EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Taraxacum officinale* Weber ex Wigg., folium

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., folium
Herbal preparation(s)	Dried leaves, comminuted Liquid extract (DER 1:1), extraction solvent ethanol 25% V/V Expressed juice from fresh leaves
Pharmaceutical forms	Herbal preparations in liquid dosage forms for oral use. Comminuted herbal substance as herbal tea for oral use.
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1. Introduction

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

- Herbal substance(s)

Dandelion leaf consists of the dried leaves of *Taraxacum officinale* Weber, Compositae, collected before flowering (Bradley PR 1992).

Dandelion leaf consists of the dried leaves of *Taraxacum officinale* Weber collected before flowering (British Herbal Pharmacopoeia 1996).

Dandelion leaf consists of the dried leaves of *Taraxacum officinale* Weber *s.l.*, collected before the flowering period (ESCOP monographs 2003).

Constituents

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 as well as p-hydroxyphenylacetic acid were detected in leaves extract. 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 (Kuusi T *et al.* 1985; 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 extracts prepared in a 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., Roddick K. 1981) and β- sitosterol (Kuusi *et al.* 1985) also were found.

Two sesquiterpenes, taraxinic acid-*D*-glucopyranoside and 11β,13-dihydrotaraxinic-acid-*D*-glucopyranoside were also found (Kuusi *et al.* 1985).

T. officinale leaves contain a high potassium concentration. In a three-year experiment values between 30.37 and 47.73 mg potassium/g of herbal substance 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/g were determined by wavelength-dispersive x-ray fluorescence method. So, potassium exhibits a high degree of solubility in infusion – approximately 67% (Queralt I *et al.* 2005).

- Herbal preparation(s)

  a) dried leaves (British Herbal Pharmacopoeia 1996)

  b) liquid extract (1:1) extraction solvent ethanol 25% (V/V) (British Herbal Pharmacopoeia 1996)

  c) 5-10 ml of juice from fresh leaf, twice daily (British Herbal Compendium 1992).

- 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.

No mono-preparations from Taraxaci folium or its combinations with other herbal substances/herbal preparations are currently registered or authorised in Europe. This report discusses Taraxaci folium only.

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

Regulatory status overview

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

MA: Marketing Authorisation

TRAD: Traditional Use Registration

Other TRAD: Other national Traditional systems of registration

Other: If known, it should be specified or otherwise add 'Not Known'
This regulatory overview is not legally binding and does not necessarily reflect the legal status of the products in the MSs concerned.

1.3. Search and assessment methodology

The electronic databases of Pubmed, Scopus and International Pharmaceutical Abstracts were searched with the search terms 'Taraxacum officinale' combined with 'human', 'clinical trial' , 'Randomised Controlled Trial' and 'Review'.

2. Historical data on medicinal use

2.1. Information on period of medicinal use in the Community

The monograph Taraxaci folium is discussed in HagerROM 2006. However, the synonyms Taraxaci herba and Herba taraxaci (according German Commission E - Blumenthal M *et al.* 1998) are mentioned, too. In the later reference, dandelion herb consists of the fresh or dried above-ground parts of *Taraxacum officinale* G. H. Weber ex Wigg. s.l. (Asteraceae) – without any collection time specified. So, this drug may theoretically contain also flower and stem from the plant (= herb). This confirms the macroscopic analysis of dandelion herb described in a handbook (Wichtl 1984). So, both references (Blumenthal M *et al.* 1998, HagerROM 2006) do not describe **explicitly** leaf drug from dandelion. In this relation, no clear separation of literature data for dandelion herb and/or leaf as herbal substance can be done.

Three preparations from Taraxaci folium could be found in literature. A period of at least 30 years in medical use as requested by Directive 2004/24 EC for qualification as a traditional herbal medicinal product is fulfilled for Taraxaci folium.

In parallel to the medicinal use, dandelion inflorescences, leaves and roots are processed into different food products. Young leaves of cultivated or wild species are consumed fresh as salad. Additionally, extracts are used as flavour components in various food products, including alcoholic beverages and soft drinks, frozen dairy desserts, candy, baked goods, gelatins and puddings and cheese (Rivera-Núňez 1991; Leung and Foster 1996).

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 folium:

As an adjunct to treatments where enhanced urinary output is desirable, e.g. rheumatism and the prevention of renal gravel (Weiss RF 1991).

Water retention due to various causes, insufficient production of bile (Bradley PR 1992).

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

Evidence regarding the specified posology

Dried leaves daily 4-10 g or by infusion; Liquid extract (1:1), extraction solvent ethanol 25% (V/V), 4-10 ml (British Herbal Pharmacopoeia 1976).
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 folium preparations in the recommended traditional indications.

Evidence regarding the duration of use

No restriction on the duration of use has been reported for Taraxaci folium. As clinical safety studies are lacking, the duration of use is limited to 2 weeks.

Assessor's overall conclusion on the traditional medicinal use

Preparations from Taraxaci folium have been used for diuresis stimulation. 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

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

The diuretic action of aqueous extracts obtained from dandelion leaves was reported to be more pronounced 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). In another study, an even higher potassium content – 4.89% – was determined (Hook I *et al.* 1993).

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

Choleretic action

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

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

Anti-inflammatory action

Extract of *Taraxacum officinale* methanol leaf exhibited a 69% inhibition, in the TPA-induced paw oedema assay in mice, while inhibition by indomethacin was 96% (Yasukawa K *et al.* 1998).

Per os (p.o.) administration of a decoction from aerial parts of *Taraxacum officinale* (10 mg/kg), followed by 75 µg/kg cholecystokinin (CCK) octapeptide injected subcutaneously three times after 1, 3 and 5 h for 5 days significantly decreased the pancreatic weight/body weight ratio in CCK octapeptide-induced acute pancreatitis. The treatment 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).

An ethanolic extract (ethanol 70%) from dried aerial parts produced a radical-scavenging activity in the DPPH assay, a diminishing effect on intracellular reactive oxygen species (ROS) level, and an anti-angiogenic activity in the chicken chorioallantoic (CAM) assay. In a carrageenan-induced air pouch model the extract inhibited production of exudate, and significantly diminished nitric oxide (NO) and leukocyte levels in the exudate. 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 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 aerial parts of *Taraxacum officinale* may 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 inducible NO synthase protein was observed after stimulation of mouse peritoneal macrophages with water decoction from the aerial parts of *Taraxacum officinale* after the treatment of 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 tumour necrosis factor-α secretion (Hyung M *et al.* 1999).

Antidiabetic action

A water extract from aerial parts of *Taraxacum officinale* is reported to inhibit α-amylase by 20-45 %. This effect might be associated with possible positive action on diabetes mellitus Type 2 (Funke I and Melzig MF 2005).

A water infusion from a non-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 infusion may be a weak *in vitro* α-glucosidase inhibitor (Őnal S *et al.* 2005).

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

Antiplatelet action

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

Antioxidative action

Effects of dandelion water lyophilisates on Wistar rats liver microsomes were studied (Hagymási K *et al.* 2000a). The malondialdehyde products were decreased by folium extracts, in a dose-dependent manner. The extract from leaves exerted a more effective membrane protection, (IC_{50}=0.55 mg/ml), compared with the root extract (IC_{50}=1 mg/ml). Root and leaf extracts did stimulate the NADPH-cytochrome P-450 reductase activity even without NADPH cofactor, but at a smaller rate. The lyophilisate from leaves 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 extract from leaves correlates with the approximately 3 times higher polyphenol content as compared to extract from roots (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 Fe^{2+} and ascorbic acid, with the exception of the ethyl acetate extract from flowers, in combination with CCl_4, the chloroform and aqueous extract from stems, either alone or in combination with CCl_4, and the aqueous extract from roots, 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 inhibition of hydroxyl radical production by different dandelion extracts. Pronounced inhibitory effects were obtained using chloroform and ethyl acetate extracts of leaves (Kaurinovic B *et al.* 2003).

Pharmacological activities of some constituents

Taraxinic acid (an aglycone from taraxinic acid-1-O-β-D-glucopyranoside), exhibited antiproliferative activity in HL-60 cells. This compound was found to be an inducer of HL-60 cell differentiation. These results may suggest that taraxinic acid induces the differentiation of human leukemia cells to monocyte/macrophage lineage (Choi JH *et al.* 2002).

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

Bitter principles are reported to enhance excretion from salivary and stomach glands by reflectory irritation of bitter receptors (Wagner H and Wiesenauer M 1995). 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 and at 70 mg/kg i.v. did not affect histamine-stimulated gastric acid secretion in the lumen-perfused rat stomach (Wu SH *et al.* 2002). As in roots, the bitter taste of dandelion leaves has been associated with the two sesquiterpenes taraxinic acid-*D*-glucopyranoside and 11β, 13-dihydrotaraxinic-acid-*D*-glucopyranoside as well as p-hydroxyphenylacetic acid and β-sitosterol (Kuusi T *et al*. 1985).

Assessor's overall conclusions on pharmacology

Pharmacological activities of leaves extracts contribute to support the traditional use of preparations containing Taraxaci folium in the proposed indication.

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

No data available.

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

Cytotoxicity

The effects of unspecified part(s) of dandelion on tumours was investigated in mice with subcutaneously transplanted tumours (Ehrlich adenocarcinoma, Lewis lung carcinoma - LLC). The effects of chemotherapy with cyclophosphamide was evaluated by tumour weight, percentage of tumour growth inhibition (GI), number of metastases in lungs and their area, and incidence of

metastasing by index of metastases inhibition (IMI). Dandelion extract did not modify metastatic process when it was used alone (IMI = 57%, GI = 21%), but increased the efficiency of cytostatic therapy (IMI = 77%, GI = 30%). Effects for extract without cyclophosphamide were negligible (IMI = 4%, GI = 11%). In the LLC model, dandelion extract decreased the number of animals with metastases from 100% to 67%, and the number of metastatic nodes in the lungs per animal from 34.4 to 4.1. Water soluble polysaccharides were identified as potentially active substances (Goldberg ED *et al.* 2004, Lopatina KA *et al.* 2007).

In another study, aqueous extract was prepared from the leaves 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 many cancers types development). Furthermore, dandelion root extract 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 identified after oral administration of 3–6 g/kg body weight dried whole dandelion plants in rats (Akhtar MS *et al.* 1985).

Different types of extracts presented low toxicity when administered: a fluid herb and root extract showed intraperitoneal LD_{50} of 28.8 and 36.6 g/kg body weight, respectively, in mice (Rácz-Kotilla E *et al.* 1974), ethanolic extracts up to doses 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-Is, 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, and 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.

The ACE-Is 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 (HF) varies from 1.2 to 4.9% (Kober L *et al.* 1995; Kostis; JB *et al.* 1996).

Severe hyperkalemia that develops during ACE-Is therapy 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 HF (Palmer BF 2004).

According to the guidelines for the diagnosis and treatment of chronic HF, potassium levels should be < 5 mmol/l to warrant the addition of potassium-sparing diuretic spironolactone to standard treatment in patients with HF. 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 HF. 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 HF 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-Is, 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).

For the proposed posology – up to 10 g of dandelion leaves, 3 times daily as tea (British Herbal Pharmacopoeia 1976) – the daily intake up to 3114 mg of potassium could be possible. This intake represents about 66% of the recommended intake for healthy adolescents and adults, 103% for children 1 to 3 years of age, 82% for children 4 to 8 years of age, and 69% for 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 hrs) complete excretion of an oral potassium load (Dietary Guidelines for Americans 2005), the above mentioned high daily potassium intake could cause an expressive elevation of serum potassium concentration. This could lead to harmful complications of patients with renal failure and/or diabetes, and/or heart failure. Concomitant dandelion tea drinking and treatment with e.g. β-blockers, ACE-Is, cyclosporine, digitalis therapy, heparin, ketoconazole, NSAIDs, pentamidine, potassium-sparing diuretics, tacrolimus or trimethoprim should be avoided. The potassium content in other dandelion herbal preparations (extracts prepared with an aqueous ethanol extractant, expressed fresh juice or comminuted dried drug) is not known, therefore the same intake restrictions should be realised for all above-mentioned situations.

3.4. Overall conclusions on non-clinical data

Reliable data on acute toxicity are only available for whole crude drug and some extracts. Oral administration of preparations from Taraxaci folium can be regarded as safe at traditionally used doses with the exception of patients with renal failure and/or diabetes, and/or heart failure. Toxicological data on dandelion are very limited, but neither the European traditional use nor known constituents suggest that there is a potential serious risk associated with the dandelion leaves use. Due to the lack of data on genotoxicity, mutagenicity, carcinogenicity, reproductive and developmental toxicity, a list entry for Taraxaci folium 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 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.

4.2.1. Dose response studies

There are no dose response studies available.

For information about posology and duration of use, see section 2.3.

4.2.2. 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

In absence of clinical studies well established use cannot be supported.

The traditional use of *Taraxacum officinale* Weber ex Wigg., folium, as a herbal tea or hydroalcoholic extract, or juice for the increase of the amount of urine to achieve flushing of the urinary tract as an adjuvant in minor urinary complaints is documented in handbooks. The traditional use is supported by some 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

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

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).

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 activity (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 case of overdose has 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

Occlusion of the bile ducts, gall-bladder empyema, obstructive ileus (Weiss RF 1991).

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 almost lacking. 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 folium for the diuresis stimulation (increase the amount of urine to achieve flushing of the urinary tract as an adjuvant in minor urinary complaints) have long been recognised empirically. There are no data available from clinical studies using herbal preparations containing Taraxaci folium.

Its medicinal use has been documented in relevant handbooks. Taraxaci folium preparations fulfil the requirements of Directive 2004/24 EC for use in traditional herbal medicinal products. Their use in the above-mentioned disorder is considered plausible on the basis of bibliography and pharmacological data.

The diuretic action of preparations from Taraxaci folium may be associated with high potassium content.

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

In absence of clinical studies, a well-established use cannot be supported.

The traditional use of *Taraxacum officinale* Weber ex Wigg., folium, as a herbal tea or hydroalcoholic extract, or juice for the increase of the amount of urine to achieve flushing of the urinary tract as an adjuvant in minor urinary complaints is sufficiently documented in handbooks.

Taraxaci folium preparations can be regarded as traditional herbal medicinal products.

There are no clinical safety data on extracts of Taraxaci folium. 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 folium 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 folium is also regarded as a contraindication.

Pharmacotherapeutic group

Preparations for the diuresis enhancement – ATC level C03.

Annex

List of references