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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Prunus avium* L.; *Prunus cerasus* L., peduncle

Draft

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

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Prunus avium* L.; *Prunus cerasus* L., peduncle
Herbal preparation(s)	Comminuted dried herbal substance
Pharmaceutical form(s)	Dried herbal substance as herbal tea for oral use
Rapporteur(s)	H. Kuin
Peer-reviewer	I. Chinou

Note: This draft assessment report is published to support the public consultation of the draft European Union herbal monograph on *Prunus avium* L.; *Prunus cerasus* L., peduncle. 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
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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1. Introduction

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

- Herbal substance(s)

The herbal substance is described in the monograph for Griottier in the 11th edition of the French Pharmacopoeia (1992) as the fruit stalk of *Prunus cerasus* or *Prunus avium* after fruit ripening and drying (Ph.Fr. 1992).

As of 2014 the monograph has been deleted from the Ph.Fr. (Journal officiel de la République Française). At present the herbal substance is published in the "Liste A des plantes médicinales (the vernacular name is Griottier, plant part is pédoncule du fruit) and herewith recognised as traditional herbal medicine under pharmaceutical monopoly but also regulatory authorised to be sold out of a retail pharmacy, as such. (ref: https://ansm.sante.fr/documents/reference/pharmacopee/la-pharmacopee-francaise#origine_vegetale).

As the monograph of the French Pharmacopoeia refers to the peduncles of both *Prunus avium* L., as well as *Prunus cerasus* L., the two are considered to be exchangeable for the purpose of this assessment report.

According to the botanical and taxonomical overview through KEW knowledge database "Plants of the World online", *Prunus cerasus* L. is native to the Northern Caucasus and has 157 synonyms, such as *Prunus acida* Ehrh., *Cerasus acida* (Ehrh.) Borkh., *Cerasus vulgaris* Mill., Cerasus avium subsp. acida (Ehrh.) Bonnier & Layens and *Prunus avium subsp. cerasus* (L.) Rouy & E.G.Camus (https://powo.science.kew.org/taxon/urn:lsid:ipni.org:names:729574-1). *Prunus avium* L. originates from Europe to Afghanistan and North Africa and has 218 synonyms, among which *Cerasus avium* (L.) Moench and *Prunus cerasus subsp. avium* (L.) Brandis (https://powo.science.kew.org/taxon/urn:lsid:ipni.org:names:30093848-2/general-information).

The herbal substance, in particular the part of the plant used, is referred to in literature using different terms. Common terms are stem, stalk, pedunculus and stipites. Throughout the assessment report the different terms for the plant part are exchangeable.

Constituents

Polyphenols:
The amount of polyphenols in the stalks of 17 different varieties of *Prunus avium* were determined colorimetrically in a 70% aqueous acetone solution, using gallic acid as reference standard. The total amount of polyphenols varied from 13-32 mg of gallic acid equivalents/g of dry plant material. The amount of tannins varied from 6.31-9.99 mg of gallic acid equivalents/g dry plant material. (Prvulovic 2011) Total phenolic content in a water extract of *Prunus avium* stalks was 118±9.12 mcg expressed as gallic acid equivalent per mg extract (Bursal *et al*., 2013).
In another reference, Peixoto *et al*. (2020) showed a total phenolic content between 24-39 mcg gallic acid equivalents per mL water extract.

Acids:
The main acids identified in the stems of *Prunus avium* are malic acid, citric acid, oxalic acid and shikimic acid; the total amount is quantified to be 0,94 g/100g. (Bastos *et al*., 2015).

Several organic acids have been identified in extracts of *Prunus avium* and *Prunus cerasus* stems (Bastos *et al*., 2015; Svarc-Gajic *et al.,* 2017; Aires *et al.,* 2017; Jesus *et al,.* 2019; Önem *et al.,* 2021 and Nunes *et al.,* 2022i).

Furthermore flavonoids, flavonols and isoflovones have been identified in *Prunus avium* and *Prunus cerasus* stipites (Khalid *et al.,* 1989; Prvulovic *et al.,* 2011; Bastos *et al.,* 2015; Aires *et al.,* 2017; Jesus *et al.,* 2019; Önem *et al.,* 2021 and Peixoto *et al*., 2020).

Fatty acids: In a subcritical water extract (SWE; DESR 1:90) of Prunus avium and *Prunus cerasus* stems hexadecanoic acid has been identified. In the SWE of *Prunus cerasus* stems furthermore 3-3-methyl-5-keto-hexenoic acid, nonanoic acid and octadecanoic acid have been identified (Svarc-Gajic *et al.,* 2017).

Alcohols: In a subcritical water extract (SWE; DESR 1:90) of *Prunus avium* and *Prunus cerasus* stems the following alcohols have been identified: arabitol, glycerol and sorbitol. Furthermore, in the SWE of *Prunus cerasus* stems also 3-hydroxy-4-methoxyphenyl-ethylene glycol has been identified (Svarc-Gajic *et al.,* 2017).

Sugars: In a subcritical water extract (SWE; DESR 1:90) of *Prunus avium* and *Prunus cerasus* stems the following sugars have been identified: arabinose, D-fructose, D-glucose, xylulose, D-ribose, D-xylose. In the SWE of *Prunus avium* stems also mannose has been identified. In the SWE of *Prunus cerasus* stems also D-galactose has been identified (Svarc-Gajic *et al.,* 2017).

Minerals:
The following minerals have been identified in the stems of *Prunus avium* in a recent article from Portugal: sodium 80 mg/kg dw, phosphorus 1345 mg/kg dw, copper 25 mg/kg dw, iron 32 mg/kg dw, manganese 11 mg/kg dw, zinc 18 mg/kg dw, aluminium 7 mg/kg dw, barium 43 mg/kg dw, lithium 0.07 mg/kg dw, lead 0,4 mg/kg dw, rubidium 8 mg/kg dw and strontium 19 mg/kg dw.(Nunes *et al*., 2022i).

Other components:
Nunes *et al.* (2022i) identified volatile compounds in the stems of *Prunus avium* grown in Portugal, where aldehydes were the most prominent group, followed by alcohols, ketones, esters, monoterpenes, nor-isoprenoids and hydrocarbons.

- Herbal preparation(s)

Comminuted herbal substance as herbal tea for oral use (infusion): Van Hellemont 1985 and product on the market in France.

Comminuted herbal substance as herbal tea for oral use (decoction): Muszynsky 1954, Font Quer 1961, Constantinescu& Hatieganu-Buruiana 1986, Delflosse 1998, Parvu 2006, Verhelst 2010 and product on the market in France.

Powdered herbal substance in hard capsules (product on the market in France).

- 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.

Not applicable.

1.2. Search and assessment methodology

This assessment report is based on the data search for *Prunus avium* and *Prunus cerasus*. The call for data started 15-02-2023 and ended on 15-05-2023. The literature search in medical and scientific databases was performed as follows:

- PubMed search March 2023; search terms used *Prunus avium*, *Prunus cerasus*.
- EMA library herbal text books were searched for *Prunus cerasus*, *Prunus avium* in March 2023.

- Eudravigilance was searched with search terms *Prunus avium* stems, *Prunus cerasus* in June 2023
- WHO Vigibase was searched using search terms *Prunus avium*, *Prunus cerasus*, June 2023

Search engines used: PubMed

Pharmacovigilance resources:
Eudravigilance
WHO Vigibase

Data from EU and non-EU regulatory authorities: marketing presence May 2023.

Other resources: EMA herbal library.

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

In May 2023 a request was sent for information on marketed products containing *Prunus avium* L. or *Prunus cerasus* L., pedunculus to the member states. The information is based on data obtained from the National Competent Authorities.

Information on medicinal products marketed in the EU/EEA

Table 1: Overview of data obtained from marketed medicinal products

Herbal substance/preparation	**Indication**	**Posology and method of administration**	**Regulatory Status**
Prunus cerasus L., pedunculus	Facilitate the functions of elimination of the kidneys and digestives	Hard capsule containing 350 mg dried powder of the herbal substance; 2 capsules with a large glass of water, twice daily	France MA Authorized 1997 Withdrawn 2011
Prunus avium L., pedunculus	mild diuretic	Infusion of the dried herbal substance (3-5 min in hot water); decoction (immerse in water and boil during 10-20 min)	France MA authorized 1976 Withdrawn 1994

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

Information on a combination marketed product containing a mixture of herbal extracts among which also cherry's and sour cherry's stems (ingredients: *Arctostaphylos* uva-ursi (L.) Spreng. folium; *Prunus avium* L. subs.(var.) duracina or *Prunus cerasus* L. subs. cerasus, stipes; *Equisetum arvense* L., herba; *Betula pendula* Roth et/aut *Betula pubescens* Ehrh., folium; *Solidago canadensis* L. et *Solidago gigantea* Ait., herba; ethanolic extracts (DER 1:5) with the ratio 2:3:3:4:8; extraction solvent 45% (V/V) ethanol) and used as diuretic, anti-inflammatory, mild antiseptic herbal extract. For gentle

urination. In the Hungarian market between 1992 and 2021 (1992-2013 as natural healing product; 2013-2021 as medicinal product).

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

Table 2: Overview of data obtained from marketed herbal products

Herbal substance/preparation	**Healthclaim**	**Posology and method of administration**	**Regulatory Status**
Prunus cerasus L., pedunculus	Facilitate the functions of elimination of the kidneys and digestives.	Hard capsule containing 350 mg dried powder of the herbal substance; 2 capsules with a large glass of water, twice daily.	France after 26-05-2011
Prunus avium L., pedunculus	Facilitate the elimination functions of the body and contribute to the normal functioning of the urinary system.	Infusion of 1 tablespoon (about 6 g) herbal substance per 200 mL (3-5 min in hot water); decoction (immerse in water and boil during 10-20 min) then filter.. Drink one cup 2-4 times per day.	France after 19-12-1994
Prunus cerasus L. pedunculus	improves intestinal function: mild laxative effect. Calms inflammation of the urinary tract: cystitis, gout. Facilitates the elimination of urine, water and toxins: diuretic and depurative properties. Has an antioxidant and anti-inflammatory effect on the liver and stomach: regulatory effect.	Hard capsule containing 350 mg dried powder of the herbal substance; 2 capsules with a large glass of water, twice daily.	Belgium

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

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 use of *Prunus cerasus* L. and *Prunus avium* L., pedunculus, or cherry stalks as a diuretic has been described in various herbal textbooks. Synonyms for *Prunus cerasus* L. that are used are *Cerasus acida* Dur. L., *Cerasus avium* L. Much. and *Cerasus vulgaris* Mill. In older textbooks the plant part is often referred to as stipites, cerasi stipites or stipites cerasorum. The oldest references that could be found that described the use of *Prunus cerasus* L., pedunculi as a diuretic were by Cazin in 1868 and Hagers Handbuch in 1949. Through the years descriptions in herbal textbooks from different European countries show that the use as a diuretic was known throughout Europe. Muszynsky (1954) described the traditional use of stipites cerasorum (*Cerasus acida* Dur. L., pedunculus) in Poland as a diuretic and mentioned that the tradition came originally from France. Hoppe (1958, 1975) describes the use of *Prunus cerasus* or *Cerasus acida* as diureticum, antidiarrhoicum and as component of "entfettungstees" (degreasing tea). In Spain the use of cherry stalks (*Prunus avium* L.) as diuretic has been described by dr. Pio Font Quer (1961). Leclerc (1973) describes the use of the cherry stalks (*Cerasus vulgaris* Mill.) as a very popular remedy to promote diuresis and prevent inflammation of the urinary tract. He refers to Cazin (1868) who described that a decoction of *Prunus cerasus* L., pedunculi increases rapidly and abundant urinary secretion when other diuretics have been used without success.

In Germany the use of *Prunus cerasus* L. *ssp. acida* (Dum) Aeth. as an antidiarrhoicum was described by Gessner (1974). In 1985 Van Hellemont described the use of stipites cerasorum (*Prunus cerasus* L., or *Cerasus vulgaris*, *Cerasus acida*) as a diuretic and sedative in urinary tract inflammations, later referenced by De Cleene & Le Jeune (1999). In 1986 Constantinescu described the use of stipites cerasorum (*Cerasus avium* L. Much. or *Cerasus vulgaris* Mill.) as a diuretic in Romania. Van Wyk (1997) made reference to *Prunus avium* fruit stalk as a diuretic and astringent. A description of the traditional use of the pedunculus of *Prunus cerasus* L. or *Prunus avium* L. as diuretic and in inflammation of the lower urine tract was given by Delflosse in 1998. Bruneton (1999) added in a note that the pedunculus of the fruit of the morello cherry trees (*Prunus cerasus* L.) was traditionally used to facilitate the digestive functions and the enhancement of the renal elimination of water. Parvu (2006) describes the traditional use of Cerasi stipes in Romania to be much broader, also including cystitis, pyelocystitis, pleurisy, migraine, dermatitis, arthritis, ascites, edema and gout. Verhelst (2010) also documented the traditional use of cherry stalks (from *Prunus cerasus* L., *Cerasus acida* or *Cerasus vulgaris* Mill.): "The cherry stems are sometimes attributed diuretic properties, as well as a sedative (calming) effect on the mucous membranes of the urinary tract. They are sometimes used for edema (water retention), impaired kidney function and urine production, hyperuricemia (increased uric acid level), rheumatic diseases, to prevent urolithiasis (kidney stones) and as an adjuvant for nephritis (inflammation of the kidneys) and cystitis (inflammation of the bladder). Laxative properties are also reported in constipation."

The peduncles of both *Prunus avium* L and *Prunus cerasus* L. (syn. *Cerasus vulgaris* L.) are taken up in the Belgium State journal in 2017 as herbs that are allowed to be manufactured and sold. In France Griottier, peduncules du fruit has been taken up in the general monograph tisanes in de French Pharmacopoeia (2013) and since 2021 Griottier, which is defined as "pédoncule du fruit" of both *Prunus avium* L. and *Prunus cerasus* L. is in the Liste des Plantes Medicinales utilisees traditionellement of the Pharmacopée Française and herewith recognised as traditional herbal medicine under pharmaceutical monopoly but also regulatory authorised to be sold out of a retail pharmacy, as such. (ref: https://ansm.sante.fr/documents/reference/pharmacopee/la-pharmacopee-francaise#origine_vegetale)

Table 3: Overview of historical data

Herbal substance/ preparation	**Documented use / Traditional use**	**Posology and method of administration**	**Reference**
Dried *Cerasus acida* Dur. L., fruit stalk decoction	Mild diuretic.	A handful (about 30 g) is boiled in 1 L water, smeared with cherry or raspberry syrup and drunk as daily dose.	Fytoterapia by Muszynsky 1954
Prunus avium stalk decoction	Diuretic.	Herbal tea is prepared by boiling 1 ounce (28 grams) of stalks in 1 L of water; drink from a glass.	Plantas Medicinales el dioscorides renovado By Dr. Pio Font Quer 1st ed. 1961
Cerasus vulgaris Mill. pedunculus, decoction	Diuretic and urinary tract inflammation.	Decoction: boil in 1 Liter of water 30 grams (a good handful) of cherry stalks.	Leclerc, 1973 Like Muszynsky 1954
Dried cherry stalk (*Prunus cerasus* L.)	Diuretic and sedative in urinary tract inflammations; laxative.	Infusion (6g in 200 mL boiling water during 2 hours), subsequently boiled for 10 min, drink one cup 3 times per day. Extractum 2-3 g per day.	Van Hellemont, 1985
Stipites cerasorum (*Cerasus avium* L. Much. or *Cerasus vulgaris* Mill.), decoction	To be used as diuretic.	One hand of stipites in 1 L water, boiled for 30 min and then divided in 3-4 cups.	Constantinescu & Hatieganu-Buruiana 1986
Dried stalks of *Prunus cerasus* or *Prunus avium* decoction	Used as diuretic and in inflammation of the lower urine tract.	10 g in 1L boiling water during 15 min.	Delfosse, 1998
Cerasi stipites decoction	treatment of kidney, urinary tract, bladder, cystitis, pyelocystitis, pleurisy, migraine, dermatitis, arthritis, ascites, edema, gout.	Decoction: 1 tablespoon of dried cherry stalks (6 grams) in 200 mL water, boiling for 10 min, then filter, 2-3 cups per day.	Parvu, 2006
Cherry stems decoction (*Prunus cerasus* L., *Cerasus acida*, *Cerasus vulgaris* Mill.)	diuretic properties, sedative (calming) effect on the mucous membranes of the urinary tract, used for edema (water	Drinking 1/2 liter per day of a decoction (10 min) of a handful of cherry stems (30 grams) previously macerated.	Verhelst 2010

Herbal substance/ preparation	Documented use / Traditional use	Posology and method of administration	Reference
	retention), impaired kidney function and urine production, hyperuricemia (increased uric acid level), rheumatic diseases, to prevent urolithiasis (kidney stones) and as an adjuvant for nephritis (inflammation of the kidneys) and cystitis (inflammation of the bladder). Laxative properties are also reported in constipation.	For 12 hours in cold water) in 1 L of water or 3 times a day a decoction (10 min) of 6 g cherry stems in 200 mL of water (macerate the stems in cold water for 2 hours) or 2 to 3 g of extract per day.	
Griottier (pédoncule du fruit) of *Prunus avium* L. and/or *Prunus cerasus* L.	Not indicated.	Infusion: pour boiling water over the vegetable drug. Leave in contact for approximately 10 to 15 min. Decoction: keep the plant drug in contact with water, boiling, for a duration of 15 to 30 min. The daily dose is 250-500 mL for a quantity of 5-10 g/L.	French Pharmacopoeia, 2013

2.3. Overall conclusions on medicinal use

Traditional use of *Prunus cerasus* L. and *Prunus avium* L., pedunculus, or cherry stalks, has been documented in several herbal textbooks originating from different European countries as early as 1868. Herbal textbooks refer to the dried cherry stalks of both *Prunus avium* L. and *Prunus cerasus* L. to be used as an infusion or decoction for diuretic purposes and in urinary tract complaints. (Cazin, 1868; Leclerc 1973; Van Hellemont 1985; Delflosse 1998) Nowadays, several products are still on the EU market containing dried cherry stalks in whole, comminuted or powdered form, to be used as a tea or in a solid dosage form as a diuretic.

One product, containing the comminuted herbal substance *Prunus avium* L., pedunculus to be used as a tea has been authorised in 1976 in France with indication, as a mild diuretic. Although the registration as medicinal product has been withdrawn in 1997, the product is still present on the French market as a food supplement for the same purpose (health claim). For this product the provided information justifies 30 years of traditional use of which at least 15 years within the EU for a decoction or infusion with a daily dose of 2-6 g in 200 mL, 2-4 times per day. The preparation and posology are justified by the product information, together with the monograph on tisanes in the French Pharmacopoeia, and is in line with the traditional herbal literature. Due to the description of the French pharmacopoeia the traditional use of the pedunculus of both species *Prunus avium* L. and

Prunus cerasus L. are considered exchangeable and therefore the monograph is on the pedunculus of both species to be prepared as a herbal tea.

The other product on the French market containing the powdered herbal substance of *Prunus cerasus* L., pedunculus for oral use has been authorized in 1997 and withdrawn in 2011, but is since then still present on the market in France as well as in Belgium. However, with the market presence since 1997 the period of 30 years of traditional use has not been completed yet and therefore at the moment the powdered herbal substance of *Prunus cerasus* L., pedunculus for oral use is not taken up into the monograph.

Table 4: Overview of evidence on period of use

Herbal substance/ preparation	**Indication**	**Posology and method of administration**	**Period of use**
Dried cherry stalks (*Prunus avium L.*, pedunculus)	Mild diuretic.	Infusion of 2-6 g herbal substance per 200 mL (3-5 min in hot water); decoction (immerse in water and boil during 10-20 min) then filter. Drink one cup 2-4 times per day.	Since 1976 in France, including monograph on tisanes in the French Pharmacopoeia

Accepted traditional use indication in the Monograph:

The wording of the indication in the monograph is harmonised with other traditional use monographs in the same therapeutic area: "Traditional herbal medicinal product used for the relief of symptoms associated with minor urinary tract complaints in addition to the general recommendation of a sufficient fluid intake to increase the amount of urine."

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

***In vivo* experiment:**

Diuretic effect

The diuretic potential of cherry stalks (*Prunus cerasus* L., stipites and/or *Prunus avium* L., stipites) decoction (CSD) and a hydroethanolic (70% V/V) extract (CSE) was studied *in vivo* in Wistar rats and compared with control (saline) and furosemide 10 mg/kg as a positive control (n=6 per treatment arm). The CSD was prepared from 100 g powdered cherry stems in 1L boiling water (decoction time 20 min, personal communication), filtered and dried. The CSE was prepared by maceration of 100 g powdered cherry stems in 500 mL ethanol (70% V/V) and after filtration the procedure was repeated with the residue. Both extracts were combined and dried. The tested concentrations for both CSD and CSE were 125, 250 and 500 mg/kg isotonic saline solution. CSD and CSE produced a dose-dependent gradual increase of the urine output. After 5h the diuretic effect of 500 mg/kg CSE and all concentrations of CSD were significantly increased in comparison with the saline control ($p<0.05$).

After 24h the urine output with CSE (250 and 500 mg/kg) and all concentrations of CSD were significantly increased ($P<0.05$). The urine output with 500 mg/kg CSD and CSE at 24h was 6.5±0.4 mL and 6.1±0.4 mL respectively. The saline control gave a urine output at 24h of 4.16±0.37 mL and the positive control furosemide reached maximum urine output of 7.96±0.37 mL. The diuretic action of CSE (250 and 500 mg/kg) relative to the saline control was 1.34 and 1.45 respectively. For CSD (125, 250 and 500 mg/kg) the diuretic action in comparison with the saline control was respectively 1.26, 1.46 and 1.56. The diuretic action of furosemide was 1.91. In comparison to furosemide the diuretic activity was 0,7 and 0,8 respectively for CSE (250 and 500 mg/kg) and for CSD (125, 250 and 500 mg/kg) it was 0.65, 0.76 and 0.81 respectively (Babota *et al*. 2021).

The saluretic effect was also researched. CSE and CSD were both associated with an increase of urinary excretion of Na^+ (U_{Na}) and K^+ ions (U_K). The most significant excretion was produced by the 500 mg/kg dose of CSD with U_{Na} and U_K values of 3.84±0.64 and 2.71±0.32 mEq/kg, 24 h after administration, compared with 6.32±0.84 and 5.31±0.44 mEq/kg respectively for furosemide. Both CSE and CSD produced a clear kaliuretic effect. The fractional excretion of sodium ions (FE_{Na}), defined as the percentage of sodium ions filtered by the kidneys and not reabsorbed, was calculated at 24 h. The experiment showed a net increase of FE_{Na} (6.81%) for the reference diuretic drug furosemide, which specifically inhibits the sodium–potassium–chloride symporter in the thick ascending limb of the loop of Henle, and a moderate increase of FE_{Na} (2.14–2.42 and 3.72–4.58%) for CSE and CSD at doses of 250 and 500 mg/kg (Babota *et al*. 2021).

Table 5: Overview of the main non-clinical data/conclusions

Herbal preparation tested	**Posology**	**Experimental model**	**Reference**	**Main non-clinical conclusions**
Dried aqueous extract from 100g powdered cherry stems in 1L boiling water (decoction); Dried hydroethanolic extract (70% V/V) 100 g in 1L.	For both extracts: 125, 250 and 500 mg/kg	Wistar rats *in vivo* (n=6 per treatment arm)	Babota *et al*. 2021	Dose dependent statistically significant increase in urine output after 5h for dried hydroethanolic extract 500 mg and dried decoction (125, 250 and 500 mg) and after 24 h for dried hydroethanolic extract (250 and 500 mg) and dried decoction at all concentrations.

3.1.2. Secondary pharmacodynamics

***In vitro* experiment:**

- Antioxidant activity

Two different types of methanol/water (7:3) extracts of *Prunus avium* L., stipites (with or without ultrasonification) were tested for their total antioxidant activity (TAA) in an *in vitro* bioassay, using 2,2'-azinobis-3-ethylbenzothiazoline-6-sulphonate (ABTS). For each sample, several dilutions (100 µL) in decreasing concentrations starting from 5 mg × mL–1, were allowed to react with a fresh ABTS solution (900 µL), and then the absorbance was measured 6 min after initial mixing. Both extracts showed an antioxidant activity that was concentration dependent. The half maximal inhibitory concentration (IC_{50}) was determined in order to compare the TAA, and lower IC_{50} means better radical scavenging activity. The IC_{50} was 2.2 mg/mL and 4.2 mg/mL respectively (Aires *et al*., 2017).

Chemical analysis of subcritical water extracts of *Prunus avium* L. and *Prunus cerasus* L., stipites showed that the two samples were similar. GC-MS showed that they contained alcohols, fatty acids,

organic acids and other organic compounds. Bioassays showed that the extracts were powerful antiradicals and antioxidants. Anti-proliferative properties measured by MTT-test showed cytotoxicity against different tumor cell lines (Svarc-Gajic *et al*., 2018).

Jesus (2019) showed that an infusion of *Prunus avium* L., stalks had antioxidant activity in the DPPH assay (IC_{50} 38.29 mcg/mL), the Nitric oxide assay (IC_{50} 99.99 mcg/mL) and in the superoxide radical assay (IC_{50} 23.28 mcg/mL).

Water extract (1 g sample in 100 mL hot water during 5 min) of 4 different commercial brands of *Prunus avium L.,* stipites showed antioxidant activity in an in vitro bioassay using DPPH, FRAP or ORAC (Peixoto *et al.*, 2020).

Nunes (2022ii) showed that a water extract from *Prunus avium* L., stems had a significant positive influence on 24 h cell viability in an *in vitro* assay with RAW macrophages that were treated with lipopolysaccharide.

- Antimicrobial activity

Two different types of methanol/water (7:3) extracts of *Prunus avium* L., stipites (with or without ultrasonification) were tested for their antimicrobial properties. The min inhibitory concentration (MIC) was between 0.13-0.25 mg/mL on three different *E. coli* strains (Aires 2017).

Methanolic extracts of two different varieties of *Prunus avium* stalks were tested for their antimicrobial properties. The MIC against *Bacillus cereus* was between 7.5-270 mcg/mL. It was also shown that the stalk extracts had significant inhibitory effect on bacterial swarming motility. Swarming is an important factor in biofilm formation (Önem *et al.*, 2021).

- Other effects

Jesus (2019) reported that an infusion of *Prunus avium* L., stalks inhibited α-glucosidase (IC_{50}=3.18 mcg/mL), haemoglobin oxidation (IC_{50}=25.77 mcg/mL), lipid peroxidation (IC_{50}=47.29 mcg/mL) and haemolysis (IC_{50}=3.36 mcg/mL). None of the tested preparations have shown hepatotoxicity against normal primary cells (Bastos *et al.*, 2015).

3.1.3. Safety pharmacology

No data available.

3.1.4. Pharmacodynamic interactions

No data available.

3.1.5. Conclusions

A diuretic effect of *Prunus avium* L., stipites (decoction and hydroethanolic extract) was demonstrated in a four arm study in rats using furosamide as a positive control. The results of the study by Babota *et al.* (2021) support the traditional use of *Prunus avium* L., stipites as a diuretic. The clinical relevance of these effects in rats are not known.

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

3.3.1. Single dose toxicity

No data available.

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 toxicology data are not available.

3.4. Overall conclusions on non-clinical data

Results from experimental studies on cherry stalks to support the proposed indication are limited to one relevant study in rats. The reported pharmacological effect is supporting the traditional use as a diuretic.

Specific data on pharmacokinetics and interactions are not available.

No toxicological data are available.

As there is no signal of a safety risk together with the fact that the product has a long tradition of use, oral administration of cherry stalks can be regarded as safe in the specified condition of use.

There is no information on reproductive and developmental toxicity, the use during pregnancy and lactation is not recommended. The use in children and adolescents under 18 years is not recommended due to lack of adequate data.

Tests on genotoxicity and carcinogenicity have not been performed.

A European Union List entry cannot be recommended from a non-clinical point of view.

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

The diuretic potential of powdered cherry stalk (*Prunus avium* L.) was evaluated in 13 healthy volunteers (5 males, 8 females; 20-40 years old) by measuring urinary volume, osmolality and concentration of electrolytes (sodium, potassium, chloride and calcium) (Hooman *et al.*, 2009). The posology was based on folk medicine: two capsules containing 335 mg powdered cherry stalk per 8 hours for 24 hours (equivalent to a daily dose of 2 g). The control group was given equivalent amount of corn starch per capsule. Evaluation was performed for a 24 hours period after administration of the last dose. After 1 week the verum and placebo-groups were switched.

The powdered cherry stalks was associated with a significant increase in the mean urine volume (p=0.001). Furthermore, an association was found with a significant increase in the concentration of urine-calcium, -sodium and -chloride, but the amount of urine-potassium and osmolality did not change (see table below).

Table 6: The mean (SD) of urinary analyses before and after use of *Prunus avium* L., stalk powder

	Placebo (n=13)	*C. avium* stalk powder (n=13)	Point estimate	95% Confidence interval of the difference between *C. avium* and placebo Lower upper	P value
Urine volume (mL)	808.0 (311.19)	1037.5 (338.29)	-229.5	-258.19 -83.3	0.001
Urine calcium (mg/dl)	124.61 (91.20)	181.15 (90.51)	-56.54	-79.04 -34.0	0.0001
Urine sodium (mEq/L)	116.38 (50.73)	134.84 (45.65)	-18.46	-31.12 -5.8	0.008
Urine chloride (mEq/L)	109.84 (41.52)	128.30 (34.12)	-18.46	-30.39 -6.5	0.006
Urine potassium (mEq/L)	43.26 (22.4)	45.15 (16.98)	-1.89	-15.95 12.1	NS
Urine osmolality (mosm/kg/H_2O)	764.15 (240.31)	857.15 (215.63)	-93.00	-241.21 55.2	NS

The milliequivalent (mEq) is the unit of measure often used for electrolytes. It indicates the chemical activity, or combining power, of an element relative to the activity of 1 mg of hydrogen. Thus, 1 mEq is represented by 1 mg of hydrogen (1 mole) or 23 mg Na^+, 35.5 mg Cl^- or 39 mg K^+.
Mean urine volume was 808±311 mL in the control group versus 1037±338 mL for the cherry stalks (p=0.001). Mean calcium was 124.6±91 mg/dl for control vs 181±90 mg/dl for cherry stalks, an increase with 45% (p=0.0001); urine sodium 116±51 mEq/L in the control group versus 135±46

mEq/L for the cherry stalks, an increase with 16% (p=0.008) and chloride 110±42 mEq/L for the control group versus 128±34 mEq/L for the cherry stalks, an increase with 16% (p=0,006). This observation was the same for both females and males (Hooman *et al.*, 2009).

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

No data available.

4.2. Clinical efficacy

4.2.1. Dose response studies

No data available.

4.2.2. Clinical studies

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 pharmacodynamic plausibility of traditional use of cherry stalks (*Prunus avium* L.) as a diuretic is supported by one small but relevant study in healthy volunteers, however, the clinical relevance in symptoms associated with minor urinary tract complaints has not been established. The published clinical data are not sufficient to support a WEU indication for cherry stalks.

5. Clinical Safety/Pharmacovigilance

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

Hooman *et al*. (2009) stated that no adverse reaction was observed (see section 4.2.2).

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

Delflosse (1998) indicated that the literature consulted did not indicate any secondary toxic effect for *Prunus cerasus* pedunculus.

Verhelst (2010) stated that cherry (*Prunus avium* L.) stalks can be used safely.

Babota *et al.* (2021) state that cherry (*Prunus avium* L.) stalks are a valuable and less exploited by-product with potential applications as a mild and safe diuretic agent.

Vigibase was searched on 5 June 2023 with the search terms *Prunus avium* L. and *Prunus cerasus* L. stems.

Two cases were retrieved. One was a report on the use of the French product that is taken up in this AR. The reaction that was reported was hyponatraemia. A causal relationship could not be assessed, because the description of the case was limited and there were also other herbal products used concomitantly.

The 2nd report was from Morocco. The reported side effects were vertigo and abdominal pain. Also in this case the use of *Prunus cerasus* L. was combined with another herb and also the description of the case was limited, not allowing a causal relation assessment.

In both cases the patients were recovered after having stopped the intake of the herbal products.

Eudravigilance was searched on 7 June 2023 with search term "Prunus avium stem".

One case was retrieved reporting headache and cloudy/unclear urine. No concomitant medicines were reported.

Assessors comment:

Only one case report was retrieved from Eudravigilance and two from Vigibase. The available information is not sufficient to include an adverse reaction in the MO section 4.8.

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.

5.5.2. Contraindications

The accepted wording in the Monograph: Hypersensitivity to the active substance.

5.5.3. Special warnings and precautions for use

Hooman *et al*., 2009 stated that cherry stalks have also been used as a traditional medicine for treating renal stones and because of the increased urinary excretion of calcium, sodium and chloride they warn that it should be used with precaution in patients with kidney stones and also in patients having any disorders associated with calcium, sodium and chloride deficiency.

The accepted wording in the Monograph: The use is not recommended in children under 18 years of age because of lack of available experience. If urinary tract complaints worsen and symptoms such as fever, dysuria, spasm, or blood in the urine occur during the use of medicinal product, a doctor or a qualified health care professional should be consulted.

5.5.4. Drug interactions and other forms of interaction

No data available.

5.5.5. Fertility, pregnancy and lactation

No data available.

5.5.6. Overdose

The accepted wording in the monograph: No case of overdose has been reported.

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

According to the available data presented, cherry stalks can be safely used in the usual dosage and in the traditional dosage form.

However, cherry stalks cannot be recommended during pregnancy or breast-feeding and in children under 18 years of age due to lack of adequate data.

The use of cherry (*Prunus avium* L.) stalks is contraindicated in patients with hypersensitivity to cherry stalks.

As the effect on calcium, sodium and chloride excretion were within the normal values and the studies population was very limited the results do not warrant a warning.

6. Overall conclusions (benefit-risk assessment)

In this assessment report all available information has been gathered about the traditional use of *Prunus avium* L., pedunculus and *Prunus cerasus* L., pedunculus (cherry stalks), safety and pharmacodynamic plausibility. The peduncles of both species are considered exchangeable, because both are mentioned in the monograph of the French pharmacopoeia. There is sufficient evidence for a traditional use of more than 30 years of which at least 15 years in the European Union, therewith fulfilling the requirement as a traditional herbal medicinal product.

A diuretic effect of *Prunus avium* L., pedunculus was measured *in vivo* in rats, using furosemide as positive control (Babota *et al*., 2021). In a cross-over clinical trial, although the amount of subjects tested in the clinical trial was limited (13), a statistical significant effect on excreted urine volume was measured with cherry stalks in comparison to the control (Hooman *et al.*, 2009). The published clinical study is not sufficient to support a WEU indication for cherry stalks, but nonetheless is in support of traditional use based on pharmacodynamic plausibility and on long standing use and experience.

Thus, the following indication is considered justified:

Traditional herbal medicinal product used for the relief of symptoms associated with minor urinary tract complaints in addition to the general recommendation of a sufficient fluid intake to increase the amount of urine.

For the preparations in the monograph all the requirements for TU (self-medication character, specified strength/posology, appropriate route of administration, period of traditional use, plausibility and safety) are met for *Prunus avium* L. and/or *Prunus cerasus* L., pedunculus.

Based on the ongoing traditional use as a diuretic and the absence of reported safety issues it can be concluded that the product is not intrinsically harmful in the specified condition of use. We can consider that the safety of cherry stalks is proper in the usual dosage. However, cherry stalks cannot be recommended during pregnancy or breast-feeding and in children under 18 years of age due to lack of adequate data. Furthermore, the following warnings should be taken up:

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

Because adequate fluid intake is required during treatment (see section 4.2. Posology and method of administration), *Prunus avium* L. and/or *Prunus cerasus* L., pedunculus is not recommended for patients with conditions where reduced fluid intake is advised by a medical doctor.

If the symptoms worsen during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.

No constituent with known therapeutic activity or active marker can be recognised by the HMPC.

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

Annex

List of references