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Assessment report on *Taraxacum officinale* F.H. Wigg., radix

Draft

Based on Article 16d(1), Article 16f and Article 16h of Directive 2001/83/EC as amended (traditional use)

Herbal substance(s) (binomial scientific name of the plant, including plant part)	Taraxaci officinalis radix
Herbal preparation(s)	a) Comminuted dried root b) Expressed juice (DER 1:1) from fresh root boiled in ethanol c) Juice from fresh root d) Liquid extract (DER 1:1), extraction solvent ethanol 30% (V/V) e) Tincture (ratio of herbal substance extraction solvent 1:5), extraction solvent ethanol 45% (V/V)
Pharmaceutical form(s)	Herbal preparations in liquid dosage form for oral use. Comminuted herbal substance as herbal tea for oral use.
Rapporteur(s)	M Nagy
Peer-reviewer	M Heroutová

Note: This draft assessment report is published to support the public consultation of the draft European Union herbal monograph on *Taraxacum officinale* F.H. Wigg., radix. It is a working document, not yet edited, and shall be further developed after the release for consultation of the monograph. Interested parties are welcome to submit comments to the HMPC secretariat, which will be taken into consideration but no 'overview of comments received during the public consultation' will be prepared on comments that will be received on this assessment report. The publication of this draft assessment report has been agreed to facilitate the understanding by Interested Parties of the assessment that has been carried out so far and led to the preparation of the draft monograph.

Official address Domenico Scarlattilaan 6 • 1083 HS Amsterdam • The Netherlands

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1. Introduction

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

- Herbal substance(s)

Taraxaci officinalis radix is described in the European Pharmacopoeia 10.2 (1852) as follows:

Whole or cut, dried underground parts of *Taraxacum officinale* F.H. Wigg.

Identification according European Pharmacopoeia (simplified): The dark brown or blackish taproot shows little branching and is deeply wrinkled longitudinally on the outer surface. The thickened crown shows many scars left by the rosette of leaves. The fracture is short. A transverse section shows a greyish-white or brownish cortex containing concentric layers of brownish laticiferous vessels and a porous, pale yellow, non-radiate wood.

Reduce to a powder. The powder is yellowish-brown. Examine under a microscope using chloral hydrate solution. The powder shows the following diagnostic characters: fragments of brown or reddish-brown cork, in surface view and transverse section with flattened, thin-walled cells, sometimes accompanied by parenchyma; reticulate lignified vessels fragments of parenchyma, some containing branched laticiferous vessels, in longitudinal section and transverse section; granular contents of laticiferous vessels. Examine under a microscope using glycerol. The powder shows numerous irregular, angular inulin fragments, free or included in the parenchyma cells.

Constituents:

Sesquiterpenic lactones

1. Eudesmanolide type: $4\alpha,11\beta$, 13,15-tetrahydroridentin B and taraxacolide-*O*-glucopyranoside (Hänsel *et al.* 1980),
2. Guaianolide type: $11\beta,13$ -dihydrolactucin and ixerin D (Kisiel and Barszcz 2000),
3. Germacranolide type: taraxinic acid D-glucopyranoside, its $11\beta,13$ -dihydro-derivative and aglycone (taraxinic acid), and ainslioside (Hänsel *et al.* 1980, Kuusi *et al.* 1985, Kisiel and Barszcz 2000).

Sterols and triterpenes

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 and Simpson 1938, Hänsel *et al.* 1980, Akashi *et al.* 1994).

Triterpenic 3β -hydroxylup-18(19)-ene-21-one in fresh roots (Kisiel and Barszcz 2000). Recently, five new triterpenoids (3β -acetoxy- $18\alpha,19\alpha$ -epoxylupan-21 β -ol, $18\alpha,19\alpha$ -epoxy-21 β -hydroxylupan-3-one, lup-18-ene-3,21-dione, lupa-18,21-dien-3 β -yl acetate, and (17*S*)-17,18-seco-lup-19(21)-ene-3,18,22-trione = officinatrione) were described (Saeki *et al.* 2013). Subsequently, beside officinatrione, nine triterpenoids were isolated from roots: $18\beta,19\beta$ -epoxy-21 β -hydroxylupan-3 β -yl acetate, 21-oxolup-18-en-3 β -yl acetate, betulin, 11α -methoxyolean-12-en-3-one, eupha-7,24-dien-3-one, 24-oxoeupha-7,24-dien-3 β -yl acetate, $18\beta,19\beta$ -epoxy-21 β -methoxylupan-3 β -yl acetate, 3β -acetoxybauer-7-en-6-one, and 3β -acetoxyeupha-7,24-dien-6-one (Kikuchi *et al.* 2016).

Phenolics

Chicoric acid and its isomer; monocaffeoyltartaric, 4-caffeoylquinic, chlorogenic, caffeic, *p*-coumaric,

ferulic, *p*-hydroxybenzoic, protocatechuic, vanillic, syringic and *p*-hydroxyphenylacetic acids, coumarins (umbelliferone, esculetin, scopoletin), benzyl-*O*- β -glucopyranoside, dihydroconiferin and a mixture of syringin and dihydrosyringin (Clifford *et al.* 1987, Williams *et al.* 1996, Kisiel and Barszcz 2000).

p-Hydroxyphenylacetic acid (Kuusi *et al.* 1985) and its derivative β -*O*-[4-*O*-(*p*-hydroxyphenylacetyl)]- β -D-glucopyranosyl]- β -hydroxy- γ -butyrolactone (Rauwald and Huang 1985) are also present. Five *di*-4-hydroxyphenylacetate inositol derivatives and three *tri*-4-hydroxyphenylacetate inositol ones with different stereochemical inositol core (*chiro*-inositol, *scyllo*-inositol, *neo*-inositol and *muco*-inositol) were isolated (Kenny *et al.* 2014). Recently, as major ester derivative of inositol, 1,5-*di*-4-hydroxyphenylacetate inositol was characterized beside further, by high resolution mass spectrometry detected, *di*- and *tri*- esters of inositol (Huber *et al.* 2015).

Eight flavone and eight flavonol glycosides were extracted from a dandelion root and characterized by high-performance liquid chromatography /electrospray ionization mass spectrometry: luteolin-7-*O*-glucoside, luteolin-4'-*O*-glucoside, luteolin-7-*O*-rutinoside, as well as unknown five quercetin diglycosides, three triglycosides and one pentaglycoside, three unknown luteolin diglycosides and one triglycoside, and chrysoeriol diglycoside (Schütz *et al.* 2005). In contrast to Hörhammer and Wagner (1962) neither apigenin 7-*O*-glucoside nor other apigenin derivatives were detected in the dandelion root investigated.

Polysaccharides

Inulin contents of roots range from 2% in spring to 40% in autumn (Bisset *et al.* 1994). Two new polysaccharides were isolated and their preliminary structures were proposed (Cai *et al.* 2017): DRP1 was mainly composed of glucose, galactose and arabinose, while DRP2 was mainly composed of rhamnose, glucuronic acid, glucose, galactose and arabinose. The average molecular weights of DRP1 and DRP2 were determined to be 5695 Da and 8882 Da, respectively. The backbone of DRP1 was mainly composed of (1 \rightarrow 6) linked- α -D-Glc and (1 \rightarrow 3,4)-linked- α -D-Glc, and DRP2 was mainly composed of (1 \rightarrow)-linked- α -D-Ara and (1 \rightarrow)-linked- α -D-Glc.

Inorganics

Average root ash was 7.50% w/w; mean root potassium content was 2.45% w/w, mean root sodium contents was 0.33% w/w; while value for calcium in root was 0.33% w/w (Hook *et al.* 1993).

- Herbal preparation

Comminuted herbal substance

Expressed juice (DER 1:1) from fresh root boiled in ethanol.

Juice from fresh root

Liquid extract (DER 1:1), extraction solvent ethanol 30% (V/V).

Tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent ethanol 45% (V/V).

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

See Section 2.1.1. *Taraxaci officinalis radix* is used in many combinations with many other herbal substances/herbal preparations. The European Union herbal monograph EMA/HMPC/475726/2020 refers exclusively to *Taraxaci officinalis radix*.

1.2. Search and assessment methodology

This assessment report is based on the data search for “*Taraxaci officinalis radix*”. Call for data started on 1.3.2020 and ended on 31.5.2020. The results of a literature search in medical and scientific databases (Scopus, Web of Science, PubMed, Embase, MEDLINE, Cochrane Database of Systematic Reviews, HealLink, ToxNet, Micromedex, HerbMed, Central Register of Controlled Trials) was performed in June 2020 using the following logical terms: ((*Taraxacum officinale*) OR (*Taraxaci radix*) OR (dandelion) OR (dandelion root) AND ((human) OR (clinical) OR (pharmacolog*) OR (pharmacokinetic) OR (toxicolog*) OR (safety) OR (composition) OR (constituent*) OR (extract*) OR (preparation*)) AND (time period from January 1985-March 2021). Also analogical search with these logical terms equivalents in all official languages in EU member states was performed. 85 articles on “root/radix” of *Taraxacum officinale* F.H. Wigg. were found, evaluated and included in this assessment report and in the relevant reference list, too.

Pharmacovigilance resources: EudraVigilance database search on 12 August 2020, active substance (high level): contain *Taraxacum officinale* root, *Taraxaci radix*, Dandelion root. 12 cases retrieved.

2. Data on medicinal use

2.1. Information about products on the market

2.1.1. Information about products on the market in the EU/EEA Member States

The information is mainly based on data obtained from the National Competent Authorities on documents on information exchange (EMA/HMPC/137093/2006 rev.2).

In February 2020 a request was sent for information on marketed products containing *Taraxaci officinalis radix* to the member states.

Information on medicinal products marketed in the EU/EEA

Table 1: Overview of data obtained from marketed medicinal products

Active substance	Indication	Pharmaceutical form Strength (where relevant) Posology Duration of use	Regulatory Status (date, Member State)
<i>Taraxaci radix</i> , comminuted herbal substance	Cholagogue in indigestion and as a mild diuretic.	Herbal tea, decoction. 3 g for 200 ml. Adults and adolescents from 12y: Drink the prepared decoction 3 times a day. Duration not	19.04.2003, PL

Active substance	Indication	Pharmaceutical form Strength (where relevant) Posology Duration of use	Regulatory Status (date, Member State)
		limited.	
Taraxaci radicis succus stabilised The product contains expressed juice (DER 1:1) from fresh root boiled in ethanol.	Traditionally used for indigestion, lack of appetite and incidentally as a mild diuretic.	Oral liquid. Adults and adolescents from 12y: Dosage 5 ml of product, diluted in small amount of water, 3 times a day.	08.12.1987, PL
Dandelion Root Dry Extract, DER 3-5:1, Extraction solvent: Ethanol 60% (V/V)	A traditional herbal medicinal product used to relieve the symptoms of mild digestive disorders, such as dyspepsia and flatulence and temporary loss of appetite; increase the amount of urine for the purpose of flushing the urinary tract to assist in minor urinary complaints, based on traditional use only	Capsule, hard. Adults and the elderly: one capsule twice a day.	07.11.2011, UK

This overview is not exhaustive. It is provided for information only and reflects the situation at the time when it was established.

Information on relevant combination medicinal products marketed in the EU/EEA

Taraxaci officinalis radix is used in combinations with other herbal substances / herbal preparations: in mild dyspepsia (such as feeling of abdominal fullness, flatulence) and loss of appetite. Typical examples of such combination partners are: *Acorus calamus* L., rhizoma, *Angelica archangelica* L., radix, *Artemisia absinthium* L., herba, *Cinnamomum verum* J.S. Presl, cortex, *Commiphora molmol* Engler, gummi-resina (myrrh), *Curcuma zedoaria* (Christm.) Roscoe, rhizoma, *Elettaria cardamomum* (L.) Maton, fructus, *Gentiana lutea* L., radix, *Juglans regia* L., folium, *Marubium vulgare* L., herba, *Potentilla erecta* (L.) Raeusch., rhizoma, and *Valeriana officinalis* L., radix.

Information on other products marketed in the EU/EEA (where relevant)

Not applicable

2.1.2. Information on products on the market outside the EU/EEA

Not applicable.

2.2. Information on documented medicinal use and historical data from literature

The following indications have been reported for *Taraxaci officinalis radix*: diuretic, hepatic tonic, in progressive cirrhosis, liver injury caused by hepatotoxic compounds, disturbance of biliary flow, dyspeptic complaints, loss of appetite, in achylia, cholecystitis, gall-stones, jaundice, atonic dyspepsia with constipation, muscular rheumatism, oliguria (see Table 2 below).

Table 2: Overview of historical data

Herbal preparation	Documented use / Traditional use	Pharmaceutical form Strength (where relevant) Posology Duration of use	Reference
Extractum Taraxaci (expressed fresh root)	Diuretic and feebly hepatic tonic	n/a	Southall (1900, reprinted 2013)
Cut or powdered herbal substance	In diseases of the liver with reduced bile production, in progressive cirrhosis, liver injury caused by hepatotoxic compounds. Also in diseases of the biliary tract, especially its smooth muscle atony or spasms. In addition, in renal failure, edema, also in achylia [lack of gastric juice] and the digestive disorders caused by it.	A decoction of a tablespoon* of roots for 1-1.5 glass** of warm water, slowly heat to boil, boil for exactly 5 minutes, leave for 10 minutes, strain. Drink half a glass of the decoction 2 - 3 times a day, 10 - 15 minutes before meals.	Ożarowski <i>et al.</i> (1978)
Cut or powdered herbal substance	Cholecystitis, gall-stones, jaundice, atonic dyspepsia with constipation, muscular rheumatism, oliguria	Three times daily. 2-8 g or by infusion or decoction.	British Herbal Pharmacopoeia (1983)
Liquid extract (DER 1:1), extraction solvent ethanol 30% (V/V)	Cholecystitis, gall-stones, jaundice, atonic dyspepsia with constipation, muscular rheumatism, oliguria	Three times daily 2-8 ml.	British Herbal Pharmacopoeia (1983)
Tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent ethanol 45%	Cholecystitis, gall-stones, jaundice, atonic dyspepsia with constipation, muscular	Three times daily, 5-10 ml.	British Herbal Pharmacopoeia (1983)

Herbal preparation	Documented use / Traditional use	Pharmaceutical form Strength (where relevant) Posology Duration of use	Reference
(V/V)	rheumatism, oliguria		
Juice of fresh root	Cholecystitis, gall-stones, jaundice, atonic dyspepsia with constipation, muscular rheumatism, oliguria	Three times daily, 4-8 ml.	British Herbal Pharmacopoeia (1983)
Cut or powdered herbal substance	Mild choleric, dyspeptic complaints, diuretic, amarum, problems with fat digestion	Unless otherwise prescribed one cup in the morning and in the evening. As decoction: 1.0-1.5 g of cut drug in 150 ml of cold water. Slowly heat to boil, leave for 10 minutes, strain.	Wichtl (1984)
Cut or powdered herbal substance	Hepato-biliary disorders, dyspepsia, lack of appetite	Unless otherwise prescribed, three times daily; 3.0-5.0 g or in infusion or decoction	Bradley (1993)
Tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent ethanol 25% (V/V)	Hepato-biliary disorders, dyspepsia, lack of appetite	Unless otherwise prescribed, three times daily, 5-10 ml.	Bradley (1993)
Expressed juice from fresh root	Hepato-biliary disorders, dyspepsia, lack of appetite	Unless otherwise prescribed, three times daily, 4-8 ml.	Bradley (1993)
Cut or powdered herbal substance	Restoration of hepatic and biliary function, dyspepsia, loss of appetite	Three times daily. 3.0-5.0 g of the drug.	ESCOP (2003)
Tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent ethanol 25%	Restoration of hepatic and biliary function, dyspepsia, loss of	Three times daily, 5-10 ml.	ESCOP (2003)

Herbal preparation	Documented use / Traditional use	Pharmaceutical form Strength (where relevant) Posology Duration of use	Reference
(V/V)	appetite		
Cut or powdered herbal substance	Disturbance of biliary flow; dyspeptic complaints	As infusion or decoction: 1.5 g of drug per cup of water.	HagerROM (2006)

* Based on an article Dymowski and Jaczkiewicz (2020) a weight of *Taraxaci radix* in a tablespoon is 7.2 ± 0.3 g.

**As noted in the Polish information exchange for the preparation of the assessment report: "in those times (1978) in Poland a cup meant 200-250 ml".

2.3. Overall conclusions on medicinal use

Table 3: Overview of evidence on period of medicinal use

Herbal preparation Pharmaceutical form	Indication	Strength Posology	Period of medicinal use
Cut or powdered herbal substance	Diseases of the liver with reduced bile production, in progressive cirrhosis, liver injury caused by hepatotoxic compounds. Also in diseases of the biliary tract, especially its smooth muscle atony or spasms. In addition, in renal failure, edema, also in achylia [lack of gastric juice] and the digestive disorders caused by it.	Decoction. 3 g of roots for 200-300 ml of warm water. To drink the decoction 2 - 3 times a day, 10 - 15 minutes before meals.	Since 1978 (Ożarowski <i>et al.</i>)
Cut or powdered herbal substance	Cholecystitis, gallstones, jaundice, atonic dyspepsia with constipation,	Decoction or infusion. Three times daily.	Since 1983 (British Herbal Pharmacopoeia)

Herbal preparation Pharmaceutical form	Indication	Strength Posology	Period of medicinal use
	muscular rheumatism, oliguria	2-8 g. Age of users and amount of water not specified.	
Cut herbal substance	Mild choleric, dyspeptic complaints, diuretic, amarum, problems with fat digestion	Decoction. Unless otherwise prescribed one cup in the morning and in the evening. As decoction: 1-1.5 g of cut drug in 150 ml of cold water. Slowly heat to boil, leave for 10 minutes, strain. Age of users not specified.	Since 1984 (Wichtl)
Liquid extract (DER 1:1), extraction solvent ethanol 30% (V/V)	Cholecystitis, gallstones, jaundice, atonic dyspepsia with constipation, muscular rheumatism, oliguria	Oral liquid. Three times daily 2-8 ml. Age of users not specified.	Since 1983 (British Herbal Pharmacopoeia)
Tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent ethanol 45% (V/V)	Cholecystitis, gallstones, jaundice, atonic dyspepsia with constipation, muscular rheumatism, oliguria	Oral liquid. Three times daily, 5-10 ml. Age of users not specified.	Since 1983 (British Herbal Pharmacopoeia)
Juice of fresh root	Cholecystitis, gallstones, jaundice, atonic dyspepsia with constipation, muscular rheumatism, oliguria	Oral liquid. Three times daily, 4-8 ml. Age of users not specified.	Since 1983 (British Herbal Pharmacopoeia)
Expressed juice (DER 1:1) from fresh root boiled in	Traditionally used for indigestion, lack	Oral liquid.	Since 1987 (registered in

Herbal preparation Pharmaceutical form	Indication	Strength Posology	Period of medicinal use
ethanol	of appetite and incidentally as a mild diuretic.	Adults and adolescents from 12y: Dosage 5 ml of product, diluted in small of water, 3 times a day.	Poland)

Preparations from *Taraxaci officinalis radix* 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 plausibility is based on the traditional use.

Therefore *Taraxaci officinalis radix* 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 for:

- a) Traditional herbal medicinal product for the relief of symptoms related to mild digestive disorders (such as feeling of abdominal fullness, flatulence, and slow digestion).
- b) Traditional herbal medicinal product for temporary loss of appetite.
- c) Traditional herbal medicinal product to increase the amount of urine to achieve flushing of the urinary tract as an adjuvant in minor urinary complaints.

3. Non-Clinical Data

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

3.1.1. Primary pharmacodynamics

Effects on the urine and urinary tract

***In vivo* results**

From the roots (*Radix Taraxaci*) and the herb (*Herba Taraxaci*) a fluid aqueous extracts (1 mL extract corresponds to 1 g dry drug) were prepared, from which various dilutions have been obtained from 0.5% to 6% (i.e. 0.5-6 g fluid extract to 100 mL distilled water). The diuretic action of aqueous extracts obtained from *Herba Taraxaci* 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 control group was given the same amount of water. The diuretic and saluretic indices of 1 g herb/kg body weight was comparable to 4 g root/kg body weight, respectively. The very high saluretic index concerning potassium excretion may be due to the high potassium content (Rácz-Kotilla *et al.* 1974). As in many *in vivo* experiments a biphasic effect could be seen for following concentrations (%): 0.5, 1, 2, 4 and 6. For a diuretic index (= urine volume of test group/urine volume of control group): 1.08,

1.12, 1.42, 1.09 and 0.90. For a "sodium" saluretic index (= urinary excretion of sodium of test group/urinary excretion of sodium of control group): 1.12, 1.25, 2.58, 1.64 and 1.23. For a "kalium" saluretic index (= urinary excretion of kalium of test group/urinary excretion of kalium of control group): 1.04, 1.09, 1.98, 1.66 and 1.32. The calculation of a single dose in the rat is not applicable to the setted single dose in an adult human as used in a monograph. Here we always rely on data from scientific articles or textbooks.

Purified fractions isolated from dandelion roots collected in autumn were examined using saline-loaded mice. A petrol ether fraction and two methanol fractions (all prepared by subsequent Soxhlet extraction and chromatographic separation) in concentration of 50 mL/kg body weight slightly increased the final urine volume in male mice (Hook *et al.* 1993).

Other authors could not confirm a diuretic activity: *per os* (p.o.) or intraperitoneal (i.p.) application of an ethanolic extract (4 g of dry drug/kg) (Tita *et al.* 1993) or of an aqueous root extract (4g/1000 ml, ad libitum drunk for 24 hrs, urine collected during 24 hrs) in female Wistar rats (Grases *et al.* 1994).

***In vitro* results**

Renal cells represent putative physiological targets of dandelion extracts. Gerbino *et al.* (2018) showed that exposure to ethanolic root extract (400 µg/mL, 15 g of roots were extracted by maceration with EtOH 95% at 1:10 w/v (plant material–solvent ratio)) induced Ca²⁺ transients similar to those obtained in HEK293 cells either in the presence or absence of extracellular Ca²⁺ also in a renal model of epithelial cells (MCD4, mouse collecting duct cells). This could be related mechanism of diuresis increase as described for spilanthol (Gerbino *et al.* 2016). Recently, Gerbino *et al.* (2020) investigated by whole-cell patch-clamp measurements on HEK293 cells co-expressing CIC-Ka (tagged with GFP) and the accessory subunit barttin (tagged with m-Cherry) the effect of a above mentioned 95% ethanolic extract from dandelion roots (DRE), activating PKC, on CIC-Ka activity. Treatment with 400 µg/mL DRE significantly inhibited Cl⁻ currents time-dependently within several minutes. The authors report that the activity of CIC-Ka in renal cells could be significantly inhibited by the activation of PKC elicited by exposure to herbal extract that activates a PKC-dependent pathway.

Pharmacological activities of some constituents:

Bitter principles are thought to enhance excretion from salivary and stomach glands by reflectory irritation of bitter receptors (Wagner and Wiesenauer 1995). 11β,13-dihydroactucin can be quantified and correlated to its bitterness by ELISA method (Hance *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 *et al.* 2002). The bitter taste of dandelion 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 *et al.* 1985). Taraxinic acid D-glucopyranoside was found to increase Nrf2 transactivation in a dose-dependent manner (Esatbeyoglu *et al.* 2017). However, it acts as the contact sensitizer (Hausen 1982). Its content (ca. 7%) in the latex originating from dandelion main root was determined by HPLC-MS (Huber *et al.* 2015).

The study of Ghale-Salimi *et al.* (2018) was designed to evaluate and compare the antiurolithiatic effects of taraxasterol and potassium citrate in the ethylene glycol induced urolithiatic rat. Taraxasterol (2, 4 and 8 mg/kg) and potassium citrate (2.5 g/kg) were treated for 33 days by gavage. The results showed that taraxasterol decreased liver and kidney coefficients ($p < 0.001$), serum calcium ($p < 0.01$) level, serum alanine aminotransferase ($p < 0.001$), aspartate aminotransferase ($p < 0.001$), lactate dehydrogenase ($p < 0.05$) activities, urine magnesium ($p < 0.05$) and oxalate ($p < 0.001$) levels, number of crystal deposits ($p < 0.001$), score of crystal deposits ($p < 0.01$), score of histopathological damages ($p < 0.001$) and score of inflammation ($p < 0.01$) in kidney sections, while increased urine pH ($p < 0.01$), calcium ($p < 0.001$) and citrate ($p < 0.05$), serum magnesium ($p < 0.001$) and albumin ($p < 0.01$) levels, superoxide dismutase and glutathione peroxidase in serum ($p < 0.01$), kidney ($p < 0.05$ and $p < 0.001$, respectively) and liver ($p < 0.01$ and $p < 0.001$, respectively) tissue homogenates in treated urolithiatic rats in comparison to the control urolithiatic rats. The effect of potassium citrate is the same as taraxasterol in treated urolithiatic rats. The authors conclude that the effect of taraxasterol could be by improving liver function, changing serum and urine parameters, maintaining the antioxidant environment, reducing crystal deposition, excretion of small deposits from kidney and reducing the chance of them being retained in the urinary tract (Ghale-Salimi *et al.* 2018).

Table 4: Overview of the main non-clinical data/conclusions

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions
<i>Comparable/similar preparations to preparations of the monograph</i>				
A fluid aqueous extract	1 mL extract corresponds to 1 g dry drug, various dilutions (from 0.5% to 6% = 0.5 - 6 g fluid extract to 100 mL distilled water), administered at a dose of 50 mL/kg body weight	<i>In vivo</i> By gastric tube to male rats	Rácz-Kotilla <i>et al.</i> 1974	diuretic action characterized by diuretic index, sodium saluretic index, and kalium saluteric index (and compared to furosemide)
An aqueous root extract	4g/1000 ml, <i>ad libitum</i> drink for 24 hrs	female Wistar rats	Grases <i>et al.</i> 1994	a diuretic activity was not confirmed
<i>Other preparations</i>				
Petrol ether fraction and two methanol fractions (all prepared by	dose of 50 mL/kg body weight taken orally	<i>In vivo</i> Male mice (strain Laca)	Hook <i>et al.</i> 1993	No significant increases in urine volume and sodium excretion

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions
subsequent Soxhlet extraction and chromatographic separation)				
An ethanolic extract	4 g of dry drug/kg, per os or intraperitoneal application	female Wistar rats	Tita <i>et al.</i> 1993	a diuretic activity was not confirmed
An ethanolic root extract	400 µg/mL, 15 g of roots extracted by maceration with EtOH 95% at 1:10 w/v (plant material–solvent ratio)	<i>In vitro</i> mouse collecting duct cells	Gerbino <i>et al.</i> 2018	Ca ²⁺ transients similar to mechanism of diuresis increase
A 95% ethanolic extract from roots	400 µg/mL	<i>In vitro</i> HEK293 cells coexpressing CIC-Ka channels	Gerbino <i>et al.</i> 2020	CIC-Ka channels deactivation involved in the diuresis process

3.1.2. Secondary pharmacodynamics

In vitro

α -Glucosidase inhibition

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) – IC₅₀ (mg plant/mL): 2.3, 3.5 and 1.83, respectively. For comparison, IC₅₀ 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 (Ónal *et al.* 2005).

Antiadipogenic-like activity

González-Castejón *et al.* (2014) have investigated the ability of *Taraxacum officinale* roots 60% ethanolic extract (500 µg/mL) to inhibit adipocyte differentiation and lipogenesis in 3T3-L1 preadipocytes. Root extract reduced intracellular lipid droplet accumulation at the highest concentration tested (600 µg/mL) by ~20% compared with control cells. It significantly reduced triglycerides (TG) content at almost all the concentrations tested (0.139 ± 0.003 – 0.148 ± 0.007 mg TG/mg protein), a dose-dependent effect was not observed. The cellular TG content decreased up to ~20% in cells treated with extract. To gain insight into the mechanism leading to reduced adipogenesis and lipid accumulation by dandelion extract, gene expression was analysed using DNA microarrays. The findings indicate dandelion root extract reduce adipogenesis in an *in vitro* model of adipocyte differentiation, probably by modulating the expression of genes related to this process or by regulating other long noncoding RNAs.

Anti-adipogenic effects of dandelion root with 78-82% ethanol in reducing differentiation and increasing lipolysis and apoptosis were studied. Analyses were performed on human primary visceral pre-adipocytes after 10 (P10) and 20 (P20) days of treatment during differentiation and on mature adipocytes after 7 days of treatment (A7). At the dose of 30 µg/mL the cell viability (in %) was as follows for P10, P20 and A7: 81, 68, and 93, respectively. Corresponding apoptosis (in %) was 76, 81, and 10. Triglyceride accumulation for P10 and P20 was decreased for 22% and 12%, respectively. Lipolysis in P20 and A7 cells was affected (measured as glycerol release) for ca. 30% and ca. 0%, respectively (Colitti and Stefanon 2016).

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 *et al.* 1996).

Antioxidative action

Effects of dandelion root water lyophilisate on Wistar rats liver microsomes was studied

(Hagymási *et al.* 2000a). The malondialdehyde products were decreased in a dose-dependent manner. For the membrane protection $IC_{50}=1$ mg/mL was determined. Root extract can stimulate the NADPH-cytochrome P-450 reductase activity even without NADPH cofactor, but at a smaller rate. The same authors described also the hydrogen-donating ability, reducing power property and radical scavenging capacity of lyophilisate (Hagymási *et al.* 2000b, 2000c).

Antioxidant effects were observed for root dandelion extract by measuring liposomal lipid peroxidation induced by Fe^{2+} and ascorbic acid. Fullerenol exhibited an antioxidant effect in combination with the extracts accompanied by a decreased lipid peroxidation (Popovic *et al.* 2001).

Inhibitory effects were also obtained using n-butanol extracts of roots (Kaurinovic *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 *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, peroxidase levels significantly (Sumanth and Rana 2006).

Jung *et al.* (2015) evaluated the antioxidant activities of water extracts from dandelion (*Taraxacum officinale*) aerial parts, roots, and mixed extracts. Mixed extract of *Taraxacum officinale* was a mixture of aerial parts and roots at 9:1 and 8:2 weight ratios. Extracts from aerial parts (DAE), roots (DRE), and mixture of aerial parts and roots (DME) were measured for cell viability and catalase activity in HepG2 cells, and DPPH radical scavenging activity. Cell viabilities of HepG2 cells treated with DAE, DRE, DME 8:2, and DME 9:1 against H_2O_2 -induced oxidative damage were 63.4%, 54.6%, 76.7% and 83.4% at a concentration of 400 µg/mL, respectively. Catalase activity was highest in DME 9:1 (12.2

U/min/mg protein) compared with DAE (9.0 mU/min/mg protein) and DRE (9.7 mU/min/mg protein). DPPH radical scavenging activity of DME showed a significantly lower EC50 value than DAE (EC50 value of DME 9:1=163.3 µg/mL, DME 8:2=172.4 µg/mL, and DAE=173.7 µg/mL).

Bifidogenic action

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 *et al.* 2004).

Cytoprotective activity

Recently was found that an aqueous extract of dandelion root increases cell viability and decreases apoptosis in dextran sodium sulfate (DSS)-incubated NCM460 human colonic epithelial cells. Analyzed extract efficiently ameliorates progressive acute injury as demonstrated by a reduction in body weight loss, severity scores of disease index and shortened colon length during DSS treatment, as well as reducing the inflammatory conditions and oxidative stress in the colon of DSS-induced mice (Ding and Wen 2018).

Nemacitidal activity

Root dandelion extract was tested *in vitro* at a range of 250–1000 µg/mL concentrations on nematode juveniles and eggs against the root-knot nematode *Meloidogyne incognita*. Peak 50% juvenile mortality and 23.8% egg hatchability reduction were recorded at the maximum concentration of root extract (Laquale *et al.* 2018).

Antimicrobial activity

The dandelion root was evaluated for its antimicrobial properties against Gram positive and Gram negative bacterial strains. The methanolic crude extract (DRE3) demonstrated the strongest inhibition of microbial growth against *Staphylococcus aureus*, methicillin-resistant *S. aureus* and *Bacillus cereus* strains. Normal phase (NP) fractionation of DRE3 resulted in two fractions (NPF4 and NPF5) with enhanced antimicrobial activity. Further NP fractionation of NPF4 resulted in two fractions (NPF403 and NPF406) with increased antimicrobial activity (Kenny *et al.* 2015).

UV-B protecting activity

Dandelion water extracts are able to protect HDFs against UV-B damage, before irradiation and also when added promptly after irradiation, via increased UV absorption and reduced MMP activity and oxidative stress. Dandelion leaf and flower but not root extracts stimulated glutathione generation and glutathione reductase mRNA expression in the presence or absence of UV-B irradiation. The extracts are also able to prevent oxidative stress-induced premature senescence; however, with both UV protection and antiageing, the root extracts have the smallest effect compared with leaf and flower extracts (Yang and Li 2015).

Cytotoxicity

In an earlier study, an aqueous extract was prepared from roots of *Taraxacum officinale* and investigated on tumour progression related processes such as proliferation and invasion. The results showed that the extract had no effect on the growth of either cell line. Furthermore, it was found to block invasion of MCF-7/AZ breast cancer cells (Sigstedt *et al.* 2008).

Ovadge *et al.* (2016) examined the cancer cell-killing effectiveness of an aqueous dandelion root extract in human colon cancer cell lines HT-29 (p53 mutant) and HCT116 (p53 WT). Extract induced programmed cell death selectively in >95% of colon cancer cells, irrespective of their p53 status, by 48 hours of treatment. The anti-cancer efficacy of this extract was confirmed in *in vivo* studies in mice, as the oral administration of extract retarded the growth of human colon xenograft models by more than 90%. Authors found the activation of multiple death pathways in cancer cells by extract treatment, as revealed by gene expression analyses showing the expression of genes implicated in programmed cell death.

Zhu *et al.* (2017) showed that an aqueous dandelion root extract (3 mg/mL) could suppress the proliferation and decrease the metastatic capacity of gastric cancer cells (SGC7901 and BGC823) by targeting lncRNA colon cancer-associated transcript-1 (CCAT1). Downregulation of CCAT1 inhibited proliferation and migration of gastric cells.

Pharmacological activities of some constituents:

Taraxinic acid, an aglycone from taraxinic acid-1-O- β -D-glucopyranoside 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).

In vivo

Anti-inflammatory action

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

Extract of *Taraxacum officinale* methanol roots exhibited inhibition of 51%, respectively, in the TPA-induced paw oedema assay in mice, while indomethacin inhibition was 96 % (Yasukawa *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 *et al.* 2001).

Liu *et al.* (2018) found that dandelion root extract may exert some of its anti-inflammatory effects by affecting the activity of AKT (protein kinase B) in lipopolysaccharides-induced inflammatory reaction in isolated Sprague-Dawley rat skeletal muscle cells. The optimal concentration and treatment time of dandelion extract for the following study were 5 mg/mL and 4 days, respectively. Although AKT activation is crucial for the recovery phase after skeletal muscle injury, moreover, dandelion extract can inhibit AKT in muscle cells after LPS induced. As this was a preliminary study, they have not yet investigated the potential signalling pathways involved in the inflammatory process in skeletal muscle cells, so cannot elucidate the mechanism by which dandelion extract suppressed inflammation.

Effects on liver cells

The protective effects of dandelion root against alcoholic liver damage were investigated in HepG2/2E1 cells and ICR mice. When an increase in the production of reactive oxygen species was induced by 300 mM ethanol *in vitro*, cell viability was drastically decreased by 39%. However, in the presence of hot water extract (TOH, 1 g/kg bw/day), no hepatocytic damage was observed in the cells treated with ethanol (as evidenced by the significant reductions of serum aspartate aminotransferase, alanine

aminotransferase, alkaline phosphatase, and lactate dehydrogenase activities), while ethanol extract (TOE) did not show potent hepatoprotective activity. The mice receiving ethanol plus TOH exhibited significant increases in hepatic antioxidant activities, including catalase, glutathione-S-transferase, glutathione peroxidase, glutathione reductase, and glutathione (You et al 2010).

Abdel-Magied *et al.* (2019) investigated the effect of dandelion root extract (DRE) on radiation-induced hepatic tissue injury in male Wistar rats. Animals were exposed to 8.5 Gy of gamma radiation applied as a shot dose and DRE (200 mg/kg/day), was orally supplemented to rats 14 days before and after irradiation. The results showed that DRE administration attenuated oxidative stress in the liver denoted by a significant reduction in the level of MDA and PCO with a marked elevation in GSH and the activity of SOD, CAT and Gpx. Additionally, these alterations were associated with a significant decrease in the activity of ALT, AST, ALP, and LDH with a marked increase of AL level. Administration of DRE significantly diminished the histopathological changes in the hepatic tissues, denoted by a reduction in the necrotic and degenerative changes of hepatocytes.

Cytotoxicity

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 *et al.* 2004, Lopatina *et al.* 2007).

In a recent study (Nassan *et al.* 2018) was shown that expression of PIK3R1 (gene is known to play a tumour suppressor) increased in 7,12-dimethylbenz[a]anthracene (DMBA) rats group treated with water decoction of dandelion root (500 mg/kg) in comparison with control, decoction+DMBA groups. Average tumour weight was 18.3±3.8 g in DMBA administered group. Treatment with dandelion root decoction decreased tumour size to an average of 6.3±1.5 g.

3.1.3. Safety pharmacology

No data available.

3.1.4. Pharmacodynamic interactions

No data available.

3.1.5. Conclusions

Results from relevant experimental studies on dandelion root to support the proposed indications are very limited. The reported pharmacological effects are not considered contradictory to the traditional uses.

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

Effect on hepatic drug metabolizing enzymes

Activity of CYP1A2 in the liver microsomes of rats receiving dandelion tea (plant part not known) was significantly decreased ($P < 0.05$) to 15% of the control value. No alterations were observed in the activities of CYP2D and CYP3A. Activity of CYP2E in rats receiving dandelion tea was significantly lower than in the control group, 48%. There was a dramatic increase (244% of control) in the activity of phase II detoxifying enzyme UDP-glucuronosyl transferase in the dandelion tea-pretreated group. There was no change in the activity of glutathione-S-transferase (Maliakal and Wanwimolruk 2001).

Assessor's comment:

No clinical drug interactions were mentioned in available literature until June 2020.

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

No data available.

3.3.1. Single dose toxicity

Fluid aqueous root extract (1ml extract corresponds to 1 g dry drug) demonstrated very low toxicity: intraperitoneal LD50 36.6 g/kg body weight in mice (Rácz-Kotilla *et al.* 1974), a not specified ethanolic extract showed very low toxicity up to doses of 10 g/kg (per os) and 4 g/kg (intraperitoneal), doses referred to dried drug in rats and mice (Tita *et al.* 1993).

3.3.2. Repeat dose toxicity

No data available.

3.3.3. Genotoxicity

No data available.

3.3.4. Carcinogenicity

No data available.

3.3.5. Reproductive and developmental toxicity

No data available.

3.3.6. Local tolerance

No data available.

3.3.7. Other special studies

No data available.

3.3.8. Conclusions

Non-clinical information on the safety of dandelion root is scarce.

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

Tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed. A European Union list entry is not supported due to lack of data on genotoxicity.

3.4. Overall conclusions on non-clinical data

Results from relevant experimental studies on dandelion root to support the proposed indications are very limited. The reported pharmacological effects are not considered contradictory to the traditional uses.

Non-clinical information on the safety of *Taraxaci officinalis radix* is scarce.

As there is no information on reproductive and developmental toxicity, the use during pregnancy and lactation cannot be recommended. Tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed.

4. Clinical Data

4.1. Clinical pharmacology

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

No data available.

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

No data available.

4.2. Clinical efficacy

No data available.

4.2.1. Dose response studies

No data available.

4.2.2. Clinical studies (case studies and clinical trials)

No data available.

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

No data available.

4.4. 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* F.H. Wigg., radix, as a comminuted herbal drug, herbal tea, juice from fresh root, 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.

5. Clinical Safety/Pharmacovigilance

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

No data available.

5.2. Patient exposure

Aside from market presence and data from studies, there are no concrete data concerning patient exposure.

5.3. Adverse events, serious adverse events and deaths

The dandelion has reported to elicit allergic contact dermatitis.

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

Many cases from daily dermatological practice and patch testing with standard sesquiterpenic lactones mix as well as with dandelion (unfortunately plant parts not exact described) were recently summarized (Minciullo *et al.* 2017). However, children who test positive to dandelion extract have been reported to test negative to SQL and Compositae mix. This is thought to be because dandelion extract may be a monosensitizer, which does not cross-react with other Compositae allergens. Of those who tested positive for Compositae sensitization, a significantly higher prevalence rate was found in children with atopic dermatitis compared with those without (4.7% vs 1.3%; $P = 0.03$) (Jovanović *et al.* 2004). Low sensibility to sesquiterpenic lactones mix, and/or Compositae one could explain why these procedures detect > 90%, but no 100% of the patients (Paulsen and Andersen 2017).

A 56-year-old afro-american man presented with black discoloration of his fingertips associated with severe pain and loss of function for 8 weeks. He had type 2 diabetes and hypertension but took no medication relevant to the presenting symptoms. Three months previously he had been admitted to the intensive care unit with renal failure and had become intermittent haemodialysis dependent. He had no relevant family history. He was an ex-smoker, was unemployed and had no hobbies. He had

been drinking 10–15 cups of dandelion tea (no plant part known) daily for 6 months. Examination revealed digital ischaemia with necrosis of the distal phalanges of both thumbs and the lateral three digits of both hands. Both hands were cool, with reduced capillary refill time. No peripheral pulses were palpable in the limbs. Vasculitic and clotting screens were normal. Hyperoxalaemia had been recorded around the onset of his hand symptoms (plasma oxalate 87 µmol/L; normal level < 10 µmol/L). As the patient was anuric, urinary oxalate could not be quantified. X-rays of the patient's hands, and arterial Doppler measurements of his limbs, revealed heavily calcified vessels. Cardiac echo did not demonstrate thrombus. Skin biopsy from a finger revealed tissue necrosis. Renal biopsy, which had been undertaken just prior to his current presentation, showed deposition of oxalate crystals in the proximal tubules on a background of diabetic glomerulopathy. Liver biopsy excluded primary hyperoxaluria. Dandelion tea (plant part not described) from the same source as the patient's, prepared in a similar way, produced a high oxalate level of 258 µmol/L. A diagnosis of secondary hyperoxalaemia due to high dietary oxalate with reduced renal clearance was made. The patient died 9 months after diagnosis. As in this patient, reduced renal function leads to impaired renal oxalate clearance. Hyperoxalaemia has consistently been demonstrated in patients with chronic kidney disease, with oxalate crystal deposition evident in tissues. The differential diagnosis for digital gangrene in mentioned patient, who had end-stage renal disease and diabetes and was an ex-smoker, was broad. With no clotting abnormalities and no evidence of a systemic vasculitis, the possibility of thromboembolic disease or calciphylaxis was considered and excluded after extensive investigation. The presence of anuria in our patient contributed to the diagnostic difficulty, and it was the presence of hyperoxalaemia and renal tubular oxalate deposition that eventually lead to the diagnosis of digital ischaemia secondary to excessive dietary oxalate ingestion in dandelion tea in the context of impaired renal function (Moriarty *et al.* 2013).

A hyperacidity (Schulz *et al.* 2001) or gastric complaints (Capasso 2003) may occur.

In addition to literature reports, a screening for adverse reactions in the EudraVigilance database was conducted on 12 August 2020 utilizing the active substance (high level) field to contain *Taraxacum officinale* root, Taraxaci radix or Dandelion root terms, retrieving 12 cases.

Out of the 12 identified cases, 2 cases had high number of suspected/interacting drugs (52 and 20 respectively) which precluded a proper causality assessment.

Nine cases were identified for herbal medicinal product „HRI water balance tablets“ (tablets for fluid retention) or herbal classic retention tablets, which contain Taraxaci radix in combination with other herbal substances such as Taraxaci herba, Uvae ursi folium/extract and Buchu leaf/extract. Out of these 9 cases, 3 were classified as serious in EV and 6 classified as non-serious. Here are the 3 identified serious cases:

1. A women 20 years old took „HRI water balance tablets“ for 7 days (4 tablets a day) to relieve symptoms of mild water retention and experienced nausea, vomiting, stomach pain, weakness and diarrhoea. Outcome was selected as recovering/resolving and suspected drug was withdrawn. No more information was available.
2. A 34 years old female has taken „HRI water balance tablets“ for 3 days (2 tbl daily) to relieve symptoms of mild water retention and after the first day of use (time to onset 1 day) experienced myalgia, peripheral oedema and fatigue. The suspected drug was withdrawn and peripheral oedema resolved after 7 days. Myalgia and fatigue remained. Concomitant medication listed in the report was paracetamol and ibuprofen. No more information was available.

3. This is a case reported by a physician of medically confirmed kidney failure and severe hypokalaemia induced by suspected abuse of „HRI water balance tablets“. The reported LLTs were also dehydration and drug abuse. This case affected a young woman who was admitted into hospital with dehydration related kidney failure with severe low potassium. Further investigation by the physician suggested high levels of sodium and potassium loss through urine. The patient admitted that she had used the water balance product in the past and was denying the continued use. The conclusion of the physician was that the patient was abusing this product. No information on dosage/TTO/ duration of use was available.

From the assessors point of view the first two cases were wrongly classified as serious, seriousness was selected as other medically important information with no further explanation and these preferred terms do not meet the criteria of EMA IME term list. All these cases contained limited information, which precluded a valid assessment. Causality assessment was also not possible due to the several herbal substances contained in the medicinal product and the role of *Taraxaci radix* is not clear.

The other 6 non-serious cases all patient reports, contained limited information and reported following PTs: Candida infection, Cystitis, Dysuria, Ineffectiveness of the drug, Headache, Nausea, Flatulence, Dyspepsia, Dizziness, Polyuria and Abdominal discomfort. No significant safety information was identified by reviewing these cases.

The remaining one case was reported by a physician who suggested an interaction between herbal medicinal product „Adios“ and oral contraceptives. The case reported a 34-years old woman who became pregnant despite taking oral contraceptives (long term). The patient was also taking „Adios“ (contains *Taraxaci* root, *Peumus boldus* leaf and *Juglans cinerea* and maybe others, the exact composition not clear) to aid „slimming“. The exact duration of use of Adios was not reported. The case contains limited information, causality association with *Taraxaci radix* was not possible to determine based on the information available.

Assessor’s comment:

Due to possible stimulation on bile secretion reported from traditional medicinal use, the warning that dandelion root is not recommended in case of obstruction of the bile duct, cholangitis, liver disease, gallstones and any other biliary diseases has been included in the monograph, paragraph 4.4. not in 4.3. because of the lack of pharmacovigilance data and also the lack of preclinical and clinical scientific data as well as lack of supporting data for registered products.

5.4. Laboratory findings

No data available.

5.5. Safety in special populations and situations

No data available.

5.5.1. Use in children and adolescents

No data available. Inclusion of adolescents in the Monograph is based on data given for product registered in Poland (Table 1).

5.5.2. Contraindications

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

5.5.3. Special Warnings and precautions for use

Indication 1) in the monograph:

Due to possible stimulation on bile secretion dandelion root is not recommended in case of obstruction of the bile duct, cholangitis, liver disease, gallstones and any other biliary diseases. (Capasso *et al.* 2003)

The use in children under 12 years of age has not been established due to lack of adequate data.

Indication 3) in the monograph:

If complaints or symptoms such as fever, dysuria, spasms or blood in urine occur during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.

Conditions where a reduced fluid intake is recommended (e.g. severe cardiac or renal disease).

For extracts containing ethanol, the appropriate labelling for ethanol, taken from the 'Guideline on excipients in the label and package leaflet of medicinal products for human use', must be included.

5.5.4. Drug interactions and other forms of interaction

No data available.

5.5.5. Fertility, pregnancy and lactation

No data available. In the absence of sufficient data, the use during pregnancy and lactation is not recommended.

5.5.6. Overdose

No data available.

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

No data available.

5.5.8. Safety in other special situations

Not applicable.

5.6. Overall conclusions on clinical safety

Clinical safety data are limited. However, up to now no serious side effects have been reported. Allergic reactions may occur and should be included as undesirable effects in section 4.8 of the monograph. The frequencies are not known.

Due to possible stimulation on bile secretion reported from traditional medicinal use, dandelion root is not recommended in case of obstruction of the bile duct, cholangitis, liver disease, gallstones and any other biliary diseases.

The use in children under 12 years of age has not been established due to lack of adequate data.

Related to Indication 3) in the monograph the following warnings is included in the monograph:

“If complaints or symptoms such as fever, dysuria, spasms or blood in urine occur during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.

Conditions where a reduced fluid intake is recommended (e.g. severe cardiac or renal disease).”

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

6. Overall conclusions (benefit-risk assessment)

Taraxaci officinalis radix is a well-known traditional herbal substance that is therapeutically used for centuries in European region. This fact has been documented continuously in a lot of well-known textbooks. For following Taraxaci officinalis radix preparations as listed in the monograph, a period of at least 30 years in medicinal use as requested by Directive 2004/24/EC for qualification as a traditional herbal medicinal product is fulfilled: a) comminuted dried root, b) expressed juice (DER 1:1) from fresh root boiled in ethanol, c) juice from fresh root d) liquid extract (DER 1:1), extraction solvent ethanol 30% (V/V), and e) tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent ethanol 45% (V/V). None of the data fulfils the requirements to demonstrate a well-established medicinal use with recognised efficacy, thus the monograph is restricted to traditional use. The efficacy is plausible on the basis of long-standing use and experience. All existing literature data support traditional use of Taraxaci officinalis radix for the following indications suitable for self-medication:

- a) Traditional herbal medicinal product for the relief of symptoms related to mild digestive disorders (such as feeling of abdominal fullness, flatulence, and slow digestion).
- b) Traditional herbal medicinal product for temporary loss of appetite.
- c) Traditional herbal medicinal product to increase the amount of urine to achieve flushing of the urinary tract as an adjuvant in minor urinary complaints.

All the requirements for “traditional use” (self-medication character, specified strength/posology, appropriate route of administration, period of traditional use, plausibility and safety) are met.

The duration of administration is limited to two weeks. If the symptoms persist longer than 2 weeks during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.

The use of Taraxaci officinalis radix preparations is not recommended during pregnancy and lactation and they should not be taken by children under 12 years of age.

Undesirable effects included in the monograph are: Allergic reactions may occur. The frequency is not known.

Contraindications are: Hypersensitivity to the active substance or to plants of the Asteraceae (Compositae) family.

Due to possible stimulation on bile secretion reported from traditional medicinal use, the warning that dandelion root is not recommended in case of obstruction of the bile duct, cholangitis, liver disease, gallstones and any other biliary diseases has been included in the monograph.

Related to **Indication 3** in the monograph the following warnings is included in the monograph:

“If complaints or symptoms such as fever, dysuria, spasms or blood in urine occur during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.

Conditions where a reduced fluid intake is recommended (e.g. severe cardiac or renal disease).”

No cases of overdose have been documented in the past 30 years for herbal preparations. There are no reports on drug interactions, drug abuse, withdrawal and rebound, effects on ability to drive or operate machinery or impairment of mental ability.

No data from investigations of repeat-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, local tolerance or other special studies of preparations from *Taraxaci officinalis* radix in animals, are available.

A European Union list entry is not supported due to lack of data on genotoxicity.

The above-cited *Taraxacum officinale*, radix preparations can be accepted as traditional herbal medicinal products in the following indications:

- a) Traditional herbal medicinal product for the relief of symptoms related to mild digestive disorders (such as feeling of abdominal fullness, flatulence, and slow digestion). Therapeutic area for browse search: Gastrointestinal disorders
- b) Traditional herbal medicinal product for temporary loss of appetite. Therapeutic area for browse search: Loss of appetite
- c) Traditional herbal medicinal product to increase the amount of urine to achieve flushing of the urinary tract as an adjuvant in minor urinary complaints. Therapeutic area for browse search: Urinary tract and genital disorders

Annex

List of references