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Passiflora Incarnata Linn: A Review on Morphology, Phytochemistry and Pharmacological Aspects

Sita Sharan Patel[1], Neelesh Kumar Verma[1], Karunakaran Gauthaman*

**Department of Pharmacognosy, Himalayan Pharmacy Institute, Majhitar, Rangpo, East Sikkim, India. Phone: 03592-246462, e-mail: gauthamank@gmail.com*
[1]Department of Pharmacology, Himalayan Pharmacy Institute, Majhitar, Rangpo, East Sikkim, India. e-mail: sitasharan.ss@gmail.com; neeleshosho@gmail.com

ABSTRACT
This review gives an account of the current knowledge on the morphology, phytochemistry and pharmacological aspects of *Passiflora incarnata.* A wide range of chemical compounds has been isolated, mainly alkaloids, flavonoids, phenols and carbohydrates. *P. incarnata* has been described as passion flower and used extensively for treatment of several diseases like anxiety, insomnia, convulsion, sexual dysfunction, cough and cancer. Hence the present article includes the detailed exploration of morphology, phytochemistry and pharmacological aspects of *P. incarnata* is an attempt to provide a direction for further research.
KEY WORDS: *Passiflora incarnata,* Aphrodisiac, Benzoflavone, Anti cancer, Cannabinoids

INTRODUCTION

The genus Passiflora consists of 500 species which are mostly found in warm and tropical regions.Passiflora comes from 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). This plant was used widely in traditional medicine in West India, Mexico, Netherland, South America, Italia and Argentina. One of species of this genus named as *P. incarnata* (Passifloraceae) is more popular than its other species. *P. incarnata* (Passion flower Family) is a wide spreading climber, native of South East United State of America, grown frequently in gardens as an ornamental. Stems wiry, leaves three lobed and serrate, flower pale pink in colour, fruits ovoid or globose. This is a fine climber suitable for covering arbours, verandahs and arches. It can be propagated by seed or layering. The fruit is edible when ripe (3). Its medicinal usage has been reported in the traditional systems of medicine such as Ayurveda, Siddha and Unani. Passiflora contains several compounds including alkaloids, phenols, glycosyl flavonoids and cyanogenic compounds (2). In the some experiments, it has potential effects for treatment of some diseases like anxiety, opiates withdrawal, insomnia, attention-deficit hyperactivity disorder and cancer (4-10).

TAXONOMY

Kingdom: Plantae – Plants
Division: Magnoliophyta – Flowering plants
Class: Magnoliopsida – Dicotyledons
Family: Passifloraceae – Passion-flower family
Genus: *Passiflora* L. – Passionflower
Species: *P. incarnata* L. – Purple Passionflower

MORPHOLOGY

The plants of genus Passiflora are shrubs and herbs, mostly climbers with auxillary tendrils. Stem is herbaceous or woody, generally climbing, very rarely arborescent. Leaves alternate, sometimes simple, entire, lobed or palmate, sometimes compound, imparipinnate; stipules germinate at the base of petioles, rarely absent; tendril axillary, arising from sterile pedicels. Flowers are bisexual or unisexual, regular. The large receptacle is often hollowed out like a cup or basin, and bears numerous filamentous or annular appendages between the corolla and stamens, which may be brightly colored and form a conspicuous corona of great diversity. Stamens 3–5 {10} inserted either at the bottom of the perianth, or at the base or top of gynophore; filaments subulate or filiform, free or monoadelphous and sheathing the gynophore; anthers versatile, introrse, two-celled, dehiscence longitudinal. Ovary is superior, more or less stipitate, very rarely sessile, unilocular, of 3–5 united carpels containing several or many anatropous ovules on parietal placentas. Styles equal in number to the placentas, cohering at the base, distinct at the top, spreading, simple or branched, or 3–5 separate styles; stigmas clavate or peltate, sometimes sub-two-lobed; ovules numerous, anatropous, 1–2 seriate, attached to 3–5 parietal linear placentas by longer or shorter funicles, enlarged into a cupule at the umbilicus. Fruits are 1-celled, an indehiscent berry or a capsule with 3–5 semi-placentiferous valves. Seeds numerous; funicle dilated into a pulpy cupuliform or saccate aril; testa crustaceous, foveolate, easily separable from the membranous endopleura, which bears a longitudinal raphe. Pollination is effected by insects, in the attraction of which the remarkable corona developments play an important part; the flowers are often strongly scented and nectar is secreted on the receptacle. Extrafloral nectories occur on the leaf stalks (2). The taxonomy, morphology, growth form, site requirements and the related horticulture aspects of *P. incarnata* have been extensively reviewed (11). Since Passiflora is an exotic genus and many of the species are cultivated for their beautiful ornamental flowers, the information pertaining to the cultivation and gardening aspects of the Passion flowers can be gathered from the Passiflora Society International (2).

PHYTOCONSTITUENTS

Alkaloids, phenols, glycosyl flavonoids and cyanogenic

compounds are known in the genus. Literature survey has revealed that a number of reports are available on *P. incarnata*.

Flavonoids

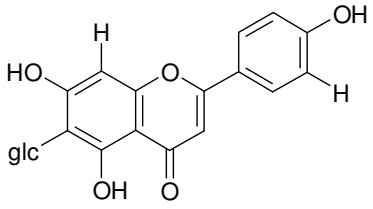
Flavonoids are chemical phenylbenzopyrones, which, usually conjugated with sugars, are present in all vascular plants (12). Flavonoids are reported to be the major phyto-constituents of *P. incarnata*. It contains mainly C-glycosylflavones based on apigenin and luteolin. Concerning the qualitative composition, the previous studies (13-15) that reported isovitexin, vitexin, isoorientin, orientin and saponarin as main components are refuted by recent well-documented and reliable investigations (16-17). The authors found schaftoside, isoschaftoside, isovitexin-2"-O-β-glucoside and isoorientin-2"-O-β-glucoside (17), furthermore vicenin-2 and lucenin-2 beside notable amounts of isovitexin and isoorientin (16) as major compounds. Saponarin, vitexin and orientin occurred in very small concentrations (16, 18). The presence of some of these flavonoids was confirmed in other studies. 6-β-D-glucopyranosyl-8-β-D-ribopyranosyl apigenin and swertisin also investigated (19). The greatest accumulation of flavonoids has been reported to be in leaves and the highest concentration of isovitexin was found to be between the pre-flowering and flowering stages (20). A newly reported benzoflavone moiety chrysin has also been estimated within *P. incarnata* extract (12). During various quantitative studies, it was observed that the ethanol free liquid extract of *P. incarnata* contains higher contents of flavonoids as compared to the commercial preparations. Amongst various other species of the genus, *P. incarnata* contains highest content of isovitexin (20, 2).

Alkaloids

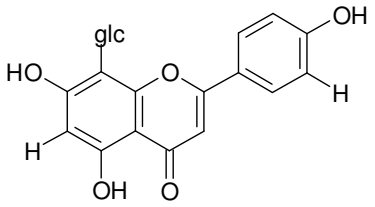
P. incarnata contains simple indole alkaloids based on β-carboline ring system namely harman, harmol, harmine, harmalol and harmaline (21). Content of harman and harmine, determined by direct spectrofluorimetric methods on TLC plates, and has been reported to be 10–20 μg/100 ml in the medicinal fluid extract of *P. incarnata* (22). Recently, all types of β-carboline alkaloids have been analyzed quantitatively by HPLC with selective fluorometric detection (23). The vegetative parts of green house grown *P. incarnata* contain 0.012 and 0.007% of harman and harmine, respectively, while the content of these alkaloids in the plant grown in fields has been reported as 0.005% and nil, respectively (24-26).

Miscellaneous Phyto-constituents

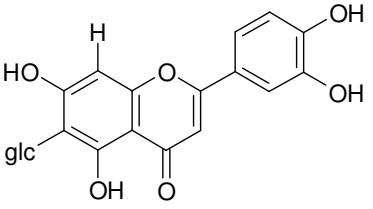
Various other constituents which have been reported from *P. incarnata* include γ-benzo-pyrone derivative maltol (27), carbohydrates such as raffinose, sucrose, D-glucose and D-fructose (28); essential oil containing hexanol (1.4%), benzyl alcohol (4.1%), linalool (3.2%), 2-phenylethyl alcohol (1.2%), 2-hydroxy benzoic acid methyl ester (1.3%), carvone (8.1%), trans-anethol (2.6%), eugenol (1.8%), isoeugenol (1.6%), β-ionone (2.6%), α-bergamotol (1.7%) and phytol (1.9%); various constituents responsible for typical odor of *P. incarnata* such as limonene, cumene, α-pinene, prezizaene, zizaene, and zizanene (29); twenty one amino acids (30), and a cyanogenic glycoside gynocardin (31, 2).



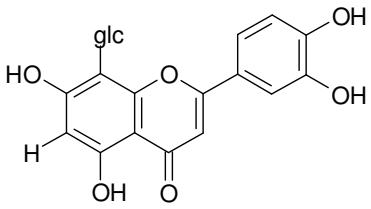
Isovitexin



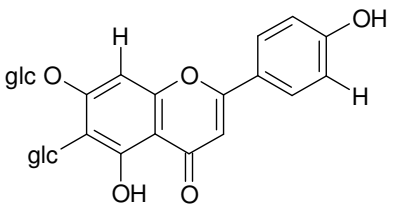
Vitexin



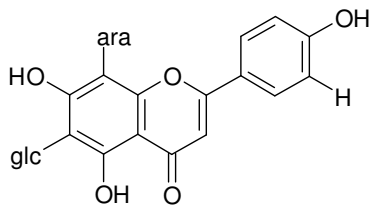
Isoorientin



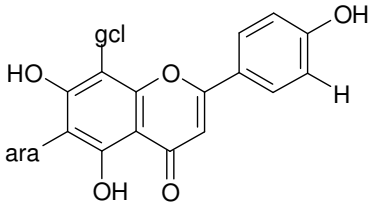
Orientin



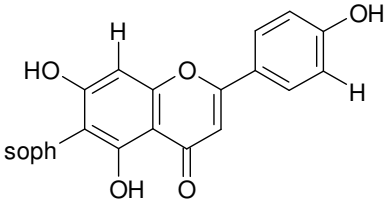
Saponarin



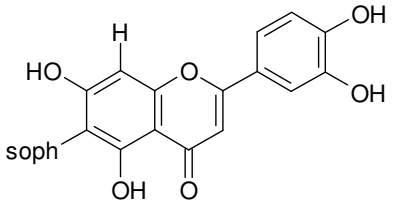
Schaftoside



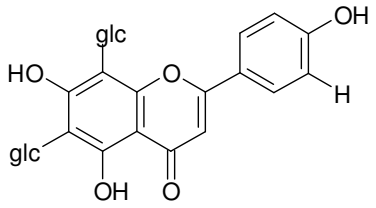
Isoschaftoside



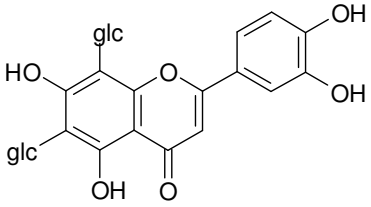
Isovitexin-2"-O-beta-glucoside



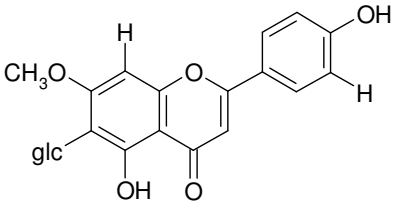
Isoorientin-2"-O-beta-glucoside



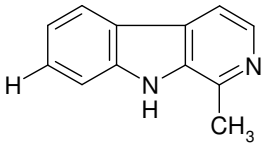
Vicenin-2



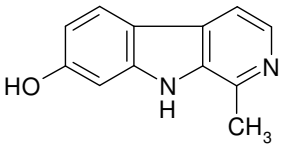
Lucenin-2



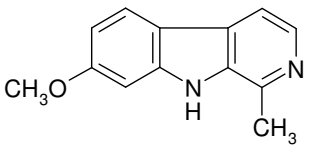
Swertisin



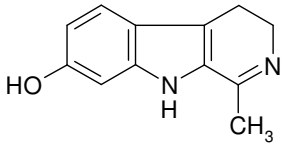
Harman



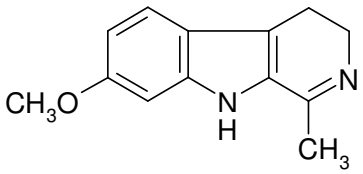
Harmol



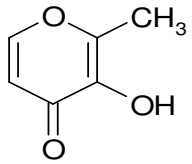
Harmine



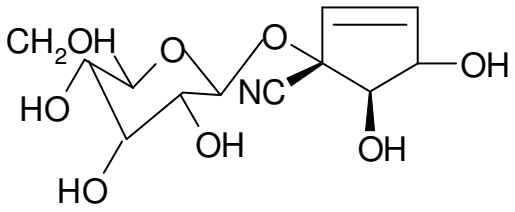
Harmalol



Harmaline



Maltol



Gynocardin

PHARMACOLOGICAL ASPECTS

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. In this study the mice were given a 10 mg/kg twice-daily dose of delta9-tetrahydrocannabinol (delta9-THC) by oral route for six days to make them dependent upon cannabinoids. Concurrently, other groups of mice were administered delta9-THC along with a 10 or 20 mg/kg twice-daily dose of the BZF moiety from *P. incarnata* orally for 6 days. Upon measuring locomotor activity during the treatment regimen, it was noticed that the mice receiving the *P. incarnata* extract and delta9-THC together developed significantly less tolerance and dependence, relative to the mice receiving delta9-THC alone. 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 beneficial role in cannabinoids reversal (32).

Nicotine Reversal

In light of various reports mentioning the usefulness of *P. incarnata* in tobacco addiction, studies have been performed using four doses (1, 5, 10 and 20 mg/kg) of the bioactive BZF moiety isolated from the aerial parts of *P. incarnata*. In a 7-day experimental regimen, mice were given nicotine hydrogen tartrate (2 mg/kg) and combinations of nicotine with four doses of BZF by the subcutaneous route. At the end of the 7 days of treatment, naloxone was given to the mice from all groups to induce a nicotine withdrawal syndrome. The mice that had been treated with 10 and 20 mg/kg dose of BZF concurrently with nicotine showed a significantly fewer number of withdrawal jumps relative to the group treated with nicotine alone. Separately, in a 14-day treatment regimen, mice were administered nicotine (2 mg/kg) and combinations of nicotine with four doses of BZF by the subcutaneous route. Spontaneous physical and behavioural signs of nicotine dependence were observed 3 hours after cessation of treatments on the 14th day. Mice administered with combinations of nicotine and 5, 10 and 20 mg/kg doses of BZF, exhibited less intensity and severity of withdrawal effects compared to the mice treated with nicotine alone. Those mice treated with the two highest doses of BZF, in combination with nicotine, showed significantly fewer nicotine-abstinence withdrawal jumps and normal ambulatory behaviour. BZF treatment prevented weight loss and resulted in normal performance in the swimming endurance test, which may be a measure of stress and/or depression. Similarly, acute administration of a single 20 mg/kg dose of BZF prevented some of the nicotine-withdrawal effects; lower doses were almost inert. These studies, although preliminary, suggest that the BZF may have value in treating nicotine addiction (33).

Alcohol Withdrawal

A BZF moiety has been reported recently to be responsible for the multifarious CNS effects of *P. incarnata*. 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, in order 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 safe and alternative drug for alcohol withdrawal (34).

Anticonvulsant

The current therapeutic 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 anticonvulsant activity of *P. incarnata* in the clonic seizure of pentylenetetrazole model has been tested in mice. As the protective effects of *P. incarnata* in clonic seizure, it suggests that it could be useful for treatment of absence seizure. Furthermore, the important role of benzodiazepine receptor in the effects of *P. incarnata* should be considered (10).

Antianxiety

Herbal medicines are popularly used worldwide and could be

an option for treating anxiety if shown to be effective and safe. Passion flower extract is one of these compounds (35). *P. incarnata* has been used to cure anxiety and insomnia since time immemorial. A fraction derived from the methanol extract of *P. incarnata* has been observed to exhibit significant anxiolytic activity in mice using elevated plus-maze (EPM) model of anxiety. The possibility of a phytoconstituent having BZF nucleus as the basic moiety being responsible for the bioactivity of *P. incarnata* is highly anticipated (36). The potential anxiolytic effects of chrysin, a Passiflora extract, and the purported modulation of the benzodiazepine receptor on the GABA (A) receptor in laboratory rats has been tested. It has been hypothesized that chrysin decreases anxiety via interaction with the GABA (A) receptor in laboratory rats as measured by elevated plus-maze, corticosterone, and catecholamine assays (37). In this study, each group of animal received an intraperitoneal injection of vehicle (DMSO 4%), chrysin, 2 mg/kg, midazolam, 1.5 mg/kg, or flumazenil, 3 mg/kg and chrysin, 2 mg/kg. The EPM was used to evaluate the behavioral component of anxiolysis, and catecholamine and corticosterone assays were examined to measure the neurohormonal effects of anxiety. No statistical difference was found among groups in catecholamine and corticosterone levels. The data suggested that chrysin may have anxiolytic properties similar to midazolam but to a lesser magnitude at the 2 mg/kg dose used in this study (37).

Aphrodisiac

The isolation of a tri-substituted BZF moiety as the main bioactive phyto-constituent of *P. incarnata* has been an encouraging breakthrough in elucidating the mode of action of this plant, which finds mention in the ancient ayurvedic medical writings as a promising cure for male-impotence, post-menopausal decline in libido in females, menstrual irregularity, morphinism, alcoholism and tobacco addiction (38). 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 vigor. BZF, the strongest inhibitor of aromatase enzyme (a member of cytochrome P-450 enzyme family, i.e., CYP3A4) prevents the metabolic conversion of androgens (testosterone) to its metabolites, thereby, increasing the testosterone levels in the gonadal tissue, thus, increasing the free testosterone and decreasing free estrogen (39). The testosterone levels in the plasma have an effect upon the gonadotropins (luteinizing hormone *LH* and follicle-stimulating hormone *FSH*) which regulate spermatogenesis and maturation of sperms. BZF, when administered concurrently with substances like alcohol and nicotine restores sexual virility, libido and vigor in male rats by maintaining the blood-testosterone levels high (40).The aphrodisiac properties of the methanol extract of leaves of *P. incarnata* has been evaluated in mice by observing the mounting behavior. So this study suggested that the *P. incarnata,* may cause sexual desire in human beings as well (41).

Antiasthmatic

The methanol extract of the leaves of *P. incarnata* was evaluated for its antiasthmatic effects against acetylcholine chloride-induced bronchospasm in guinea-pigs. This may be due to defective alpha-adrenoceptor function reported after excessive or continuous administration of an alpha-receptor agonist (42).

Antitussive

The methanolic extract of leaves of *P. incarnata* (100 and 200 mg/kg, p.o.) exhibited significant antitussive activity on sulfur dioxide-induced cough in mice, the cough inhibition being comparable to that of codeine phosphate (43). These results corroborate the folklore claims on the effectiveness of the plant in managing 'tough' cough conditions. Moreover, *P. incarnata*, that has not been reported anywhere to possess addiction-liabilities, could present advantages over available cough-suppressants (opiates, antihistaminics) which, though acting fast, have several adverse effects including CNS depression, dryness of mouth, blurred vision, severe gastrointestinal effects, and burning micturition (44). Further studies are, therefore, necessary to evaluate better the potential of *P. incarnata* as an effective cough suppressant.

Anticancer

The phytochemical composition of passion fruit juice was hypothesized to have valuable anti-cancer activity (9). Chrysin, a passion flower extract, may be beneficial because of its potential to attenuate surgical suppression of natural killer (NK) cell activity, thereby minimizing metastatic spread of cancer (45).

Hypertension

Despite improved pharmacotherapies and mechanical treatments, cardiovascular disease remains a principal cause of morbidity and mortality worldwide, with every chance that this burden will increase (46). *P. incarnata* which is an allied species of *Passiflora nepalensis* has already been reported to possess antihypertensive effects. The antihypertensive effect of *P. incarnata* is contributed due to presence of water soluble substance isolated as a mercury salt ($C_{10}H_{22}O_8NHgCl_2$) (3) and flavonoids. *P. nepalensis* is used in folklore medicine for treating hypertension.

TOXICOLOGICAL PROFILE

Though herbal products are generally regarded as safe, yet, on account of the occurrence of cyanogenic constituents in *Passiflora* species, their toxicity can't be ruled out at higher levels. *P. incarnata* is listed as "safe herbal sedative" by the FDA of America and none of the available monographs of *P. incarnata* mention the toxicity or any contra-indication of this plant. Since the physiological actions and the mode of CNS depressant activity have not been well documented, it has been advised to take *P. incarnata* with caution when taken along with other CNS depressants or stimulants (47). A few individuals have experienced emesis with this plant even at medicinal doses. Moderate doses act as anti-spasmodic or somewhat narcotic. Excessive doses have produced spasms and even paralysis in animals. It has been advised not to take *P. incarnata* with procarbazine anti-neoplastic drugs, possibly to minimize CNS depression. The neuromuscular relaxing effects of *P. incarnata* have been enhanced by the use of the aminoglycoside antibiotic like clindamycin. There has been a report that a 34 years old female patient developed severe

nausea, vomiting, drowsiness and ventricular tachycardia following self medication with *P. incarnata* (48). The extract of the plant is being evaluated in Japan for its possible teratogenic effects (49). Herbal preparations containing *P. incarnata* as one of the ingredients have caused vasculitis in patients suffering from insomnia (50). The popular American Magazine US Pharmacist has discouraged the use of *P. incarnata* in lactating mothers (2). Due to the presence of passiflorine and harmin alkaloids, the plant is reported as a general environmental toxic grass by the University of California in their Environmental Toxicological Newsletter (51) and a severe contra-indication of *P. incarnata* with a synthetic MAO inhibitor drug phenelzine has been highlighted (52).

CONCLUSION

The therapeutic efficacy of *P. incarnata* extensively used in Indian System of Medicine has been established through modern testing and evaluation (pre-clinical and clinical trials) in different disease conditions. These studies place this indigenous drug a novel candidate for bioprospection 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, countless possibilities for investigation still remain in relatively newer areas of its function. Hence, phytochemicals and minerals of these plants will enable to exploit its therapeutic use. Therefore further studies may be carried out to prove the potential of this plant. The plant is becoming the endangered species now so more work can be done on agricultural and climatic conditions to grow this plant.

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ABBREVIATIONS USED

P. incarnata (*Passiflora incarnata*); glc (*β*-3-D-glucopyranosyl); soph (sophorose); ara *a*-L-arabinopyranosyl); BZF (benzoflavone); delta9-THC (delta9-tetrahydrocannabinol); AEDs (antiepileptic drugs); EPM (elevated plus-maze); GABA (gama amino butyric acid).

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