



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Tilia tomentosa* Moench, flos

Based on Article 10a of Directive 2001/83/EC as amended (well-established use)

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

Draft

Herbal substance(s) (binomial scientific name of the plant, including plant part)	<i>Tilia tomentosa</i> Moench, flos
Herbal preparation(s)	
Pharmaceutical forms	

Note: This Assessment Report is published to support the release for public consultation of the draft Public statement on *Tilia tomentosa* Moench, flos. It should be noted that this document is a working document, not yet fully edited, and which shall be further developed after the release for consultation of the Public statement. Interested parties are welcome to submit comments to the HMPC secretariat, which the Rapporteur and the MLWP will take into consideration but no 'overview of comments received during the public consultation' will be prepared in relation to the 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 Public statement.



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1. Introduction

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

- Herbal substance(s)

Lime tree (Linden) is a tall deciduous tree native throughout Europe as far north as 65° in latitude, which can grow to heights approaching to 30 metre. It is found in the wild and purposely planted in gardens. It is also cultivated in Europe and North America while the material of commerce originates mainly from Balkan countries such as Bulgaria, Romania, former Yugoslavia, Turkey and in part from China. Lime tree bark is smooth and gray and its leaves are white heart-shaped especially underneath contrary to the hairless ones of *Tilia cordata/platyphyllos*. The 5-petalated, yellow white flowers are collected in full bloom, dried and preserved under low-moisture conditions (Blumenthal *et al.* 1998).

These species are preferred because the tannin and mucilage content in their flowers produce more favourable teas and extracts (Blumenthal *et al.* 1998)

Tiliae tomentosae flos (fam. *Tiliaceae*), common silver lime flower, consists of the whole dried inflorescence of *Tilia tomentosa* Moench, gathered during the flowering season, as well as their preparations in effective dosages (Blumenthal *et al.* 1998; PDR for Herbal Drugs 2007).

Common names: silver lime flower, silver linden, common silver lime flower, basswood, lime tree, Linden tree.

Synonym(s)

Tilia tomentosa Moench = *Tilia argentea* Desfontaines

Chemical constituents according to existing references (Blumenthal *et al.* 1998, PDR for herbal Medicines 2007, Duke *et al.* 1985, Review Nat Prod 2005)

- **Acids** - caffeic acid, chlorogenic acid and p-coumaric acid
- **Amino acids**
- **Carbohydrates** - mucilage polysaccharides (3%).
- **Flavonoids** - kaempferol, quercetin, myricetin and their glycosides (mainly Kaempferol-3-O-β-D-(6"-E-p-coumaroyl)-glucopyranoside – tiliroside, hyperoside) (Nowak 2003)
- **Volatile oil** - (0.02% to 0.1%) Many components including alkanes, phenolic alcohols and esters, and terpenes including citral, citronellal, citronellol, eugenol, limonene, nerol, α-pinene and terpineol (monoterpenes), and farnesol (sesquiterpene) (Fitsiou *et al.* 2007; Toker *et al.* 1999)
- **Other constituents** - saponin (unspecified), tannin (condensed) and tocopherol (phytosterol)

Tilia tomentosa = *Tilia argentea* is referred to as common adulteration of *Tilia cordata* which detected via microscopic tests (Blumenthal *et al.* 2000, Ph.Eur. 2011).

The fragrant components of the flowers degrade rapidly under conditions of high moisture (HagerROM 2010, PDR for Herbal Medicines 2007, Review Nat Prod 2005).

- Herbal preparation(s)

To be completed by the Rapporteur.

- 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.

This monograph refers only to *Tiliae tomentosae flos*.

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

Regulatory status overview

Member State	Regulatory Status				Comments
Austria	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No prod. on the market
Belgium	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No prod. on the market
Bulgaria	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No prod. on the market
Cyprus	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No prod. on the market
Czech Republic	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	One herbal tea, since 2000
Denmark	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No prod. on the market
Estonia	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No prod. on the market
Finland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No prod. on the market
France	<input type="checkbox"/> MA	<input checked="" type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No prod. on the market
Germany	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input checked="" type="checkbox"/> Other Specify:	No prod. on the market
Greece	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No prod. on the market
Hungary	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No prod. on the market
Iceland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Ireland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Italy	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Latvia	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Liechtenstein	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Lithuania	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No prod. on the market
Luxemburg	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Malta	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
The Netherlands	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No prod. on the market
Norway	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No prod. on the market
Poland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No prod. on the market
Portugal	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No prod. on the market
Romania	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Slovak Republic	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No prod. on the market
Slovenia	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No prod. on the market
Spain	<input type="checkbox"/> MA	<input checked="" type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No prod. on the market
Sweden	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No prod. on the market
United Kingdom	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No prod. on the market

MA: Marketing Authorisation

TRAD: Traditional Use Registration

Other TRAD: Other national Traditional systems of registration

Other: If known, it should be specified or otherwise add 'Not Known'

This regulatory overview is not legally binding and does not necessarily reflect the legal status of the products in the MSs concerned.

1.3. Search and assessment methodology

Search terms: *Tilia tomentosa* Moench, *Tiliae tomentosae*, flos., *Tilia argentea* Desfontaines, flos, *Tilia* sp., tiliroside,

Databases: Pubmed, Medline, HealLink, scopus.

Libraries: University of Athens, Lab. Of Pharmacognosy and Chemistry of Natural Products of the University of Athens.

2. Historical data on medicinal use

2.1. Information on period of medicinal use in the Community

Since the Middle Ages, the flowers of the lime trees have been used as a diaphoretic to promote perspiration. In addition, the flowers have been used traditionally as tranquiliser and to treat headaches, indigestion and diarrhoea. Infusions of the flowers make a pleasant-tasting tea. Traditionally lime flowers were added to baths to quell hysteria and steeped as a tea to relieve anxiety-related indigestion, heart palpitation and vomiting (Blumenthal *et al.* 1998; 2000, Duke *et al.*1985, Review Nat Prod 2005).

In Germany, silver lime flower is approved in the Commission E monographs, and it is used for catarrh of the respiratory tract, as an antispasmodic, expectorant, diaphoretic and a diuretic (Blumenthal *et al.*1998) drug.

The Commission E approved silver lime flower for colds and cold-related coughs and there is no objection to its use as a corrigent for aroma and flavour (Blumenthal *et al.* 1998, PDR for Herbal Medicines 2007).

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

There are no Herbal preparations according to the overview of the European market, while in literature only two references show its activity without fulfilling the criteria of at least 30 years (Blumenthal *et al.* 1998; PDR for herbal Medicines 2007), as requested by Directive 2004/24 EC for qualification as a traditional herbal medicinal product.

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

No data available.

3. Non-Clinical Data

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

In vitro and animal studies

Hepatoprotective activity

Diuretic, sedative and antispasmodic effects

Tilia species are traditional medicinal plants widely used as sedatives and tranquilizers (Zhang, 2004). For this purpose, the infusion of their inflorescences is used to prepare a tea. In this study extracts of inflorescences from *Tilia tomentosa* Moench, one of the species found in the market, were purified using a benzodiazepine (BZD) binding assay to detect BZD receptor ligands in the different fractions. One of the ligands was identified as kaempferol, but it had low affinity ($K(i) = 93 \mu\text{M}$) for this receptor, and did not produce sedative or anxiolytic effects in mice. On the other hand, a complex fraction, containing as yet unidentified constituents, but probably of a flavonoid nature, when administered intraperitoneally in mice, had a clear anxiolytic effect in both the elevated plus-maze and holeboard tests, two well validated pharmacological tests to measure anxiolytic and sedative compounds. This active fraction had no effect on total and ambulatory locomotor activity. In conclusion, these results demonstrate the occurrence of active principle(s) in, at least, one species of *Tilia* that may explain its ethnopharmacological use as an anxiolytic (Viola *et al.* 1994).

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

No data on silver lime flower extracts have been found or reported.

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

Single-dose and repeated-dose toxicity studies

No data have been found.

Genotoxicity studies

No data on genotoxicity studies carried out on silver lime flower in the scientific literature.

Carcinogenicity studies

No carcinogenicity studies carried out on silver lime flower in the scientific literature.

Reproduction and developmental toxicity studies

No reproductive and developmental toxicity studies carried out on silver lime flower in the scientific literature.

The safety of silver lime flower during pregnancy and lactation has not been established.

3.4. Overall conclusions on non-clinical data

Silver lime flower has officially been recognised as adulterations of *Tilia* flos in Eur. Phar., 2008 on the other hand it is approved by the German Commission E Monograph. No herbal medicinal products containing silver lime have been reported within the European market overview.

The published data referring to the indications and preparations is limited, and could not support the traditional use of *Tilia tomentosa* and preparations.

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

4.2.1. Dose response studies

No data available.

4.2.2. Clinical studies (case studies and clinical trials)

Antidiabetic activity

There is a lack of clinical research, assessing the effects of silver lime flower and rigorous randomised controlled clinical trials are required.

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

None reported.

4.3. Overall conclusions on clinical pharmacology and efficacy

Not specified by the Rapporteur.

5. Clinical Safety/Pharmacovigilance

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

There is a lack of clinical and preclinical safety and toxicity data for silver lime flower and further investigation of these aspects is required.

5.2. Patient exposure

No data available.

5.3. Adverse events and serious adverse events and deaths

It has been advised that silver lime flower should be avoided by individuals with an existing cardiac disorder (Duke 1985); as excessive use may result in cardiac toxicity.

5.4. Laboratory findings

No data available.

5.5. Safety in special populations and situations

Special patient population

No data on use in children are available, therefore *Tilia tomentosa* flos can be intended only for use in adolescences and adults.

Use in pregnancy and lactation

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

Overdose

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

Drug abuse

No information in the literature search.

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

No data in the literature search.

5.6. Overall conclusions on clinical safety

No data for use in children are available, therefore *Tilia tomentosa* flos can be intended only for use in adolescences and adults.

In the absence of data available and in accordance with general medical practice, it is recommended not to use the herbal medicinal products containing *Tilia tomentosa* flos (silver lime flowers) during pregnancy and lactation.

Some cases of allergic reactions have been reported while the frequency is not known.

Moreover no adverse effects have been reported, showing enough safety data for the proposed traditional use of the herbal medicinal product.

No data on genotoxicity, carcinogenicity and reproducibility on silver lime flowers are available.

6. Overall conclusions

After reviewing information on the products containing *Tilia tomentosa* Moench, flos and preparations thereof marketed in the Community, it appears that there are no products (single-ingredient and/or combination) available.

A comprehensive literature search was conducted and available data, including information on products on the market in the EU are assessed vis-à-vis the requirements laid down in Directive 2001/83/EC and its Annex I, in particular Article 1, Article 10a and Chapter 2a.

The HMPC/MLWP concluded that the following requirements for the establishment of a Community herbal monograph on traditional and well-established herbal medicinal products containing *Tilia tomentosa* Moench, flos are not fulfilled:

- the requirement laid down in Article 10a of Directive 2001/83/EC that the active substance has a recognised efficacy and an acceptable level of safety and that the period of well-established medicinal use has elapsed
- the requirement laid down in Article 16a(1)(d) of Directive 2001/83/EC that “the period of traditional use as laid down on Article 16c(1)(c) has elapsed”

Based on the above-mentioned information, the HMPC is of the opinion that no Community herbal monograph on *Tilia tomentosa* Moench, flower can be established.

Annex

List of references