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Full Length Research Paper

Pharmacological studies of *Passiflora* sp. and their bioactive compounds

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Human infections particularly those involving microorganisms that is, bacteria, fungi, viruses, nematodes, can cause serious infections in tropical and subtropical countries of the world. In recent years, multiple drug resistance in human pathogenic microorganisms has been developed due to indiscriminate use of commercial anti-microbial drugs commonly used in the treatment of such diseases. Plants have been the basis of many traditional medicines throughout the world for thousands of years and have continued to provide new remedies to mankind. They are one of the richest sources of bioactive compounds. In India, local empirical knowledge about medicinal properties of plants is the basis for their use as home remedies. It has been generally accepted by many people in India and elsewhere in the world that beneficial medicinal effects can be obtained by ingesting plant products. *Passiflora* is one of the plants used in Ayurveda for several remedies such as sedative, anxiety and hypertension etc. This review focused on the various virgin areas of research on the *Passiflora* sp. This study supports the use of traditional medicines (herbal extracts) to cure many diseases like diarrhea, intestinal tract, throat, ear infections, fever and skin diseases.

Key words: *Passiflora,* bioactive molecules, antimicrobial activity.

INTRODUCTION

Passion flower is also known as maypop, apricot vine, passion vine, and granadilla. It grows as much as 30 ft (10 m) tall, with a thick, woody stem. The passion flowers or passion vines (*Passiflora*) have a genus of about 400 species of flowering plants and the largest in the family of Passifloraceae (Montanher, 2007; Beninca, 2007). They are mostly vines, with some being shrubs, and a few species being herbaceous.The species of this genus are distributed in the warm temperate and tropical regions of the world, but they are much rarer in Asia, Australia, and tropical Africa. Species of *Passiflora* have been naturalized beyond their native ranges. For example, Blue Passion Flower (*P. caerulea*) now grows wild in Spain (Dana et al., 2001).

The medical utility of very few species of *Passiflora* has been scientifically studied (Akhondzadeh et al., 2001). Passionflower extracts have been classified into several categories of chemical activities like anxiolytic, spasmolytic, hypnotic, sedative, narcotic and anodyne (Ozarko, 2001). These extracts are part of a treatment that has successfully treated outpatients with adjustment disorder and anxious mood (Broutin et al., 1997). Many species have been found to contain beta-carboline harmala alkaloids with anti-depressant properties. The flower and fruit has only traces of these chemicals, but the leaves and the roots are often more potent and have been used to enhance the effects of mind-altering drugs. Once dried, the leaves can also be smoked. *Passiflora quadrangularris* is used by traditional healers for snake bites. Snake bites cause blood clotting and eventually burst blood vessels around the bite, this is known as haemorrhaging (Worldnet, 2001).

When an extract of the leaves and branches of *P. quadrangularris* was administered orally either before or after a venom injection, haemorrhaging neutralizes and dropped below 25% in mice (Otero et al., 2000). Several monoterpenoid compounds (compounds with 10 carbons) have been isolated from *P. quadrangularris.* (Osorio, 2001); some dietary monoterpenes have been proven chemopreventive against rat mammary cancer (Crowell,

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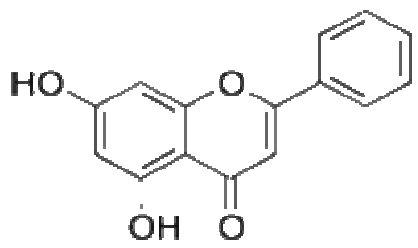
1997). *Passiflora alata* can induce occupational allergic disease in humans (Giavina et al., 1997). Shatfocide, which is a glycoside of apigenin, was isolated from *Passiflora incamata* L. (Li et al., 1991). Also experiments done with wheat sprouts extract suggest that shaftocide is responsible for the antimutagenic properties of the extract (Peyrt et al., 1992). In this review, phytochemical, pharmacological data, together with the clinical and adverse effect of *Passiflora* and its bioactive components, will be briefly discussed. The review will then focus on industrial and medical uses of *Passiflora.*

Bioactive compounds

The genus *Passiflora* may be suitable for the screening of bioactive molecules, since ethnobotanical use, chemotaxonomic information, and observation of the interaction of the plants with their environment have been suggested as selection criteria for potential sources of natural molecules of pharmacological relevance (Rates et al., 2001). Phytochemical investigation of *P. incarnata* and *P. edulis* and the occasional analysis on other species revealed that the members of this genus contain alkaloids, phenols, cyanogenic compounds and glycosyl flavonoids (Dhawan et al., 2004). The pharmacological activity of some of these compounds, such as chrysin in *P. edulis (*Medina et al.,1990) and maltol, ethyl maltol, flavonoids and harman alkaloids in *P. incarnata* has also been reported (Aoyagi et al., 1974; Soulimani et al., 1997). *P. Incarnata* has aromatase properties due to the presence of two flavonoid compounds: chrysin and benzoflavone moiety, the latter being more potent (Dhawan et al., 2002).

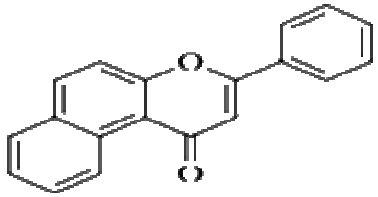
Many species have been found to contain beta-carboline harmala alkaloids. The majority of the active components in this plant are *C*-glycosyl flavones based on apigenin and luteolin, while harman alkaloids are found in trace amounts (Hiremath et al., 2000; Rehwald et al., 1994; Raffaelli et al., 1997). Several flavonoids have been isolated from *P. incamata L., chrysin* and apigenin, (Zanoli et al., 2000) along with orientin, isoorientin, vitexin and isovhexin (Soulimani et al., 1997). The largest accumulations of *P. Incarnata* flavonoids were found in the leaves between the pre-flowering and flowering stages of the plant (Menghini and Mancini, 1988).

Chrysin: $C_{15}H_{10}O_4$ (5, 7-dihydroxy-2-phenyl-(9CI)



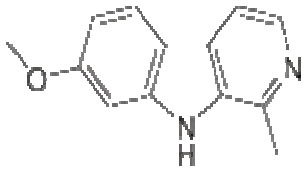
Chrysin is a naturally occurring flavone chemically extracted from the blue passion flower (*Passiflora caerulea*). Chrysin acts as an aromatase inhibitor supplement to bodybuilders and athletes. It has been shown to induce an anti-inflammatory effect, most likely by inhibition of COX-2 expression via IL-6 signaling (Woo et al., 2004*).* In rodent *in vivo* studies, chrysin was found anxiolytic (Brown et al., 2007; Wolfman et al., 1994). In herbal medicine, It is recommended as a remedy for anxiety, but there are no controlled data in humans available (Balch, 2002). Chrysin exhibited an anxiolytic effect, which was showed by an increase in locomotor activity in rats when injected at 1 mg/kg. This effect was linked to GABA benzodiazepine receptors in the brain because the anxiolytic effect was blocked by an injection of Flumazenil, which is a benzodiazepine antagonist (Zanoli et al., 2000). Chrysin and apigenin have been shown to inhibit the growth of breast carcinoma cells (Yin et al., 2001), human thyroid cancer cells (Yin et al., 1999) and human prostate tumors (Knowles et al., 2000). Apigenin is considered antimutagenic because it reduces the effects of mutagens in rats (Nagasugi et al., 2000).

Benzoflavone



The β-Naphthoflavone, also known as 5,6-benzoflavone, is a potent agonist of the aryl hydrocarbon receptor and an inducer of detoxification enzymes as cytochromes P450 (CYPs) and uridine 5'-diphospho-glucuronosyltransferases (UGTs) (Chlouchi et al., 2007). β-Naphthoflavone is a putative chemopreventive agent (Izzotti et al., 2005).

Harmala alkaloids: $C_{13}H_{12}N_2O$ (7-Methoxy-1-methyl-9*H*-pyrido[3,4-*b*]indole)

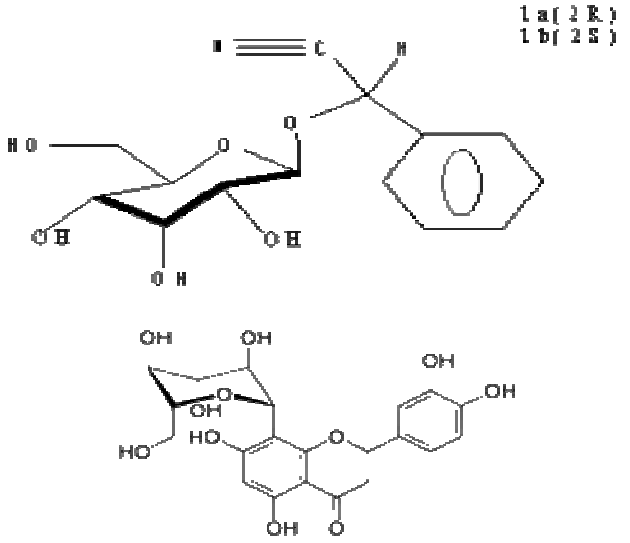


The *passiflora* family contains small amounts of harmala alkaloids, harmane (passaflorine), and possibly harmine (telepathine), harmaline, harmol, and harmalol. The presence of the last four in *P. incarnata* is disputed (Bennati*,* 1968) because they are contained in only very small amounts (0.01% or less) (Lawrence, 1989).

Furthermore, they have been identified as stimulants and monoamine oxidase inhibitors (Fernandez et al., 1994; Rommelspacher et al., 1994; Ergene and Schoener, 1993) which would give antidepressant rather than sedative effects. Wild rue *(Peganum harmala)* which contains significant amounts of these substances (and after which they were named) is used therapeutically as a stimulant rather than a sedative (U.S. Dispensatory, 1947).The harmala alkaloids which is the active principle in *passiflora* might also be a cause for concern for kidney toxicity, as these substances are toxic to the kidneys (Hagiwara et al., 1992).

Extracts of the aerial parts of *P. incamata* L. contain the beta-carbolines: harman, hamun, hannalin, harmol, and harmalol, along with an aroma compound, maltol (Soulimani et al., 1997). Beta-carbolines, like those of *P. incamata* L., induce voluntary ethanol intake in rats (Baumn et al., 1996). Some people may be interested in the fact that harman has been identified in beer, wine (Bosin and Faull, 1988) and cigarette smoke (Totsuka et al., 1999). Beta-carbolines have been found to prevent neuron damage to the brain mitochondria of dopamine-induced mice by acting as an antioxidant and scavenging hydroxyl radicals (Lee et al., 2000a). Harman and related compounds are mutagenic and have become more mutagenic after nitrosarion occurs in the acidic conditions of the stomach. Harman acts as a vasorelaxant (something that reduces inflammation or edema), it functions by releasing GABA, serotonin and noradrenaline (Dolzhenko and Komissarov, 1987).

Glycosides



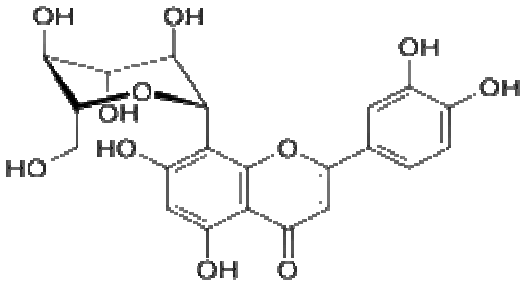
Glycosides

Orientin

Glycosides are molecules in which a sugar is bound to a non-carbohydrate moiety, usually a small organic molecule. Glycosides play numerous important roles in living organisms. Many plants store chemicals in the form of inactive glycosides which can be activated by enzyme hydrolysis (Brito-Arias, 2007). Leaf and stem material of *P. edulis* contain the new cyanogenic glycosides (2R)–α-allopyranosyloxy-2-phenylacetonitrile and (2S)– α -D-allopyranosyloxy-2-phenylacetonitrile , along with smaller amounts of (2R)–prunasin, (2S)-sambunigrin. Many different types of glycosides are present in passion flower such as apigenin, homoorientin, 7-isoorientin, isoshaftoside, isovitexin, kaempferol, lucenin, luteolin, n-orientin, passiflorine (named after the genus), quercetin, rutin, saponaretin, saponarin, shaftoside, vicenin and vitexin.

In some cases this glycoside occurs with simple β-D-glucopyranosides: tetraphyllin A, deidaclin, tetraphyllin B, volkenin, epivolkenin and taraktophyllin. P. citrina contains passicapsin, a rare glycoside with the 2, 6-dideoxy-β-D-xylo-hexopyranosyl moiety, while P. herbertiana contains tetraphyllin A, deidaclin, epivolkenin and taraktophyllin, P. discophora tetraphyllin B and volkenin, and P. xviolacea tetraphyllin B (Jaroszewski and olafsdottir, 2002*). S*ome other glycosides present in *Passiflora* are the hydrocarbon nonacosane and the anthocyanidin pelargonidin-3-diglycoside (Duke, 2008). *Passiflora morifolia* extracts contain the cyanohydrin glycoside and linamarin (Jaroszewski et al., 1996). Linamarin causes an increase of lactic acid and total cholesterol in the liver and brain in addition to the depletion of brain phospholipids in rabbits (Padmaja and panikkar 1989).

Isoorientin (Luteolin-8-C-glucoside)



Orientin is a flavone, a chemical flavonoid-like compound found in the passion flower, the Açai palm and *Anadenanthera peregrina*. Orientin is also reported to be in millets. Isoorientin (or homoorientin) is the luteolin-6-C-glucoside. It can be isolated from the passion flower, *Vitex negundo*, the Açaí palm and *Swertia japonica (*Linda and Rooney, 2006)

Other organic compounds

Passion flower contains many alkaloids, flavonoids as

well as many organic compounds such as organic acids. This genus is rich in formic, butyric, linoleic, linolenic, malic, myristic, oleic and palmitic acids as well as phenolic compounds, and the amino acid α-alanine. Some species contain ester such as ethyl butyrate, ethyl caproate, n-hexyl butyrate and n-hexyl caproate which give the fruits their flavor and appetizing smell. Sugars, contained mainly in the fruit, are mostly d-fructose, d-glucose and raffinose. Among enzymes, *Passiflora* was found to be rich in catalase, pectin methyl esterase and phenolase (UMMC, Drugs.Com 2008). Apart from glycosides, phenols and alkaloids, various miscellaneous phyto-constituents which were also reported to be in *P. edulis* include, Edulans I and II (Dhawan et al., 2004) and pectins (Pinheiro et al., 2008).The pectin fractions contain mainly sugars (83 - 85%, w/w). However, non-sugar components such as nitrogen-containing material (3 - 8%, w/w) and ash (5 - 7%, w/w) are also present in these fractions (Yapo and Koffi, 2008).

EXPERIMENTAL STUDY

Medicinal plants are finding their way into pharmaceuticals, neutralceuticals, cosmetics and food supplements. The World Health Organization estimated that 80% of the population of developing countries still relies on traditional medicines, mostly plant drugs, for their primary health care needs. Herbs are supposed to be safe but many unsafe and fatal side effects have recently been reported (Ikegami et al., 2003; Izzo, 2004).

Antimicrobial activity

In *Passiflora* species, many of the chemical components of passion flower (passicol) have antimicrobial activity (Nicolls, 1970; Birner and Nicolls, 1973; Nicolls et al., 1973).The ethanol leaf extracts exhibited variable degrees of antibacterial activity against *P. putida*, *V. cholerae*and moderate activity was noted in *S. flexneri* and *S. pyogenes* respectively. The acetone extracts exhibited strong to moderate activity against *V. cholerae* followed by *P. putida, S. flexneri* and *S. pyogenes.* The ethanol fruit extracts showed moderate activity against the bacterial pathogens namely *V. cholerae, P. putida, S. pyogenes* and *S. flexneri*. Among the two parts tested, the leaf extracts exhibited better antibacterial activity than the fruits (Afolayan and Meyer, 1997). The earlier reports focused on the antibacterial properties of *Passiflora* species by different methods. Perry et al. (1991) reported the antibacterial activity of *Passiflora* which has got activity against *Pseudomonas tetrandra, Escherichia coli, Bacillus subtilis* and *Pseudomonas aeruginosa.*

The antibacterial properties of leaf and fruit (ethanol and acetone) extracts of *Passiflora foetida* (stinking passion flower) were screened against four human pathogenic bacteria that is *Pseudomonas putida, Vibrio cholerae, Shigella flexneri* and *Streptococcus pyogenes* using well-in agar method. The results showed the leaf extract having remarkable activity against all bacterial pathogens compared to fruits (Mohanasundari et al., 2007). Perry et al. (1991) also found that 4-hydroxy-2-cyclopentenone was cytotoxic to leukemia cells. The 4-Hydroxy-2-cyclopentenone is responsible for the anti-bacterial activity of an extract of leaves from *Passiflora tetrandra* against the bacteria: *E. coli*, *B. subtilis* and *P. aeruginosa,* during the course of this experiment. Apigenin and luteolin were found to be toxic against the methicillin-resistant bacteria, *S. aureus* (Sato et al., 2000). Nicolls (1970) described the presence of antifungal activity in plants of the Passifloraceae, particularly in the *Passiflora* species of *P. caerulean* (passion flower), *P. edulis* (purple passion fruit), and *P. mollissima* (banana passion fruit). In fungal molds and yeasts, an actinomycete, gram-positive and gram negative bacteria were tested qualitatively with an antimicrobial substance, here called "Passicol," obtained from *Passiflora* species.

A wide range of organisms were found susceptible to Passicol (Nicolls et al., 1973). The crude Passicol extracts in phosphate buffer (pH 7) solutions were tested against *Trichophyton mentagrophytes* (ringworm) and *Candida albicans* growing at 28°C. The fungi *Microsporum* and *Trichophyton* required additional amounts of extract on each for 2 or 3 days because of their slow growth. There is presence of Acetylenic compounds which inhibit germination or mycelial growth of some fungi (Allen and Thomus, 1971; Lechner et al., 1970).

Antioxidant activity

P. nitida leaf and *P. palmeri* stem extracts were characterized by a high antioxidant power that correlates with high catechin and *o*-diphenol contents and shows antimicrobial activity. However, *P. foetida* leaf extracts, which also show high antimicrobial activity, have a low antioxidant power and low amounts of *o*-diphenol and catechin. *P. tenuifila* leaves show very high amounts of flavones and total phenols, but intermediate levels of antioxidant activity, probably due to the lower contribution of *o*-diphenols and gallocatechins relative to the phenol content (Bendini et al., 2006). The antioxidant activity of leaf and stem extracts of *P. edulis* was determined using the 1, 1-diphenyl- 2-picrylhydrazyl (DPPH) free radical scavenging assay (Blois, 1958). DPPH offers a convenient and accurate method for titrating the oxidizable groups of natural or synthetic anti-oxidants (Cao et al., 1997). The crude extracts (leaf and stem) of *P. edulis* were mixed with 95% methanol to prepare the stock solution (10 mg/100 mL).

All the four extract exhibited potential antioxidant activity (Table 1). The chloroform extract of stem scavenged 50% DPPH free radical at the lowest inhibitory concentration (IC50: 51.28 µg/ml). The petroleum ether extract of stem also revealed strong antioxidant activity (IC50: 54.01 µg/ml). On the other hand, petroleum ether and chloroform extracts of leaf showed antioxidant activity with IC50 of 58.88 and 56.85 µg/ml, respectively. These results denote the presence of antioxidant principles in the extractives. *P. nitida* and *P. palmeri* also showed high antioxidant activity. *P. tenuifila* and *P. coriacea* demonstrated antioxidant power but not antimicrobial activity. Natural antioxidants derived from plant extracts have been claimed to have multiple biological activities including vasodilatatory, anti-inflammatory, anticancerogenic, antiviral, and antibacterial effects (Halliwell et al., 1995; Halliwell, 1997).

Maltol, an aromatic compound, shows antioxidant properties when inhibiting the oxidation of hexanal by 84% (Lee and Shibamoto, 2000b). Maltol was also shown to be responsible for the development of dialysis-related diseases in patients with renal dysfunction and may play a role in the development of certain neurodegenerative disorders. Maltol was shown to be a strong enhancer of aluminum accumulation in rat brain and blood (Van-Ginkel et al., 1993).

Cytotoxic activity

Brine shrimp lethality bioassay is widely used in bioassay for bioactive compounds (Meyer et al., 1982; Zhao et al., 1992). Simple zoological organism (*Artemia salina*) was used as a convenient monitor for the screening. The eggs of the brine shrimp were

Table 1. Antioxidant activity of *P. edulis*.

S/No.	Sample	IC_{50} (µg/ml)
1.	Ascorbic Acid	43.04
2.	Petroleum ether extract of leaf	58.88
3.	Chloroform extract of leaf	56.85
4.	Petroleum ether extract of stem	54.01
5.	Chloroform extract of stem	51.28

Table 2. The lethality of the crude petroleum ether and chloroform extracts of *P. edulis.*

S/No.	Sample	IC_{50} (µg/ml)
1.	Vincristine Sulphate	5.68
2.	Petroleum ether extract of leaf	11.17
3.	Chloroform extract of leaf	7.91
4.	Petroleum ether extract of stem	6.89
5.	Chloroform extract of stem	6.63

collected and hatched in artificial seawater (3.8% NaCl solution) for 48 h to mature shrimp called nauplii. The cytotoxicity assay was performed on brine shrimp nauplii using Meyer method (Meyer et al., 1982).

The lethality of the crude petroleum ether and chloroform extracts of *P. edulis* leaf and stem to brine shrimp was determined on *A. salina* after 24 h of exposure of the samples with the positive control, vincristine sulphate. This technique was applied for the determination of general toxic property of the plant extractive. The LC50 values for standard vincristine sulphate and extracts of *P. edulis* were presented in Table 2. The chloroform extract of stem showed the lowest LC50 value and the petroleum ether extract of leaf showed highest value which was 6.63 and 11.17 µg/ml, respectively.

Anti-inflammatory activity

The aqueous leaves extract of *Passiflora* species exhibited potent anti-inflammatory action in the experimental model *in vivo* (Beninca et al., 2007). The aqueous leaves extract of *P. edulis* possess a significant anti-inflammatory activity on mice (Vargas et al., 2007). The systemic administration of *P. edulis* exhibited pronounced anti-inflammatory actions, characterized by inhibition of leukocyte influx to the pleural cavity and associated with marked blockade of myeloperoxidase, nitric oxide, TNFα and IL-1α levels in the acute model of inflammation caused by intra pleural injection of mice. In one experiment, *P. edulis* was more effective in suppressing the TNFα and IL-1α levels than dexamethasone (Montanher et al., 2007). *P. edulis* therefore, may be a source of new therapeutic candidates with a spectrum of activity similar to the current anti-inflammatory steroids such as dexamethasone.

Anti-tumor activity

Fruit's decoction of different *passiflora* species has been evaluated for the inhibition of activity of gelatinase matrix metalloproteinases (MMP-2 and MMP-9). Two metallo-proteases were involved in the tumour invasion, metastasis and angiogenesis. Water extract of *P. edulis*, at different concentrations was inhibited by the enzymes (Puricelli et al., 2003).

Hemolytic activity

Plants used in traditional medicine are rich sources of hemolysins and cytolysins, which are potential bactericidal and anticancer drugs (Dhawan et al., 2001). The present study demonstrates for the first time the presence of a hemolysin in the leaves of *Passiflora quadrangularis* L. This hemolysin is heat stable, resistant to trypsin treatment, has the capacity to froth, and acts very rapidly. The hemolysin activity is dose-dependent, with a slope greater than 1 in a double-logarithmic plot (Petry et al., 2001). Polyethylene glycols of high molecular weight were able to reduce the rate of hemolysis, while liposomes containing cholesterol completely inhibited it. In contrast, liposomes containing phosphatidylcholine were ineffective. The *Passiflora* hemolysin markedly increased the conductance of planar lipid bilayers containing cholesterol but was ineffective in cholesterol-free bilayers. Successive extraction of the crude hemolysin with n-hexane, chloroform, ethyl acetate, and n-butanol resulted in a 10-fold purification, with the hemolytic activity being recovered in the n-butanol fraction (Shao et al., 1996).

The data suggest that membrane cholesterol is the primary target for this hemolysin and that several hemolysin molecules form a large transmembrane water pore (Nippon, 1993). The properties of the *Passiflora* hemolysin, such as its frothing ability, positive color reaction with vanillin, selective extraction with n-butanol, HPLC profile, cholesterol-dependent membrane susceptibility, formation of a stable complex with cholesterol, and rapid erythrocyte lysis kinetics indicate that it is probably a saponin (Lutomski and Malek, 1975). Many different species of *passiflora* contain the saponins. Saponins are common constituents of plants that exhibit a broad spectrum of biological activities (Birner and Nicolls, 1973; Perry et al., 1991) and frequently possess hemolytic, cytolytic and bactericidal activities (Rao and Song, 1995; Li et al., 2005).

Furthermore, saponins also have plasma cholesterol-lowering activity (Chandel and Rastogi, 1980) and are widely utilized as a component of potent adjuvants to boost the immune response, principally when complexed with cholesterol. However, not all *Passiflora* species contain saponins in their leaves (Akiyama et al., 1980). It effectively decreased the concentrations of serum triglycerides and total cholesterol, but showed no apparent effect on the concentrations of HDL and liver cholesterol. Yuldasheva et al. (2005) demonstrates for the first time that leaves of *P. quadrangularis* possess a potent, heat-stable, non-proteinaceous hemolysins and its activity is increased by trypsin treatment.

Anti anxiety

Generalized Anxiety Disorder (GAD) is the most common anxiety disorder but is generally less severe than panic disorder. GAD is probably the disorder most often found with a coexisting mental disorder, usually another anxiety disorder or a mood disorder (Blazer et al., 1991). *Passiflora* extract is potentially a significant improvement over benzodiazepines in the management of GAD.

Passion flower (*P. incarnata*) is a woody, hairy, climbing vine and is reputed to have sedative/ anxiolytic properties. It has been used widely as an ingredient of herbal remedies, chiefly in the form of a liquid tincture (Bergne, 1995).

Passion flower (*P. incarnata*) is used for the cure of nervous restlessness, sleep disorders, restlessness, nervous stress and anxiety (Bergne, 1995; Bruneton, 1995; Bradley, 1992). *Passiflora* (or Passionflower) is a folk remedy used for anxiety (Miyasaka et al., 2007; Reginatto et al., 2006). Several species of *Passiflora* have been employed widely as a folk medicine because of its sedative and tranquillizer activities (Barbosa et al., 2008). Anti

anxiety activity of *P. edulis* has been evaluated on the performance of mice in the elevated plus maze, open field, and horizontal-wire tests (Coleta et al., 2001). The aqueous extract of passion flower presented an anxiolytic-like activity (Coleta et al., 2006).

Antihypertensive

Despite improved pharmacotherapies and mechanical treatments, cardiovascular disease remains a principal cause of morbidity and mortality worldwide (Benson et al., 2008). *P. edulis,* which is an allied species of *Passiflora,* has already been reported to possess antihypertensive effects and *P. nepalensis* is used in folklore medicine for treating hypertension. Ichimura et al. (2006) reported that the orally administered methanol extract of this plant (10 or 50 mg/kg) or luteolin (50 mg/kg), which is one of consistent polyphenols of the extract, significantly lower systolic and diastolylic blood pressure in spontaneously hypertensive rats (SHRs). Quantitative analysis by liquid chromatography tandem mass spectrometry (LC-MS/MS) showed that the extract contained 20 µg/g dry weight of luteolin and 41µg/g dry weight of luteolin-6-C-glucoside. It also contained gama amino butyric acid (GABA, 2.4 mg/g dry weight by LC-MS/MS) which has been reported to be an antihypertensive material. The extract contained a relatively high concentration of GABA, the antihypertensive effect of the extract in SHRs might be due mostly to the GABA-induced antihypertensive effect and partially to the vasodilatory effect of polyphenols including luteolin (Ichimura et al., 2006).

CLINICAL APPLICATIONS

Allergies few reports of the use of passion flower products on allergic reactions, asthma, irritated sinuses, skin rashes, and skin blood vessel inflammation (vasculitis) have been reported in the available literature. It is believed that some reactions may have been caused by impurities in combination products, not by passion flower itself (Giavina et al., 1997).

Side effects and warnings

Passion flower is generally considered to be a safe herb with few reported serious side effects. In cases of side effects, the products being used have rarely been tested for contamination, which may have been the cause. Cyanide poisoning has been associated with *passiflora* fruit, but this has not been proven in human studies. Rapid heart rhythm, nausea, and vomiting have been reported. Side effects may also include drowsiness /sedation and mental slowness. Patients should be cautious when driving or operating heavy machinery. Passion flower may theoretically increase the risk of bleeding and affect blood tests that measure blood clotting (Kapadia et al., 2002). There is a reported case of liver failure and death of a patient taking a preparation of passion flower with kava. Caution should be applied in taking any kava-containing products, as kava has been associated with liver damage. It has been suggested that the cause of the liver damage is less likely related to the presence of passion flower.

Pregnancy and breastfeeding

Flavonoids exhibit significant hormone activity (Zand et al., 2000); apigenin and luteolin (another flavonoid) were found to be more effective at preventing pregnancy than ethinyl estradiol (Hiremath et al., 2000). There is not enough scientific evidence to recommend the safe use of passion flower in any dose during pregnancy or breastfeeding. During the 1930s, animal studies found uterine stimulant action in components of *Passiflora.* Many tinctures contain high levels of alcohol and should be avoided during pregnancy. Most herbs and supplements have not been thoroughly tested for interactions with other herbs, supplements, drugs, or foods. The interactions listed below are based on reports in scientific publications, laboratory experiments, or traditional use. One should always read product labels. If one has a medical condition, or is taking other drugs, herbs, or supplements, he should speak with a qualified healthcare provider before starting a new therapy.

Pharmacological effect

Passiflora have been tested in humans or animals. Its safety and effectiveness have not always been proven. Some of these conditions are potentially serious, and should be evaluated by a qualified healthcare provider.

Congestive heart failure

An extract containing passion flower and hawthorn has been studied as a possible treatment for shortness of breath and difficult use of exercise in patients with congestive heart failure. Although, the results are promising, the effects of passion flower alone are unclear. The high quality human research of passion flower alone compared to prescription drugs used for this condition is needed before a strong recommendation can be made (Capasso and Sorrentino, 2005).

Sedation (agitation, anxiety and insomnia)

Passion flower has a long history of use for symptoms of restlessness, anxiety, and agitation. Early evidence from animal studies and weak human trials supports these uses. Better research is needed before a firm conclusion can be drawn (Dhawan et al., 2003a; Dhawan et al., 2003b).

Dosing

The doses noted here are based on scientific research, publications, traditional use, or expert opinion. Many herbs and supplements have not been thoroughly tested,

therefore safety and effectiveness may not be proven. Brands may be made differently, with variable ingredients, even within the same brand. The doses noted here may not apply to all products. One should read product labels, and discuss doses with a qualified healthcare provider before starting. Safety and effectiveness have not been established for any dose. Standard or well-studied doses of passion flower are currently lacking. Different preparations and doses have been used traditionally. Doses of 0.5 - 2 grams of dried herb were required to be taken 3 - 4 times daily by mouth. Doses of 1 - 4 milliliters of tincture (1:8) were taken 3 - 4 times daily by mouth. Tea made from dried herb (four to eight grams) was taken daily. A dose of 2.5 grams in an infusion were used 3 - 4 times daily (Smith et al., 1993).

Children (younger than 18 years)

There is not enough scientific data to recommend passion flower to be used for children at any dose (Werneke et al., 2006).

Interactions with drugs

Certain substances (harmala alkaloids) with monoamine oxidase inhibitory (MAOI) action have been found in small amounts in some species of *Passiflora.* Although, levels of these substances may be too low to cause noticeable effects, passion flower may theoretically increase the effects of MAOI drugs, such as isocarboxazid, phenelzine and tranylcypromine. Increased sedation or low blood pressure could also result from taking passion flower with tricyclic antidepressants, such as amitriptyline, and selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine. Based on animal research, use of passion flower with alcohol or other sedatives may increase the amount of drowsiness caused by some drugs. Examples include benzodiazepines, such as lorazepam or diazepam; barbiturates, such as phenobarbital; narcotics, such as codeine; some antidepressants; and alcohol. Caution is advised while driving or operating machinery.

In theory, passion flower may increase the risk of bleeding when taken with drugs that increase this risk. Some examples include aspirin, anticoagulants (blood thinners) such as warfarin or heparin; anti-platelet drugs such as clopidogel and nonsteroidal; anti-inflammatory drugs such as ibuprofen or naproxen. Many tinctures contain high levels of alcohol and may cause nausea or vomiting when taken with metronidazole or disulfiram.

Passion flower may also interact with anti-anxiety drugs, antibiotics, anticonvulsants, antifungals, antihistamines, anti-cancer drugs, antispasmodics, antitussives, caffeine, CNS depressants, and drugs broken down by the liver, flumazenil, naloxone, and other neurologic agents.

Interactions with herbs and dietary supplements

In theory, use of passion flower with herbs or supplements with MAOI activity may cause additive effects. Kava (*Piper methysticum*) is believed to have weak monoamine oxidase inhibitor effects and may thus interact with passion flower. In addition, tricyclic antidepressants or selective serotonin reuptake inhibitors may lead to increased sedation or low blood pressure when taken with passion flower. Based on animal research, use of passion flower may increase the amount of drowsiness caused by some herbs or supplements, such as valerian and kava. Passion flower may have additive effects when taken with herbs or supplements that increase the risk of bleeding. Multiple cases of bleeding have been reported with the use of ginkgo (*Ginkgo biloba*), and fewer cases with garlic and saw palmetto.

Numerous other agents may theoretically increase the risk of bleeding, although this has not been proven in most cases. When taken with caffeine or herbs containing caffeine or caffeine-like compounds, passion flower may increase blood pressure. Passion flower contains lycopene and may have additive effects when taken with lycopene supplements. Passion flower may also interact with herbs or supplements taken for pain, anxiety, seizures, fungal infections, bacterial infections, or cancer. In addition, interactions with antihistamines, antispasmodics, antitussives, CNS depressants, herbs and supplements broken down by the liver, and other neurologic agents are possible.

USES

Traditional uses

The uses here are based on tradition or scientific theories of *Passiflora* species. Some of these conditions are potentially serious, and should be evaluated by a qualified healthcare provider. These traditional uses includes alcohol withdrawal, antibacterial, anti-seizure, anti-spasm, aphrodisiac, asthma, attention deficit hyperactivity disorder (ADHD), burns (skin), cancer, chronic pain, cough, drug addiction, Epstein-Barr virus, fungal infections, gastrointestinal discomfort (nervous stomach), *Helicobacter pylori* infection, hemorrhoids, high blood pressure, menopausal symptoms (hot flashes), nerve pain, pain (general), skin inflammation, tension and wrinkle prevention (Dhawan et al., 2002).

Industrial uses

A number of species of *Passiflora* are cultivated outside their natural range because of their beautiful flowers. *P. incarnatea* L. commonly used in many herbal remedies is well known for its sedative properties, while several other species are cultivated for the production of fruit juice

(*P. edulis*, *P. quadrangularis*, *P. ligularis*) (Bendini et al., 2006). Passicol can also be produced from fruit rinds of the purple passion fruit, which are waste products from the manufacture of passion fruit juice. The resulting rich juice, which has been called a natural concentrate, can be sweetened and diluted with water or other juices (especially orange or pineapple), to make cold drinks. In South Africa, passion fruit juice is blended with milk and an alginate; in Australia the pulp is added to yogurt.

In Brazil, the fruits are commonly known as “maracuja” and the fruit pulp yields a delicious juice which is exported to the several countries (Machado et al., 2008; Dhawan et al., 2004). *Passiflora* is available on the market in a range of different preparations, mainly in tablet form (500 mg) of the dried herb for oral use or by infusion, as liquid extract or as tincture (Fisher et al., 2000). In addition to variation in preparation, several different manufacturers produce formulations of passiflora, making it even more difficult to compare the efficacy of the distinct preparations. Maypop (*P. incarnata*) leaves and roots have a long history of use among Native Americans in North America and were adapted by the colonists. The fresh or dried leaves of Maypop are used to make an infusion, a tea that is used to treat insomnia, hysteria, and epilepsy. It is also valued for its painkilling properties. *Maracujá* (*P. edulis*) and a few other species are used in Central and South America for similar purposes. *P. Incarnata* has aromatase properties due to the presence of two flavonoid compounds: chrysin and benzoflavone moiety, the latter being more potent (Dhawan et al., 2002).

Many species have been found to contain betacarboline, harmala and alkaloids which are MAOIs with antidepressant properties. The flower and fruit has traces of aromatase inhibitor properties only. Passiflora quadrangularis has an antihelminthic action and is also frequently used to treat bronchitis, asthma, and whooping cough (Mowrey, 1993). It has even been patented for treatment of diabetic complications and hypertension (Nippon, 1993). Plants used in traditional folk medicine have a vast source of pharmacologically active components, including hemolysins and cytolysins, potential bactericidal and anticancer drugs (Chandel and Rastogi, 1980; Rao and Sung, 1995; Shao et al., 1996).

Conclusion

Species of *Passiflora* are commonly found throughout world. Studies have revealed its use in anti-inflammatory, antimicrobial, anti-oxidant and antitumour. Further studies are needed to examine the potential use of species of *Passiflora* extract in the prevention of pathologies, such as cardiac ischemia, renal ischemia and neurodegenerative diseases, where oxidative stress damage to protein seems to play a major role. A comprehensive account of the chemical constituents is given in this review.

Various types of preparations, extracts and individual compounds derived from this species have been found to possess a broad spectrum of pharmacological effects on several organs such as the brain, blood, cardiovascular and nervous systems as well as on different biochemical processes and physiological functions including proteosynthesis, work capacity, reproduction, and sexual function. The plant is becoming an endangered species now so more work need to be done on agricultural and climatic condition in order to grow this plant. Therefore, further studies may be carried out to prove the potential of this plant.

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