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A PHARMACOLOGICAL REVIEW: *PASSIFLORA SPECIES*

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ABSTRACT: 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 most abundant sources of bioactive compounds. The genus *Passiflora* L. comprises about 520 species of dicotyledonous plants in the family Passifloraceae. *Passiflora incarnata* and *P. alata*, also commonly known as passion flower, are two species of a perennial climbing vine with beautiful exotic flowers and delicious fruit that grow worldwide, preferring subtropical, frost-free climates. They are native to the tropical and semi-tropical United States (Virginia to Florida and as far west as Texas), Mexico, Central American, and from Brazil to Paraguay through northern Argentina. It is used extensively for the treatment of some diseases like anxiety, insomnia, convulsion, sexual dysfunction, cough, and cancer. Passionflower is currently official in the national Pharmacopeia's of Egypt, France, Germany, and Switzerland, and also monographed in the British Herbal Pharmacopoeia and the British Herbal Compendium, the ESCOP monographs, the Commission E, the German Standard Licenses, the German Homeopathic Pharmacopoeia, and the Homeopathic Pharmacopoeia of the United States. The present article including the detailed exploration of pharmacological properties of *P. incarnata* is an attempt to provide a direction for further research.

INTRODUCTION: The genus *Passiflora* consists of 500 species that are mostly found in warm and tropical regions. *Passiflora c*omes from the Latin word "Passio" that was first time discovered by Spanish discoverers in 1529 and was described as a symbol for "Passion of Christ" [1, 2]. 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 [3, 4]. They are mostly vines, with some being shrubs, and a few species being herbaceous.

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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. The medical utility of very few species of *Passiflora* has been scientifically studied [5]. Passionflower extracts have been classified into several categories of chemical activities like an anxiolytic, spasmolytic, hypnotic, sedative, narcotic and anodyne [6].

These extracts are part of a treatment that has successfully treated outpatients with adjustment disorder and anxious mood [7]. Many species have been found to contain beta-carboline harmala alkaloids with anti-depressant properties. The flower and fruit have 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 hemorrhaging [8].

Classification:

Botanical source : *Passiflora incarnata* L.

Family : Passifloraceae

Genus : Passiflora L.

Species : *Passiflora incarnata* L.

Identifying Characteristics: The stems wiry; three-lobed leaves, serrate; pale pink flowers 5-7 cm across; fruits ovoids or globose, 3-5 cm long **Fig. 1-3** [9].

FIG. 1: PASSIONFLOWER

FIG. 2: WHOLE PLANT

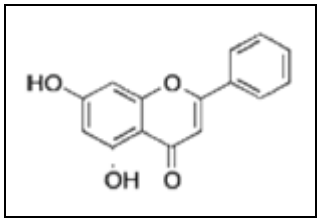
FIG. 3: FRUITS

Bioactive Compounds: The chemical content of *Passiflora* species is also not well delineated. Investigators have differed on whether its sedative effects are due to indole alkaloids such as harmane, harmaline, and harmol; flavonoids such as apigenin, luteolin, and scopoletin; or an isolated trisubstituted benzoflavone.

Also, recently it was determined that Passiflora contains more gamma-aminobutyric acid (GABA) than 20 other plants examined [10]. One of six alkaloids isolated from *P. incarnata* has been called "passiflorine," and is believed by some to be the plant's active compound, although the Agricultural Research Service's web site describes passiflorine as inactive. The Chemical Abstract Service's database's only similar entry is "passiflorine," a steroid-like molecule found in *P. edulis* stems and leaves that is not an alkaloid. Passionflower extracts consist of fresh or dried aerial parts of *P. incarnata* or *P. alata*, collected during the flowering and fruiting period. Botanical identity is confirmed by thin-layer chromatography, microscopic and macroscopic examination, and organoleptic evaluation.

Extracts contain 0.825% apigenin and luteolin glycosides, vitexin, isovitexin and their C glycosides, kaempferol, quercetin, and rutin; indole alkaloids (0.01%), mainly harman, harmaline, harmine; coumarin derivatives; cyanogenic glycosides (gynocardin); amino acids (including GABA); fatty acids (linoleic and linolenic); gum; maltol; phytosterols (stigmasterol); sugars (sucrose); and a trace of volatile oil [11, 12, 13, 14, 15, 16].

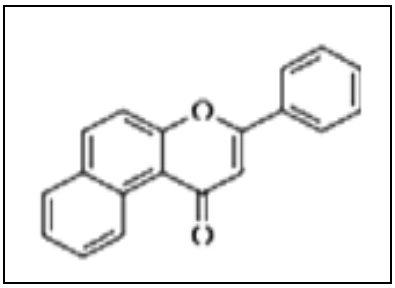
Chrysin: $C_{15}H_{10}O_4$ (5, 7-dihydroxy-2-phenyl-(9CI)



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 [17].

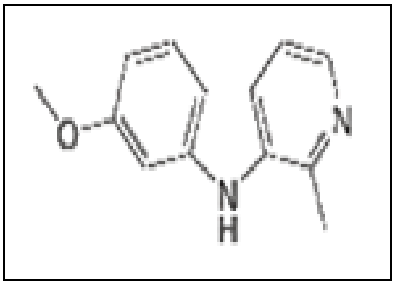
In rodent *in-vivo* studies, chrysin was found anxiolytic [18, 19]. In herbal medicine, it is recommended as a remedy for anxiety, but there are no controlled data in humans' available [20]. Chrysin exhibited an anxiolytic effect, which was slowed by an increase in locomotor activity in rats when injected 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 [21]. Chrysin and apigenin have been shown to inhibit the growth of breast carcinoma cells [22], human thyroid cancer cells [23] and human prostate tumors [24]. Apigenin is considered anti-mutagenic because it reduces the effects of mutagens in rats [25].

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'-diphosphate glucuronosyl-transferases (UGTs) [26]. β -Naphthoflavone is a putative chemopreventive agent [27].

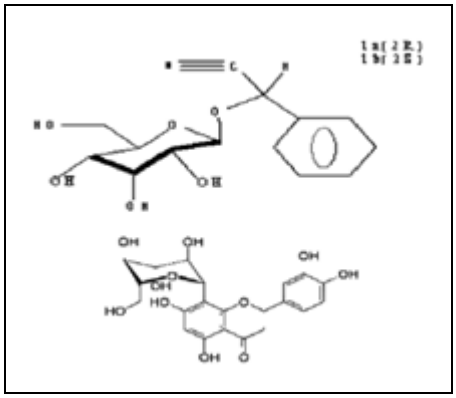
Harmala Alkaloids: $C_{13}H_{12}N_2O$ (7-Methoxy-1-methyl-9*H*-pyrido [3, 4-*b*] indole)



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 [28] because they are contained in only very small amounts (0.01% or less) [29]. Furthermore, they have been identified as stimulants and monoamine oxidase inhibitors [30, 31, 32] 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. The harmala alkaloid 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 [33].

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 [34]. Beta-carbolines, like those of *P. incamata* L., induce voluntary ethanol intake in rats [35]. Some people may be interested in the fact that harman has been identified in beer; wine [36] and cigarette smoke [37]. 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 [38]. 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 [39].

Glycosides:



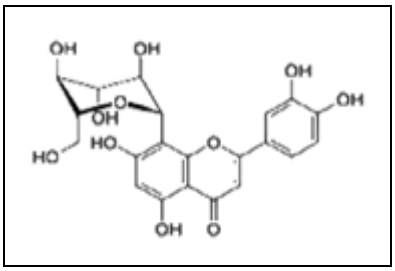
Orientin: Glycosides are molecules in which a sugar is bound to a non-carbohydrate moiety, usually a small organic molecule. Glycosides play numerous essential roles in living organisms. Many plants store chemicals in the form of inactive glycosides which can be activated by enzyme hydrolysis [40].

Leaf and stem material of *P. edulis* contain the new cyanogenic glycosides (2R)–α-allopyranosyloxy-2-phenylacetonitrile and (2S)–α-Dallopyranosyloxy-2-phenylacetonitrile, along with smaller amounts of (2R)–prunasin, (2S)-sambunigrin. Many different types of glycosides are present in passion flowers such as apigenin, homoorientin, 7-isoorientin, isoschaftoside, isovitexin, kaempferol, lucenin, luteolin, norientin, 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. citrine* 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 [41]. *S*ome other glycosides present in *Passiflora* are the hydrocarbon nonacosane and the anthocyanidin pelargonidin-3-diglycoside [42].

Passiflora morifolia extracts contain the cyanohydrins glycoside and linamarin [43]. 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 [44].

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* [45].

Other Organic Compounds: Passionflower 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 esters 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 methylesterase and phenolase. Apart from glycosides, phenols, and alkaloids, various miscellaneous phytoconstituents which were also reported to be in *P. edulis* include, Edulans I and II [46] and pectins [47]. 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 [48].

Pharmacology:

Cannabinoids Reversal: The newly reported benzoflavone (BZF) moiety from the plant *P. incarnata* (Linn) has been evaluated in light of traditional reports on the use of this plant in breaking down cannabis addiction. In the modern or allopathic system of therapeutics, there has been no suitable remedy to combat the severe withdrawal effects of various cannabis products, including marihuana, marijuana, bhang, hashish, ganja, *etc*., the world-wide consumption of which has attained alarming proportions, especially among the younger generation. It has been reported that the BZF of *P. incarnata*, when administered concurrently with cannabinoids, prevented the development of tolerance and dependence of cannabinoids in mice. Even an acute administration of the BZF significantly blocked the expression of withdrawal effects in cannabinoid dependence. So these studies suggested that the BZF may have a beneficial role in cannabinoids reversal [49].

Nicotine Reversal: Some of the pharmacological studies on the BZF moiety also confirmed that the BZF moiety isolated from *P. incarnata* was very effective in countering the menace of addiction-prone substance nicotine in laboratory animals. In light of various reports mentioning the usefulness of *P. incarnata* in tobacco addiction, studies have been performed by using the bioactive BZF moiety isolated from the aerial parts of *P. incarnata*. So these studies, although preliminary,

suggested that the BZF may have value in treating nicotine addiction [50].

Alcohol Withdrawal: A BZF moiety has been reported recently to be responsible for the multifarious CNS effects of *P. incarnata* Linn. In the light of the established usefulness of the BZF moiety in counteracting the withdrawal effects of substances like cannabinoids and nicotine by the authors, the bioactive BZF moiety has been tested in mice treated with an addictive dose of ethyl alcohol, to evaluate its effectiveness in countering alcohol dependence. The chronic administration of *P. incarnata* with alcohol had better preventive effects than the single acute treatment with *P. incarnata* in alcohol-dependent mice. These results suggested that the treatment of *P. incarnata* extract could be used as a safe and alternative drug for alcohol withdrawal [51].

Anticonvulsant Activity: The current treatment of epilepsy with modern antiepileptic drugs (AEDs) is associated with side effects, dose-related and chronic toxicity, and teratogenic effects, and approximately 30% of the patients continue to have seizures with current AEDs therapy. Natural products from folk remedies have contributed significantly in the discovery of modern drugs and can be an alternative source for the discovery of AEDs with novel structures and better safety and efficacy profiles. Evidence for the anticonvulsant activity of *P. incarnata* in the clonic seizure of the pentylenetetrazole model has been tested. As the protective effects of *P. incarnata* in clonic seizure, it suggests that it could be useful for the treatment of an absent seizure. Furthermore, the important role of the benzodiazepine receptor in the effects of *P. incarnata* should be considered [52].

Antimicrobial Activity: In *Passiflora species,* many of the chemical components of passion flower (passicol) have antimicrobial activity [53, 54, 55]. The ethanol leaf extracts exhibited variable degrees of antibacterial activity against *P. putida, V. Cholera* and moderate activity were 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 [56]. The earlier reports focused on the antibacterial properties of *Passiflora* species by different methods. Antibacterial activity of *Passiflora* which has got activity against *Pseudomonas tetrandra, Escherichia coli, Bacillus subtilis,* and *Pseudomonas aeruginosa.*

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 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 [57].

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 [58]. DPPH offers a convenient and accurate method for titrating the oxidizable groups of natural or synthetic anti-oxidants [59]. The crude extracts (leaf and stem) of *P. edulis* were mixed with 95% methanol to prepare the stock solution (10 mg/100 mL).

Anti-inflammatory Activity: The aqueous leaves extract of *Passiflora* species exhibited potent anti-inflammatory action in the experimental model *in-vivo* [60]. The aqueous leaves extract of *P. edulis* possess a significant anti-inflammatory activity on mice [61]. 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, TNF-α and IL-1α levels in the acute model of inflammation caused by intrapleural injection of mice. In one experiment, *P. edulis* was more effective in suppressing the TNF-α and IL-1α levels than dexamethasone [62]. *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 the activity of gelatinase matrix metalloproteinases (MMP-2 and MMP-9). Two metalloproteases were involved in the tumor invasion, metastasis, and angiogenesis. Water extract of *P. edulis*, at different concentrations, was inhibited by the enzymes [63].

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 [64].

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 passionflower itself [65].

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.

Passionflower may theoretically increase the risk of bleeding and affect blood tests that measure blood clotting [66]. 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.

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 [67].

Industrial Uses: Some species of *Passiflora* are cultivated outside their natural range because of their beautiful flowers. *P. incarnate* 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*) [68]. 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 alginate; in Australia, the pulp is added to yogurt.

CONCLUSION: Species of *Passiflora* are commonly found throughout the world. These studies place this indigenous drug as a novel candidate for bio-prospection and drug development for the treatment of such diseases as anxiety, insomnia, convulsion, sexual dysfunction, cough, cancer, and postmenopausal syndrome. The medicinal applications of this plant and countless possibilities for investigation remain in relatively newer areas of its function.

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. Hence, phytochemicals and minerals of these plants will enable to exploit its therapeutic use.

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