Journal of Ethnopharmacology 150 (2013) 791–804

Contents lists available at ScienceDirect

Journal of Ethnopharmacology

journal homepage: www.elsevier.com/locate/jep

Review

Passiflora incarnata L.: Ethnopharmacology, clinical application, safety and evaluation of clinical trials ☆

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ARTICLE INFO

Article history:
Received 5 July 2013
Received in revised form
23 September 2013
Accepted 24 September 2013
Available online 17 October 2013

Keywords:
Passiflora incarnata
Insomnia
Sleep disorders
Anxiety

ABSTRACT

Ethnopharmacological relevance: The genus *Passiflora incarnata* Linnaeus comprises approximately 520 species belonging to the Passifloraceae family. The majority of these species are vines found in Central or South America, with rare occurrence in North America, Southeast Asia and Australia. The genus *Passiflora incarnata* has long been used in traditional herbal medicine for the treatment of insomnia and anxiety in Europe, and it has been used as a sedative tea in North America. Furthermore, this plant has been used for analgesic, anti-spasmodic, anti-asthmatic, wormicidal and sedative purposes in Brazil; as a sedative and narcotic in Iraq; and for the treatment of disorders such as dysmenorrhoea, epilepsy, insomnia, neurosis and neuralgia in Turkey. In Poland, this plant has been used to treat hysteria and neurasthenia; in America, it has been used to treat diarrhoea, dysmenorrhoea, neuralgia, burns, haemorrhoids and insomnia. *Passiflora incarnata* L. has also been used to cure subjects affected by opiate dependence in India. This review aims to provide up-to-date information about the pharmacology, clinical efficacy and clinical safety of *Passiflora incarnata* L. based on the scientific literature. In particular, the methodological accuracy of clinical trials is analysed in accordance with current consolidated guidelines on reporting the clinical efficacy of herbal medicine, offering new insight into opportunities for future research and development.

Methods: A bibliographic investigation was performed by examining the available data on *Passiflora incarnata* L. from globally accepted scientific databases and search engines (Pubmed, Scopus and Web of Science, SciFinder and Google Scholar). We selected studies, case reports, and reviews addressing the pharmacology and safety of *Passiflora incarnata*.

Results: Although numerous *Passiflora incarnata* L. derivative products have been commercialised as alternative anxiolytic and sedative remedies based on their long tradition of use, their supposed efficacy does not appear to be adequately corroborated by the literature, with clinical studies often featuring inadequate methodologies and descriptions of the products under investigation. This medicinal plant has shown a wide spectrum of pharmacological activities in preclinical experiments, including anxiolytic, sedative, antitussive, antiasthmatic, and antidiabetic activities. The plant has a good safety profile. The clinical trials that we included in this review were designed to evaluate and in some cases confirm promising observations of preclinical pharmacological activity, and the methodological limits of these studies are characterised here.

Conclusion: In conclusion, clinical studies on the effects of products containing herbal preparations based on *Passiflora incarnata* reveal crucial weaknesses such as poor details regarding the drug extract ratio, limited patient samples, no description of blinding and randomisation procedures, incorrect definition of placebo, and lack of intention to treat analysis. In conclusion, the results of this review suggest that new clinical trials should be conducted using a more rigorous methodology to assess the traditional putative efficacy of *Passiflora incarnata* L.

☆Chemical compounds studied in this article Chrysin (PubChem CID: 5281607); Vitexin (PubChem CID: 5280441); Isovitexin (PubChem CID: 25202038); Kaempferol (PubChem CID: 5280863); Harman (PubChem CID: 5281404); Harmine (PubChem CID: 5280953); Harmaline (PubChem CID: 5280951); Palmitic Acid (PubChem CID: 985); Apigenin (PubChem CID: 5280443); Myristic Acid (PubChem CID: 11005).

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http://dx.doi.org/10.1016/j.jep.2013.09.047

Contents

1. Introduction

This article summarises and critically analyses the scientific literature on *Passiflora incarnata* L. (English common name: passionflower), an herbal medicine with a long tradition of medicinal use worldwide. The genus *Passiflora incarnata* L. comprises approximately 520 species of dicotyledonous plants belonging to the family Passifloraceae (Wohlmuth et al., 2010).

The word Passiflora comes from the Latin word "Passio" because in 1529, Spanish "conquistadores" described its flowers as symbols of the "passion of Christ" (Kinghorn, 2001; Dhawan et al., 2004). The majority of these species are vines, with most found in Central or South America and some species occurring in North America, Southeast Asia and Australia (Ulmer et al., 2004). A number of species, including *Passiflora edulis* Sims and *Passiflora laurifolia* L., are widely cultivated for their edible fruits, while many others are grown as ornamentals for their particular and spectacular flowers (Wohlmuth et al., 2010). Several species have a long history of use as traditional herbal medicines. *Passiflora incarnata* L., which originated in North America, is the most common variety used in contemporary Western phytotherapy. This species, commonly known by the English name maypop, is native to the south-eastern United States, but is also cultivated in Europe, Asia, Africa and Australia, both as an ornamental and as a medicinal plant (Dhawan et al., 2004).

This plant exhibits various pharmacological properties and possesses a complex phytochemistry. The present review aims to evaluate and comment on the scientific evidence regarding the therapeutic use of *Passiflora incarnata*, to summaries the chemical constituents of therapeutic preparations, to analyse the pharmacological aspects of the plant by examining both preclinical and clinical research, and to assess the toxicity and safety profile.

The putative clinical efficacy of *Passiflora incarnata* has been evaluated for the treatment of a variety of diseases, but the current most common use in clinical practice is in the treatment of anxiety and sleep disorders.

In several preclinical experiments, Passiflora extracts have exhibited potential effects for the treatment of anxiety and insomnia as well as for attention-deficit hyperactivity disorder, hypertension and cancer. Recent studies also showed that preparations obtained from leaves exert anticonvulsant effects (Dhawan, et al. 2003a; Nassiri-Asl et al., 2007). Although a variety of other preparations are available, dried extracts are the most important product derived from passionflower. Many practitioners actually use passionflower extracts alone or in combination with other herbal medicines to treat anxiety and sleep disorders in a wide range of patients (Newall, 1996; Zhou et al., 2008). This review also highlights the scientific basis for future research on *Passiflora incarnata*, and its real potential for the development of the market for herbal medicinal products.

2. Research method and inclusion criteria

Two investigators independently conducted a systematic search of the scientific literature published prior to December 2012 regarding *Passiflora incarnata* L. using MEDLINE, the Cochrane library, EMBASE and Google Scholar. The investigators used the following keywords or combinations of them:

- Passiflora
- *Passiflora incarnata*
- Passionflower
- Maypop

The articles included in the analysis were reviews, meta-analyses, clinical trials, and case reports. The selected articles report traditional uses of *Passiflora incarnata*, assess its phytochemistry, present both in vitro and in vivo preclinical experimental evidence, and present clinical evidence regarding its efficacy and safety profile.

We excluded clinical trials of treatments with herbal medicine combinations containing *Passiflora incarnata* extracts, or based on only one active compound from the phytocomplex of the plant. Scientific literature in English, German, French, Spanish and other languages has been considered, although in the case of one article in Chinese (Zhou et al., 2008), we could only evaluated the abstract written in English. We included recently published studies.

3. Botanical description

Passiflora edulis Sims has often been taken to be synonymous with *Passiflora incarnata* L. (www.plantlist.org, last accessed December 2012) because the plants possess identical morphological and microscopic characteristics. *Passiflora edulis*, as the name of the species reflects, is mainly cultivated for edible purposes and does not exert pharmacological effects on the central nervous system. Although one article attempted to eliminate potential confusion between these two similar plants (Dhawan et al., 2001b), this confusion remains, potentially leading to the selection of the wrong plant, thus accounting for the inconclusive and contradictory pharmacological reports on these two plants. Dhawan et al. established key identification parameters to differentiate between the two

plants: various leaf constants, the vein-islet number, the vein-termination number, the stomatal number, and the stomatal index; as well as physicochemical parameters such as ash values, extractive values, and the thin layer chromatography profile of the petroleum ether extracts of *Passiflora incarnata* and *Passiflora edulis* (Dhawan et al., 2001b).

Passiflora incarnata is an evergreen climber, rapidly growing up to 6 m (19 ft 8 in). This plant is in leaf from December to January, in flower from June to July, and its seeds ripen from September to November. This plant possesses hermaphrodite flowers (possessing both male and female organs) which are pollinated by insects such as bees. *Passiflora incarnata* can grow in light (sandy), medium (loamy) or heavy (clay) soils, with a preference for well-drained soil, and it cannot grow in the shade due to the soil moisture in shady areas.

Description of the different parts of the plant

- **Stems** – Vining, glabrous to minutely pubescent, herbaceous. Tendrils present.
- **Leaves** – Alternate, 3-lobed, serrulate, petiolate, up to +15 cm long, +13 cm wide, glabrous. Petioles with two glands near the base of the leaf blade.
- **Inflorescence** – Single pedicillate flowers from leaf axils.
- **Flowers** – A corona consisting of a structure of appendages situated between the corolla and the stamens. As shown in the graphical abstract, the corona is the ring-like structure of purple and white appendages above the petals and sepals. The flower is typically 6–7 cm in diameter. The flower has 5 petals and 5 sepals, which are purplish to whitish, similar, and alternating. The flower has 3 styles, typically 3 stamens, 5 greenish-white sepals with terminal appendages.
- **Fruit** – Fleshy, ovoid to globose, initially green, yellowish-red at maturity.
- **Flowering** – June – September.
- **Habitat** – Thickets, waste ground, disturbed sites, roadsides, railroads. The plant is also cultivated (ESCOP, 1997).

4. Traditional use/ethnomedicinal uses

The prehistoric use of *Passiflora incarnata* can be dated back to the Late Archaic period in North America, which ranges between 8000 and 2000 B.C. Archaeological evidence indicates that native Americans developed human-plant mutualism during the pre-Colombian period, and *Passiflora incarnata* was a common weed crop that often occurred in anthropogenic habitats. Ethnobotanists hypothesised that passionflower represented a minor food plant for native Americans rather than a staple, and for this reason the mutualism occurred without any intentional behaviour such as planting, seed storage, or cultivation. The two important aspects of seed dispersal and environmental modification can explain the geographic diffusion of *Passiflora incarnata* in various areas in North America, despite the demographic decline of the aboriginal population and the subsequent replacement by European–American populations characterised by different dietary and agricultural traditions. In addition, the horticultural practice of raising this plant as ornamental because of its spectacular flowers contributed to extending its presence in North America (Gremillion, 1989; Iwu, 2002). In American aboriginal medicine, the passionflower has been used in particular by the Cherokees of the southern Allegheny mountains, the Houmas of Louisiana and the Aztecs of Mexico (Vogel, 1977; Taylor, 1996).

Spanish conquerors first learned of passionflower from pre-Colombian people who traditionally used it as a sedative to treat insomnia and nervousness. *Passiflora incarnata* or 'Passionflower' (Flos passionis) acquired its name from the descriptions of the parts of its flower by Spanish missionaries in South America. It was known by the Spanish as 'La Flor de las Cinco Llagas' or the 'The Flower With The Five Wounds.' 'Passionis' refers to Christ's passion, representing various elements of the Crucifixion (Ratsch, 1998). Early European travellers in North America noted that the Algonquin Indians in Virginia and the Creek people in Florida ate the fruits of *Passiflora incarnata* from cultivated as well as wild sources. They wrote in a report: "*they plant also the field apple, the maracock, a wyld fruict like a kind of pomegranett, which increaseth infinitlye, and ripens in August*" (Major 1849:72). Passionflower was brought to Europe, where it became widely cultivated and was introduced to European folk medicine, becoming a popular traditional phyotherapeutic remedy as well as a homoeopathic remedy for the relief of mild symptoms of mental stress, anxiety and mild sleep disorder (Beverley, 1947; Bradley, 1992; EMA AR 2008; European Pharmacopeia 7th Edition). Traditional medicinal use in Europe has been documented continuously in several books published in 1938, 1958, 1977 and 2003 (Madaus, 1938; Hoppe, 1958; List and Hörhammer, 1977; ESCOP, 2007). Today, passionflower is officially included in the national pharmacopeias of France, Germany, and Switzerland and is also monographed in the British Herbal Pharmacopoeia and the British Herbal Compendium, the ESCOP monographs, the Community Herbal Monographs of the EMA, the German Standard Licences, the German Homoeopathic Pharmacopoeia, the Homoeopathic Pharmacopoeia of the United States, and the Pharmacopeia of Egypt (VA, 1978, 1987, 1992, 1996, 1997; Dhawan et al., 2004). In European traditional medicine, passionflower has long been prescribed for various indications such as anxiety, nervousness, constipation, dispepsia, mild infections and insomnia. In Poland, it has been prescribed to cure disorders such as hysteria and neurasthenia. Presently, *Passiflora incarnata* is commonly used in phytotherapy as a mild sedative and anxiolytic. The botanical drugs included in the current European and British Pharmacopoeias are the dried aerial parts of the plant (Taylor, 1996; Wohlmuth et al., 2010). In Turkey, passionflower is used for the following conditions: dysmenorrhoea, epilepsy, insomnia, neurosis and neuralgia (Taylor, 1996). In South America, it is still commonly used in folk medicine. In Argentina and Mexico, it is currently consumed for its sedative effects (Rodriguez-Fragoso, et al., 2008); in Brazil it is used as an analgesic, anti-spasmodic, anti-asthmatic, wormicidal and sedative (Taylor, 1996). In North America, it is used for the treatment of diarrhoea, premenstrual syndrome, dysmenorrhoea, neuralgia, burns, haemorrhoids, insomnia, muscle cramps, hysteria, neuralgia, and as a pain reliever for various conditions. Native Americans still continue to use this plant in folk medicine, with Cherokees consuming the root tea as a tonic for the liver and for skin boils. The roots are pounded for topical anti-inflammatory use. It is also used for nervousness, abdominal cramps and anxiety (Dhawan et al., 2004). *Passiflora incarnata* is also used as an herbal medicine in Asia; it has been used to treat morphine dependence in traditional medicine in India (Ingale and Hivrale, 2010). In Vietnam, it has been used for sleeplessness, anxiety and high blood pressure (Van Dan and Chuong, 1990). In the African countries of Rwanda, Kenya and Congo it is employed as a folk remedy by herbalists and natural health practitioners for its sedative, nervine, anti-spasmodic and analgesic effects (Neuwinger, 2000). It has been used as a sedative and narcotic in Iraq, and it is cultivated and commonly prescribed in Australia as a sedative and anxiolytic (Wohlmuth et al., 2010).

5. Phytochemistry

A considerable body of literature has explored the chemical composition of the raw material and of various products derived from passionflower.

The results of this literature clearly show that various bioactive constituents can contribute to the reported clinical effects, probably in a synergistic manner. Currently, researchers believe that only a portion of the pharmacologically active compounds have been precisely identified (Abourashed et al., 2002; Grundmann et al., 2008; Zucolotto et al., 2012). The aerial parts of *Passiflora incarnata.* are phytochemically characterised by the presence of a pattern of several primary constituents consisting of flavonoids, maltol, cyanogenic glycosides and indole alkaloids (Poethke et al., 1970; Spencer and Seigler, 1985, Qimin et al., 1991; Krenn, 2001; Marchart et al., 2003). The indole alkaloids are represented by harman, harmin, harmalin, harmol and harmalol, which can act as monoamino-oxidase inhibitors, but they are present in small amounts (Poethke et al., 1970; Spencer and Seigler, 1985; Rehwald et al., 1995; Sampath et al., 2011).

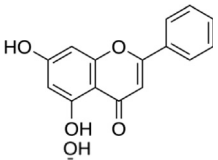
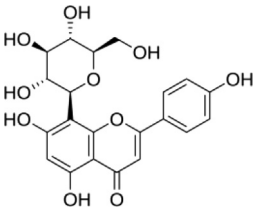
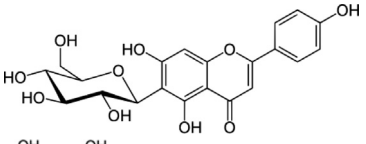
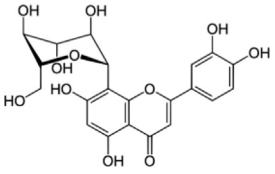
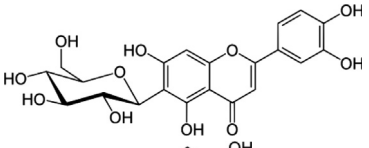
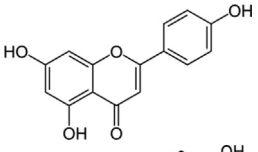
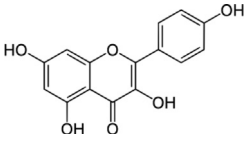
Flavonoids represent 2.5% of the compounds in this plant (Table 1), with vitexin, isovitexin, orientin, isoorientin, apigenin, kaempferol, vicenin, lucenin and saponarin identified (Lutomski et al., 1981; Krenn, 2001; Marchart et al., 2003). Furthermore, phenolic, fatty, linoleic, linolenic, palmitic, oleic and myristic acids are present, as well as formic and butyric acids, coumarins, phytosterols and essential oils (Sampath et al. 2011; Bruneton, 1995; di Wohlmuth 2010).

Different groups of researchers from Australia, Austria, Germany, Italy, and other countries have carried out analytical studies on different *Passiflora incarnata* samples with the goal of verifying and assessing the putative variability in C-glycosyl flavone content. This issue is important because some of the C-glycosyl flavones are considered to be marker compounds useful to distinguish between different passionflower extracts. Samples analysed in these experiments had different origins and different destination markets (e.g., Germany, Austria, USA, etc.) the results showed considerable qualitative and quantitative variability with respect to C-glycosyl flavone content (Raffaelli et al.,1997; Yockteng et al., 2011).

In 2004, Pereira et al. developed a high-performance thin layer chromatographic (HP-TLC) method to quantitatively determine the flavonoid contents in leaves of *Passiflora alata*, *Passiflora edulis*, *Passiflora caerulea* and *Passiflora incarnata*. The orientin and isoorientin contents were determined, and the results were compared with those obtained using a quantitative HPLC-UV method. The authors reported qualitative and quantitative differences in flavonoid content among different *Passiflora incarnata* and other *Passiflora* species (Pereira et al., 2004). Wohlmuth et al. performed analytical tests using thin layer chromatography (TLC), high performance liquid chromatography (HPLC) with photodiode array detection and liquid chromatography–mass spectrometry LC/MS on 11 samples of *Passiflora incarnata* pharmaceutical raw material obtained from different Australian cultivations. These data indicated little variability, in contrast with previous results published by other authors. According to their analytical assessment, the isovitexin chemotype is the most common in commercialised plants (Wohlmuth, 2010).

Seminal studies attributed an anti-anxiety action to *Passiflora incarnata* flavonoids, but recently published data revised this role, suggesting that these compounds do not contribute exclusively to the anxiolytic activity and that other substances are likely responsible for this effect as well. Recently, in vivo and in vitro studies demonstrated that flavonoids can be metabolised by the intestinal microflora to their corresponding hydroxyphenylacetic acids; the route of administration has been demonstrated to determine the biological activity of flavonoids. For example, when kaempferol and quercetin are administered intraperitoneally in mice, they do not exert anxiolytic effects. Vissiennon et al. hypothesised that anxiolytically active flavonoids like kaempferol have to be metabolised by bacteria in the gut and that the resulting phenylacetic acid derivative metabolites could be the main pharmacologically active substances. Flavonoids present in *Passiflora incarnata* seem to have a pharmacological profile similar to that of prodrugs, which require metabolic activation (Vissiennon et al., 2012).

Table 1
Main flavonoids as secondary compounds of *Passiflora incarnata* L. phytocomplex.

Flavonoid	Molecular formula	Skeletal formula
Chrysin	$C_{15}H_{10}O_4$	
Vitexin	$C_{21}H_{20}O_{10}$	
Isovitexin	$C_{21}H_{20}O_{10}$	
Orientin	$C_{21}H_{20}O_{11}$	
Isoorientin	$C_{21}H_{20}O_{11}$	
Apigenin	$C_{15}H_{10}O_5$	
Kaempferol	$C_{15}H_{10}O_6$	

Various experiments assessed the pharmacological activities of a tri-substituted benzoflavone compound, termed BZF. The results regarding the potential beneficial effects of BZF against anxiety were not conclusive, even though BZF-like compounds are only present in trace amounts in some passionflower extracts (Dhawan et al., 2001a; Holbik et al., 2010; Sampath et al., 2011). Additionally, Elsas et al. (2010) repeated TLC and LC analytical examination according to the methodology described in other studies (Dhawan et al., 2003a; Dhawan et al., 2004). These authors did not detect any substances matching BZF compounds in the analysed extracts, and revealed little variation in the relative abundance of specific flavonoids (Elsas et al., 2010). The *Passiflora incarnata* extracts were found to contain a certain amount of gamma-aminobutyric acid (GABA) (Carratù et al. 2008), suggesting that the bioactivity of this plant could result from the synergistic action of GABA with additional phytochemicals that may facilitate membrane permeation, leading to the positive modulation of GABAA receptors by flavonoids (Campbell et al., 2004).

6. Preclinical data supporting pharmacological effects

The potential therapeutic properties of *Passiflora incarnata*, reported extensively in folk medicine, have been evaluated by modern preclinical pharmacological studies with the aim of characterising pharmacological activities (Table 2). Although its extracts have been tested in numerous preclinical experiments, the mechanism of action of the extract is still under discussion.

The well-known sedative action has been demonstrated in various experiments conducted on mice and rats (Soulimani et al., 1997; Speroni and Minghetti, 2007). Passionflower extracts were shown to significantly prolong the sub-hypnotic pentobarbital-induced sleep (Soulimani et al., 1997). Other experiments demonstrated, in contrast with previous evidence, that the flavonoids apigenin and chrysin present in *Passiflora incarnata* did not significantly influence various sleep parameters such as sleep duration (Zanoli et al., 2000), and sleep onset latency, number of awakenings, duration of rapid eye movement (REM) and non-REM sleep were measured via electroencephalography. This discrepancy might be related to the variability of extract constituents and to the small sample size of 8–12 rats, preventing the observation of statistically significant differences between treatment conditions (Shinomiya, et al., 2005).

Related to effects on sleep, anxiolytic activity is one of the most intensively investigated pharmacological roles of *Passiflora incarnata* (Dhawan et al., 2001c; Miyasaka et al., 2007). As some studies showed that pre-administration of flumazenil, the antagonist of the $GABA_A$ benzodiazepine binding site receptor, attenuates in vivo the anxiolytic effect of *Passiflora incarnata*, passionflower and diazepam were assumed to share the same mechanism of action (Medina et al., 1990; Grundmann et al., 2008). Dysfunction of the GABA system is implicated in many neuropsychiatric conditions, including anxiety and depressive disorders. Numerous pharmacological effects of *Passiflora incarnata* are mediated via the modulation of the GABA system, including affinity to the $GABA_A$ and $GABA_B$ receptors and effects on GABA uptake. It appears to be unlikely that *Passiflora incarnata* extract acts by binding to the benzodiazepine site. However, it is plausible that binding to the GABA-site of the $GABA_A$ receptor is one mode of action of the plant extract (Appel et al., 2011). Anxiolytic activity has been assessed in a series of in vivo experiments based on various experimental animal models such as the Elevated Plus Maze (EPM) Grundmann et al. 2009 test, the staircase test and the light/dark box choice test (non-familiar environmental tests). Soulimani et al. (1997) treated mice with a lyophilised hydroalcoholic extract or an aqueous extract of the aerial parts of this medicinal plant and subjected the mice to the staircase test (non-familiar environmental test) and the light side of the light/dark box choice test (non-familiar environmental test). Both extracts exhibited anxiolytic properties, with decreases in rears and steps climbed in the staircase test and decreases in rears and locomotion in the free exploratory test (Soulimani et al., 1997). The anxiolytic effect, as assessed in mice by the EPM test, is lower for extracts obtained from roots and flowers, which contain lower amounts of active compounds, making it desirable to separate the most active parts to maximise the anxiolytic action of extracts (Dhawan, 2010).

Among the chloroform, butanol, and petroleum ether fractions (without BZF-like compounds) of a hydroethanol extract of *Passiflora incarnata*, the chloroform fraction exerted the highest sedative effect in mice (Holbik, et al., 2010). Elsas et al. tested five different extracts of passionflower on rats and measured anxiety using EPM. Surprisingly, the results showed anxiogenic activity for every extract. This unexpected anxiogenic action could be due to the lower baseline anxiety levels compared with the higher baseline levels of anxiety measured in other animal studies (Elsas et al., 2010).

Speroni et al. observed the efficacy of *Passiflora incarnata* in the control of convulsions induced by pentylenetetrazole (PTZ) (Speroni and Minghetti, 2007). More recently, five different extracts of passionflower with various flavonoid and GABA concentrations revealed different anticonvulsant properties against PTZ-induced seizures in mice (Elsas et al., 2010). In another experiment, a hydroethanolic extract significantly reduced PTZ-induced seizures and ameliorated associated post-ictal depression, which diazepam usually worsens (Singh et al., 2012). Furthermore, *Passiflora incarnata* was shown to possess analgesic action, increasing the nociceptive threshold in the tail-flick and hot-plate tests in rats (Speroni and Minghetti, 2007).

A significant body of scientific literature highlighted the preclinical evidence regarding the beneficial properties of passionflower as a treatment for addictive behaviours linked to substances such as amphetamine, nicotine, cannabis and ethanol, and benzodiazepines (Capasso and Sorrentino, 2005; Dhawan et al., 2002a,b,c; Dhawan and Sharma, 2003). In particular, BZF has been tested in various experiments for its ability to counter chronic drug use and substance dependence (Dhawan et al., 2003a). An aqueous passionflower extract was demonstrated to antagonise the locomotor sensitisation in a group of rats with previously developed nicotine dependence (Breivogel and Jamerson, 2012). The chronic co-administration of the BZF moiety along with morphine significantly attenuated the occurrence of signs of morphine dependence and naloxone-precipitated withdrawal jumps in mice. BZF-morphine co-treatment also reduced the induction of tolerance measured using the tail-flick test (Dhawan et al., 2002d). In another experiment, BZF exerted protective action against the development of Δ-9-tetrahydrocannabinol (THC) tolerance, preventing the expression of the typical signs of withdrawal (Dhawan et al., 2002b). Administration of BZF together with nicotine showed beneficial effects preventing the development of nicotine tolerance and dependence. The severity and intensity of nicotine cessation withdrawal behaviours were significantly reduced in the group of mice treated with nicotine and BZF compared to the group that received nicotine alone (Dhawan et al., 2002c). The passionflower BZF compound can decrease the levels of anxiety measured using the EPM in ethanol-dependent mice. Additionally, mice treated with ethanol-BZF combinations exhibited less dependence and fewer withdrawal signs in comparison to the group of mice that only received ethanol, and these effects were dose-dependent. The signs of diazepam dependence and cessation were less severe in mice treated with BZF (Dhawan, 2003b).

The administration of a passionflower extract can influence sexual behaviour in experimental animals, increasing the number of mounts, even though the sedative effect dominates over the "aphrodisiac effect" at high doses (Dhawan et al., 2003c). Studies of aging showed that the BZF moiety can counteract the detrimental effects on libido, fertility, and sperm count caused by chronic ethanol and nicotine consumption in 2 years old male rats (Dhawan and Sharma, 2002a; Dhawan et al., 2003e).

In experimental studies, a methanol extract demonstrated antitussive action in a murine model of sulphur dioxide-induced cough (Dhawan and Sharma, 2002b), and antiasthmatic dose-dependent action against acetylcholine-induced bronchospasms in guinea pigs (Dhawan et al., 2003d). Potential beneficial metabolic effects have been suggested by the demonstration of anti-hyperglycaemic and hypolipidemic actions on streptozotocin-induced diabetic mice (Gupta et al., 2012). Two chemical compounds present in passionflower extracts, chrysin and apigenin, have been found to exhibit antitumoural activity by inhibiting the growth of breast carcinoma cells, human thyroid cancer cells and human prostate tumours (Ingale and Hivrale, 2010).

7. Overview of clinical studies

Passiflora incarnata has long been used in the folk medicine of West India, Mexico, the Netherlands, South America, Italy and

Table 2
Preclinical data about pharmacological activities of *Passiflora incarnata* L.

Pharmacological activity	Tested extract or other derivative product	In vitro/in vivo	Model	Administration (in vivo)	Dose range	Active concentration	Reference
Anxyolitic activity	Methanol extract of aerial parts	In vivo	Elevated Plus Maze test in mice	Oral	10 mg/kg	10 mg/kg	Dhawan et al., 2001a
	Methanol extract of aerial parts and underground parts	In vivo	Elevated Plus Maze test in mice	Oral	100, 125, 200 and 300 mg/kg for both aerial and underground parts	100, 125, 200 and 300 mg/kg	Dhawan et al., 2001b
	Petrol extract $CHCl_3$ extract MeOH extract Water extract	In vivo	Elevated Plus Maze test in mice	Oral	75, 100, 125, 200 and 300 mg/kg	75, 100, 125, 200 and 300 mg/kg	Dhawan et al., 2001c
	Mother tincture vs methanol extract of aerial parts	In vivo	Elevated Plus Maze test in mice	Oral	Mother tincture:100, 200, 300, and 400 mg/kg Methanol extract: 125 mg/kg	Mother tincture:100, 200, 300, and 400 mg/kg Methanol extract: 125 mg/kg	Dhawan et al., 2002c
	Fractions of hydroethanolic extract: – Butanol fraction (BF) – Petroleum ether fraction (PEF) – Chloroform fraction (CHCl3)	In vivo	Elevated Plus Maze test in mice	Oral	Fractions of total extract (rispectively150mg, 300 mg, 750 mg): – BF: 2.1 mg, 4.2 mg,10.5 mg – PEF: 0.17 mg 0.34 mg 0.85 mg – CHCl3: 0.15 mg 0.30 mg 0.75 mg	Fractions of total extract (rispectively 150 mg/kg, 300 mg/kg, 750 mg/kg): – BF: 2.1 mg, 4.2 mg,10.5 mg – PEF: 0.17 mg 0.34 mg 0.85 mg – CHCl3: 0.15 mg 0.30 mg 0.75 mg	Sampath et al., 2011
Sedative effect	0.5% carboxymethyl cellulose (CMC)	In vivo	Rat model of sleep disturbance	Oral	300, 1000, 3000 mg/kg	300, 1000, 3000 mg/kg	Shinomiya et al., 2005
Modulation GABA system	Dry extract (DER=5-7:1, extraction solvent: 50% ethanol (V/V))	In vitro ex vivo	Rat brain neurons (hippocampus and cerebellum)	N/A	0,1–1000 mcg/ml	0,1–1000 mcg/ml	Appel et al., 2011
Anticonvulsivant/ anti-epileptic activity (and positive effect on post-ictal depression)	Hydro-alcoholic extract	In vivo	Pentylentetrazole (PTZ) induced seizures model in mice	Intraperitoneal	0.4–0.05 mg/kg	0.4–0.05 mg/kg	Nassiri-Asl et al., 2007
	Hydro-alcoholic extract	In vivo	Pentylentetrazole (PTZ) induced seizures model in rats	Intracerebroventricular	0.125, 0.25, 0.55 and 1.5 mcg	0.125, 0.25, 0.55 and 1.5 mcg	Nassiri-Asl et al., 2007
	Hydro- alcoholic extract		Pentylentetrazole (PTZ) induced seizures model in rats	Intraperitoneal	150, 300 and 600 mg/kg	150, 300 and 600 mg/kg	Singh et al., 2012
Drug/substance reversal effects on withdrawal	Benzoflavone (BZF) moiety from methanol extract	In vivo	Elevated Plus Maze test in mice in which anxiety was induced by withdrawn after an addictive dose 2 g/kg, bid for 6 days of ethanol	Oral	– -10, 20 and 50 mg/kg of twice daily for 7 days – 10, 20 and 50 mg/kg on 6th day of ethanol	– 10, 20 and 50 mg/kg	Dhawan et al., 2002a
	Benzoflavone (BZF) moiety from methanol extract	In vivo	Detrimental effects upon the libido, fertility, and sperm count in 3 groups of male rats treated with: – ethanol 3 g/kg, p.o. – nicotine 2 mg/kg, s.c. – ethanol 3 g/kg, p.o.+ nicotine 2 mg/kg, s.c.	Oral	10 mg/kg for 7 days	10 mg/kg	Dhawan et al., 2002d

	Benzoflavone (BZF) moiety from methanol extract	In vivo	Withdrawal in mice treated with 10 mg/kg dose of morphine for 9 days. Tail-flick and naloxone precipitated withdrawal jumps.	Oral	10, 50 and 100 mg/kg doses along with 10 mg/kg	10, 50 and 100 mg/kg doses along with 10 mg/kg	Dhawan and Sharma, 2002b
	Benzoflavone (BZF) moiety from methanol extract	In vivo	Withdrawal in mice treated with addictive dose of delta9-tetrahydrocannabinol (delta9-THC)	Oral	a 10- or 20-mg-kg$_{-1}$ twice-daily for 6 days.	10- or 20-mg-kg$_{-1}$	Dhawan et al., 2002b
	Benzoflavone (BZF) moiety from methanol extract	In vivo	Withdrawal in mice treated with diazepam addictive dose	Oral	10, 50 or 100 mg/kg	10, 50 or 100 mg/kg	Dhawan et al., 2003c
	Acqueous extract	In vivo	Locomotor activity in rats treated with nicotine addictive dose	Oral	800 mg/kg of one dose	800 mg/kg	Breivogel and Jamerson, 2012
Aphrodisiac activity	Methanol extract	In vivo	Mounting behaviour with non-oestrous female mice	Oral	75, 100 and 150 mg/kg	75, 100 and 150 mg/kg	Dhawan et al., 2003a
Aphrodisiac activity (restoration sexual decline after delta-9-THC)	Benzoflavone (NZF) moiety from methanol extract	In vivo	Mounting behaviour of rats treated with addictive doses of delta-9-THC with non-oestrous female rats – decrease in sperm count – number of impregnated pro-oestrous female rats	Oral	10 and 20 mg/kg^{-1}	10 and 20 mg/kg^{-1}	Dhawan et al., 2003b
Anti-tussive effect	Methanol extract of the leaves	In vivo	Sulphur dioxide-induced cough in mice	Oral	100 and 200 mg/kg	100 and 200 mg/kg	Dhawan et al., 2003d
Anti-asthmatic effect	Methanol extract of leaves	In vivo	Acetylcholine chloride induced-bronchospasm in guinea-pigs	Oral	50, 100 and 200 mg/kg	50, 100 and 200 mg/kg	Dhawan et al., 2003d
Anti-diabetic activity	Methanolic extract aerial parts petroleum ether (200 ml) and methanol (200 ml).	In vivo	Streptozotocine induced diabetes in mice	Oral	100 and 200 mg/kg for 15 days	100 and 200 mg/kg for 15 days	Gupta et al., 2012

Table 3
Summary of clinical trials on *Passiflora incarnata* L.

Reference	Study design	Condition	Participants and sample size (treatment/control)	Age (treatment group/control group) in years	Treatment group	Control group	Treatment duration	Outcomes measures	Main results
Schulz et al., 1998 "The quantitative EEG as a screening instrument to identify sedative effects of single doses of plant extracts in comparison with diazepam"	RCT; DB; CR	Healthy subjects	12	53.7 ± 5.6	Passiflora i. 1200 mg extract (drug-extract ratio: 5.9:1) plus caffeine 100 mg	Placebo or active control (Diazepam 10 mg) plus caffeine 100 mg	Single administration after 3 days of wash-out other administration	Qualitative EEG (qEEG) and self-rating of alertness with a Visual Analogue Scale (VAS)	Changes in qEEG consistent with sedative effects
Akhondzadeh et al., 2001a "Passionflower in the treatment of generalized anxiety: a pilot double-blind randomized controlled trial with oxazepam"	RCT; DB	Generalized anxiety disorders (GAD)	36 (18/18)	Between 19 and 47	Passiflora i. extract 45 drops/day plus placebo tablet	Oxazepam 30 mg/day plus 45 drops of placebo	4 weeks	Hamilton Anxiety scale	No significant difference between the two treatments
Akhondzadeh et al., 2001b "Passionflower in the treatment of opiates withdrawal: a double-blind randomized controlled trial"	RCT; DB	Opiates addiction	65 (30/35), 30 pt. completed the trial (15/15)	34.8 ± 7.6 35.9 ± 8.1	Passiflora i. extract 60 drops plus clonidine tablet 0.8 mg/daily	Placebo 60 drops plus clonidine tablet 0.8 mg/daily	2 weeks	Short Opiate Withdrawal Scale (SOWS)	Same efficacy on physical symptoms of withdrawal. Passiflora i. plus clonidine showed a more significant improvement over clonidine on mental symptoms
Akhondzadeh et al. 2005 *"Passiflora incarnata* in the treatment of attention-deficit hyperactivity disorder in children and adolescents"	RCT; DB	Attention-deficit hyperactivity disorder (ADHD)	34	School-aged children (Age is not expressed in years)	0.04 mg/kg/day (twice daily) Passiflora i. extract	Methylphenidate 1 mg/kg/day (twice daily)	8 weeks	Parent and Teacher ADHD Rating Scale	No significant diffence between the two treatment groups on Parent and Teacher Rating Scale scores
Movafegh et al., 2008 "Preoperative oral *Passiflora Incarnata* reduces anxiety in ambulatory surgery patients: a double-blind, placebo-controlled study"	RCT; DB	Presurgery anxiety	60 (30/30)	32.0 ± 4.6 31.7 ± 5.1	Passiflora i. extract 500 mg	Placebo	Single administration	Psychomotor function was assessed with the Trieger Dot Test and the Digit-Symbol Substitution Test	Reduction of anxiety without sedation
Fahami et al., 2010 "A comparative study on the effects of Hypericum Perforatum and passion flower on the menopausal symptoms of women referring to Isfahan city health care centers"	RCT	Menopausa	59 (29/30)	51.7 ± 3.3 51.8 ± 2.6	30 mg, 20% Pass P drop (a Passiflora i. extract), 10 drops, three times daily and 30 drops before sleeping	160 mg effervescent tablet of Hypericum p. (three times daily)	6 weeks	Cooperman's index for menopausal symptoms	Decrease of score of menopause symptoms in the two treatment groups
Ngan and Conduit, 2011 "A Double-blind, Placebo-controlled Investigation of the Effects of Passiflora incarnata (Passionflower) Herbal Tea on Subjective Sleep Quality"	RCT; DB	Sleep disorders	41	22.73 ± 6.22	Passiflora i. teabags (containing 2 g of dried plant parts)	Petroselinum c. teabags (containing 2 g of dried plant parts)	1 week, after 1 week of wash-out another 1 week	PSG recording (for objective PSG sleep measures) for 10 pt, sleep diary, State Anxiety Inventory score (STAI)	Improvement of sleep quality. No effects on STAI
Aslanargun et al., 2012 "Passiflora incarnata Linneaus as an anxiolytic before spinal anaesthesia"	RCT; DB	Pre-spinale anaesthesia anxiety	60 (30/30)	50 (26–55) 44 (25–55) (median, minimum an maximum in brackets)	Passiflora i. 700 mg/5 ml aqueous extract	Placebo	Single administration	State Anxiety Inventory score	Suppression of anxiety without changing psychomotor performance, sedation level, or hemodynamics

RCT = randomized controlled trial; DB = double blind; CR = crossover.

Argentina for the treatment of bronchitis, asthma, whooping cough, pneumonia, nervousness and insomnia. Furthermore, this plant is generally believed to possess sedative, antispasmodic and mild anti-microbial effects.

Currently, products containing passionflower extracts are mainly utilised in modern phytotherapy as mild sedatives and anxiolytic agents. The results from various clinical trials support this use by demonstrating potential effects for the treatment of generalised anxiety disorder, pre-surgery anxiety, insomnia, attention-deficit hyperactivity disorder, opiate withdrawal symptoms and control of menopausal symptoms (Tables 3–5) (Nassiri-Asl et al., 2007).

8. Anxiety (general anxiety disorder and pre-operative anxiety)

Anxiety disorders are the most prevalent psychiatric disorders (Kessler et al., 2010), and this spectrum of pathologies imposes high individual and societal burdens, sometimes becoming chronic and disabling. These disorders impose further costs including hospitalisation, prescription medications, decreased productivity, absenteeism from work, and sometimes suicide (Movafegh et al., 2008).

Different anxiety disorders have the following common features: excessive, irrational fear and avoidance of anxiety triggers (American PA, 2013 DSM-5 2013). Benzodiazepines (BZDs) are a common class of drugs used to cure anxiety disorders. Although these drugs are effective, BZD treatment suffers from several problems: a significant percentage of patients are non-responders (approximately 25%), the development of tolerance and potential dependence; and sedation, resulting in cognitive and psychomotor impairment. For this reason, safe alternative treatments are desired (Miyasaka et al., 2007; Movafegh et al., 2008; Koen and Stein, 2011).

Some clinical trials have been performed to assess the putative anxiolytic effect of *Passiflora incarnata* already reported in folk medicine. One of these trials was designed to evaluate *Passiflora incarnata* treatment of Generalised Anxiety Disorder (GAD), and another two clinical trials were performed to assess its effectiveness in treating pre-surgery anxiety. Akhondzadeh et al. (2001a,b) compared the supposed antianxiety effect of an extract of *Passiflora incarnata* with the benzodiazepinic drug oxazepam in a double-blind randomised clinical trial carried out by recruiting 36 patients suffering from GAD.

Patients were enroled if they matched the following inclusion criteria: previous diagnosis of GAD according to DSM IV criteria (duration of illness at least 6 months) and a score of 14 or more measured by the Hamilton Anxiety Rating Scale. History of a serious suicide attempt or current acute suicidal ideation, psychosis, major depression, substance abuse and dementia were considered as exclusion criteria. In a 4-week trial, a group of 18 volunteers was treated with a passionflower extract (commercialised in Iran as Passipay™ Iran Daroo) at a dose of 45 drops/day plus placebo tablet, and another 18 volunteers received 30 mg oxazepam per day plus placebo drops. The decrease in the HAM-A score from baseline was used as the main response measure. The patients were assessed at baseline and 4, 7, 14, 21 and 28 days after the beginning of the treatment. Four subjects dropped out of the trial due to non-compliance (two from each group), for a total of 32 patients completing the trial. The results demonstrated that both herbal extract and oxazepam exerted positive effects, producing similar reductions in HAM-A scores with respect to baseline. In particular, oxazepam reduction was evident starting from day 4, leading to a more rapid onset of action. The results indicated that *Passiflora incarnata* is as effective as oxazepam for the treatment of GAD. Patients treated with the extract experienced a small but

Table 4
Quality assessment according to Jadad Scale.

Reference	Was similarity between the two (or more) groups at baseline?	Was the trial described as randomized?	Was the randomization procedure described and was appropriate?	Was the treatment allocation concealed?	Was the trial described as double-blind?	Was the method of double blinding described and appropriate?	Was the number of withdrawals/dropouts in each group mentioned?	Was an analysis conducted on the intention – to-treat sample?	Jadad score
Schulz et al., 1998	Description not adequate	Yes	No	Not reported	Yes	Not reported	Not reported	Not reported	1+1+0+0+0=2
Akhondzadeh et al. 2001a	Yes	Yes	No	Not reported	Yes	Not reported	Not reported	Not reported	1+1+0+0+0=2
Akhondzadeh et al., 2001b	Yes	Yes	No	Not reported	Yes	Not reported	Yes	Not reported	1+1+0+0+0=2
Akhondzadeh et al. 2005	Yes	Yes	No	Not reported	Yes	Not reported	Yes	Yes	1+1+0+0+0=2
Movafegh et al., 2008	Yes	Yes	Yes	Not reported	Yes	Not reported	Yes (all pt completed the trial)	N/A	1+0+0+1+0=2
Fahami et al., 2010	Yes	Yes	Yes	Not reported	No	N/A	Yes	Not reported	1+1+0+1+0=3
Ngan and Conduit, 2011	Description not adequate	No	N/A	Not reported	Yes	Not reported	Not reported	Not reported	1+1+0+0-1=1
Aslanargun et al., 2012	Yes	Yes	Yes	Not reported	Yes	Not reported	Yes (all pt completed the trial)	N/A	1+1+0+0+0=2

Table 5
Section 4 of Elaboration of CONSORT Items for Randomized Controlled Trials of Herbal Medicine Interventions.

Reference	Herbal medicinal product name	Characteristics of the herbal product	Dosage regimen and quantitative description	Qualitative testing	Placebo/control Group (rationale for the type of control or placebo used)	Practitioner
Schulz et al., 1998	Yes (only name of the manufacturer)	Yes	Yes	No	No	No
Akhondzadeh et al. 2001a	No	No	Yes	No	No	No
Akhondzadeh et al., 2001b	No	No	Yes	No	No	No
Akhondzadeh et al. 2005	No	No	Yes	No	No	No
Movafegh et al., 2008	Yes	No	Yes	No	No	No
Fahami et al., 2010	Yes	No	Yes	No	No	No
Ngan and Conduit, 2011	Yes (only name of the manufacturer)	Yes	Yes	No	No	No
Aslanargun et al., 2012	Yes	No	No	No	No	No

statistically significant impairment of job performance compared with the oxazepam group. No other significant differences were observed between the two treatments in terms of side effects (Akhondzadeh et al., 2001b).

The anxiolytic activity of passionflower has been tested in two clinical studies conducted on patients undergoing surgery. One study was designed with the aim of comparing the effect of oral administration of a *Passiflora incarnata* extract with placebo as a premedication before anaesthesia. The study enroled 60 patients (aged between 25 and 45 years) with ASA (American Society of Anaesthesiology patient classification status) physical status (Pt) I and II (ASA I corresponds to normal healthy Pt; ASA II corresponds to Pt with mild systemic disease but no functional limitation) undergoing inguinal herniorrhaphy. The subjects were randomly allocated in two groups of 30, one receiving *Passiflora incarnata* (500 mg, Passipay™) 90 min before the surgical operation, with each tablet containing 1.01 mg of benzoflavone (BZF). The other group of 30 patients received a placebo. Anxiolytic and sedative effects were assessed, in addition to psychomotor performance and discharge time. A numerical rating scale (NRS) was used to assess each patient's anxiety and sedation before and 10, 30, 60, and 90 min after premedication. Psychomotor function was assessed with the Trieger Dot Test (TDT) and the Digit-Symbol. The TDT deviation represents the cumulative distance (in millimetres) between the drawn line and missed dots. The DSST is a subtest of the Wechsler Adult Intelligence Scale, a timed pen-and-paper test in which patients are required to appropriately match numbers and symbols.

Furthermore, the time interval between arrival in the postanaesthesia care unit and discharge to home (discharge time) was recorded. The NRS anxiety scores were significantly lower in the passionflower group compared with the control group ($P < 0.001$). No significant differences were observed in psychological variables in the postanaesthesia care unit, and the recovery of psychomotor function was comparable in both groups. Patients did not report side effects, although the sample size was very small. In conclusion, using *Passiflora incarnata* as a premedication reduced anxiety without causing sedation (Movafegh et al., 2008).

Aslanargun et al. (2012) conducted a prospective, randomised, double-blind placebo-controlled study on 60 patients between 25 and 55 years of age who underwent regional anaesthesia with the aim of evaluating whether treatment with *Passiflora incarnata* extract before spinal anaesthesia could reduce anxiety. This study included ASA I–II patients. The participants, allocated in 2 groups using a random procedure, received the medication under investigation (700 mg/5 ml of an aqueous extract of passionflower, produced by Sandoz, Kocaeli, Turkey) or a corresponding identical placebo, 30 min before the spinal anaesthesia baseline. Hemodynamic parameters, State-Trait Anxiety Inventory (STAI) score, alertness-sedation score (OAA/S), and psychomotor function measured using the perceptive accuracy test (PAT) and the finger tapping test (FTT) were evaluated. All tests (STAI-S2, STAI-T2, PAT2, and FTT2) were repeated for a second time, just before spinal anaesthesia. The psychomotor function was again evaluated at the end of the operation and 60 min after the operation. A statistically significant difference was observed between the two groups in the increase in the State Anxiety Inventory (STAI-S) score obtained just before spinal anaesthesia when compared to the baseline. No statistically significant difference from baseline was observed in psychomotor function for either group. Furthermore, no statistically significant difference was observed between groups in terms of the characteristics of the sensory and motor blocks, the time to first analgesic requirement, the time to discharge, and side effects.

Placebo and *Passiflora. incanata* extract resulted in comparable side effects, with no observations of nausea, vomiting, respiratory depression, shivering, or postoperative complications. The results suggested that passionflower treatment reduces clinical symptoms anxiety before spinal anaesthesia without affecting psychomotor function, sedation level, or hemodynamic parameters (Aslanargun et al., 2012).

While the clinical studies described above investigating the effects of passionflower on anxiety are well designed, some weak points are evident. The sample of patients in the study of GAD is much too small, and none of these three studies describe randomisation methods. A major limitation of these studies is that for the most part they do not contain any description of the type of herbal preparation used, giving health professionals incomplete information on the potential therapeutic use of the *Passiflora incarnata* products investigated in these studies. The trade name of the preparation is reported without providing any information on the part of the plant, the type and percentage of extraction solvent (alcohol, water, chloroform, etc.) used, and the drug extract ratio (D.E.R.). This information is fundamental to link the results with a well-defined herbal preparation. Only in this way will clinicians be able to know and identify what preparations derived from *Passiflora incarnata* can be effective in curing a specific condition, in this case GAD. While more data on the product used in these studies may be available on the website of the company that produces it, a detailed description of the extract is needed to enable a more complete evaluation of clinical efficacy. The more recent study by Aslanargun on preoperative anxiety is an exception, as the ratio between the extract and water is reported and the randomisation method is adequately described. Neither of these studies adequately describes how the sample size was determined. In the Movafegh et al. trial, blinding is mentioned but the adopted procedure is not sufficiently described.

9. Treatment of opiate withdrawal

Opiate addicts and dependent subjects who attempt to quit opiate consumption commonly experience withdrawal syndrome.

During the process of detoxification, these individuals can suffer from anxiety and sleep disorders, but the use of benzodiazepines is not indicated because this class of drugs can induce dependence itself. Alternative non-opiate detoxification therapies have been tested to overcome some of the limitations of methadone-based detoxification regimens. Clonidine is an α_2-adrenergic agonist that attenuates symptoms caused by the disregulation of the noradrenergic system. The main disadvantage of clonidine-based detoxification, in addition to hypotensive side-effects, is the lack of effectiveness in addressing mental symptoms.

To verify the possible adjuvant activity of an extract of *Passiflora incarnata* on the treatment of opiate withdrawal based on clonidine, a clinical double-blind randomised trial vs. placebo has been performed. A total of 65 participants with opiate addictions were randomly assigned to treatment with *Passiflora incarnata* extract plus clonidine tablet or clonidine tablet plus placebo. The patients were considered eligible if they met the DSM IV criteria for opiate dependence. The severity of the withdrawal syndrome was measured using a revised version of the Short Opiate Withdrawal Scale (SOWS) at baseline (day 0) and days 1, 2, 3, 4, 7 and 14 after the start of the treatment. Fifteen subjects dropped out from the passionflower group and 20 from the placebo group over the course of the trial, leaving 30 subjects (15 per group). The results showed that the group of patients treated with clonidine plus *Passiflora incarnata* extract exhibited earlier symptom reductions than patients treated with placebo and clonidine. Statistical analysis of data regarding mental and physical symptoms showed that treatment consisting of *Passiflora incarnata* plus clonidine reduced mental symptoms (e.g., insomnia/sleeping problems, dysphoria, anxiety, agitation, irritability and craving for substances) to a greater extent than physical symptoms of opiate withdrawal (Akhondzadeh et al., 2001a).

This clinical trial does not describe the randomisation and blinding methods. The trial is characterised by a high number of drop-outs. Because of the small “intention to treat group”, a small number of patients were finally treated. For this reason, adding an “intention to treat” analysis could be useful. Details about the characteristics of passionflower extract are not reported, and even the trade name is not indicated. The absence of this information prevents other researchers from reproducing the study or finding further information on the product.

10. Treatment of menopausal symptoms

The increase in women's lifespans implies a major quality of life impact of the physiological changes and disorders related to menopause. Vasomotor disorders, sleep disorders and psychological changes are prevalent in this period of life for women. Hormone therapy is a common treatment, and results in some unwanted effects for most individuals. Herbal medicines can act as additional therapeutic tools with fewer side effects than hormone therapy (Vesco et al., 2007; Freeman et al., 2011). A clinical study compared the effects of two extracts derived from the medicinal herbs *Hypericum perforatum* L. and *Passiflora incarnata* on menopausal symptoms. The entrance conditions for this study were as follows: women who experienced menopause in the last year and women who were in the first 5 years of menopause. The study recruited 59 menopausal women and randomly divided them into two groups, with 30 patients undergoing *Hypericum perforatum* treatment and 29 patients treated with *Passiflora incarnata*. The following doses were administered: *Hypericum perforatum*, 160 mg effervescent tablet made by Goldaroo Company, three times a day; *Passiflora incarnata*, 30 mg, 20% Pass P drop™, made by Iran Daroo Company, 10 drops, three times a day and 30 drops before sleeping. The women filled out an interview, Personal Characteristics Questionnaire, and Cooperman's Index for menopause symptoms at the three stages of pre-intervention, the third week of intervention, and the sixth week of intervention. The results showed that the average score for menopause symptoms in the two treatment groups decreased significantly through the third and sixth weeks of the treatment period ($P < 0.05$), with no statistically significant differences observed between the two groups. The authors concluded that *Hypericum perforatum* and *Passiflora incarnata* can exert beneficial effects on precocious menopause symptoms (vasomotor signs, insomnia, depression, anger, headaches, etc.) and that health professionals can use them as an alternative to hormone therapy (Fahami et al., 2010).

The analysis of this study reveals several critical points. The randomisation procedure is not described, and no placebo treatment is included. The authors correctly report this issue, but there is no ability to compare the results in this study with the normal evolution of menopausal symptoms. As we highlighted for other studies, the herbal preparation is not described, and only the product name is provided.

11. Treatment of insomnia/sleep disorders

Sleep disturbances contribute to increased healthcare utilisation and associated morbidity, and consequently have major societal and individual impact. Several studies have examined the possible sedative effects of *Passiflora incarnata* on human sleep. As anxiety has been shown to be positively correlated with sleep disturbance (Spoormaker and van den Bout, 2005; Spira et al., 2008), Schulz et al. investigated the potential effects of passionflower in improving sleep quality in humans as a secondary consequence of its anxiolytic effects (Schulz et al., 1998).

A randomised double-blind vs. placebo clinical trial of twelve healthy females (age: 53.7 ± 5.6 years) was conducted to study the effects of different medicinal herbs (including *Passiflora incarnata*) on sleep quality. The experiment was designed as a randomised crossover study with six treatments: placebo, diazepam, valerian extract, lavandula extract, passionflower and kava–kava extract. *Passiflora incarnata* extract (drug-extract ratio: 5.9:1) was administered in a single dose of 1200 mg, and the effects were compared with placebo and diazepam (10 mg). Quantitative EEG and the level of alertness (rated by a visual analogue scale) were measured at 120 and 180 min after the co-administration of the medication with 100 mg of caffeine. Diazepam, placebo and passionflower extract all exerted effects, producing a similar decrease in mental alertness. EEG did not show any effect of passion flower extract in comparison with placebo (Schulz et al., 1998).

Another randomised double-blind placebo control clinical study tested the potential efficacy of passionflower on 41 volunteers suffering from primary insomnia, 14 males and 27 females, aged 18–35 years. The treatment was based on an infusion of dried *Passiflora incarnata* parts in teabags (each containing 2 g of dried leaves, stems, seeds and flowers), and the placebo was parsley teabags (each containing 2 g of dried *Petroselinum crispum* L.); both with dosages of 3 cups of tea per day. PolySomnoGraphy (PSG) and subjective sleep parameters were analysed, but only 10 subjects underwent PSG testing. The results revealed that in subjects receiving passionflower, only subjective sleep quality was significantly improved compared with the placebo group. *Passiflora incarnata* did not lead to any significant changes in the PSG parameters.

As reported noted in the study, the small sample size limits the power of the statistical analysis to detect significant differences. In addition to this limitation only a portion of the sample was assessed by PSG. Furthermore, the fact that the patients were not adapted to sleeping in uncomfortable environments such as the laboratory may have limited the treatment effectiveness.

The authors suggested that the administered dose may not have been sufficient because it was only administered in the night time to avoid daytime sedation (Ngan and Conduit, 2011).

The article by Ngan et al. does not provide sufficient details about the features of the herbal preparation, instead only indicating the name of the manufacturer. Randomisation and blinding procedures were also not explained. According to several articles, a placebo should be an inert substance or procedure, and the placebo effect (or response) is the response following placebo administration (Finiss et al., 2010). In the present clinical trial, the placebo is an herbal preparation containing *Petroliseum crispum,* which does not fit the definition of placebo widely accepted by the scientific community, consequently revealing a substantive methodological weakness. The article published by Schulz et al. provides little information regarding the extract used, and the patient sample is highly limited, with only 12 subjects. On the other hand, this study provides useful information because it compares the effects of extracts obtained from different herbal medicines on sleep.

12. Treatment of ADHD

Attention Deficit Hyperactivity Disorder (ADHD) is a psychiatric condition characterised by age-inappropriate levels of inattention, hyperactivity-impulsiveness or a combination of these problems (Shaw et al., 2012). The symptoms of ADHD often lead to functional impairment in multiple domains and lower quality of life. Stimulants are currently the first-line treatment for ADHD. Nevertheless roughly 30% of children and adolescents are either non-responders or experience severe side effects, so the use of herbal medicine could provide therapeutic benefit. As *Passiflora incarnata* is a folk remedy for anxiety and ADHD, its potential beneficial activity against ADHD has been evaluated in a double-blind, randomised clinical trial on a sample of 34 children with ADHD. This disorder was diagnosed according the Diagnostic and Statistical Manual of Mental Disorders (DSM IV). The authors hypothesised that a therapy based on *Passiflora incarnata* tablets could lead to clinical improvements in ADHD patients. The children were divided among two groups: group 1 received passionflower tablets 0.04 mg/kg/day (twice daily) and group 2 received methylphenidate tablets 1 mg/kg/day (twice daily), both for a duration of 8 weeks. The authors defined as outcome measures the Parent and Teacher ADHD Rating Scale. A child psychiatrist assessed the children at baseline, 14, 28, 42 and 56 days after the treatment began. No significant differences were observed between the two medications in the Parent and Teacher Rating Scale scores over the course of the trial ($F=0.007$, $df=1$, $p=0.93$; and $F=0.006$, $df=1$, $p=0.94$, respectively), although patients who received methylphenidate experienced decreased appetite and anxiety/nervousness more often than those in the *Passiflora incarnata* group. An intention to treat (ITT) analysis was performed. Two patients dropped out from the methylphenidate group and one from the passionflower group due to failure to follow up, resulting in 31 patients completing the protocol. Although the number of dropouts in the methylphenidate group was higher than that in the *Passiflora incarnata* group, no statistically significant differences have been reported between the two branches of the study. In addition, decreased appetite and anxiety/nervousness occurred more often in the methylphenidate group. These results suggest that the main advantage of the *Passiflora incarnata* treatment is a more tolerable side-effect profile (Akhondzadeh et al., 2005).

The analysis of this study reveals critical issues including a lack of description of randomisation and blinding procedures. The authors correctly report the small patient sample as a limitation. As we found in other studies, details about the characteristics of the *Passiflora incarnata* extract are not reported, and even the trade name is not indicated. Thus, it is difficult for other researchers to reproduce the results of this study.

13. Safety profile and pharmacovigilance data

No acute toxicity was observed after intraperitoneal injection of doses larger than 900 mg/kg in mice (Fisher et al., 2000). The acute oral administration of the methanolic extract of *Passiflora incarnata* in various doses of 50, 100, 200, 400, 800 and 1600 mg/kg did not lead to any mortality up to 7 days after treatment (Gupta et al., 2012). No case of overdose has been reported in humans, and the US Food and Drug Administration classified passionflower extracts as "generally regarded as safe" (GRAS) (Burdock and Carabin, 2004).

One case of toxicity has been published for a woman consuming *Passiflora incarnata* at therapeutic doses of 500–1000 mg 3 times daily. The authors did not provide details about the type of extract used to produce the tablets, but only reported that one tablet contained the "equivalent [of] 500 mg of the active ingredients" of the plant. A 34-year-old woman developed severe nausea, vomiting, drowsiness, prolonged QT and episodes of non-sustained ventricular tachycardia. The possible association of symptoms with *Passiflora incarnata* was not recognised for several days, at which point she required hospitalisation for cardiac monitoring and received intravenous fluid therapy (Fisher et al., 2000).

In another case, a patient self-medicated with *Valeriana officinalis* L. and *Passiflora incarnata* while on lorazepam treatment developed handshaking, dizziness, throbbing and muscular fatigue within the 32 h before clinical diagnosis. The patient's medical history revealed GAD but no neurological disorder. An additive or synergistic effect was hypothesised as the cause of these symptoms. The active chemical constituents of *Valeriana officinalis* and *Passiflora incarnata* might enhance the action of benzodiazepine binding to the GABA receptors (Carrasco et al., 2008). Furthermore *Passiflora incarnata* is associated with IgE-mediated occupational asthma and rhinitis (Giavina-Bianchi et al., 1997). A case of hypersensitivity with cutaneous vasculitis and urticara has been reported, with lesions appearing over the shins and the ankles, and also over the shoulder and one thumb after the ingestion of tablets containing *Passiflora incarnata* extract (Smith et al., 1993). As passionflower may induce uterine contractions, the consumption of this herbal medicine is contraindicated during pregnancy (Fisher et al., 2000).

14. Conclusion

Interest in the clinical use of medicinal plants has increased dramatically over the past decade throughout the world (Frass et al., 2012), and the benefits of these products are increasingly cited in the media (Kelly et al., 2005). The high consumption of these types of products by an extensive number of patients has led to growing concerns about their efficacy and safety (Bishop and Lewith, 2010). In many countries, these products are regulated both as medicinal products and as food supplements, and they are often labelled as natural food supplements (Miroddi et al., 2013).

In light of its long tradition of use and the growing demand for *Passiflora incarnata* derivative preparations, this study reviewed and commented on the current knowledge provided by preclinical and clinical research on the effects of this plant.

Although the data provided here show that this medicinal plant may exert beneficial effects in the treatment of several pathological conditions, further studies are needed to clarify issues regarding the composition of the phytocomplex, the replicability of preclinical experiments, the lack of translation of the preclinical

results to humans, the lack of methodological accuracy in clinical trials, and the types of extracts causing adverse effects. To date, no standardised composition has been defined for this plant, and the concentrations of the various chemical constituents in its preparations that are necessary to achieve specific pharmacological effects remain unknown. Furthermore, because the mechanisms of action of the different compounds present in *Passiflora incarnata* remain unclear, studies should be carried out to explore the structure–activity relationships among the constituents.

We evaluated the methodological accuracy of published clinical trials on this plant according to current and consolidated guidelines for the reporting of the clinical efficacy of herbal medicine provided by the Consort Statement (Table 5) (Gagnier et al., 2006). Furthermore, we assessed the methodological quality of clinical studies using the Jadad Scale (Table 4) (Clark et al., 1999), finding that only one of the eight trials considered here had a score of 3 (a score ≥ 3 means "good quality"), while the other studies had scores of 1 or 2. The clinical trials included in this review exhibit crucial weaknesses such as insufficient details regarding the drug extract ratio, limited patient samples, no description of blinding and randomisation procedures, unclear placebo definition, and a lack of intention to treat analysis. Thus, some of the potential therapeutic effects of *Passiflora incarnata* need to be evaluated in new studies.

In conclusion, this review highlights the fact that the common therapeutic uses of *Passiflora incarnata* are not sufficiently supported by clinical evidence. Future research should be conducted using a more rigorous methodology with the ability to corroborate and ascertain the therapeutic potential of *Passiflora incarnata*.

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