International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 2 Mar-Apr 2022, pp: 1070-1084 www.ijprajournal.com ISSN: 2456-4494

Passiflora species: -Active constituents and its pharmacokinetic profile and pharmacological activity Reported.

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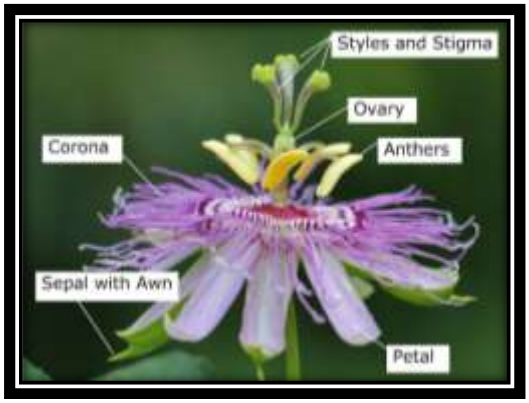
Submitted: 01-04-2022 Accepted: 11-04-2022

ABSTRACT: -This reviewarticle isabout**Passiflora species** active compound and its pharmacokinetic and pharmacological activity which is done most recently.
Passiflora Species have wide range of genus about 550 which are highest in Passifloraceae.
The species of this genus aregenerally found in the warm temperate and tropical regions ofthe world, but they are much rarer in Asia, Australia, andtropical Africa.
Its active constituent is potent against various disease and disorders like anti-inflammatory, anti-cancer, neuro-protective, anti-platelet activity, anti-bacterial/anti-fungal, Cardioprotective, radio protective action, anti-depressant and spasmolytic activity.
The most recent study regarding pharmacokinetic profile and pharmacological activity of Passiflora species are reviewed in this article for better understanding of medicinal uses of this particular species.
But further more research is necessary for more specific action on specific body organs in betterment of its therapeutic effect.
KEYWORDS: -Passiflora species, Activeconstituents, Pharmacokinetic profile,Pharmacological activity.

I. INTRODUCTION

Passiflora derived from Latin word "Passio" which was first time discovered by Spanish in 1529 and was described as a symbol for "Passion of Christ." [1,2]
The Passiflora or passion vines (Passiflora) have a genus of about 550 species of flowering plants and the largest in the family of Passifloraceae. [3,4]
Passiflora is also known as maypop, apricot vine,passion vine, and granadilla. It grows as much as 30 ft(10m) tall, with a thick, woody stem. [5,6]



FlowerOfPassifloraSpecies

The medical utility of very few species of Passiflora hasbeen scientifically studied. [8]
Passionflower extracts have been classified into severalcategories of chemical activities like anxiolytic, spasmolytic, hypnotic, sedative, narcotic and anodyne. [9]
These extracts are part of a treatment that hassuccessfully treated outpatients with adjustment disorderand anxious mood. [10]

Many specieshave been found to contain beta-carboline alkaloids with anti-depressant properties.
The flower andfruit have only traces of these chemicals, but the leavesand the roots are often more potent and have been usedto enhance the effects of mind-altering drugs. [11]

When an extract of the leaves and branches of P.quadrangularriswas administered orally either before orafter a venom injection, haemorrhaging neutralizes anddropped below 25% in mice. [12]
Passiflora alatacan induce occupational allergic disease in humans. [13].
Shatfocide, which is a glycoside of apigenin, was isolated from Passiflora incamataL. [14]

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 2 Mar-Apr 2022, pp: 1070-1084 www.ijprajournal.com ISSN: 2456-4494

The plants belonging to this Genus have been used in traditional medicine for a variety of conditions such asgastrointestinal conditions, neurological complications, cardiovascular conditions, inflammation and anxiety. (15)

The main chemical constituents of the Passiflora Species are the flavonoids (0.25%) such as vitexin, iso-vitexin, orientin, iso-orientin, apigenin, kaempferol and quercetin. The indole alkaloids (0.1%) based on the beta-carboline ring system such as harman, harmin, harmaline, harmol and harmalol.

Two important constituents like chrysin and tri-substituted Benzoflavone Moiety (BZF) have been isolated, some other isolated plant constituents have been identified such as glycosides, carbohydrates, amino acids, benzopyrones, cyanogenic glycosides such as gynocardin, pyrone derivatives such as maltol and ethyl maltol. (16)

I am representing below review article comprehensively, Passiflora species: - Activeconstituentsand itspharmacokineticprofileandpharmacologicalactivity. Most of the references I have mentioned in this review are recent ones and were published in the past decade. Also, several recognized sources of literature were referred for obtaining the information.

This current review demonstrates the usefulness of the Passiflora Species plant parts, their significant role in traditional medicine and the continuing in pharmacokinetic profile and pharmacological activity evidence-based studies that are being reported for better understanding and utilizing these plants for human medicine.

Apart from these reasons, the previous review in similar terms was published and there is a need for an update the potential research information for drug discovery that these plant species offer.

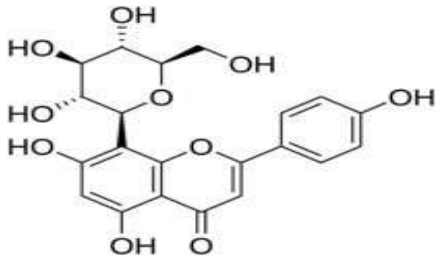
ACTIVE CONSTITUENTS OF PASSIFLORA SPECIES

The major phytochemicals of these parts include flavonoids, sterols, phenolics compounds, polyphenols and carotenoids are given below:

1. Flavonoids (0.25%)

Vitexin: - $C_{21}H_{20}O_{10}$

8-(β-D-Glucopyranosyl)-4′,5,7-trihydroxyflavone]



PHARMACOKINETIC PROFILE

Vitexin is absorbed in the upper gastro-intestinal tract, vitexin is only absorbed to a relatively small extent (4.9-5.8%) and is largely resistant to molecular transformations. (17)

Crucial metabolic transformation of vitexin takes place in the colon, where the gut microbiota plays significant roles in degrading it. (18)

The transformation of vitexin is dependent on the presence of specific bacteria for key degradation steps, such as the cleavage of the C-C bond. (19)

For example, the intestinal Lachnospiraceae strain is able to deglycosylate the vitexin, while Eubacterium cellulosolvens cannot.

they were excreted with faces at 24 hours. (20)

PHARMACOLOGICAL ACTIVITY

1. Anti-inflammatory activity of vitexin: -

Vitexin shows prominent effect on inflammation as follow mechanism high calcium ion (Ca2þ) transition though the endoplasmic reticulum membrane Ca^2 channel in T lymphocytes and mast cells leads to the secretion of inflammatory mediators and further contributes to allergic responses. (21)

Vitexin was found to alleviate allergies by inhibiting calcium release-activated calcium currents and b-hexosaminidase, which suggests the importance of Ca^2 transition as the target for the amelioration of inflammation. (22)

Other animal studies have shown that vitexin ameliorated peritonitis, lung edema, kidney injury, and inflammatory osteolysis by regulating targets commonly found in cell culture results. (23)

2. Anti-cancer activity of vitexin: -

It has also been shown vitexin to be a potent compound in the inhibition of carcinogenesis and tumour growth, it exerts antineoplastic effects on cancer in various organs and systems, including the liver, colon, breast, skin, bladder, lung, etc. (24)

In recent years there have been many studies focusing on the inhibitory effects of vitexin on tumour progression for these cancers and cancer

International Journal of Pharmaceutical Research and Applications
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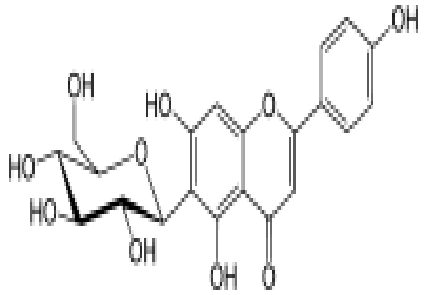
cell lines. Additionally, more mechanisms have been explored.

3.Neuro-protective activity of vitexin: -

Neuron disorders, including epilepsy seizure, brain infarction, retinal damage, hypoxic-ischemic injury, bradykinesia, depression, and memory loss, are closely associated with the loss of neurons, reduced stress resistance, and inflammation. [25]

Vitexin attenuated these neuron disorders and improved the learning behaviours in mice and rats mainly by promoting neuron survival, decreasing ROS levels, and reducing the release of pro-inflammatory factors. [26]

Iso-vitexin: $C_{21}H_{20}O_{10}$
[6-(β-D-Glucopyranosyl)-4′,5,7trihydroxyflavone]



PHARMACOKINETICPROFILE

Flavone C-mono-glucosides such as iso-vitexin were poorly absorbed in the gastrointestinal tract of rats and consequently, they reached the colon, no flavone C-glucosides were detected in the brain and liver of rats within 12 hours after administration, they were excreted with faces at 24 hours. [27]

PHARMACOLOGICALACTIVITY

1. **Antiviral Activity: -**

Iso-vitexin showed cell cytotoxicity and inhibitory effects against influenza virus (type A) in vitro. Other three flavonoid C-glycosides did not exhibit significant activity. [28]

Iso-vitexin from exhibited antimicrobial activities against Staphylococcus aureus, Escherichia coli and Bacillus subtilis. [29]

2. **Antiplatelet Activity: -**

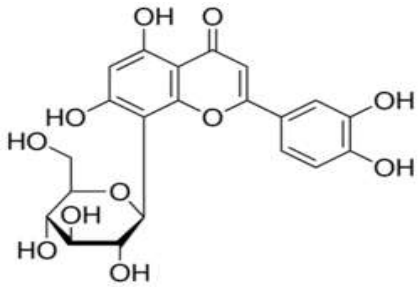
Isolated iso-vitexin, it was found that C-glycosyl flavones hardly inhibited platelet aggregation and further O-glycosylation of C-glycosyl flavones did not improve the antiplatelet activity. [30]

3. **Antibacterial and Antifungal Activity: -**

Identified iso-vitexin act as quorum sensing inhibitors by means of biosensors. [31]

Iso-vitexin exhibited antimicrobial activities against Staphylococcus aureus, Escherichia coli and Bacillus subtilis. [32]

Orientin:$C_{21}H_{20}O_{11}$
[8-(β-Glucopyranosyl)3′,4′,5,7tetrahydroxyflavone]



PHARMACOKINETICPROFILE

Orientin mainly absorbed by colon and distributed into rat liver, lung, and kidney while the blood-brain barrier prevented it from entering the brain.

Orientin did not have long-standing build up in rat organs, compared to alkaloids, both distributions and eliminations of Orientin in rats were fast. [33]

PHARMACOLOGICALACTIVITY

1. **Vasodilatation and Cardioprotective activity: -**

Orientin has been identified to have **vasodilatation** effects on removed thoracic aortic rings from the New Zealand rabbit.

It was found that orientin with an IC_{50} value of 2.28 μM and 7.27 μM relaxed phenylephrine-induced contractions in the endothelium-intact and endothelium-isolated aortic rings, respectively. [34]

The possible pathway that orientin acts as a vasorelaxant on thoracic aortic rings is by the nitric oxide-cGMP pathway, while in the vascular smooth muscle, it relaxes the muscle via activation of voltage-dependent calcium channels. [34]

Besides that, orientin has been massively studied for its in vivo **cardioprotectiv**e effect.

Orientin was demonstrated to reduce myocardium apoptosis of rat heart with ischemia reperfusion. The apoptosis of rat cardiomyocytes that were injured by hypoxia/reoxygenation also decreased upon pre-treatment with orientin at 3, 10, and 30 μmol L−1. [35]

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 2 Mar-Apr 2022, pp: 1070-1084 www.ijprajournal.com ISSN: 2456-4494

2. Neuroprotective activity: -

Neurodegenerative diseases are the incurable and weakening conditions where there are aggregation and deposition of misfolded intracellular and extracellular proteins, which lead to progressive central nervous system diseases. [36-37]

Law et al. concluded that this antiapoptotic effect of orientin could have been attributed to the inactivation of caspases 3/7 and caspase-9 activities based on the caspase assays. [38]

3. Radioprotective activity: -

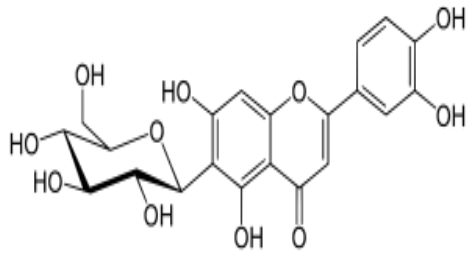
Isolated orientin have been frequently examined for radioprotective effect. The pre-treatment of optimal dose at 50 μg/kg body weight of orientin 30 minutes on mice before being exposed to 11 **Gy** of gamma radiation showed protection against fatality, but the post-treatment of orientin was not as effective as pre-treatment. [39]

The possible mechanisms of action of this protective effect were then determined.

Orientin have given protection against whole-body 3 **Gy**of gamma radiation-induced lipid peroxidation in mouse liver and also scavenged free radical activities include diphenyl picrylhydrazyl (DPPH) and 2,2 - azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) in vitro. [39]

Therefore, the antioxidant activity of the flavonoids might be the possible pathway of the radiation protective effect.

ISO-ORIENTIN:$C_{21}H_{20}O_{11}$
[6-(β-D-Glucopyranosyl)-3′,4′,5,7tetrahydroxy flavone]



PHARMACOKINETICPROFILE

Iso-orientin is poorly absorbed in humans with very few metabolites in urine and blood and are deglycosylated and degraded by human intestinal bacteria in colon. However, the transcellular movement of the intact molecule across the intestinal epithelium was predominantly facilitated. [40]

And iso-orientin is eliminated by urine and faces.

1. Anticancer and Antitumor Activity: -

Iso-orientin induced apoptosis by mitochondrial dysfunction, activating the Fast receptor-mediated apoptotic pathway and MAPK signalling pathway and inactivating the p53 and PI3K/Ak dependent NF-kB signalling pathway. Orientin remarkably inhibited the proliferation and induced apoptosis of EC 109 cells. [41]

Iso-orientin is a common flavonoid found in Passiflora species and has been isolated from many plant species. [42]

Several studies have reported a pharmacologic effect of ISO on cancer cells. [43]

Iso-orientin exerts cytotoxic effects on HT-29 human colorectal adenocarcinoma,

In this study, demonstrated for the first time the effects of ISO causing decreased cell viability and proliferation of HT-29 human colorectal adenocarcinoma cells. [44]

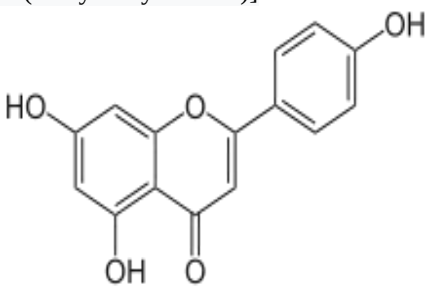
2. Anti-inflammatory Activity: -

Iso-orientin inhibit thromboxane B2 (TXB2) and leukotriene B4 (LTB4) synthesis in peritoneal leukocytes. Both mediators derive from arachidonic acid via the cyclooxygenase (COX) and 5-lipoxygenase (5-LO) pathways, respectively and have pro-inflammatory effects.

Iso-orientin showed a strong inhibitory activity on TXB2 synthesis (54.33%, 56.34%, and 66.42% inhibition at 25, 50, and 100 mg/mL, respectively) while it hardly inhibited LTB4 synthesis (only 28.24% inhibition at 100 mg/mL).

The selective inhibition on TXB2 synthesis was attributed to the luteolin type structure and 6-C-glycosylation. [45-46]

Apigenin: - $C_{15}H_{10}O_5$
[4′,5,7- (Trihydroxy flavone)]



PHARMACOKINETICPROFILE

About 5-10% of total polyphenol intake, mostly monomers and dimers, may be absorbed in the small intestine. [47]

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 2 Mar-Apr 2022, pp: 1070-1084 www.ijprajournal.com ISSN: 2456-4494

The absorbed apigenin may go through extensive Phase I and Phase II metabolism. [47]
In the rat liver, metabolism of apigenin was found to involve Phase I Enzymes in the presence of NADPH (nicotinamide adenine dinucleotide phosphate), P450 (cytochrome P450 enzymes), or FMO (favin-containing monooxygenase). [48]
Phase II biotransformation of apigenin involves both enteric and enterohepatic cycling.[49]
Excretion of apigenin after oral intake through faeces is a good indication. [50]
By using rats, after a single oral administration of radiolabelled apigenin, 51.0% of the radioactivity was recovered in urine and 12.0% in faeces within 10 days. In the same research, it was discovered that sex and age of the rats affected apigenin conjugates eliminated via the urinary route. [50]

PHARMACOLOGICALACTIVITY

1. Antibacterial Activity: -

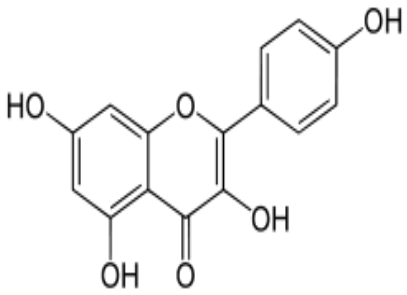
The antibacterial potential of apigenin has been tested against many bacteria species and various strains within the same species. Broth microdilution and agar dilution methods are the most popular methods in which the minimal inhibitory concentrations (MICs) are determined as the lowest concentration of treatment that showed no growth after incubation. [51-54]
Apigenin could not inhibit the growth of Staphylococcus aureus.
Despite the reported lack of activity against S. aureus, apigenin was found to remarkably decrease the level of hemolysin at low concentrations in a concentration dependent manner in S. aureus culture supernatants. [54]

2 Antiviral Activity: -

Apigenin is reported to be able to inhibit multiple viruses, including enterovirus 71 (EV71), herpes simplex virus HSV-1 and HSV-2, hepatitis C virus, infuenza virus, hand, foot, and mouth disease virus, and African swine fever virus (ASFV), but not coxsackie virus A16 (CAV16). [55]

Apigenin inhibited EV71-mediated cytopathogenic effect and EV71 replication in vitro, Viral polyprotein expression, EV71-induced cell apoptosis, intracellular reactive oxygen species (ROS) generation and cytokines up-regulation were inhibited. [56]
Apigenin could interfere with viral internal ribosome entry site (IRES) activity and inhibit EV71- induced c-Jun N-terminal kinase (JNK) activation which is critical for viral replication. [56]

Kaempferol:-$C_{15}H_{10}O_6$
(3,4′,5,7Tetrahydroxyflavone)



PHARMACOKINETICPROFILE

It has been reported that kaempferol is absorbed by passive diffusion, facilitated diffusion as well as by active transport due its lipophilicity. Kaempferol is metabolized by a glucuronide conjugation as well as by a sulphate conjugation in the liver. [57-58]
Kaempferol is also metabolized in the small intestineby intestinal enzymes.

The normal floras of the colon metabolize the kaempferol glycoside into aglycones and further convert it into 4-methylphenol, 4-hydroxyphenylacetic acid and phloroglucinol which are absorbed into the systemic circulation and then distributed to different tissues and finally excreted via faeces or urine. [59-60]
It has been reported that about 1.9% to 2.5% of the ingested kaempferol was excreted in urine. [61-62]

PHARMACOLOGICALPROFILE

1. Anti-Cancer Activity: -

Prostate cancer has been reported to be one of the most common cancers for male both in incidence rate and morbidity. It is well known that the androgen/AR signalling pathway is crucial for prostate cancer development. [63]

Several studies showed therapeutic effect of kaempferol on different types of cancers, including lung cancer [64], gastric cancer [65], pancreaticcancer [66], breast cancer [67], ovarian epithelial carcinoma [68], renal caner [69], bladder cancer [70-71] and prostate cancer. [72]

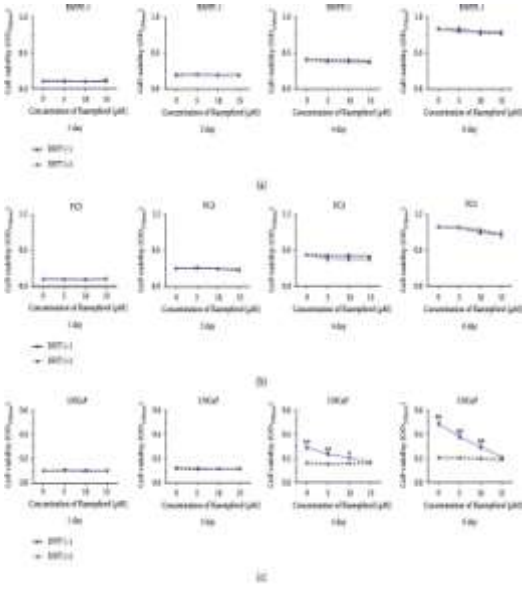
The effect of kaempferol on the cell growth of LNCaP, PC-3, and RWPE-1 cells was investigated in study.
It is well known that LNCaP cells were AR-positive cells and PC-3 cells were known as AR-negative cells. RWPE-1 cells were non-malignant prostate epithelial cells. 1 nM DHT was added to mimic androgen hormone level after castration. Data of MTT assay showed that cell viability of LNCaP decreased 33% by 5 μM kaempferol, about

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 2 Mar-Apr 2022, pp: 1070-1084 www.ijprajournal.com ISSN: 2456-4494

60% by 10 μM kaempferol, and almost 100% by 15 μM kaempferol (Figure 1(c)) on days 4 and 6. On the contrary, the cell growth of PC-3 and RWPE-1 was not inhibited significantly by the same dosage of kaempferol, regardless of the presence of DHT (Figures 1(a) and 1(b)).[63]

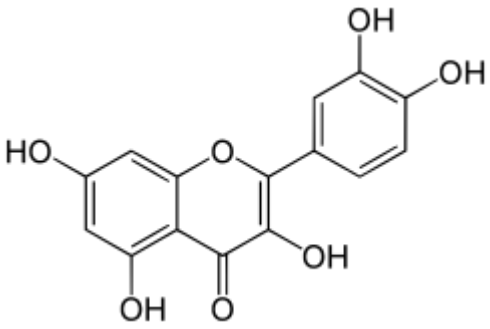
2. Anti-atherosclerosis Activity: -

An Experiment conducted by Kong and his co-workers to explore the anti-inflammatory effect of kaempferol as an atherosclerosis remedy. They administered kaempferol for 10 weeks to rabbits. After the study, they found that the cholesterol level and arteriolar lesions of rabbits were markedly reduced.



Kong and his co-workers found that the serum level of TNF-α, cytokines, leukocytes, IL-1β, Intracellular adhesion molecule-1 (ICAM-1) and E-selectin were significantly decreased after the treatment of kaempferol. Thus, they found kaempferol as a potential anti-atherogenic agent which prevents vascular inflammation.[73]

Quercetin: $C_{15}H_{10}O_7$
(3,3′,4′,5,7Pentahydroxyflavone)



PHARMACOKINETIC PROFILE

Animal and human research have reported poor oral bioavailability of quercetin after a single oral dose due to macronutrient absorption.[74]

For instance, quercetin is ingested in the form of glycosides, and glycosyl groups are released during chewing, digestion, and absorption. Afterward, quercetin glycosides are converted into aglycone in the intestine before they are absorbed into enterocytes by the action of β-glycosidases enzymes.[75]

Quercetin is a lipophilic compound, so it is assumed that it can cross the intestinal membranes by simple diffusion, and theoretically, this absorption is better than its glycoside forms which reach the intestines without degradation.[76]

PHARMACOLOGICALACTIVITY

1. Hepatoprotective and Antihypertensive Activity: -

Recently, an in vivo study found that quercetin increased heme oxygenase 1 activity in D-galactosamine- and LPS-treated rats by lowering plasma concentrations of alanine aminotransferase and stimulating its hepatotoxic and hepatoprotective activity.[77]

Moreover, Liu et al. revealed the ability of quercetin to treat ethanol-induced oxidative damage in rat hepatocytes, suggesting that quercetin may be an appropriate hepatoprotective natural product.[78]

Duarte et al. reported that quercetin had antihypertensive activity in spontaneously hypertensive rats, and noted that quercetin had induced a dose-dependent, advanced, and potential reduction in pressure of the blood when given chronically to several hypertensive rat models.[79]

2. Anti-Alzheimer activity: -

Quercetin's beneficial effects against AD are ascribed due to its inhibitory efficacy against acetylcholinesterase (AChE).[80]

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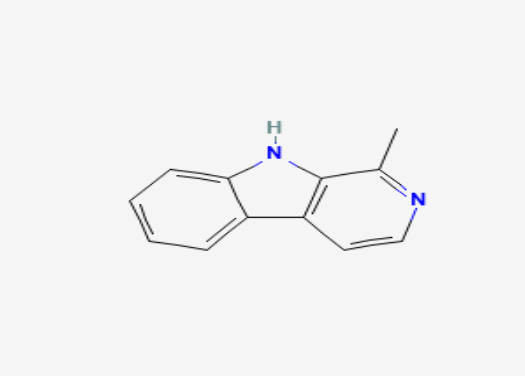
Recently, in vivo experiments have documented the ability of quercetin to reduce the oxidative stress caused by 6-hydroxydopamine in the neurons of rats. (81)

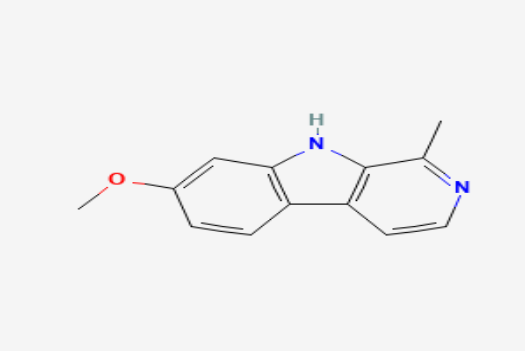
Another study conducted on healthy P19 neurons revealed that neuron survival is not affected by quercetin, while it depletes the glutathione content that may affect the functioning of the nervous system. (82)

Indole alkaloids (0.1%)

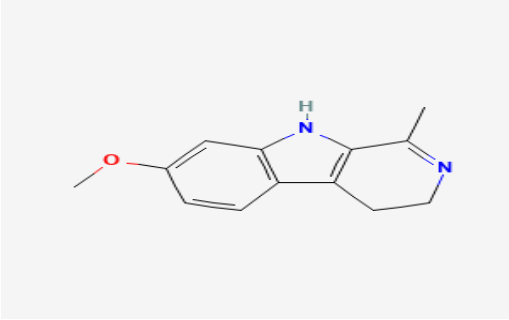
Harman: -($C_{12}H_{10}N_2$)
(1-methyl-9H-pyrido[3,4-b] indole)



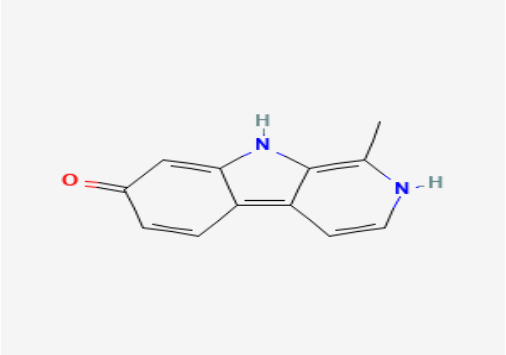
Harmine: - ($C_{13}H_{12}N_2O$)
(7-methoxy-1-methyl-9H-pyrido[3,4-b] indole)



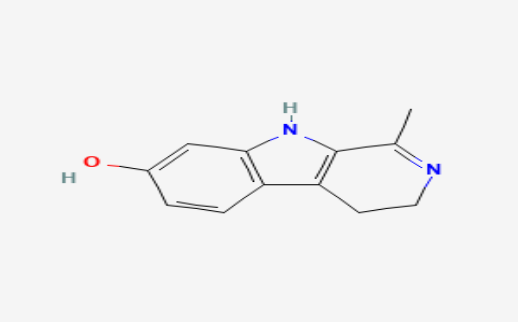
Harmaline: -$C_{13}H_{14}N_{2O}$
(7-Methoxy-1-methyl-4,9-dihydro-3H-pyrido[3,4-b]indole)



Harmol: -$C_{12}H_{10}N_2O$
(1-methyl-2,9-dihydropyrido[3,4-b] indol-7-one)



Harmalol: -$C_{12}H_{12}N_2O$ (1-methyl-4,9-dihydro-3H-pyrido[3,4-b] indol-7-ol)



PHARMACOKINETIC PROFILE

Harmane was immediately absorbed into the blood circulation, with a high Cmax of 1059.56 ± 91.06 ng/mL and a short Tmax of 0.23 ± 0.06 h after the administration of a single oral dose at 30.0 mg/kg body weight in rats. The plasma concentration-time curve for harmane displayed a rapid decrease, with an elimination half-life (T1/2e) of 2.26 ± 0.53 h, and the levels fell below the detection limits within 8 h after administration. (83)

The oral bioavailability of harmane was 19.41%. The absorption rate constant (Ka), distribution rate constant (Kd), and elimination rate constant (Ke) were 3.64, 1.51, and 0.32 per hour. Other parameters were also evaluated in that study. (83)

PHARMACOLOGICALACTIVITY

1. Antidepressant Activity: -

Harmane, norharmane, and harmine exhibited antidepressant-like activity when administered to mice subjected to the FST. In a dose-dependent manner, these compounds decreased the immobility duration with a 50% effective dose (ED50) of 11.5 mg/kg by

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 2 Mar-Apr 2022, pp: 1070-1084 www.ijprajournal.com ISSN: 2456-4494

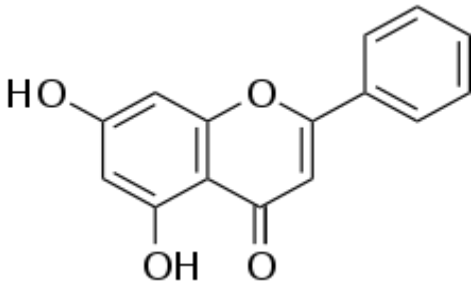
intraperitoneal (i.p.) administration for harmane, 8.5 mg/kg i.p. for norharmane, and 8 mg/kg i.p. for harmine. These effects do not appear to be mediated by presynaptic monoaminergic mechanisms but are likely caused by an inverse-agonistic mechanism that involves the benzodiazepine receptors. (84)

2. Spasmolytic Activity: -

Harmine, harman, and harmaline have relaxation potency against histamine, carbachol, and KCl-The relaxation potency of these compounds against histamine, carbachol, and KCL induced contractions revealed EC_{50} values for harmane, harmine, and harmaline of 28 ± 3, 16 ± 51 ±,5, 37 ± 3, and 131 ± 30 µM against KCl, respectively.

Harmine displayed the most potency among the three-indole alkaloid. (85)

Chrysin: -$C_{15}H_{10}O_4$
(5,7-dihydroxy-2-phenylchromen-4-one)



PHARMACOKINETIC PROFILE

After oral consumption by a human, the bioavailability of chrysin is low due to poor intestinal absorption, rapid metabolism, and exertion. The scientific evidence indicated that absorbed chrysin is catalysed mainly by glucuronidation and sulfation. (86) Small amounts of chrysin are found as conjugates in the plasma and urine. (87)

Although chrysin has low oral bioavailability, its metabolites can reach high concentrations in body fluids (e.g., plasma, bile, and urine) (88-90)

PHARMACOLOGICAL ACTIVITY

1. Anti-hyper lipidemic activity: -

It is also reported that chrysin (200 mg/kg, PO, for 15 days) decreased the serum levels of total cholesterol, TGs, LDL-c, and VLDL-c serum levels also increased the serum levels of HDL-c in rats fed with an atherogenic diet. (119)

It was indicated that chrysin decreased the intestinal absorption of cholesterol by decreasing the incorporation of dietary and biliary cholesterol into micelles. (91)

It has been suggested that chrysin has hypolipidemic effects by reducing lipid absorption. In addition, chrysin increased the activities of the LPL in liver tissue and HMG-CoA reductase in the rats fed with an atherogenic diet. (91)

2. Dermatological activity: -

Chrysin has the ability to attenuate psoriasis-like skin lesions. (92)

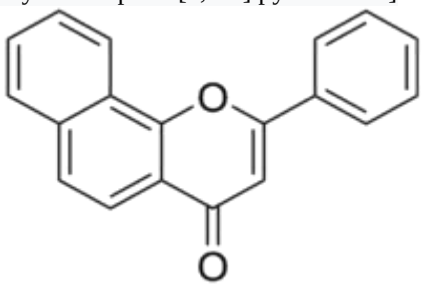
Its hydroxy ethylated derivatives obtained by gamma irradiation may find an application in the treatment of atopic dermatitis because they decrease the levels of pro-inflammatory cytokines IFN-γ, IL-5, IL-4 and IL-17. (93)

In addition, by targeting IκB kinase in the atopic dermatitis-like inflammatory microenvironment, chrysin inhibits NF-κB-dependent CCL5 transcription. (94)

Administration of chrysin to BALB/c mice with dermatitis induced by 2,4 dinitrochlorobenzene and the house dust mite resulted in reduced levels of blood histamine and inhibited the secretion of Th1, Th2, Th17, CCl17 and CCl22 cytokines. (94)

chrysin also protects the skin from photoaging and melanogenesis. (95)

Benzoflavone:$C_{19}H_{12}O$
[2-Phenyl-4H-naphtho[1,2-b] pyran-4-one]



PHARMACOKINETIC PROFILE

7,8-Benzoflavone was rapidly absorbed after oral administration with an absorption rate constant ka of 0.29 min.

The rapid oral absorption is possibly due to the highly lipophilic nature of 7,8-benzoflavone. (96)

plasma concentrations of 7,8-benzoflavone after oral dosing are similar or lower than those observed at the lowest intravenous dose.

The bioavailability of 7,8-benzoflavone was very low, ranging from 0.61% to 13.2%. The increase in bioavailability with the increase of dose again

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 2 Mar-Apr 2022, pp: 1070-1084 www.ijprajournal.com ISSN: 2456-4494

suggested nonlinearity in 7,8-benzoflavone pharmacokinetics.
Since the urinary excretion of parent 7,8-benzoflavone is minimum. (96)

PHARMACOLOGICAL ACTIVITY

1. Cannabinoid's reversal activity: -

The newly reported benzoflavone (BZF) moiety from the plant P. incarnata (Linn) has 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 beneficial role in cannabinoids reversal. (97)

2. Nicotine reversal activity: -

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. (98)

II. CONCLUSION

Passiflora plant have broad range of 550 species with wide geographical distribution which is available easy in hot climate.

The main chemical constituents of the Passiflora Species are the flavonoids (0.25%) such as vitexin, iso-vitexin, orientin, iso-orientin, apigenin, kaempferol and quercetin. The indole alkaloids (0.1%) based on the beta-carboline ring system such as harman, harmin, harmaline, harmol and harmalol.

Two important constituents like chrysin and tri-substituted Benzoflavone Moiety (BZF) have been isolated, some other isolated plant constituents have been identified such as glycosides, carbohydrates, amino acids, benzopyrones, cyanogenic glycosides such as gynocardin, pyrone derivatives such as maltol and ethyl maltol.

As previously mentioned above chemical constituents of Passiflora species in this review have different pharmacokinetic activity i.e., absorption, distribution, metabolismand excretion.

And pharmacological activity on different body system like nervous system, cardiovascular system, blood system, hepatic system, dermatological system.

Active constituents of Passiflora species like vitexin and iso-vitexin show anti-inflammatory, anti-cancer, neuro-protective and anti-platelet activity.

From above review article we can give conclusion that, Passiflora species are widely studied because of its broad range of medicinal importance beside that this review article included with more recent studies on animals and some studies are on humans.

But some more research is yet to be performed for better understanding of pharmacokinetics and pharmacological activity of active constituents of Passiflora species.

III. ACKNOWLEDGMENT

We are sincerely thankful to all our references because without them our review article can't get complete.
We also give thanks to our pharmacology department staff for their valuable suggestions.

CONFLICT OF INTEREST

All authors declare solemnly no conflict of interest on this review article.

ABBREVIATIONS

1. **BZF:** - Benzoflavone Moiety
2. **Ca^2**: - Channel Calcium channel
3. **ROS**: -Reactive oxygen species
4. **IC_{50}**: -Half-maximal inhibitory concentration
5. **μM**: - Micrometre
6. **cGMP**: -Cyclic guanosine monophosphate
7. **PI3K**: - Phosphatidylinositol 3-kinase
8. **Akt**: -Protein kinase B
9. **SK-N-SH**: - A neuroblastoma cell line
10. **DNA**: - Deoxyribonucleic acid

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 2 Mar-Apr 2022, pp: 1070-1084 www.ijprajournal.com ISSN: 2456-4494

11. **Gy**: - The Gray is a derived unit of ionizing radiation.
12. **DPPH: -** Diphenyl picrylhydrazyl
13. **ABTS**: - 3-ethylbenzothiazoline-6-sulfonic acid
14. **MAPK: -**Mitogen-activated protein kinase
15. **TP53: -** A gene that instructs the cell to produce tumour protein
16. **NF-kB: -**Nuclear factor kappa B
17. **EC 109: -**Esophageal squamous **cell** line
18. **ISO: -** Iso-orientin
19. **HT-29: -**Human colorectal adenocarcinoma cell line
20. **XTT:-**2,3-Bis-(2-Methoxy-4-Nitro-5-Sulfophenyl)-2H-Tetrazolium-5-Carboxanilide
21. **TXB2: -** Thromboxane B2
22. **LTB4: -**Leukotriene B4
23. **COX: -** Cyclooxygenase
24. **5-LO: -** lipoxygenase
25. **NADPH: -**Nicotinamide adenine dinucleotide phosphate
26. **P450: -**Cytochrome P450 enzymes
27. **FMO: -** Flavin-containing monooxygenase
28. **MICs: -** Minimal inhibitory concentrations
29. **A549: -** Cells alveolar basal epithelial cells
30. **EV71: -** Enterovirus 71
31. **HSV: -** Herpes simplex virus
32. **CAV16: -** Coxsackie virus A16
33. **IRES: -** Internal ribosome entry site
34. **JNK: -** Jun N-terminal kinase
35. **HCV: -** Hepatitis C virus
36. **TRBP: -** Transactivating response RNA-binding protein
37. **ARpathway: -**Androgen receptor signalling pathway
38. **LNCaP: -** Prostate cancer cell line
39. **DHT: -** Dihydrotestosterone
40. **TNF-α: -**Tumour necrosis factor α
41. **IL-1β: -** Interleukin-1β
42. **ICAM-1: -** Intracellular adhesion molecule-1
43. **RAGE**: - Advanced Glycation End products
44. **AChE: -** Acetylcholinesterase
45. **AD: -** Alzheimer's Disorder
46. **Cmax: -**Maximum concentration
47. **Tmax: -**Time to reach maximum concentration
48. **KCl: -** Potassium chloride
49. **EC_{50}: -**Effective concentration
50. **VLDL: -** Very-low-density lipoproteins
51. **NAFLD: -**Non-alcoholic fatty liver disease
52. **ALT: -** Alanine aminotransferase
53. **AST: -** Aspartate aminotransferase
54. **TGs: -**Triglycerides
55. **LDL: -**Low-density lipoprotein
56. **VLDL: -** Very low-density lipoprotein
57. **HDL: -**High density lipoprotein
58. **LPL: -**Lipoprotein lipase
59. **HMG-CoA: -**3-Hydroxy-3-methylglutaryl-coenzyme A
60. **IFN-γ: -** Interferon-gamma
61. **IL: -**Interleukin

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