PASSION FLOWER

Passiflora incarnata Linnaeus

Family

Passifloraceae.

Parts Used

Herb (aerial parts).

Description

The genus Passiflora comprises approximately 520 species of dicotyledonous (flowering plants whose seed typically has two embryonic leaves or cotyledons) plants. The majority of species are vines with most found in Central or South America and some species occurring in North America, Southeast Asia and Australia. A number of species, including *Passiflora edulis* Sims, *Passiflora laurifolia* L. and *Passiflora mollissima* (Kunth) Bailey, are widely cultivated for their edible fruits, while many others are grown as ornamentals for their unusual and often spectacular flowers. Several species have a history of use as traditional herbal medicines and the North American passion flower *Passiflora incarnata* L. is an important herbal drug widely used in contemporary Western phytotherapy.

This species, commonly known as maypop or apricot vine, is native to the south-eastern United States but is also cultivated in Europe, Asia and Australia, both as an ornamental and as a medicinal plant.[1,2,3]

Passiflora edulis Sims has often been taken to be synonymous with *Passiflora incarnata* L.[4] because the plants possess identical morphological and microscopic characteristics. *Passiflora edulis*, as the name of the species reflects, is mainly cultivated for edible purposes (*edulis* means edible in Latin)

and does not exert pharmacological effects on the central nervous system. Although one article attempted to eliminate potential confusion between these two similar plants, 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*.[5]

Passiflora incarnata is a woody, perennial creeper vine that climbs with the aid of coiled tendrils and rapidly grows up to 6 metres. This plant possesses hermaphrodite flowers (possessing both male and female organs) which are pollinated by insects such as bees. It 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. It has hairless, 3-lobed leaves, large stipules (outgrowths on the base of the leaf stalk) and solitary, very characteristic, open, white and violet flowers with conspicuous flower parts that have given rise to the vernacular name passion flower (see below in Traditional and Empirical Use). The flower is typically 6 to 7cm in diameter. The fruit is fleshy and egg shaped, initially green turning to yellowish-red at maturity.[6,7]

Traditional Use

The prehistoric use of passion flower 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 (preceding Christopher Columbus's voyages of 1492), and passion flower was a common weed crop that often occurred in anthropogenic habitats. In American aboriginal medicine, the passion flower has been used in particular by the Cherokees of the southern Allegheny mountains, the Houmas of Louisiana and the Aztecs of Mexico. Spanish conquerors first learned of passion flower from pre-Colombian people who traditionally used it as a sedative to treat insomnia and nervousness.[8]

Passion flower is not a reference to earthly passions but rather the word *Passiflora* is derived from *passio*, the Latin for suffering. *Flora* comes from the Latin name of Flora, the goddess of plants, flowers, and fertility in Roman mythology. *Incarnata* means "in the flesh". *Passio* has been used to describe the sufferings of Christ between the night of the Last Supper and his death. Spanish missionaries in South America in the 1500s saw in the plant, and flower, symbols of Jesus' scourging, crowning with thorns and crucifixion. The three pistils of the stigma became the nails of the cross; the five petals and five sepals became the 10 apostles (omitting Peter, who denied Christ, and Judas the betrayer), the anthers were the five wounds and the purple corona of filaments was the crown of thorns. It was known by the Spanish as '*La Flor de las Cinco Llagas*' or the 'The Flower With The Five Wounds.[9]

Early European travellers in North America noted that the Algonquin Indians in Virginia, and the Creek people in Florida, ate the fruits of passion flower from cultivated, as well as, wild sources. Passion flower 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.

Today, passion flower 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. In European traditional medicine, passion flower has long been prescribed for various indications such as anxiety, nervousness, constipation, dyspepsia, mild infections and insomnia. In Turkey, passion flower is used for dysmenorrhoea, epilepsy, insomnia, neurosis and neuralgia. In Argentina and Mexico, it is currently consumed for its sedative effects and in Brazil it is used as an analgesic, antispasmodic, antiasthmatic,

wormicidal and sedative. In North America it is used for the treatment of diarrhoea, premenstrual syndrome, dysmenorrhoea, neuralgia, burns, haemorrhoids, insomnia, muscle cramps, hysteria 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. Passion flower is also used as a herbal medicine in Asia where it has been used to treat morphine dependence in traditional medicine in India. In Vietnam it has been used for sleeplessness, anxiety and high blood pressure. In the African countries of Rwanda, Kenya and Congo it is employed as a folk remedy by herbalists for its sedative, nervine, antispasmodic and analgesic effects. It has been used as a sedative and narcotic in Iraq.[10,11]

Constituents

A considerable body of literature has explored the chemical composition of the raw material and of various products derived from passion flower. 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, although the flavonoid and possibly the alkaloid constituents are considered to be important in this respect.[12]

Flavonoids: Pharmacopoeial standard not less than 1.5% expressed as vitexin. Aglycones apigenin, chrysin (5,7-hydroxyflavone), luteolin, quercetin and kaempferol. C-glycosides of apigenin (e.g. vitexin, isovitexin, schaftoside, isoschaftoside) and of luteolin (e.g. orientin, iso-orientin) and related flavonoids. There is considerable variation, qualitatively and quantitatively in the flavanoid composition depending on the source of the plant material.

Alkaloids: Indole alkaloids of the β-carboline type including harman, harmol, harmine, harmalol and harmaline. The alkaloids are minor constituents and may be present in parts per million or even not detectable in some samples of material.

Other constituents: Cyanogenic glycoside gynocardin, maltol and ethymaltol, essential oil (e.g. linalool, carvone, eugenol), amino acids, fatty acids (e.g. linoleic, linolenic, oleic acids), formic and butyric acids, sterols (e.g. stigmasterol) and sugars (e.g. sucrose, glucose, fructose).[13]

Actions

Anxiolytic, mild sedative, anticonvulsant, anti-inflammatory, antispasmodic, hypnotic, hypotensive, anodyne.

Pharmacological Activity

Several pharmacological properties have been described for preparations of passion flower, following preclinical studies, providing supporting evidence for some of the traditional uses. However well designed clinical trials of passion flower preparations are lacking and further studies are required to determine their clinical efficacy and effectiveness.[14] Although passion flower extracts have been tested in numerous preclinical experiments, the mechanism of action is still under discussion.[15]

Anxiolytic and Sedative Activity

Anxiolytic activity is one of the most intensively investigated roles of passion flower.[16,17,18]

Dysfunction of the gamma-aminobutyric acid (GABA - the chief inhibitory neurotransmitter in the vertebrate central nervous system) system is implicated in many neuropsychiatric conditions including anxiety and depressive disorders. The *in vitro* effects of a dry extract of passion flower (sole active ingredient in Pascoflair® 425mg) on the GABA system were investigated. The study found that numerous pharmacological effects of passion flower are mediated via the modulation of the GABA system, including affinity to the GABAa and GABAb receptors and effects on GABA uptake. It appears to be unlikely that passion flower acts by binding to the benzodiazepine site. However, it is plausible that binding to the GABA-site of the GABAa receptor is one mode of action of the plant extract.[19] In the past passion flower and diazepam (also known as

valium - a benzodiazepine drug) were assumed to share the same mechanism of action because some studies showed that flumazenil (a GABAa benzodiazepine receptor antagonist) weakened the *in vivo* anxiolytic effect of passion flower.[20]

In a pilot, double-blind, randomised controlled trial passion flower extract (commercialised in Iran as Passipay™ Iran Daroo) was found to be as efficacious as oxazepam (a benzodiazepine known as Serapax) in the treatment of generalised anxiety disorder (GAD). The low incidence of impairment of job performance with passion flower extract compared to oxazepam was an advantage. The study was performed on 36 out-patients diagnosed with GAD using DSM (Diagnostic and Statistical Manual of Mental Disorders) IV criteria. Patients were allocated in a random fashion: 18 to the passion flower extract 45 drops/day plus placebo tablet group, and 18 to oxazepam 30mg/day plus placebo drops for a 4-week trial. Passion flower extract and oxazepam were both effective in the treatment of generalised anxiety disorder. Oxazepam showed a rapid onset of action but significantly more problems relating to impairment of job performance were encountered with subjects on oxazepam.[21]

Many patients suffer from anxiety before surgery, but any premedication must be sufficiently anxiolytic without causing undue sedation or interacting with general anaesthesia. The anxiolytic activity of passion flower has been tested in two clinical studies conducted on patients undergoing surgery.

In 2012, a prospective, randomised, double-blind, placebo-controlled study was conducted on 60 patients who were aged between 25 and 55 years who underwent regional anaesthesia. The aim of the study was to investigate the effect of preoperative oral administration of an aqueous extract of passion flower on anxiety, psychomotor functions, sedation and haemodynamics in patients undergoing spinal anaesthesia. The authors concluded that oral preoperative administration of passion flower suppresses the increase in anxiety before spinal anaesthesia without changing psychomotor function test results, sedation level or haemodynamics.[22]

A novel clinical study has found that a single dose of passion flower prior to outpatient surgery reduced anxiety without increasing sedation. A double blind placebo controlled study was designed to compare the effect of oral administration of passion flower with placebo as a premedication before anaesthesia. 60 patients were randomised into two groups to receive either oral passion flower (500 mg Passipy™) (n = 30) or placebo (n = 30) as premedication, 90 minutes before surgery. A numerical rating scale (NRS) was used for each patient to assess anxiety and sedation before and 10, 30, 60 and 90 minutes after premedication. Psychomotor function was assessed with the Trieger Dot Test and the Digit-Symbol Substitution Test at arrival in the operating room, 30 and 90 min after tracheal extubation. The time interval between arrival in the post anaesthesia care unit and discharge to home (discharge time) was recorded for each patient. The authors concluded that in outpatient surgery, administration of oral passion flower as a premedication reduces anxiety without inducing sedation.[23]

A 2011 Victorian study investigated the efficacy of passion flower herbal tea on human sleep, as measured using sleep diaries validated by polysomnography (PSG). This study featured a double-blind, placebo-controlled, repeated-measures design with a counterbalanced order of treatments (passion flower vs. placebo tea or parsley, Petroselinum crispum; 2g), separated by a one week 'washout' period. Forty-one participants (18 to 35 years) were exposed to each treatment for a week, whereby they consumed a cup of the tea (prepared from passion flower dried aerial parts 2g) in 250mL of boiling water infused for 10 minutes and filled out a sleep diary for seven days and completed Spielberger's state-trait anxiety inventory on the seventh morning. Ten participants also underwent overnight PSG on the last night of each treatment period. Of six sleep-diary measures analysed, sleep quality showed a significantly better rating for passion flower compared with placebo. These initial findings suggest that the consumption of a low dose of passion flower, in the form of tea, yields short-term subjective sleep benefits for healthy adults with mild fluctuations in sleep quality.[24]

Passion flower may be a novel therapeutic agent for the treatment of attention-deficit hyperactivity disorder (ADHD) a recent double-blind, randomised clinical trial has found. ADHD is a common early-onset childhood disorder that

is estimated to occur in 3 to 5% of school-aged children. Stimulants are the first-line treatment for ADHD. Nevertheless, approximately 30% of children and adolescents either do not respond to or do not tolerate stimulants. A total of 34 children with ADHD as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM IV) were randomised to receive tablets of passion flower or methylphenidate, dosed on a weight-adjusted basis. Group one received passion flower 0.04mg/kg/day (twice daily) and group two received methylphenidate 1mg/kg/day (twice daily) in the eight week trial. The principal measure of outcome was the Parent and Teacher ADHD Rating Scale. Patients were assessed by a child psychiatrist at baseline, 14, 28, 42 and 56 days after the medication was started. No significant differences were observed between passion flower and methylphenidate on the Parent and Teacher Rating Scale scores over the course of the trial. Both treatment groups demonstrated significant clinical benefit over the period of treatment as assessed by both parents and teachers. Although the number of dropouts in the methylphenidate group was higher than in the passion flower group, there was no significant difference between the two protocols in terms of dropouts. In addition, decreased appetite and anxiety/nervousness were observed more often in the methylphenidate group. These results suggest that the main advantage of the passion flower treatment is a more tolerable side-effect profile. The authors reported that the study was relatively small and their results require confirmation in a larger study.[25]

A study using the elevated plus maze (EPM) in mice detected the reputed anxiolytic effects of an ethanolic extract of passion flower. The mice were either treated orally with three different concentrations of the extract or the positive control diazepam.[26]

Lyophilised hydroalcoholic and aqueous extracts of the aerial parts of passion flower, as well as chemical constituents of the plant, indole alkaloids (harman, harmin, harmalin, harmol, and harmalol) maltol and flavonoids (orientin, isoorientin, vitexin and isovitexin) were assessed for behavioural effects in mice. In accordance with the traditional use of passion flower, psychotropic properties were confirmed by some behavioural tests in mice. The anxiolytic properties of hydroalcoholic extract were confirmed at 400mg/kg by the increase of rears (to rise up on the back legs with the front legs in the air) and steps climbed in the staircase test (non-familiar environmental test), and the increase in locomotion and time spent in light side in the light/dark box choice test (non-familiar environmental test). The sedative properties of aqueous extract were confirmed at 400g/kg by decrease of rears and steps climbed in the staircase test and the decrease of rears and locomotion in the free exploratory test. Passion flower extracts were shown to significantly prolong the sub-hypnotic pentobarbital-induced sleep.[27]

In a 2001 study the petroleum ether, chloroform, methanol, and water extracts of passion flower, and sorted out plant parts, were evaluated for their anxiolytic activity using the elevated plus-maze model in mice. The results showed that roots and flowers of passion flower act as natural adulterants by causing a significant increase in the anxiolytic dose. Therefore, separation of these parts is recommended to maximize the anxiolytic action of the extracts.[28]

Despite the above evidence, a 2010 study which tested five different extracts of passion flower on rats, and measured anxiety using EPM, found anxiogenic (causing anxiety) activity for every extract. This unexpected anxiogenic action was explained by the lower baseline anxiety levels compared with the higher baseline anxiety levels of anxiety measured in other animal studies.[29]

Extracts of *Hypericum perforatum*, passion flower and *Valeriana officinalis* are used for the treatment of mild depression and anxiety. A 2011 study investigated whether a combination of *Hypericum* and passion flower exerts comparable effects to *Hypericum* alone. Two well-established models for investigating extracts for their antidepressant activity were used, namely the effects on synaptic uptake of serotonin and the forced-swimming-test. Passion flower significantly enhanced the pharmacological potency of *Hypericum* in both models. The data suggested that antidepressive therapeutic effects of *Hypericum* are possible with lower doses when it is combined with passion flower, than with mono-preparations of *Hypericum*.[30]

A 2007 *in vivo* study suggested definitive anxiolytic effects of passion flower are unknown however the

flavones chrysin may have anxiolytic properties similar to midazolam (the most commonly used benzodiazepine as a premedication for sedation) but to a lesser magnitude at the 2mg/kg dose used in the study. The study observed the potential anxiolytic effects of chrysin and the purported modulation of the benzodiazepine receptor on the GABA(A) receptor in laboratory rats.[31]

Anticonvulsant Activity

The results of a 2012 study concluded that the hydroethanolic extract of passion flower suppressed pentylenetetrazole (PTZ)-induced seizures, and ameliorated its associated post-ictal depression, which has been found to worsen with the standard antiepileptic drug, diazepam.[32]

The efficacy of a hydroethanolic extract of passion flower (0.4mg/kg) in the control of convulsions induced by PTZ was observed in a 2007 animal study. Passion flower prolonged the onset time of seizure and decreased the duration of seizures compared to placebo. The study concluded that these effects may be related to its effect on GABAergic and opioid systems.[33]

Antiaddictive Activity

A double-blind randomised controlled trial found that passion flower had an anxiolytic effect which may be used as an adjuvant agent in the detoxification of opiates by clonidine, an alpha2-adrenergic agonist that attenuates symptoms caused by the disregulation of the noradrenergic system. Clonidine-based therapies have been utilised as the main protocol for opiate detoxification for several years. However, detoxification with clonidine has its limitations, including lack of efficacy for mental symptoms and hypotensive side effects. A total of 65 opiate addicts were assigned randomly to treatment with passion flower plus clonidine tablet or clonidine tablet plus placebo drop during a 14-day double-blind clinical trial. All patients met the DSM IV criteria for opioid dependence. The fixed daily dose was 60 drops of passion flower extract and a maximum daily dose of 0.8mg of clonidine administered in three divided doses. The severity of the opiate withdrawal syndrome was measured on days 0, 1, 2, 3, 4, 7 and 14 using the Short Opiate Withdrawal Scale (SOWS). Both protocols were equally effective in treating the physical symptoms of withdrawal syndromes. However, the passion flower plus clonidine group showed a significant superiority over clonidine alone in the management of mental symptoms. These results suggested that passion flower extract may be an effective adjuvant agent in the management of opiate withdrawal. However, a larger study to confirm the results is warranted.[34]

A significant body of literature highlights the preclinical evidence regarding the beneficial properties of passion flower as a treatment for addictive behaviour linked to substances such as amphetamine, nicotine, cannabis, benzodiazepines and ethanol.[35]

A tri-substituted benzoflavone moiety (BZF) has been isolated from the bioactive methanol extract of passion flower. The BZF moiety has exhibited significantly encouraging results in the reversal of tolerance and dependence of several addiction-prone psychotropic drugs, including morphine, nicotine, ethanol, diazepam and delta-9-tetrahydrocannabinol (delta9-THC).[36]

A commercially available aqueous extract of passion flower was able to antagonise the expression of nicotine locomotor sensitisation using a rat model. Rats were administered 0.4mg/kg nicotine or vehicle once a day for four consecutive days. Nicotine administration produces sensitisation of locomotor activity, a phenomenon implicated in the development of nicotine dependence. On the fifth day, locomotor activity of the subjects was monitored as rats from each treatment group were administered 800mg/kg of passion flower extract (or its vehicle) followed by a challenge dose of 0.4mg/kg nicotine. When given to rats sensitised to nicotine for four days, the challenge dose of nicotine increased locomotor activity by more than two-fold over activity following nicotine challenge in rats treated with vehicle during the sensitisation phase. The difference was significant from 15 to 40 minutes after nicotine administration. Rats sensitised to nicotine then treated with passion flower extract prior to the nicotine challenge exhibited a level of locomotor activity the same as the vehicle-treated controls.[37]

BZF, when administered concurrently with delta9-THC, prevented the development of tolerance and dependence of cannabinoids in mice. Even an

acute administration of the BZF moiety significantly blocked the expression of withdrawal effects in delta9-THC-dependent mice.[38]

Aphrodisiac Activity

The aphrodisiac properties of the methanol extract of passion flower leaves have been evaluated in mice by observing the mounting behaviour. The methanol extract exhibited significant aphrodisiac behaviour in male mice at all doses, i.e. 75, 100 and 150mg/kg. Amongst these, the highest activity was observed with the 100mg/kg dose when the mountings were calculated about 95 min after the administration of the test extracts.[39]

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 two year old male rats. BZF speeds up the restoration of sexuality in rats upon cessation of the administration of substances like alcohol, nicotine and alcohol-nicotine combinations, which have severe detrimental effects upon male sexuality, fertility and vigour. BZF, the strongest inhibitor of aromatase enzyme, when administered concurrently with substances like alcohol and nicotine restores sexual virility, libido and vigour in male rats by maintaining the blood-testosterone levels to be high.[40]

Other Activity

A 2010 Iranian study comparatively examined the effects of two herbal medications, *Hypericum perforatum* and passion flower on menopause symptoms. The sample included 59 menopausal women selected via simple sampling and were assigned randomly into two groups of *Hypericum perforatum* treatment group (30 women) and passion flower group (29 women). The outcome suggested that these two herbs could be used as an alternative treatment for individuals who cannot, whatsoever, use hormone therapy for treating menopause precocious symptoms (vasomotor signs, insomnia, depression, anger, headache, etc.).[41]

The methanol extract of passion flower leaves (100 and 200mg/kg) exhibited significant antitussive activity on sulphur dioxide-induced cough in mice, the cough inhibition (39.4 and 65.0%, respectively) being comparable to that of codeine phosphate (10 and 20mg/kg respectively).[42]

The methanol extract of passion flower leaves was evaluated for its antiasthmatic effects against acetylcholine chloride (Ach)-induced-bronchospasm in guinea-pigs at doses of 50, 100 and 200mg/kg. Using a 7-day treatment regimen, significant prevention of dyspnoea-related-convulsions was noted in the animals treated with a 100mg/kg dose of this extract. No preventive effect was exhibited by the 50mg/kg dose and at a higher dose, i.e. 200mg/kg, the preventive effects against Ach-chloride-induced-dyspnoea were also reduced. This may be due to defective alpha-adrenoceptor function reported after excessive or continuous administration of an alpha-receptor agonist.[43]

Methanolic extract of passion flower exhibited significant antihyperglycaemic and hypolipidaemic activities in streptozotocin-induced diabetes in mice demonstrating potential metabolic effects.[44]

Passion flower was shown to possess analgesic action, increasing the nociceptive threshold in the tail-flick and hot plate tests in rats.[45]

Indications

- Anxiety, especially before surgery, Generalized Anxiety Disorder (GAD), attention-deficit hyperactivity disorder (ADHD)
- Insomnia
- Nervous conditions including tachycardia, headache and restlessness
- Spasmodic conditions including dysmenorrhea, asthma, whooping cough
- Neuralgic pain especially with anxiety
- Epilepsy, especially generalised seizures
- Adjuvant for opiate withdrawal and symptoms of opiate withdrawal
- Cardiac rhythm abnormalities, hypertension
- Sexual dysfunction
- Menopause

Energetics

Neutral, bitter.

Use in Pregnancy

Passion flower has demonstrated the ability to increase uterine contractions *in vivo* Whether this has any adverse effects in pregnancy remains unknown. Caution is advised until safety is better established.

Contraindications

Whether concomitant use of high doses of passion flower adversely affects people's ability to drive a car, or operate heavy machinery, should be evaluated on an individual case-by-case basis.

Drug Interactions

Caution with barbiturates, benzodiazepines and central nervous system depressant drugs.

Administration and Dosage

Liquid Extract:	1:1
Alcohol:	30%
Weekly Dosage:[46]	10 to 20mL

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