European Medicines Agency
*Evaluation of Medicines for Human Use*



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# ASSESSMENT REPORT ON
# *PASSIFLORA INCARNATA* L., HERBA



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## 1. INTRODUCTION

### 1.1 DESCRIPTION

- *Passiflora incarnata* L., herba is the dried aerial parts of *Passiflora incarnata* L. It may contain flowers and fruits [European Pharmacopoeia].
- *Passiflora incarnata* L., herba extract is the dry extract of *Passiflora incarnata* L., herba, prepared with ethanol (40% – 90% v/v) or methanol (60% v/v), or acetone (40% v/v), and containing a minimum of 2.0% flavonoids, expressed as vitexin [European Pharmacopoeia].

## 2. TRADITIONAL MEDICINAL USE

### 2.1 INFORMATION ON PERIOD OF MEDICINAL USE IN THE COMMUNITY REGARDING THE SPECIFIED INDICATION

*Passiflora incarnata* L., herba has been used in Europe for the relief of mild symptoms of mental stress and to aid sleep. The medicinal use has been documented continuously in recognised handbooks dating *e.g.* from 1938, 1958, 1977 and 2003 [Madaus, 1938; Hoppe, 1958; List and Hörhammer, 1977; ESCOP, 2003]. It is often used in combinations with other sedative herbal substances.

### 2.2 TYPE OF TRADITION WHERE RELEVANT

European phytotherapy.

### 2.3 BIBLIOGRAPHIC/EXPERT EVIDENCE ON THE MEDICINAL USE

Medicinal use of *Passiflora incarnata* L., herba for the relief of mild symptoms of mental stress and to aid sleep has been recorded *e.g.* in the following handbooks:

*Lehrbuch der Biologischen Heilmittel* [Madaus, 1938]. Daily dose: 30-50 drops or 0.250-0.375 g fresh plant material ("Teep"-tablets) before bedtime. Duration of use: No information.

*Martindale Extra Pharmacopoeia* [Todd, 1967]. Single dose: liquid extract (1 in 1): 0.5-1 ml; tincture (1 in 5): 0.5-2 ml.

*British Herbal Pharmacopoeia* (1976). Dosage (3 times daily): 0.25-1 g (powder or infusion); 0.5-1 ml liquid extract (1:1 in 25 % alcohol); 0.5-2 ml tincture (1:8 in 45% alcohol).

*Hagers Handbuch* [List and Hörhammer, 1977]. Single dose: 2 g as infusion.

*Hagers Handbuch* [Hänsel *et al.*, 1994]. Daily oral dose: 4 – 8 g of the crude drug or the corresponding amount of the extract. For tea: 15 g crude drug in 150 ml of water. Used mostly in combinations with *Valeriana officinalis* L., root, *Humulus lupulus* L., cone or *Melissa officinalis* L., leaf. Also combinations with *Pimpinella anisum* L., fruit, *Lavandula angustifolia* Mill., flower, *Citrus aurantium* L., flower or *Mentha piperita* L., leaf are used. Duration of use: No information.

*British Herbal Compendium* [Bradley, 1992]. Daily oral dose: crude drug: 2 – 8 g. Liquid extract (1:1, 25% ethanol) 2 – 8 ml. Tincture (1:8, 25% ethanol) 8 – 16 ml. Duration of use: No information.

*Herbal Drugs and Phytopharmaceuticals* [Wichtl, 2004)]. Daily oral dose: 6 g. Duration of use: No information.

*Herbal Medicines. A guide for healthcare professionals* [Barnes *et al.*, 1996]. Daily oral dose: crude drug: 1,25 – 8 g. Liquid extract (1:1, 25 % ethanol) 1.5 – 3.0 ml. Tincture (1:8, 45 % ethanol) 1.5 – 6.0 ml. Duration of use: No information.

*Handbook of Medicinal Herbs* [Duke, 2002]. Daily oral dose: 2 – 8 g. Duration of use: No information.

*ESCOP Monograph* (2003). Daily oral dose: crude drug: 2 – 8 g. As infusion: crude drug 10 g. Tincture (1:8) 4 – 16 ml. Duration of use: No restriction.

*PDR for Herbal Medicines* (1998). Daily oral dose: 3 teaspoons (~ 6 g) for tea preparation. Duration of use: No information.

*Acupuncture & Médicine traditionelle chinoise* [Weniger and Anton, 1996]. Daily oral dose: 6 – 9 g for tea preparation. Powdered crude drug: 0.5 – 1 g. Duration of use: No information.

*Drogenkunde* (Hoppe, 1958). Daily oral dose: No information. Duration of use: No information.

*Précis de Matière Médicale* [Paris and Moyse, 1981]. Daily oral dose: tincture or fluid extract 2 – 5 g (unclear if this amount relates to the crude drug). Duration of use: No information.

*Phytothérapie. Les données de l´évaluation* [Bruneton, 2002]. Daily oral dose: No information. Duration of use: No information.

*The Complete German Commission E Monographs* [Blumenthal *et al.*, 1998]. Daily oral dose: 4 – 8 g. Equivalent amount of preparations. Duration of use: No information.

*Herbal Medicine, expanded Commission E monographs* [Blumenthal *et al.*, 2000]. Daily oral dose: 4 – 8 g. Equivalent amount of preparations. Duration of use: No information.

Dry extracts (5-7:1) prepared by 60% methanol have been on the German market since 1992 (Information from Germany).

Liquid extract (1:1 in 70% ethanol) has been on the market in Germany since at least 1978. Daily oral dose: 3 times 2 ml (Information from Germany).

No information on medicinal use of acetone extracts have been found in the literature or received from the Member States.

Medicinal and traditional use for the relief of mild symptoms of mental stress and to aid sleep is also described in a number of reviews [Bizet, 1998; Brasseur and Angenot, 1984; Lutomski *et al.*, 1981; Meir, 1995]. Only one reference [Lutomski *et al.*, 1981] contains information on dosage and quotes the information from Commission E and ESCOP. None of the reviews contains any information on the duration of use. An extensive review of the botany, chemistry pharmacology and clinical use of plants of the genus *Passiflora*, including *Passiflora incarnata* has been published [Dhawan *et al.*, 2004].

### 2.4 ASSESSOR'S OVERALL CONCLUSION ON THE TRADITIONAL MEDICINAL USE

Traditional medicinal use of *Passiflora incarnata* L., herba in the form of powdered herbal substance, herbal tea or ethanol extracts, for the relief of mild symptoms of mental stress and to aid sleep is well documented in a number of handbooks. The requirement for medicinal use of at least 30 years (15 years within the Community) according to Directive 2004/24/EC is considered fulfilled.

**A:** The daily dosage ranges from 0.5 – 8 g of herbal substance as powder.
**B:** For herbal tea, a daily dosage of 1 – 8 g of herbal substance is used to make an infusion.
**C:** For liquid extracts (1:8, extraction solvent 25% ethanol), the dose range 8 – 16 ml daily in divided doses is documented.
**D:** For liquid extracts (1:8, extraction solvent 45% ethanol), the dose range 2 – 6 ml daily in divided doses is documented.
**E:** For liquid extracts (1:1, extraction solvent 25% ethanol), a daily dose ranging between 0.5 and 8 ml is documented.

**F:** For liquid extracts (1:1, extraction solvent 70% ethanol), a daily dose of up to 3 times 2 ml is documented.

Extracts prepared with acetone are included in the European Pharmacopoeia but data on traditional use (30 years) of these extracts have neither been found in the literature, nor reported by Member States. Methanol extracts are also included in the European Pharmacopoeia and have been authorised in Germany since 1992. As the required 30 years of medicinal use have not elapsed, acetone and methanol extracts cannot be included in a Community herbal monograph.

## 2.5 BIBLIOGRAPHIC REVIEW OF SAFETY DATA OF THE TRADITIONAL HERBAL MEDICINAL SUBSTANCE

The following two major electronic databases were searched on 20 June 2006 with the search term "passiflora". Results:
PubMed: 160 references obtained.
Toxline: 37 references obtained in Toxline Core on PubMed and 68 references in Toxline Special.
Out of these references 1 case report on ventricular tachycardia was retrieved. The case concerned a 34-year old male [Fisher *et al.*, 2000]. One case of hypersensitivity vasculitis in connection with *Passiflora* extract intake has also been reported [Smith *et al.*, 1993]. No other signals of safety concern were identified throughout these searches.

### 2.5.1 Patient exposure

Products containing *Passiflora incarnata* L., herba are currently available in most Member States. The products have various regulatory statuses. A considerable patient/consumer exposure must be anticipated although no exact figures can be given.

### 2.5.2 Adverse events

Hypersensitivity is possible in very rare cases [ESCOP, 2003]. One case of hypersensitivity vasculitis has been reported [Smith *et al*., 1993].

### 2.5.3 Serious adverse events and deaths

One case of ventricular tachycardia accompanied by severe nausea, vomiting, drowsiness and prolonged QT interval required hospital admission for cardiac monitoring and intravenous fluid therapy [Fisher *et al.*, 2000]. The daily ingested dose corresponded to 1.5 g respectively 2 g crude drug during 2 days. Causality cannot be assessed with certainty due to incomplete data.

### 2.5.4 Safety in special populations and situations

#### *2.5.4.1 Intrinsic (including elderly and children)/extrinsic factors*

No data available.

#### *2.5.4.2 Drug-drug interactions and other interactions*

No clinical data available.

#### *2.5.4.3 Use in pregnancy and lactation*

No data available.

#### *2.5.4.4 Overdose*

No data available.

#### *2.5.4.5 Drug abuse*

No data available.

#### *2.5.4.6 Withdrawal and rebound*

No data available.

#### *2.5.4.7 Effects on ability to drive or operate machinery*

Theoretically, products containing *Passiflora incarnata* L., herba may cause drowsiness. The ability to drive a car or to operate machinery may be reduced. If affected, patients should not drive nor operate machinery [ESCOP, 2003]. Excessive doses may cause sedation [Barnes *et al.*, 1996].

#### *2.5.4.8 Contraindications*

Hypersensitivity to the active substance.

### 2.5.5 Non-clinical safety data

***Overview of available data regarding Passiflora incarnata L., herba preparation(s) and relevant constituents thereof***

Acute toxicity:
Extracts: mice, *i.p.*, 900 mg/kg. $LD_{50}$: oral: >15 g/kg (mice and rats), *i.p.*: 3510 mg/kg (rats), 3140 mg/kg (mice), *s.c.*: >10 g/kg (rats), 8300 mg/kg (mice) [Committee of experts on cosmetic products, 2001].
Maltol: $LD_{50}$ *s.c.*, mice 820 mg/kg [Hänsel *et al*., 1994], *i.p.*, mice 820 mg/kg, [Committee of experts on cosmetic products, 2001].
Ethylmaltol: $LD_{50}$ *i.p.*, mice 910 mg/kg [Committee of experts on cosmetic products, 2001].

Repeated dose toxicity:
Hydroethanolic extract, male rats, oral, 10 ml/kg body weight = 5 g/kg dried herb, 21 days, no change in weight, rectal temperature and motor coordination (ESCOP, 2003). An oral daily dose of 600 mg/kg for 4 weeks did not give any toxic symptoms in rats [Weniger and Anton, 1996].

Genotoxicity:
No genotoxic effects in the diploid strain *Aspergillus nidulans* D-30 of 1.30 mg/ml of a fluid extract (16.2% dry matter, 0.32% ethanol) [ESCOP, 2003].

No information on carcinogenicity, reproductive and developmental toxicity is available.

### 2.5.6 Assessor's overall conclusions on safe use

The non-clinical information indicates that the acute and repeated dose toxicity is low. As there is no information on reproductive and developmental toxicity the use during pregnancy and lactation cannot be recommended. Minimum required data on mutagenicity (Ames test) are not available.

Conventional clinical safety data are virtually absent. However, longstanding medicinal use and experience of *Passiflora incarnata* L., herba has been documented within the Community. During this time, no clear clinical signals that *Passiflora incarnata* L., herba is harmful under normal conditions of use have been identified. As no data on use in children are available, products containing *Passiflora incarnata* L., herba cannot be recommended for use in children below the age of 12 years.

## 3 PHARMACOLOGICAL PROPERTIES

### 3.1 OVERVIEW OF THE PHARMACOLOGICAL EFFECTS OF *PASSIFLORA INCARNATA* L., HERBA PREPARATIONS AND RELEVANT CONSTITUENTS THEREOF

**Constituents**:
Flavonoids, mainly *C*-glycosides of apigenin and luteolin, *e.g.* isovitexin, isoorientin and their 2"-β-D-glucosides, schaftoside, isoschaftoside, vicenin-2 and swertisin, with considerable variation in qualitative and quantitative composition according to source [Hänsel *et al*., 1994; Bradley, 1992; Wichtl, 2004; Barnes *et al.*, 1996; ESCOP, 2003; PDR for herbal medicines, 1998; Weniger and Anton, 1996].
Maltol which, however, may be an artefact [Hänsel *et al*., 1994; Bradley, 1992; Barnes *et al*., 1996; ESCOP, 2003; Weniger and Anton, 1996].
Essential oil in trace amounts comprising more than 150 components [Hänsel *et al*., 1994; Bradley, 1992; Wichtl, 2004; Barnes *et al.*, 1996; ESCOP, 2003; PDR for herbal medicines, 1998; Weniger and Anton, 1996].
Gynocardin (a cyanogenic glycoside) [Hänsel *et al*., 1994; Bradley, 1992; Wichtl, 2004; ESCOP, 2003; PDR for herbal medicines, 1998; Weniger and Anton, 1996].
β-carboline alkaloids (e.g. harman, harmol, harmalol) may be present in traces. However, these alkaloids are undetectable in most commercial materials [Hänsel *et al*., 1994; Bradley, 1992; Wichtl, 2004; Barnes *et al*., 1996; ESCOP, 2003; PDR for herbal medicines, 1998; Weniger and Anton, 1996].
A tri-substituted benzoflavone derivative [Dhawan *et al.*, 2004].

A number of early pharmacological studies have been reviewed by Hänsel *et al*., [1994], most of which are said to be of poor quality. Newer studies are reviewed in the ESCOP monograph [2003], which indicate a sedative effect in rodents of hydroethanolic extracts, including reduction of spontaneous locomotor activity and prolongation of pentobarbital-induced sleeping time at doses of 50 – 400 mg/kg administered intraperitoneally or *per os*. The authors conclude that the available pharmacodynamic studies generally support, with some conflicting results, the empirically acknowledged sedative and anxiolytic effects of passion flower but it is not yet clear which constituents are responsible for these effects.

A tri-substituted benzoflavone derivative, comprising a benzene ring fused at positions 6, 7 of a flavone compound has recently been isolated and claimed to be the main bioactive phyto-constituent of *Passiflora incarnata*. It exhibits significant anxiolytic activity at an oral dose of 10 mg/kg in mice. It also causes reversal of morphine tolerance in mice (dose 10 – 100 mg/kg), prevention of nicotine addiction in mice (10 – 20 mg/kg), prevention of $\Delta^9$-THC dependence and tolerance in mice (10 – 20 mg/kg) and prevention of ethanol dependence in mice (10 – 50 mg/kg). The compound was also found to counteract dependence on benzodiazepines in mice and to increase libido in aged rats and to prevent loss of libido induced by ethanol, $\Delta^9$-THC or nicotine. The authors postulate that the mechanism for all these effects is inhibition of the enzyme aromatase (a member of the cytochrome P-450 family), resulting in inhibition of the metabolic conversion of androgens to oestrogens thereby increasing free testosterone and decreasing free oestrogen [Dhawan *et al.*, 2004].

#### Assessor's comments on pharmacological effects of *Passiflora incarnata* L., herba preparations and relevant constituents thereof

Published data on the pharmacodynamics of *Passiflora* extracts and its constituents, particularly the tri-substituted benzoflavone derivative, give some support to the traditional use of *Passiflora* for the relief of mild symptoms of mental stress and to aid sleep. The chemical structure of the benzoflavone derivative does not appear to be known and the amounts of substance present in the herbal substance/preparations have not been reported in the literature. No data from direct studies of inhibition of the enzyme aromatase have been found in the literature.

In summary, the doses employed in the animal experiments seem high compared to the doses of *Passiflora*/benzoflavone derivative that humans are exposed to during use of herbal medicinal products containing *Passiflora*. The mechanism of action cannot, at present, be regarded as clarified.

### 3.2 CLINICAL STUDIES

Four clinical studies have been identified in the literature.
In one small pharmacological screening study (12 healthy female volunteers), the effect of a passion flower extract (1.2 g) was compared with that of placebo and diazepam (10 mg). Alertness was rated by the subjects on a VAS scale after receiving the medication and after challenge with 100 mg of caffeine. Diazepam and, to an apparent lesser degree, placebo and passion flower extract, all decreased mental alertness. The effects of the passion flower extract on qualitative EEG signals could not be distinguished from placebo [Schulz *et al.*, 1998].

The effect of an extract (45 drops/day) of passion flower on patients with general anxiety was compared with the effect of oxazepam (30 mg/day) in a study during 28 days. Eighteen patients were treated with passion flower extract and 18 with oxazepam. Patients were assessed by a psychiatrist at baseline and days 4, 7, 17, 21 and 28 after the medication started. The score on the Hamilton anxiety rating scale was the same for both groups on days 0, 21 and 28. The authors concluded that the extract was equally effective as oxazepam [Akhondzadeh *et al*., 2001a].

Another study by Akhodzadeh *et al*., [2001b] comprised 65 opiate addicts undergoing withdrawal. Treatment was 60 drops of an extract of passion flower + 0.8 mg of clonidine or placebo + the same dose of clonidine for 14 days. Both treatments were equally effective with regard to the physical symptoms of withdrawal. However, the combination of passion flower and clonidine was superior to clonidine alone with respect to psychological symptoms.

In a randomized, double-blind study in 34 children (between 6 and 13 years of age) recently diagnosed with ADHD, the efficacy of passion flower tablets was compared with methylphenidate [Akhondzadeh *et al*., 2005]. Seventeen children were treated with passion flower tablets (0.04 mg/kg/day) for 8 weeks. A control group of 17 children received methylphenidate (1 mg/kg/day). The primary efficacy parameter was outcome on a parent and teacher ADHD rating scale that has been extensively used in Iran in school-age children. Both groups improved significantly over the 8 weeks trial compared to the baseline value. There was no statistically significant difference in treatment result between the two groups. No placebo group was employed.

#### 3.2.1 Assessor's comments on the clinical studies

In the first study in 12 healthy volunteers [Schulz *et al.*, 1998], the effect of passion flower could not be distinguished from that of placebo. No statistical evaluation of the results was performed.

In the second study [Akhondzadeh *et al*., 2001a], major deficiencies in methodology include that the type of herbal preparation and details of the posology are unclear. Concerning the design of the study, the number of patients involved (18 treated with passion flower) is too small to provide robust information. No placebo group was used, but the patients visited a psychiatrist 6 times during the 28 days trial. It appears very reasonable to assume that this extensive contact with a doctor may in itself have a beneficial effect on patients with general anxiety. In the absence of a placebo group, the intrinsic effect of the medication cannot be assessed. The trial has been discussed in the literature, and it has been pointed out that the study was not designed as an equivalence study and conclusions about efficacy cannot be drawn [Ernst, 2006]. This study does not give conclusive evidence of efficacy of passion flower extract for treatment of anxiety, but as a pilot study it may be seen as supportive of the traditional use to relieve mild symptoms of mental stress.

The third study [Akhondzadeh *et al*., 2001b] is a report of the use of passion flower as an adjuvant to clonidine in the treatment of opiate withdrawal symptoms in opiate addicts. The type of herbal preparation was not reported. The indication and study population used in this study cannot be considered relevant for evaluation of the traditional use of passion flower. This is the first report of the

use of passion flower in the treatment of opiate withdrawal symptoms. Medicinal use of passion flower in this indication cannot be recognised as well-established nor as traditional in the Community.

In the fourth study [Akhondzadeh *et al*., 2005] the efficacy of passion flower was compared to metylphenidate in children with ADHD. The type of herbal preparation was not reported, but apparently the dose (0.04 mg/kg/day) is several orders of magnitude lower than the doses used in traditional European phytotherapy (approximately 10 - 100 mg/kg/day; 70 kg body weight assumed). There are a number of limitations of the study, which the authors themselves point out. These include e.g. the lack of placebo group and the small number of patients involved. The trial must be considered as a pilot study. This is the first report of the use of passion flower in the treatment of ADHD. Medicinal use of passion flower in this indication cannot be recognised as well-established/traditional in the Community.

### 3.2.2 Assessors overall conclusions on results of clinical studies

Only 4 small clinical studies have been retrieved from literature. They all suffer from serious deficiencies from efficacy point of view such as too small number of patients involved, lack of adequate statistical design/treatment of the results, undefined testing medication or therapeutic indications of doubtful relevance to the traditional medicinal use. The clinical data cannot be considered to fulfil the criteria required for "well-established medicinal use" according to Directive 2001/83/EC as amended.

## 4 ASSESSOR'S OVERALL CONCLUSIONS

Traditional medicinal use of *Passiflora incarnata* L., herba for the relief of mild symptoms of mental stress and to aid sleep has been documented in a number of recognised handbooks. Products containing *Passiflora incarnata* L., herba are currently available in most Member States. The requirement for medicinal use of at least 30 years (15 years within the Community) according to Directive 2001/83/EC as amended is considered fulfilled. Many of the products commercially available are combination products with other herbal substances/preparations.

The non-clinical information indicates that the acute and repeated dose toxicity is low. Information on genotoxicity, carcinogenicity, reproductive and developmental toxicity is lacking. Use during pregnancy and lactation can thus not be recommended.

Insufficient data on use in children are available therefore products containing *Passiflora incarnata* L., herba are not recommended for use in children below the age of 12 years.

Conventional clinical safety data are virtually absent, however, longstanding medicinal use and experience of *Passiflora incarnata* L., herba have been documented within the Community. No clinical signals that *Passiflora incarnata* L., herba is harmful under normal conditions of use have been identified.

In view of the empirically acknowledged sedative properties of *Passiflora incarnata* L., herba a warning for use in connection with driving of cars and operation of machinery is advisable.

Only 4 clinical studies have been reported in the literature. Major methodological deficiencies have been identified in the trials. The data available are insufficient to document clinical efficacy as required for products with "well-established medicinal use" according to Directive 2001/83/EC as amended. Together with available pharmacodynamic studies in animals, however, they do support the traditional use of *Passiflora incarnata* L., herba, for the relief of mild symptoms of mental stress and to aid sleep, which altogether may be considered plausible.

Sufficient data to develop a Community herbal monograph on the traditional use of *Passiflora incarnata* L., herba are available. As the minimum required data on mutagenicity (Ames test) are not

available, an inclusion to the Community list of traditional herbal substances, preparations and combinations thereof for use in traditional herbal medicinal producs is not recommended.