Rana AC 2006).

Bifidogenic action

No data available for Taraxaci radix cum herba.

The growth of six bifidobacteria strains was significantly enhanced in the medium containing dandelion root extract, while only two strains developed slightly less intensive in this medium compared to the control. The remaining six strains exhibited equivalent growth in both media. Determination of carbohydrates before and after incubation in all bifidobacterial cultures revealed 1-48% utilisation of dandelion oligofructans (Trojanová I *et al.* 2004).

Pharmacological activities of some constituents:

Taraxinic acid, an aglycone from taraxinic acid-1-O-β-D-glucopyranoside, both typical *Taraxacum* root constituents, exhibited potent antiproliferative activity against HL-60 cells. Taraxinic acid was found to be a potent inducer of HL-60 cell differentiation (Choi JH *et al.* 2002).

A high intake of chlorogenic acid may be associated with a lower risk for diabetes by decreasing carbohydrate absorption and inhibiting glucose intestinal transport (Welsch CA *et al.* 1989, Johnston KL *et al.* 2003). Chlorogenic acid also inhibits glucose-6-phosphate translocase (Hemmerle H *et al.* 1997).

Bitter principles are thought to enhance excretion from salivary and stomach glands by reflectory irritation of bitter receptors (Wagner H and Wiesenauer M 1995). 11β,13-dihydrolactucin can be quantified and correlated to its bitterness by ELISA method (Hance P *et al.* 2007). Moreover, taraxinic acid D-glucopyranoside at the dose of 80 mg/kg p.o. inhibited significantly the development of aspirin-induced gastric lesions in the rat. 70 mg/kg i.v. did not affect histamine-stimulated gastric acid secretion in the lumen-perfused rat stomach (Wu SH *et al.* 2002). The bitter taste of dandelion leaves and roots has been associated with the two sesquiterpenes taraxinic acid-D-glucopyranoside and

11β,13-dihydrotaraxinic-acid-D-glucopyranoside as well as with p-hydroxyphenylacetic acid and with β-sitosterol (Kuusi T *et al*. 1985).

Assessor's overall conclusions on pharmacology

Only pharmacological activities of root or leaves extracts are available. A theoretical mixture of both plant parts may be expected to possess all the biological activities, which are described for both parts of the plant. No quantitative data for these effects can be calculated because of unknown root:leaf ratio in real root with herb samples. However, the traditional use of preparations containing Taraxaci radix cum herba in the proposed indications can be supported.

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

No data available for Taraxaci radix cum herba.

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

Cytotoxicity

The dandelion herb water decoction caused a time-dependent and partially dose-dependent reduction of human hepatoma cell lines cell viability by 26% (Koo HN *et al.* 2004). Furthermore, in cells treated with 0.2 mg/ml extract for 48 h, maximum secretion of TNF-α and IL-1 was observed. The increased amounts of TNF-α and IL-1 contributed to dandelion decoction-induced apoptosis, which was almost completely neutralized by addition of anti-TNF-α and IL-1 antibodies. These results suggest that the decoction induced cytotoxicity through TNF-α and IL-1 secretion. As a consequence of the induced secretion of TNF-α, increased NO production from rIFN-γ primed mouse peritoneal macrophages was observed (Kim HM *et al.* 1998, Kim HM *et al.* 1999).

Screening evaluation of the effects of medicinal composition from unspecified part(s) of dandelion on the course of tumour process was carried out on mice with subcutaneously transplanted tumours (Ehrlich adenocarcinoma, Lewis lung carcinoma - LLC). The efficiency of chemotherapy with cyclophosphamide was evaluated by tumour weight, percentage of tumour growth inhibition (GI), numbers of metastases in lungs and their area, and incidence of metastasing by index of metastases inhibition (IMI). Dandelion extract did not modify the metastatic process when it was used alone (IMI = 57%, GI = 21%), but potentiated the efficiency of cytostatic therapy (IMI = 77%, GI = 30%). Effects for extract tested alone were negligible (IMI = 4%, GI = 11%). The antimetastatic activity of dandelion on LLC metastases after removal of tumour node was documented by their decrease from 100% to 67%, and number of metastatic nodes in the lungs per animal (34.4 vs. 4.1). Potentially active substances are the water soluble polysaccharides mentioned (Goldberg ED *et al.* 2004, Lopatina KA *et al.* 2007).

In another study, three aqueous extracts were prepared from the leaves, flowers and roots of *Taraxacum officinale*, and investigated on tumour progression related processes such as proliferation and invasion. The results showed that the water extract of dandelion leaf (DLE) decreased the growth of MCF-7/AZ breast cancer cells in an ERK-dependent manner (ERK = extracellular signal-regulated kinases relevant to the development of many cancer types), whereas the extracts of dandelion flower (DFE) and root (DRE) had no effect on the growth of either cell line. Furthermore, DRE was found to block invasion of MCF-7/AZ breast cancer cells while DLE blocked the invasion of LNCaP prostate cancer cells, into collagen type I. Inhibition of invasion was further evidenced by decreased phosphorylation levels of FAK and src as well as reduced activities of matrix metalloproteinases, MMP-2 and MMP-9 (Sigstedt SC *et al.* 2008).

Toxicity

No visible signs of acute toxicity were observed after oral administration of dried whole dandelion plants at 3–6 g/kg body weight in rats (Akhtar MS *et al.* 1985).

Different types of extracts demonstrated very low toxicity: fluid herb and root extract, intraperitoneal LD_{50} 28.8 and 36.6 g/kg body weight, respectively, in mice (Rácz-Kotilla E *et al.* 1974), ethanolic extracts showed very low toxicity up to doses of 10 g/kg (per os) and 4 g/kg (intraperitoneal) of dried drug -per kilogram body weight- in rats and mice (Tita B *et al.* 1993).

Hyperkalemia related issues

Under normal physiological conditions, potassium balance is maintained by mechanisms that match potassium excretion to potassium intake mainly through the kidney. In healthy adults, the serum potassium level is controlled within the narrow range of 3.5 to 5.0 mEq/l, irrespective of the dietary potassium intake. Potassium is excreted very rapidly after large intake, e.g. 200 mmol/day, when given orally with only a small increase in plasma potassium (He FJ and MacGregor GA 2008).

Hyperkalemia may occur when the regulatory mechanisms are impaired, particularly in patients with impaired renal function or in some patients with diabetes (Evans KJ and Greenberg A 2005). The development of hyperkalemia requires the concomitant malfunction at least of one of the mechanisms that maintain potassium homeostasis. The factors that can affect these homeostatic mechanisms and result in hyperkalemia can be divided into four categories:

1. decrease in kidney potassium excretion due to acute or chronic renal failure, adrenal insufficiency, burns, bleeding into gastrointestinal tract, hyporeninemic hypoaldosteronism, potassium therapy, secretion tissue injury, suppression of insulin
2. transcellular potassium movement (acute tumour lysis, exercise, hyperglycemia, hyperkalemic familial periodic paralysis, insulin deficiency, intravascular hemolysis, metabolic acidosis, rhabdomyolysis)
3. drug-induced hyperkalemia (β-blockers, ACE-I, cyclosporine, digitalis intoxication, heparin, ketoconazole, NSAIDs, pentamidine, potassium-sparing diuretics, tacrolimus, trimethoprim)

and

4. increase in potassium load - the recommended intake of potassium for healthy adolescents and adults is 4,700 mg/day. Recommended intakes for potassium for children:
   1 to 3 years of age is 3,000 mg/day,
   4 to 8 years of age is 3,800 mg/day,
   9 to 13 years of age is 4,500 mg/day (Dietary Guidelines for Americans 2005).

However, an increase in plasma potassium to levels above 5.5 mM is uncommon until over 90% of the renal function is lost and glomerular filtration rate is less than 20 ml/min. The incidence of hyperkalemia in the general population is unknown. In hospitalised patients, the incidence ranges from 1.3% to 10%. Impaired kidney function is the major risk factor for development of hyperkalemia and is present in 33% to 83% of all cases (Evans KJ and Greenberg A 2005).

In addition to renal function, there are several other factors that also influence plasma potassium, e.g. sodium-potassium ATPase, hydrogen ion balance, plasma tonicity, and plasma insulin, adrenaline, noradrenaline and aldosterone concentrations (Gennari FJ 1998). In these situations, a high potassium intake may aggravate the hyperkalemia that could result in cardiac arrhythmias.

ACE-I's are used in 10-38% of patients hospitalised with hyperkalemia (Palmer BF 2004). The risk of increased serum potassium levels reported in randomised trials of patients with congestive heart failure varies from 1.2 to 4.9% (Kober L *et al.* 1995 Kostis; JB *et al.* 1996).

Severe hyperkalemia that develops during ACE-I use is seen mainly in patients with diabetes and renal failure. The risk of hyperkalemia increases with high doses and combinations of these drugs, and this risk is further increased when an aldosterone antagonist is also added. In addition, afterload-reducing effect of ACE-Is or A-II R blockers may contribute to the development of hyperkalemia in patients with heart failure (Palmer BF 2004).

According to the guidelines for the diagnosis and treatment of chronic heart failure, potassium levels should be < 5 mmol/l to warrant the addition of potassium-sparing diuretic spironolactone to standard treatment in patients with heart failure. Caution is advised in patients with abnormal renal function and diabetes mellitus with hyporeninemic hypoaldosteronism because severe hyperkalemia may ensue (Khan MG 2003).

Cardiac glycosides are indicated in atrial fibrillation and any class of symptomatic heart failure. Hyperkalemia depolarizes the myocytes and strengthens the suppressive effect of digoxin on the atrioventricular node (Macdonald JE and Struthers AD 2004).

Hyperkalemia may be due to digitalis toxicity, and it is believed to result from inhibition of the Na+-K+ ATPase enzyme by digitalis (Khan MG 2003).

Patients with heart failure are at high risk of thromboembolic events. Heparin can cause hyperkalemia by blocking the synthesis of aldosterone. However, severe hyperkalemia occurs in the presence of additional factors affecting potassium homeostasis. While the principle of the treatment is to discontinue the heparin, it is first recommended to discontinue other potassium-elevating drugs (ACE-I, spironolactone) if heparin therapy is vital (Day JRS *et al.* 2002).

Diabetes is a well known condition that increases the risk of hyperkalemia. Extracellular potassium is taken up intracellularly by insulin action. In diabetes in which the insulin action is insufficient or deficient, the serum potassium level increases (Jarman PR *et al.* 1995; Ahuja TS *et al.* 2000). Additionally, about 40% of patients with type 1 or type 2-diabetes will develop some level of renal impairment (Gross JL *et al.* 2005).

519 mg/l of potassium were found in an infusion prepared by using 5 g of dandelion leaves from Spain in 200 ml of water at 70°C during 2 hrs (Queralt I *et al.* 2005).

Under the proposed posology of dandelion herb and root, a high daily intake of potassium might be possible even though the exact potassium content in dandelion herbal preparations (dry extracts prepared with an aqueous ethanol, expressed fresh juice or comminuted dried herbal substance) is not known. This intake may represent a substantial part of the recommended intake for healthy adolescents and adults, children 1 to 3 years of age, children 4 to 8 years of age, and children 9 to 13 years of age, calculated for limits in Dietary Guidelines for Americans 2005. In the case of hyperkalemia, taking in account the relatively slow (6-12 hours) complete excretion of an oral potassium load (Dietary Guidelines for Americans 2005), above mentioned high daily potassium intake could cause a relevant elevation of serum potassium concentration. This could lead to harmful complications in patients with renal failure and/or diabetes, and/or heart failure. Concomitant dandelion tea drinking and treatment with e.g. β-blockers, ACE-I, cyclosporine, digitalis therapy, heparin, ketoconazole, NSAIDs, pentamidine, potassium-sparing diuretics, tacrolimus or trimethoprim should be avoided.

Assessor's overall conclusions on toxicology

Reliable data on acute toxicity are only available for whole crude drug and some extracts. Oral administration of preparations from Taraxaci radix cum herba can be regarded as safe at traditionally used doses with the exception of patients with renal failure and/or diabetes, and/or heart failure. In those conditions, the use should be avoided because of possible complications due to hyperkalemia.

Although toxicological data on dandelion are very limited, neither the European traditional use nor known constituents suggest that there is any risk associated with the use of dandelion root and herb. Due to the lack of data on genotoxicity, mutagenicity, carcinogenicity, reproductive and developmental toxicity, a list entry for Taraxaci radix cum herba cannot be recommended.

4. Clinical Data

Clinical studies could not been found. Therefore only the use as a traditional herbal medicinal product is proposed.

4.1. Clinical Pharmacology

No specific data are available.

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

No specific data are available.

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

No specific data are available.

4.2. Clinical Efficacy

No studies for clinical efficacy were found.

The following medicinal uses have been consistently reported in European handbooks:
Herbal tea for the stimulation of diuresis and in digestive disorders is often mentioned without any clinical data (Wichtl M 1984, Hänsel R 1991, Kubelka W and Länger R 1996, Hänsel R and Sticher O 2007).

4.2.1. Dose response studies

There are no dose response studies available.

4.2.2. For information on posology and duration of use, see section 2.3.Clinical studies (case studies and clinical trials)

No published data available.

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

No published data available.

4.3. Overall conclusions on clinical pharmacology and efficacy

The well established use cannot be supported, because no clinical studies were found.

The traditional use of *Taraxacum officinale* Weber ex Wigg., radix cum herba, as a comminuted herbal drug, herbal tea, juice or hydroalcoholic extract, for the relief of symptoms related to mild digestive disorders and temporary loss of appetite and to increase the amount of urine to achieve flushing of the urinary tract as an adjuvant in minor urinary complaints is well documented in a number of handbooks. The traditional use is supported by pharmacological data.

5. Clinical Safety/Pharmacovigilance

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

No specific data are available.

5.2. Patient exposure

No data available.

5.3. Adverse events and serious adverse events and deaths

A 52-year-old woman with a 13-year history of episodes of erythema multiforme (EM), after contact with weeds during home gardening, had had no recent history of herpes simplex, other infection, drug ingestion or vaccination. On examination, EM lesions were distributed on the exposed skin. Eczematous patch tests reactions were obtained with fresh dandelion leaves. Also photoaggravation was seen to dandelion. Neither blistering nor eczematous lesions have been seen on her skin, making this case very unusual (Jovanović M *et al.* 2003).

Anaphylaxis and pseudoallergic contact dermatitis is possible due sesquiterpene lactones, e.g. taraxinic acid D-glucopyranoside (Hausen BM 1982, Zeller W *et al.* 1985, Lovell CR and Rowan M 1991, Fernandez C *et al.* 1993, Hausen BM and Vieluf IK 1997, Mark KA *et al.* 1999).

Serious adverse events and deaths

No data available.

5.4. Laboratory findings

No data available.

5.5. Safety in special populations and situations

Intrinsic (including elderly and children) /extrinsic factors

No data available.

Drug interactions

None known. Theoretically, patients on lithium therapy who use herbal preparations with diuretic action (e.g. dandelion) may experience dehydration and resulting lithium toxicity (Harkness R and Bratman S 2003).

Use in pregnancy and lactation

No data available. In accordance with general medical practice, the product should not be used during pregnancy or lactation without medical advice.

Overdose

No toxic effects have been documented.

Drug abuse

No data available.

Withdrawal and rebound

No data available.

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

No data available.

Contraindications

Due to the stomach-gastro reflection stimulation of bitter ingredients, products containing *Taraxacum* root cum herba must not be used in case of active peptic ulcer disease (Bisset NG 1994).

Hypersensitivity to the active substance(s) or to plants of the Asteraceae (Compositae) family.

5.6. Overall conclusions on clinical safety

Clinical safety data are limited. However, up to now no serious side effects have been reported. Furthermore the chemical composition of dandelion does not give reasons for safety concerns, apart those mentioned in section 3.3.

As there is no information on reproductive and developmental toxicity the use during pregnancy and lactation cannot be recommended.

Data on use in children or adolescents are not available.

6. Overall conclusions

The positive effects of Taraxaci radix cum herba for the relief of symptoms related to mild digestive disorders such as feeling of abdominal fullness, flatulence and slow digestion and for diuresis stimulation have long been recognised empirically. There are no data available from clinical studies using relevant herbal preparations.

As medicinal use has been consistently documented in many handbooks, preparations from Taraxaci radix cum herba identified in the monograph fulfil the requirements of Directive 2004/24 EC for use in traditional herbal medicinal products. Their use in above-mentioned disorders is considered plausible on the basis of bibliography and pharmacological data. Some preparation types were not found in use, only mentioned in books.

The diuretic action of preparations from Taraxaci radix cum herba may be associated with the high kalium content and with certain flavonoids, although no studies confirm this hypothesis. Bitter principles (sesquiterpenoids) may be responsible for the stimulation of digestive fluids in stomach and bile flow stimulation.

Reliable data on acute toxicity are only available for whole crude drug and some extracts. Oral administration of preparations from Taraxaci radix cum herba can be regarded as safe at traditionally used doses with the exception of patients with renal failure and/or diabetes, and/or heart failure. Although toxicological data on dandelion are very limited, neither the European traditional use nor known constituents suggest that there is a potential risk associated with the use of dandelion root and herb. Due to the lack of data on genotoxicity, mutagenicity, carcinogenicity, reproductive and developmental toxicity, a list entry for Taraxaci radix cum herba cannot be recommended.

Well-established use cannot be supported, as no clinical studies were found.

The traditional use of *Taraxacum officinale* Weber ex Wigg., radix cum herba, as a comminuted herbal substance (herbal tea), juice or hydroalcoholic extract, for the relief of symptoms of mild digestive disorders and for temporary loss of appetite and to increase the amount of urine to achieve flushing of the urinary tract as an adjuvant in minor urinary complaints is well documented in a number of handbooks.

Taraxaci radix cum herba preparations can be regarded as traditional herbal medicinal products.

There are no clinical safety data on extracts of Taraxaci radix cum herba. In the documentation of the traditional medicinal use within the European Union no serious adverse effects have been reported.

Due to lack of data, Taraxaci radix cum herba preparations cannot be recommended for children and adolescents below the age of 12 years, in pregnancy and lactation and must not be used in case of obstructions of bile ducts, cholangitis, liver diseases, gallstones, active peptic ulcer and any other biliary diseases. Hypersensitivity to the Asteraceae sesquiterpene lactones or other active substances from Taraxaci radix cum herba is also regarded as contraindication.

Pharmacotherapeutic groups

Preparations for the relief of symptoms related to mild digestive disorders (such as feeling of abdominal fullness, flatulence, and slow digestion) and temporary loss of appetite - ATC level A03.

Preparations for the diuresis enhancement - ATC level C03

Annex

List of references