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Committee on Herbal Medicinal Products (HMPC)

# Assessment report on *Fumaria officinalis* L. herba

Draft – Revision 1

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) | | *Fumaria officinalis* L. herba |
| Herbal preparation(s) | | a) Comminuted herbal substance<br>b) Powdered herbal substance<br>c) Dry extract (DER 3.5-5:1), extraction solvent water<br>d) Liquid extract (DER 1:1), extraction solvent ethanol 25% V/V<br>e) Tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent ethanol 45% V/V<br>f) Juice of fresh plant |
| Pharmaceutical form(s) | | Comminuted herbal substance as herbal tea for oral use.<br>Herbal preparations in solid or liquid dosage forms for oral use. |
| First assessment | Rapporteur | I Chinou |
| | Peer-reviewer | G Calapai |
| Revision | Rapporteur | I Chinou |
| | Peer-reviewer | A Assisi |

Note: This draft assessment report is published to support the public consultation of the draft European Union herbal monograph on *Fumaria officinalis* L. herba. 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.

# *Table of contents*

# 1. Introduction

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

- Herbal substance(s)

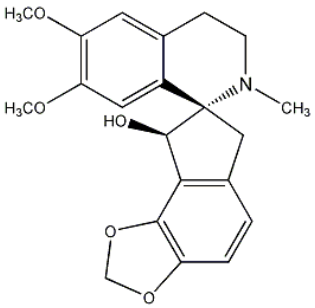
Fumariae herba, common fumitory herb, consists of the dried, above-ground parts of *Fumaria officinalis* L. (fam. Papaveraceae), gathered during the flowering season, as well as their preparations in effective dosages (Blumenthal 1998).

Fumitory is an annual plant of somewhat variable characteristics, often resembling a bush but also growing as a low trailing shrub. It has a grey, pointed leaves that at a distance give the plant a wispy appearance of smoke (hence the common name). The pink-purple flower blooms in spring. The plant is a widely dispersed and can be found in gardens, slopes and in wastelands.

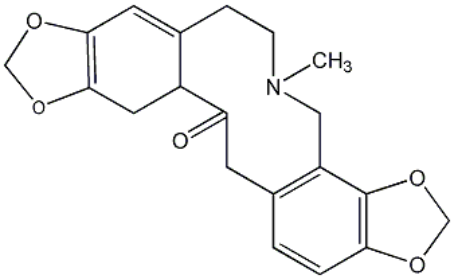
According to the European Pharmacopoeia (No 1869), the whole or fragmented dried aerial parts of *Fumaria officinalis* are harvested in full bloom. They contain a minimum of 0.40% of total alkaloids, expressed as protopine ($C_{20}H_{19}NO_5$=353.4).
Fumitory comprises of the dried or fresh flowering plant *Fumaria officinalis* is used in herbal medicine. It is an ingredient of preparations used mainly for gastrointestinal and biliary-tract disorders (Ph. Eur. 10$^{th}$ Ed. 07/2015:1869 corrected 9.2; Martindale 1996).

According to Goetz *et al.* (2009), British Herbal Pharmacopoeia (1976), British Herbal Compendium (1992) and Paris & Moyse (1981) chemical constituents are:

- Alkaloids (0.3-1% calculated as protopine (0.13%) even though several different types of alkaloids have been isolated and structurally elucidated derivatives
- Protopines, the quantitatively predominant type, as protopine (fumarine) and cryptopine. Recently fourteen isoquinoline alkaloids were identified, with the principle ones being protopine, cryptopine, sinactine, parfumine, fumariline, fumarophycine, and fumaritine (Vrancheva *et al.* 2016; Zhang *et al.* 2020; Raafat & El-Zahaby 2020). Two new isoquinoline alkaloids, named fumaranine and fumarostrejdine, have been structurally determined (Chlebek *et al.* 2016)
- Protoberberines: aurotensine, stylopine, N-methylsinactine and others
- Spirobenzylisoquinolines: fumaritine, fumaricine and fumariline and others
- Benzophenanthridines such as sanguinarine and corydamine (traces)
- Indenobenzazepines: fumaritrididine and fumaritrine (Preininger 1975; Forgacs *et al.* 1982, 1986; Wawrzynowicz *et al.* 1968; Hermansson & Sandberg 1973; Mardirossian *et al.* 1983)




Fumaricine




Protopine

- Flavonoids: principally glucosides of quercetin such as isoquercitrin, rutin, quercetin-3,7-diglucoside-3-arabinoglucoside (Torck *et al.* 1971; Massa *et al.* 1971)
- Acids: chlorogenic and caffeic acids, also fumaric acid, caffeoylmalic acid and other aliphatic acids (Massa *et al.* 1971; Boegge *et al.* 1995; Hahn & Nahrstedt 1985)
- Other constituents: bitter principles, mucilage, resin and potassium salts (Barnes *et al.* 2002)

This monograph refers only to Fumariae herba.

- Herbal preparation(s)

a) Comminuted herbal substance

b) Powdered herbal substance

c) Dry extract (DER 3.5-5:1), extraction solvent water

d) Liquid extract (DER 1:1), extraction solvent ethanol 25% V/V

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

f) Juice of fresh plant

- 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*

The assessment is based on the sources mentioned in the list of references.

Search engines used: "Search terms: *Fumaria officinalis* L., Fumariae herba, fumitory, fumitory alkaloids

Medical databases: Pubmed, Cochrane library; key words: Databases: Pubmed, Medline, Heal-Link, Scopus, google scholar (December 2020, March 2021).

Toxicological databases: Toxnet; same key words

Pharmacovigilance resources: EudraVigilance, VigiLyze (March, May 2022)

No data available from National pharmacovigilance data

Data from EU and non-EU regulatory authorities: only from EU market overview

Other resources: Library of the National and Kapodistrian University of Athens (Pharmacy and Pharmacognosy 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

The following tables abridge information provided by the National Competent Authorities (NCAs) on medicinal products on the market in the European Union (EU)/European Economic Area (EEA) Member States containing Fumariae herba (*Fumaria officinalis* L, herba) or its preparations as a single active substance or as a combination of active substances.

**Information on medicinal products marketed in the EU/EEA**

Table 1: Overview of data obtained from marketed medicinal products

| Active substance | Indication | Pharmaceutical form | Regulatory Status |
|---|---|---|---|
| Dry extract, extraction solvent water, DER 5:1, not less than 2.5 mg alkaloids calculated as protopine per film coated tablet.<br>1 film-coated tablet contains 250 mg extract | Pain in the biliary system in case of dyskinesia of the biliary duct, complaints after chole-cystectomia, cholelithiasis when surgery is not possible. | Film coated tablet<br>3 times daily, 1-2 tablets | AT, WEU<br>Since 1978 |
| Dry extract, extraction solvent water, DER not specified, not less than 1.5% alkaloids calculated as protopine.<br>1 film-coated tablet contains 250 mg extract | Dyskinesia of the biliary duct; pain in case of cholelithiasis when surgery is not possible; pain in case of cholecystitis and cholangitis; post-chole-cystectomia syndrome; post-hepatic syndrome with cholestasis | Film coated tablet<br>Adults<br>3 times daily, 1-2 tablets, single dose: 250 mg<br>Daily dose: 750 mg - 1.5 g | AT, WEU<br>Since 1992 |
| Powdered aerial parts | Traditionally used to promote urinary and digestive elimination functions. Traditionally used as a choleretic and cholagogue. | 220 mg, 3-5 times daily, (1100 mg maximum daily dose) | FR, TU<br>Since 1982 |

| Active substance | Indication | Pharmaceutical form | Regulatory Status |
|---|---|---|---|
| Dried extract (DER: 3.5-4.5:1), solvent water<br>Coated tablet | Traditionally used to promote urinary and digestive elimination functions. | Adults<br>4 times daily, 250 mg of extract/tablet (1000 mg daily) | FR, TU<br>Since 1963 |
| Dried extract (DER: 3.5-4.5:1), solvent water<br>Hard capsules | Traditionally used to promote urinary and digestive elimination functions. | 2 times daily, 200 mg of extract/capsule | FR, TU<br>Since 1987 |
| Powdered herbal substance for oral use as herbal tea | Traditionally used digestive complaints, difficult digestions. | oral use in adults<br>2g/250 ml divided in 2-3 times daily,<br>2-6 g/day | ES, TU<br>Since 1985 |
| Powdered herbal substance for oral use in capsules (160 mg) up to three times daily | Dyspeptic symptoms; THMP to facilitate difficult digestions; spastic discomfort in the gastrointestinal tract (gall bladder). | 6-8 capsules (160 mg) daily, 960-1280 mg/day | ES, TU<br>Since 1993 |
| Fumariae herba comminuted herbal substance | Spastic discomfort in the area of the gall bladder and bile ducts, as well as the gastrointestinal tract | Adolescents, adults elderly<br>Herbal tea<br>Single dose: 1.6 g of the comminuted herbal substance in 150 ml (rather 250 ml in the existing MO) of boiling water as herbal infusion<br>Daily dose: 4.8 – 6.4 g (means 3-4 times)<br>If the symptoms persist longer than 1 week or are recurrent, a doctor should be consulted.<br>The use in children under 12 years of age has not been established due to lack of adequate data. | DE, WEU<br>Since 1986<br>Standard Marketing Authorisation according to section 36 of the German Medicinal Products Act |

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**

In Austria:

| | | | |
|---|---|---|---|
| Combination 275.1 mg dry extract, extraction solvent water, DER 4-6:1, not less than 1.5% alkaloids calculated as protopine. 83.1 mg dry extract of Silybi mariani fructus (no more details) | Supportive treatment of dyskinesias of the biliary duct (also after cholecystectomia) in cases of an impairment of the liver. | Hard capsules<br>3 times daily 2 tablets | AT, WEU<br>Since 1988 |

In Poland:

Combination product containing: *Aloe ferox*, *Fumaria officinalis* L., 1 mg of boldine (tablet), 15 mg of dry extract of *Aloe ferox* Miller corresponding 3.150-2.745 mg of hydroxy-anthraquinones counted as aloin, extraction solvent: purified water; 10 mg of dry extract of *Fumaria officinalis* L., herba, DER 4-6:1, extraction solvent: purified water; 1 mg of boldine (substance)
Indication: Traditionally in digestion disturbances (bloating, feeling of fullness, belching) with bile excretion disturbances and slight spasms.
Pharmaceutical form, strength, posology and duration of use: Traditionally in digestion disturbances (bloating, feeling of fullness, belching) with bile excretion disturbances and slight spasms.
Adults: in digestive disorders - mild spasmodic gastro-intestinal complaints: 1 to 2 tablets before meals, no more than 4 times a day. Do not be taken >8 tablets a day; in occasional constipation: 3 to 5 tablets once a day, before bedtime. Up to 2-3 times a week
On the market since 2000.

**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

No data available.

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

The name of fumitory is said to be derived either from the fact that its whitish, blue-green colour gives it the appearance of smoke rising from the ground, or according to Pliny and Olivier de Serres (XIV century) because the juice of the plant brings on such a flow of tears that the sight becomes dim as with smoke (Delaveau 1980), and hence its reputed use in affections of the eye. The leaves have no odour but a bitter and salty taste.

Fumitory has been known since antiquity and was described in herbals from the Middle-Ages. It was a predominantly the Mediterranean genus that was once used medicinally.
Traditionally the plant has been used as digestive and diuretic.

Fumaria extracts may be useful in the management of disorders of hepatobiliary tract, spastic discomfort in the area of the gallbladder bile ducts as well as gastrointestinal tract.
Unproven uses: in folk medicine, the herb has been used for skin diseases, constipation, cystitis, arteriosclerosis, rheumatism, arthritis, as a blood purifier, for hypoglycaemia and infections (PDR 2007).

Traditional preparation involved expressing the juice and evaporating, while the plant has also been used to treat chronic eczema, cutaneous eruptions and other dermatological conditions (The Review of Natural Products 2005). The use as an eye lotion in conjunctivitis has been reported (British Herbal Pharmacopoeia 1976).

Physicians and writers from Dioscorides to modern times value its depurative properties. The herbal drug has been monographed in old official pharmacopoeias (e.g. Codex Medicamentarius Gallicus Pharmacopée Française 1908; British Herbal Pharmacopoeia 1976; Madaus 1979; Les Cahier de l'Agence 2008; Wichtl 1998; HagerROM 2006; Blumenthal 1998; British Herbal Compendium 1992). It was also included in the Pharmacopée Française of 1908 for its diuretic and depurative properties.

Fumitory was officially recognized in 1986 by the French Health authorities (Bulletins Officiels N° 86/20 bis and N° 90/22 bis, Direction de la Pharmacie et du Médicament) as an herbal remedy traditionally used in renal and digestive elimination functions and to help digestion. Moreover, fumitory is on the United Kingdom General Sales List (GSL) and is approved by the German Commission E Monograph (Blumenthal 1998). It has been used as a traditional remedy for a long time without safety problems, in Europe and worldwide, for more than 30 years.

The flowers are used to make a yellow dye for wool.
Fumitory is listed by the Council of Europe as a natural source of food flavouring (category N3). This category indicates that fumitory can be added to foodstuffs in the traditionally accepted manner, although there is insufficient information available for an adequate assessment of potential toxicity (Barnes *et al.* 2002).

Type of tradition: European.

Fumitory (shatara) has been used in Afghanistan for the treatment of asthma (Delaveau 1980), while in India fumitory has been reported that is used against dyspeptic disorders (Fiegel 1971).

Fumitory has been used widely ethnomedicinally in five selected remote regions of Pakistan plants against gastrointestinal complaints (Tariq *et al.* 2015).

A summary of historical data on the use of Fumariae herba (*Fumaria officinalis* L, herba) is included in Table 2.

Table 2: Overview of historical data

| **Herbal preparation** | **Documented use / Traditional use** | **Strength (where relevant), Posology, Duration of use** | **Reference** |
|---|---|---|---|
| Liquid extract (1:1), extraction solvent | Used for relief of digestive | *Adults and elderly*<br>2-4 ml (30-50 drops) before | From literature references<br>British Herbal |

| Herbal preparation | Documented use / Traditional use | Strength (where relevant), Posology, Duration of use | Reference |
|---|---|---|---|
| ethanol 25% V/V<br>Tincture (1:5), ethanol 45% V/V<br>Juice of fresh plant | /dyspeptic problems (such as dyspepsia). | meals<br>Daily dose 1-4 ml before meals<br>Daily dose 3.5-4 g | Pharmacopoeia 1976; Van Hellemont 1986; British Herbal Compendium 1992; Barnes *et al.* 2002; PDR 2007; Goetz *et al.* 2009) |

## *2.3. Overall conclusions on medicinal use*

According to the overview of the European market, the herbal preparations a), b) and c) fulfil the criteria of the thirty years of period of medicinal use, including at least 15 years in Europe. The herbal preparations d), e) and f) were found in literature references, also for at least 30 years (British Herbal Pharmacopoeia 1976 and in later versions based to that).

For Fumariae herba, 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 easily fulfilled. The evidence on traditional medicinal use is supported by a large number of publications providing consistent information.

A summary of evidence on period of medicinal use of Fumariae herba (*Fumaria officinalis* L, herba) is included in Table 3.

Table 3: Overview of evidence on period of medicinal use

| Herbal preparation Pharmaceutical form | Indication | Posology, Strength | Period of medicinal use |
|---|---|---|---|
| a) Comminuted herbal substance (Fumariae herba) as herbal tea for oral use. | Traditional herbal medicinal product used to promote digestive elimination functions (France).<br>Traditional herbal medicinal product for the symptomatic relief of digestive disorders such as dyspepsia and flatulence (Spain). | 2-6 g/day (2 g/250 ml), 2-3 times daily<br>To be taken 30 min before meals<br>**Duration of use**<br>Up to 2 weeks. | TU, Spain, Since 1985 |
| Comminuted herbal substance | Spastic discomfort in the area of the gall bladder and bile ducts, as well as the gastrointestinal tract | Adolescents, adults elderly<br>Herbal tea<br>Single dose: 1.6 g of the comminuted herbal substance in 150 ml of boiling water as herbal infusion<br>Daily dose: 4.8 – 6.4 g | Since 1986, DE, WEU, Standard Marketing Authorisation according to section 36 of the German Medicinal |

| Herbal preparation Pharmaceutical form | Indication | Posology, Strength | Period of medicinal use |
|---|---|---|---|
| | | (means 3-4 times)<br><br>If the symptoms persist longer than 2 weeks or are recurrent, a doctor should be consulted.<br><br>The use in children under 12 years of age has not been established due to lack of adequate data. In the current MO adolescents are also excluded | Products Act |
| b) Powdered herbal substance | Used to promote digestive functions | Single dose of 220 mg, up to 1100 mg of herbal substance daily | In France since 1982 |
| c) Dry extract (DER 3.5-5:1), extraction solvent water | As digestive | Single dose of 250 mg of extract, up to 1000 mg daily | In France since 1963 and in Austria since 1978 |
| d) Liquid extract (1:1), extraction solvent ethanol 25% V/V<br><br>e) Tincture (1:5), ethanol 45% V/V<br><br>f) Juice of fresh plant | As digestive | Liquid extract<br><br>2-4 ml daily (30-50 drops) before meals (divided between meals)<br><br>Tincture - daily dose 1-4 ml (divided between meals)<br><br>f) Juice<br><br>Daily dose 3.5-4 g | From the literature (British Herbal Pharmacopoeia 1976;<br><br>Van Hellemont 1986;<br><br>British Herbal Compendium 1992;<br><br>Barnes *et al.* 2002; PDR 2007; Goetz *et al.* 2009) |

# 3. Non-Clinical Data

***In vitro* and animal studies**

The herb has been used as amphocholeretic (Boucard & Laubenheimer 1966; Fiegel 1971; British Herbal Compendium 1992), mild antispasmodic on smooth muscle, mild diuretic and laxative (Reynier *et al.* 1977i).

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

### 3.1.1. Primary pharmacodynamics

A summary of the main non-clinical data/conclusions regarding Fumariae herba (*Fumaria officinalis* L, herba) is included in Table 4.

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

| **Herbal preparation tested** | **Posology**<br>*Strength*<br>*Dosage*<br>*Route of administration* | **Experimental model**<br>*In vivo/*<br>*In vitro* | **Reference**<br>*Year of publication* | **Main non-clinical conclusions** |
|---|---|---|---|---|
| Water extract (not further defined) | Oral use (no further data given) | *In vivo* | Boucard & Laubenheimer 1966 | The amphocholeretic activity of fumitory revealed showing that it has no effect on normal choleresis but modified bile flow which was artificially increased or decreased slowing down artificially increased flow and increasing reduced flow, together with light antispasmodic activity. |
| Water extract (not further defined) | Oral use (no further data given) | *In vivo* | Lagrange & Aurousseau 1973 | Fumitory extract inhibited the formation of gall bladder calculi |
| Water extract (not further defined) | Oral use (no further data given) | *In vivo* in rats | Reynier *et al.* 1977ii | preparations of the herb had no effect on normal choloresis but modified bile flow that had been artificially increased or decreased |
| *Plantago* | Oral use | *In vivo* | Denden *et al.* | The studied plant mixture showed |

| **Herbal preparation tested** | **Posology**<br>*Strength*<br>*Dosage*<br>*Route of administration* | **Experimental model**<br>*In vivo/*<br>*In vitro* | **Reference**<br>*Year of publication* | **Main non-clinical conclusions** |
|---|---|---|---|---|
| *major* together with *Fumaria officinalis* ethanolic extracts in Tunisia | | | 2010 | choleretic properties |
| Single substances alkaloid protopine from Fumitory | Oral use | *In vivo* | Van Hellemont 1986 | The alkaloid protopine has a contractile action on Oddi's sphincter in animals |

## 3.1.2. Secondary pharmacodynamics

***Antibacterial activity***

Bactericidal activity against the Gram-positive organisms *Bacillus anthracis* and *Staphylococcus* has been reported (Preininger 1975).

Antibacterial activity was evaluated using liquid medium against *Acinetobacter calcoaceticus*, *Propionibacterium acnes* and *Corynebacterium xerosis*. Evaluation of minimum inhibitory concentration (MIC) showed low values, indicating an interesting antibacterial capacity. The MIC of 0.33 mg/mL recorded against *Propionibacterium acnes* with alkaloid extracts showed the effectiveness of this plant as an antibacterial agent. The greater effectiveness of the acid fraction (AF) and the total alkaloid extract (TA) against the three strains tested was correlated to their richness in protopine with levels of 51.75% and 34.48%, respectively (Khamtache *et al*. 2016).

**Inhibition of enzymes (acetylcholinesterase, etc**

All of the investigated alkaloid extracts from fumitory have significantly inhibited acetylcholinesterase activity, ($IC_{50}$ 0.13 ± 0.01 mg extract/mL) (Vrancheva *et al*. 2016).

Several metabolites isolated in sufficient amounts were evaluated for their acetylcholinesterase, butyrylcholinesterase, prolyl oligopeptidase (POP), and glycogen synthase kinase-3β inhibitory activities. Parfumidine and sinactine exhibited potent POP inhibition activities ($IC_{50}$ 99±5 and 53±2 μM, resp.) (Chlebek *et al*. 2016).

**Antioxidant activity / antiulcer activity**

The crude extract of total alkaloids from fumitory and its fractions showed high antioxidant activity against the free radical DPPH ($IC_{50}$ NF (15.74 ± 0.04 μg/mL)), the 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid (ABTS) radical ($IC_{50}$ BF (70.71 ± 0.04 μg/mL)), and the hypochlorous acid radical ($IC_{50}$ NF (304.19 ± 0.29 μg/mL)), Total Antioxidant Capacity (TA (14.23 ± 0.04 mg eq ascorbic acid/g DM)), lipid peroxidation inhibition ($IC_{50}$ TA (41.67 ± 0.17 μg/mL))

and ferric reducing power (FRP) (BF (3.49 ± 0.11 mg eq ascorbic acid/g DM)) (Khamtache *et al*. 2016).

A methanolic extract of *Fumaria officinalis* showed inhibitory concentration ($IC_{50}$:35.5 µg/ml) and ascorbic acid the standard antioxidant showed inhibitory concentration ($IC_{50}$:20.10 µg/ml) in a DPPH assay (Khare & Upmanyu 2019).

Moreover, *in vitro* alpha-amylase inhibitory activity assay was performed on n-hexane, chloroform, methanol and water extracts of fumitory by using dinitrosalicylic acid. All the plant extracts showed variable values of alpha-amylase inhibition in terms of percentage with the aqueous extract giving the maximum inhibition (Fatima *et al*. 2019).

The antioxidant and antiulcer activities of Normacid syrup® (NS-a herbal combination containing fumitory) were evaluated in mice. Effects of NS (250 and 500 mg/kg, *p.o.*, for 14 days) were studied on pylorus ligation and diclofenac-induced ulcers. Antiulcer activity of NS was assessed from gastric secretion parameters, mucosal nitrite level and mucin content in gastric mucosa. The activity of antioxidant enzymes like super oxide dismutase (SOD), catalase (CAT), reduced glutathione (GSH) and lipid peroxidation (MDA) in the stomach tissue were quantified. Pre-treatment with NS significantly ($p<0.05$) reduced ulcer score and ulcer index in pylorus ligated (62.20–67.50 %protection) and diclofenac (64.19–70.85 %protection)-induced gastric ulcers. NS decreased the gastric volume, free acidity and total acidity and increased the pH of gastric fluid. Simultaneously, the level mucosal nitrite and mucin content were increased significantly ($p<0.001$). In addition, pre-treatment with NS significantly increased activities of SOD ($p<0.001$), CAT ($p<0.001$), GSH ($p<0.05$ to $p<0.001$), and reduced the MDA level ($p<0.001$). The antiulcer activity might be due to its antisecretory, cytoprotective and antioxidant mechanism (Maheshwari *et al*. 2014).

Petroleum ether, ethyl acetate, chloroform and methanol fumitory's extracts were investigated *in vitro* and their antioxidant activity was evaluated by DPPH and ABTS methods showing that the methanolic extract had the highest total phenolic and flavonoids contents and exhibited very strong antioxidant activity (Edziri *et al*. 2020)

**Anticoagulant activity**

The anticoagulant activity of a series of fumitory extracts (petroleum ether, ethyl acetate, chloroform and methanol ones)were evaluated by prothrombin time (PT) and activated partial thromboplastin time (aPTT) tests, showing the methanolic extract exhibited such properties. (Edziri *et al*. 2020).

**Hypoglycaemic action**

Effect of aqueous and methanolic extracts of *Fumaria officinalis* on blood glucose was evaluated in normo-glycaemic rats and alloxan induced diabetic rats. Glimepiride 0.2 mg/kg was used as standard therapy in diabetic rats. Results showed that methanolic extract exhibited the maximum percentage inhibition of DPPH (86.30%) and alpha-amylase inhibition (94.01%) at 500 µg/ml and 16 mg/ml concentration respectively. Administration in normo-glycaemic rats did not show any significant decrease in blood glucose level at 500 and 750 mg/kg dosage. Aqueous and methanolic extracts exhibited a significant hypoglycaemic effect ($p<0.05$) at all doses. (Fatima *et al*. 2019)

**Cytotoxicity**

Cytotoxicity and apoptosis induction by *Fumaria officinalis* extracts on two leukaemia and nine multiple myeloma (MM) cell lines was investigated. Chloroform (CF) and ethyl acetate (EF) fractions showed drastic cytotoxic effect on CCRF-CEM and CEM/ADR 5000 cells. NCI–H929 cell line exhibited higher sensitivity against CF, while EF demonstrated its higher cytotoxicity on OPM-2 cells with $IC_{50}$ value

14.80 ± 1.70 and 28.13 ± 1.38 µg/mL respectively. Flow cytometric and morphological studies confirmed that CF and EF induced apoptosis in NCI–H929 cells by loss of MMP, generation of ROS and obvious morphological variations. In DNA histograms, up to 50% of the cells were accumulated by CF and 44% by EF in the sub-G0/G1 phase following 72 h treatment. Moreover, two isoquinoline alkaloids and four flavonoids were identified in the active fractions (Adham *et al*. 2021).

**IBS management**

Fumitory has been used against irritable bowel syndrome (IBS) in a herb combination with *Curcuma xanthorrhiza* and did not demonstrate any benefits in IBS management (Rahimi & Abdollahi 2012), while has been also suggested among herbs for the management of colitis (Akkol *et al*. 2020).

**Other properties**

*Fumaria officinalis* L. extract has shown arrhythmic activity (no further information) (Gorbunov *et al*. 1977).

*Plantago major* together with *Fumaria officinalis* ethanolic extracts in Tunisia, after *in vivo* oral use exhibited antiallergic properties (Denden *et al*. 2010).

In two *in vivo* studies on 30 rabbits (divided in three groups of ten substances each one) received 200mg/kg and 400mg/kg of *Fumaria officinalis* hydroalcoholic extract for 28 days (groups two and three, respectively). Several haematological parameters (such as creatinine level, packed cell volume (PCV), Hb, mean corpuscular volume (MCV), Red Blood Cells (RBC) and total and differential White Blood Cells (WBC) count were measured (by enzymatic methods) after 28 days, showing that serum creatinine concentrations significantly increased in group taking high doses of fumitory (Khoshvaghti *et al.* 2013), while is exhibited decrease in PCV, Hb, MCV, RBC, total WBC and neutrophil percentage in the two experimental groups when compared with the control group. Moreover, it increased lymphocyte, eosinophil and monocyte percentages. The results could suggest a potential further use of fumitory in the experimental management of anaemia and immunity-dependent disorders (Khoshvaghti *et al.* 2014).

A preparation of the alkaloids of fumitory (mainly protopine) has showed antihistaminic, hypotensive, bradycardic and sedative activities in small doses *in vivo* in animals (Goetz *et al*. 2009).

Moreover, in another *in vivo experiment* in rats, the oral administration of a single dose (250 mg/kg bw) of fumitory produced an increase in urinary volumetric excretion as well as of excretion of $Na^+$ and $K^+$, 24h after the administration (Păltinean *et al.* 2017).

## 3.1.3. Safety pharmacology

No data available.

## 3.1.4. Pharmacodynamic interactions

No data available.

## 3.1.5. Conclusions

Fumitory has been used as an herbal remedy in digestive elimination functions and to help digestion in Europe, for more than 30 years. The published data that refers to the indications and preparations is very limited.

Non-clinical data are referred on choleretic amphocholeretic, mild antispasmodic on smooth muscle, (Reynier *et al*. 1977*;* Lagrange & Aurousseau 1973; Boucard & Laubenheimer 1966; British Herbal Compendium 1992) supporting the traditional use of fumitory in indigestion towards the suggested posology, method of administration and indication in the EU herbal Monograph on *Fumaria officinalis* herba.

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

No pharmacokinetic data on Fumaria extracts have been found or reported, while there is only limited data on protopine alkaloid purified from Fumaria extracts.

The alkaloid protopine, the major secondary metabolite was extracted from *Fumaria officinalis* and purified by column chromatography. Urine samples were collected from horses and a human volunteer that had been administered either *Fumaria officinalis* or protopine free base. Plant and urine samples were acetylated and analysed by GC-MS after solid-phase extraction (SPE). The urinary metabolites of protopine were identified as 4,6,7,13-tetrahydro-9,10-dihydroxy-5-methyl-benzo[e]-l,3-benzodioxolo [4,5-1][2] benzazecin-12(5H)-one, 4,6,7,13-tetrahydro-10-hydroxy-9-methoxy-5-methyl- benzo[e]-1,3-benzodioxolo[4,5-1][2] benzazecin-12(5H)-one and 4,6,7,13-tetrahydro-9-hydroxy-10-methoxy-5-methyl-benzo[e]-1,3-benzodioxolo[4, 5-l][2] benzazecin-12(5H)-one, chelianthifoline, isochelianthifoline and 2-O-desmethylchelianthifoline. The metabolic formation of the tetrahydroprotoberberines by closure of the bridge across N5 and C13 is rate limited and protopine-like metabolites accumulate only when the route is overloaded. Metabolism was qualitatively similar in the horse and human (Wynne *et al*. 2004).

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

The main constituents of fumitory include alkaloids (principally protopines, protoberberines, spirobenzyl-isoquinolines, benzo-phenanthridines and indeno-benzazepines types), flavonoids (principally glycosides of quercetin), acids (chlorogenic and caffeic acids, fumaric acid and other aliphatic acids).

### 3.3.1. Single dose toxicity

No data available.

### 3.3.2. Repeat dose toxicity

No data available.

### 3.3.3. Genotoxicity

Very limited genotoxicity data are available on fumitory according to scientific literature.

Very recently the antioxidant, anticoagulant and *in vitro* genotoxic properties of *Fumaria officinalis* L. have been investigated (Edziri *et al.* 2020).

*In vitro* toxic and genotoxic properties of several extracts (petroleum ether, ethyl acetate, chloroform and methanol ones) of *Fumaria officinalis* L. were assessed with respectively the Neutral red uptake method and the bacterial Vitotox test and comet assay in human C3A cells. This study showed that

methanolic extract had the highest total phenolic and flavonoids contents. The bacterial Vitotox test revealed absence of genotoxicity for all extracts. This was confirmed in the comet assay which was conducted on human C3A cells, except for the methanolic extract where DNA damage appeared to be significantly increased at non-toxic concentrations (Edziri *et al*. 2020).

### 3.3.4. Carcinogenicity

No data available.

### 3.3.5. Reproductive and developmental toxicity

No reproductive and developmental toxicity studies have been carried out on fumitory according to available scientific literature.

### 3.3.6. Local tolerance

No data available.

### 3.3.7. Other special studies

None reported.

### 3.3.8. Conclusions

Tests on reproductive toxicity and carcinogenicity have not been performed. Adequate tests on genotoxicity have not been performed.

## *3.4. Overall conclusions on non-clinical data*

Fumitory was officially recognized since 1986 by the French Health authorities (Bulletins Officiels N° 86/20 bis and N° 90/22 bis, Direction de la Pharmacie et du Médicament) as an herbal remedy traditionally used in renal and digestive elimination functions and to help digestion. Moreover, fumitory is on the United Kingdom General Sales List (GSL), and it is approved by the German Commission E Monograph. It has been used as a traditional remedy for a long time without safety problems, in Europe, for more than 30 years.

The published data that refers to the indications and preparations is very limited.

Non-clinical data on choleretic amphocholeretic, mild antispasmodic on smooth muscle, (Reynier *et al*. 1977i*;* 1977ii*;* Lagrange & Aurousseau 1973; Boucard & Laubenheimer 1966; British Herbal Compendium 1992) support the traditional use of *Fumaria officinalis* and preparations thereof in the proposed indication:
Traditional herbal medicinal product used for the relief of symptoms of indigestion (such as sensation of fullness, flatulence and slow digestion).

The efficacy of traditional herbal medicinal products is only plausible but not proven by clinical data. The reported pharmacological effects are not considered contradictory to the traditional uses Nevertheless, the safety must be guaranteed.

Specific data on pharmacokinetics and interactions are not available.

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

Tests on reproductive toxicity and carcinogenicity have not been performed. Adequate tests on genotoxicity 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.

### 4.2.1. Dose response studies

No data available.

### 4.2.2. Clinical studies (case studies and clinical trials)

There is a lack of clinical research assessing the effects of fumitory; therefore, rigorous randomised controlled clinical trials are required.

The following data on clinical studies has been found in the literature:

***Biliary disorders***

*Clinical trials*

Salembier (1967): A study on the effect of the aerosol 'Fumeterre' containing fumaria, on choleresis has been carried out in a group of 33 patients with external biliary drainage (no further information available).

Fablet *et al*. (1968): The therapeutic activity of the extract of *Fumaria officinalis* against the hepatobiliary syndrome and the depending migraines has been studied in a group of 101 patients (82 women and 19 men of 16-79 years old).

Heully *et al*. (1969): The effect of a water extract of Fumitory herba has been studied in a group of 20 persons *vis-a-vis* the choleretic result in a dose containing 500 mg of direct infusion in duodenal. The results appeared very variable and not comparable. The tolerability reported to the extract was good.

In a clinical study involving 105 patients with biliary disorders (hepatopathy, chololethiasis, post-operation cholocystectomy syndrome) favourable results were claimed (British Herbal Compendium 1992; Fiegel 1971). Doses of 2 tablets containing sprayed water extract (3-6:1) in tablets of 250 mg each, in a proposed dose of 2 tablets x 3 times per day were used for a period of 2-6 months. No detailed response has been given but a very good tolerability was reported.

In another clinical trial by Müscher (1971) an amphocholeretic herbal medicinal product (Fumitory herb water extract 4-6:1, in tablets containing 250 mg of sprayed water extract) was used for one year in a group of 178 patients with biliary disorders. Ninety-six (96) treated patients (20-70 years old) were suffering from biliary disorders (especially dyskinesia), taking doses of 3 tablets per day (two before the meals and the 3rd before sleep). The safety and tolerability were proven and for 64 patients the results were characterised as successful, especially against the symptoms of fullness and flatulence. Another 43 patients (40-70 years old) with diagnosed chololithiasis and post-operation syndrome were treated with 2 tablets containing 250 mg, 3 times daily for a period of 3 weeks, showing for 36 among them successful results, good tolerability and safety. In total, 125 patients among the 176 treated claimed favourable results. In all cases the tablets were taken before meals and the safety and tolerability were proven.

Roux (1977): In that clinical study 31 patients (16 men and 15 women, 25-78 years old) with biliary syndrome (either dyskinesia or low digestion and digestive complains (diarrhoea) have shown very positive amphocholeretic effects. The treatment lasted 15-30 days (depending on the problem) with doses of 2 dragees containing 250 mg of a water extract of fumitory (no further data were given).

The clinical experience with a *Fumaria officinalis* nebulisate (water extract of 4-6:1) as an amphocholinergic agent used in 64 patients suffering from biliary disorders (dyskinesia, hepatopathy etc) has been published by Zawodsky (1974). All patients were treated with 3 tablets containing 250 mg of the extract daily, for 21 days. No adverse effects were noticed, and a very good tolerability was reported.

Hunold (1975): The clinical experience with *Fumaria officinalis* (water extract of 4-6:1) in primary and secondary, organic or functional affections of the gall bladder and biliary system was checked in a group of 85 patients with no detailed information on the daily doses used during the trial.

Bourjat (1974): A clinical study has been carried out on the effect of trials of treatment with a water extract sprayed in tablets (nebulizate) of *Fumaria officinalis* against Xerostomia due to radiotherapy, because of pathological sclerose of salivary glands. The results were positive using 2 tablets containing 250 mg of water extract (water extract of 4-6:1) before each meal and before sleep.

*Double blind placebo clinical trial*

One double blind placebo clinical trial was performed in a group of 30 patients (20 women, 10 men of 26-57 years old) with different biliary disorders (dyskinesia, cholocystitis, hepatopathy, chololithiasis, post-operation cholocystectomy syndrome ) taking doses of 3 tablets of 'Fumaria-Nebulisat' (water extract 4-6:1) 250 mg per day (two before the meals and the 3rd before sleep) for 28 days. The safety and tolerability were proven, and for all 30 patients the results were described as positive, especially against the symptoms of fullness and flatulence (Kopp 1979).

*Open studies*

Kopp (1979): The Choleretic activity of an herbal medicinal product containing an extract of fumitory was studied in an open study in 18 patients for 10 days with favourable results. No data on the exact preparation or the posology are provided.

Zacharewicz *et al*. (1979): In an open study 45 patients (30 women and 15 men 28-59 years old) among them 27 with biliary dyskinesia problems (20 hypertonic, 7 hypotonic), were treated with 3 tablets containing 250 mg of extract per day (water extract not further specified), for 16 days. In some cases the daily doses reached 2000 mg. No adverse effects were reported, while 80% of the participants of the open study improved their daily life and their symptoms were reduced.

***Irritable bowel syndrome***

Neither fumitory nor Javanese turmeric was effective in a study in patients with irritable bowel syndrome (IBS) (Brinkhaus *et al.* 2005).
The aim of the study was to determine the efficacy of two herbal remedies used in the treatment of IBS. In a randomized, double-blind, placebo-controlled trial, IBS patients were randomly assigned to one of three treatment groups: 1) *Curcuma xanthorrhiza* 60 mg daily (curcuma group) (n=24), 2) *Fumaria officinalis* 1500 mg of herb in powder daily (fumitory group) (n=24), and 3) placebo (n=58). The study treatment was applied three times a day for 18 weeks. The main outcome parameters were changes in global patient ratings of IBS-related pain and distension on a visual analogue scale (0-50 mm) between baseline and at the end of treatment. Additional outcome parameters included global assessments of changes in IBS symptoms and psychosocial stress caused by IBS.
A total of 106 patients (mean age 48±12 years, 63% F) were included in the intention-to-treat group. IBS-related pain decreased by -0.9 ± 11.5 (mm±SD) in the fumitory group, -0.3±9.9 in the placebo group and increased by 2.0±9.5 in the curcuma group (p=0.81). IBS-related distension decreased by -1.4±12.5 in the curcuma group, -2.1±9.2 in the placebo group and increased by 0.3±9.3 in the fumitory group (p=0.48). Additionally, the global assessment of changes in IBS symptoms and psychological stress due to IBS did not differ significantly among the three treatment groups.
Neither fumitory nor curcuma showed any therapeutic benefit over placebo in patients with IBS.

A summary of the main clinical studies on humans regarding Fumariae herba (*Fumaria officinalis* L, herba) is included in Table 5.

Table 5: Clinical studies on humans

| **Type (aim) and objective(s) of Study Reference** | **Study Design and Type of Control Study duration (if available)** | **Test Product(s) herbal preparation, pharmaceutical form; Dosage** Regimen; Route of Administration Duration of treatment | **Number of subjects (including age, sex, drop out)** | **Healthy Type of subjects or Diagnosis of Patients** (inclusion criteria) | **Outcomes (primary and secondary endpoints)** | **Statistical analysis (e.g. ITT yes/no, CI 95%) Quality score** | Comments on **Clinical relevance of results** |
|---|---|---|---|---|---|---|---|
| Brinkhaus *et al.* 2005 | In a randomized, double-blind, placebo-controlled trial, for 16 days. | Determination of efficacy of two herbal remedies used in the treatment of IBS.<br><br>IBS patients were randomly assigned to one of three treatment groups: 1) *Curcuma xanthorrhiza* 60 mg daily (curcuma group) (n=24), 2) *Fumaria officinalis* 1500 mg daily (fumitory group) (n=24) and 3) placebo (n=58).<br><br>The study treatment was applied 3 times/day | A total of 106 patients (mean age 48±12 years, 63% F) were included in the intention-to-treat group. | IBS diagnosed (Patients with irritable bowel syndrome) | The main outcome parameters were changes in global patient ratings of IBS-related pain and distension on a visual analogue scale (0-50 mm) between baseline and at the end of treatment.<br><br>Additional outcome parameters included global assessments of changes in IBS symptoms and psychosocial stress caused by IBS.<br><br>IBS-related pain decreased by -0.9 ± 11.5 (mm±SD) in the fumitory group, -0.3±9.9 | No data reported | Neither fumitory nor curcuma showed any therapeutic benefit over placebo in patients with IBS.<br><br>Negative outcome |

| **Type (aim) and objective(s) of Study Reference** | **Study Design and Type of Control Study duration (if available)** | **Test Product(s) herbal preparation, pharmaceutical form; Dosage** Regimen; Route of Administration Duration of treatment | **Number of subjects (including age, sex, drop out)** | **Healthy Type of subjects or Diagnosis of Patients** (inclusion criteria) | **Outcomes (primary and secondary endpoints)** | **Statistical analysis (e.g. ITT yes/no, CI 95%) Quality score** | Comments on **Clinical relevance of results** |
|---|---|---|---|---|---|---|---|
| | | | | | in the placebo group and increased by 2.0±9.5 in the curcuma group (p=0.81). IBS-related distension decreased by -1.4±12.5 in the curcuma group, 2.1±9.2 in the placebo group and increased by 0.3±9.3 in the fumitory group (p=0.48). The global assessment of changes in IBS symptoms, psychological stress due to IBS did not differ among the three treatment | | |

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

No data available.

### 4.4. Overall conclusions on clinical pharmacology and efficacy

Eight existing clinical studies in 617 patients (British Herbal Compendium 1992; Fiegel 1971; Müscher 1971; Roux 1977; Zawodsky 1974; Hunold 1975; Bourjat 1974; Salembier 1967; Fablet *et al*. 1968) as well as one existing double blind placebo trial (30 patients) (Kopp 1979) and two open studies in 63 patients (Kopp 1979; Zacharewicz *et al.* 1979) fully support the traditional use with intended choleretic and digestive effects of fumitory. However, there is a lack of rigorous clinical research assessing the effects of preparations of fumitory as the majority of the studies are short and old ones reporting mostly on the safety than efficacy of fumitory water extracts and also offering to the plausibility impact of the proposed TU.

According the published *in vitro* and *in vivo* studies as well as the existing old small clinical trials an antispasmodic effect on the upper digestive tract is documented supporting the plausibility of the use of fumitory.

## 5. Clinical Safety/Pharmacovigilance

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

Eight existing clinical studies in 617 patients (British Herbal Compendium 1992; Fiegel 1971; Müscher 1971; Roux 1977; Zawodsky 1974; Hunold 1975; Bourjat 1974; Salembier 1967; Fablet *et al.* 1968) as well as one existing double blind placebo trial (30 patients) (Kopp 1979) and two open studies in 63 patients (Kopp 1979; Zacharewicz *et al.* 1979) fully support the traditional use with intended choleretic and digestive effects of fumitory. A good tolerability was proven, and no adverse effects have been reported, showing enough safety data for the proposed traditional use of fumitory.

Patient exposure

See sections 4.2.2 and 5.1.

### 5.2. Adverse events, serious adverse events and deaths

Raised intraocular pressure and oedema have been reported as possible effects (Anderson & Phillipson 1986).

One case of an acute hepatitis induced by a combination herbal product containing *Taraxacum officinale*, *Fumaria officinalis*, *Peumus boldus*, *Cynara cardunculus* extract, *Equisetum arvense*, to a 56-year-old female who has used it for a long period (approx. 7 months) against hyperlipidaemia has been reported by Bonnet *et al.* (2007). According to information from National data no further adverse events, have been recorded.

No new safety issues have been detected in the EudraVigilance and/or the VigiLyze databases up to March 2022, and no causal link could be established between any adverse events and herbal medicinal products containing *Fumaria officinalis.*

### 5.3. Laboratory findings

No data available.

## *5.4. Safety in special populations and situations*

No data available.

### 5.4.1. Use in children and adolescents

In the absence of adequate data, only Fumaria herbal preparation a) (comminuted herbal substance as herbal tea) is intended for adolescents, based on the evidence of traditional use.

The use in children under 12 years of age, for all the other herbal preparations [(b), c), d), e), f)] has not been established due to lack of adequate data.

### 5.4.2. Contraindications

Hypersensitivity to the active substance.

### 5.4.3. Special warnings and precautions for use

Due to possible stimulation on bile secretion *Fumaria* herba is not recommended in case of obstruction of the bile duct, cholangitis, liver disease, gallstones and any other biliary diseases.

For a)

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

For b), c), d), e) and f)

The use in children and adolescents under 18 years of age has not been established due to lack of adequate data.

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

For tinctures and 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.

### 5.4.4. Drug interactions and other forms of interaction

None reported.

### 5.4.5. Fertility, pregnancy and lactation

Safety during pregnancy and lactation has not been established. In the absence of sufficient data, and in accordance with general medical practice, the use of herbal medicinal products containing fumitory during pregnancy and lactation is not recommended.

No fertility data available.

### 5.4.6. Overdose

No cases of overdose have been reported in the scientific literature.

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

No studies on the effect on the ability to drive and use machines have been performed.

### 5.4.8. Safety in other special situations

Not applicable.

## *5.5. Overall conclusions on clinical safety*

In the absence of data in special patient populations, Fumaria as comminuted herbal substance a) for herbal tea, is intended only for adolescents, adults and elderly, while all other forms only for adults and elderly.

In the absence of data and in accordance with general medical practice, it is recommended not to use the herbal medicinal products containing fumitory during pregnancy and lactation.

Seven hundred and ten (710) patients were treated with water extracts of fumitory (mainly 1 500 mg daily) for a period from 10 days to 21 weeks with variable results, but showing good tolerability (British Herbal Compendium 1992; Fiegel 1971; Müscher 1971; Roux 1977; Zawodsky 1974; Hunold 1975; Bourjat 1974; Salembier 1967; Fablet *et al.* 1968; Kopp 1979; Zacharewicz *et al.* 1979). The results support the plausibility of traditional use of fumitory.

There is one published report suggesting that a raised intraocular pressure and oedema have been reported as possible effects (Anderson & Phillipson 1986) during the use of an herbal medicinal product containing fumitory. One case of an acute hepatitis probably induced by Fumaria combination has been reported (Bonnet *et al.* 2007). No newer data have been further reported from Eudravigilance and VigiLyze up to March 2022 linked with safety of fumitory herbal medicinal products.

# 6. Overall conclusions (benefit-risk assessment)

Considering the lack of adequate controlled clinical studies, using herbal preparations, containing the herbal substance of Fumariae herba in conclusion, Fumariae herba and its preparations can be regarded as traditional herbal medicinal products in the indications:

Traditional herbal medicinal product used for the relief of digestive disturbances, such as feelings of fullness, slow digestion and flatulence.

In the absence of data in special patient populations, Fumaria is intended as comminuted herbal substance (a) only for adolescents, adults and elderly, while all the rest herbal preparations (b, c, d, e, f) only for adults and elderly.

In the absence of data and in accordance with general medical practice, it is recommended not to use the herbal medicinal products containing fumitory during pregnancy and lactation.

Seven hundred and ten (710) patients have been treated with water extracts of fumitory (mainly 1500 mg daily) from 10 days up to 21 weeks with reported good tolerability.

No adverse effects have been reported in the above referred clinical studies except one literature report suggesting that a raised intraocular pressure and oedema (Anderson & Phillipson 1986). In addition, one case of an acute hepatitis probably induced by *Fumaria officinalis* L. and *Vitis vinifera* plant therapy products has been reported by Bonnet *et al.* (2007).

The reported pharmacological effects are not considered contradictory to the traditional uses

As there is no available data on carcinogenity and reproducibility on fumitory extracts, and not available data on genotoxicity, the establishment of a EU List Entry is not possible for safety reasons.

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

Typical analytical marker(s) are alkaloids, expressed as protopine ($C_{20}H_{19}NO_5$=353.4) (Ph. Eur. 10$^{th}$ Ed. 07/2015: 1869 corrected 9.2).

# Annex

## *List of references*