Journal of Pharmacy Sciences and Drug Research

Research Article

Pharmacological Potential of Clitoria ternatea Linn: Perspectives on Its Future as a Therapeutic Herbal Medicine

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Abstract

The present review draws attention to pharmacological actions of *Clitoria ternatea Linn* (Family *Fabaceae*). It is a twining evergreen garden flowering plant which is commonly known as Aparajita (Hindi) or Butterfly pea (English). It has been used anciently as medhya (brain tonic) in Ayurvedic system of medicine. Various primary and secondary plant metabolites including aparajitin, clitorin, triterpenoides, anthocyanins, steroids and flavonol glycosides have been isolated from *Clitoria ternatea* Linn. This article reviews various pharmacological activities of *Clitoria ternatea* including nootropic, anti-convulsant, anti-depressant, anti-anxiety, anti-stress, antioxidant, anti-inflammatory, anti-hyperlipidemic, anti-diabetic, analgesic, cytotoxicity, platelet aggregation inhibitory and hepatoprotective. The reported activities of *Clitoria ternatea* make it a potential source of drug molecules for treatment of various ailments.

Keywords: *Clitoria ternatea*; Aparajita; Butterfly pea; Medhya drug; Nootropic activity; Antioxidant; Anti-inflammatory

Introduction

Ayurvedic system of medicine is a well-known and oldest system of medicine being used centuries in India. In this system, plants with medicinal properties are used for various ailments and may be a source of drugs. Medhya drugs prescribed in Ayurvedic system of medicine are a group of herbal drugs used to improve mental abilities [1]. These herbal drugs include the extracts from *Clitoria ternatea* (CT), *Celastrus paniculatus, Acorus calamus, Centella asiatica, Bacopa monierra, Withania somnifera and Areca catechu* [2-4]. Out of several medicinal plants/herbal drugs mentioned in Ayurveda, *Clitoria ternatea* is well known Ayurvedic medicine used for the treatment of various diseases.

Clitoria ternatea is well known tropical perennial climber herb from family Fabaceae with slender downy stem, found throughout the tropical region of India, growing wild and also in gardens, bearing white or blue flowers. It is commonly known as Aparajita and Koyal in Hindi and Butterfly pea in English. The extracts of CT have been used as an ingredient in "Medhya Rasayana" a rejuvenating herbal formulation for treatment of various neurological disorders and to strengthen intellectual ability. Various traditional uses of CT are shown in Figure 1. The root part of CT has been used for its laxative, purgative, diuretic, inflammation, indigestion, constipation, fever, arthritis, eye ailments, sore throat and anthelmintic. Kirtikar and Basu [5] also reported the usefulness of CT for treatment of severe bronchitis, asthma and fever. CT is also being used by the local tribes to cause abortion, to cure abdominal swelling, sore throat, mucous disorder and fever [6]. The root juice of CT is given with cold milk to reduce phlegm in chronic bronchitis. Various known pharmacological properties of CT plant are shown in Figure 2. In this article, we have reviewed various pharmacological studies of this potential medicinal plant.

Chemical constituents

Taraxerol and taraxerone, pentacyclic triterpenoids and flavonol glycoside, 3,5,4′-trihydroxy-7-methoxyflavonol-3-O-β-d-xylopyranosyl-(1,3)-O-β-d-galactopyranosyl (1,6)-O-β-d-glucopyranoside are present in the root of CT [7-9]. Besides protein and fatty acid content, CT seeds also contain p-hydroxycinnamic acid, β-sitosterol, γ-sitosterol adenosine, flavonol-3-glycoside, ethyl-α-d-galactopyranoside,

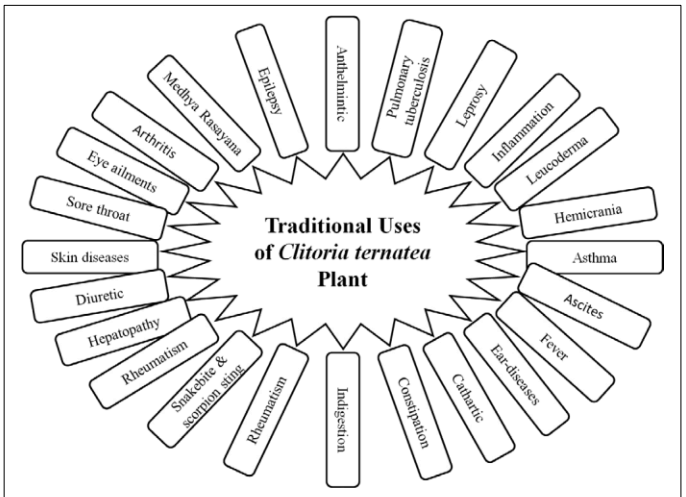


Figure 1: Traditional uses of *Clitoria ternatea* plant.

3,5,7,4′-tetrahydroxyflavone, 3-rhamnoglucoside, hexacosanol, and an anthoxanthin glucoside [10-14]. Kelemu et al. [15] reported the presence of antimicrobial and insecticidal protein finotin in the seeds of CT. The flowers of CT contain ternatins A1-3, B1-4, C1-5, D1-3 [16-24]. The flowers of CT also contain kaempferol, kaempferol 3-neohesperidoside, kaempferol 3-2G-rhamnosylrutinoside, kaempferol 3-rutinoside,

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Received: May 10 2025**, Accepted:** Jun 23 2025; **Published:** Jun 29, 2025

Citation: Gollen B, Mehla J, Gupta P (2025) Pharmacological Potential of Clitoria ternatea Linn: Perspectives on Its Future as a Therapeutic Herbal Medicine. Journal of Pharmacology and Drug Delivery, 1(1):105.

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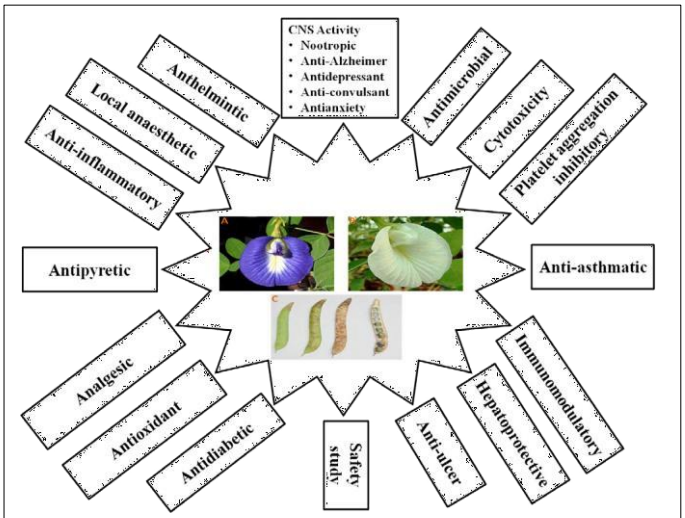


Figure 2: Various pharmacological activities of *Clitoria ternatea* plant. A and B) Blue and white flowers of *Clitoria ternatea* C) Fruit and seed of *Clitoria ternatea*.

kaempferol 3-glucoside, quercetin, quercetin 3-2G-rhamnosylrutinoside, quercetin 3-neohesperidoside, quercetin 3-rutinoside, quercetin 3-glucoside, myricetin 3-neohesperidoside, myricetin 3-rutinoside and myricetin 3-glucoside [25,26]. The leaves of CT contain β-sitosterol, flavonoids, lactones aparajitin and clitorin, essential oil, colouring-matter and mucilage [27-30].

Pharmacology of *Clitoria ternatea* (CT)

Nootropic activity: *Clitoria ternatea*, a traditional Ayurvedic medicine, has been used for centuries for neurological disorders. Taranalli and Cheeramkuzhy evaluated the influence of CT extracts on memory and central cholinergic activity in rats [31]. The memory in rats was screened by using passive avoidance test. The results of this study indicate that the extract of aerial parts showed 66.66% memory retention in electroshocked rats at the dose of 300 mg/kg, p.o. The extract of aerial part of CT (300 mg/kg, p.o.) significantly increased the acetylcholine (ACh) content in whole rat's brain whereas acetylcholinesterase (AChE) activity was increased in cortex and midbrain but there was no significant change in medulla oblongata and cerebellum. The aerial extract of CT at the dose of 500 mg/kg showed only 50% memory retention without affecting the cholinergic markers as compared to normal rats. The extract of CT root exhibited equal memory retention in electroshocked rats at doses of 300 mg/kg and 500 mg/kg, p.o as compared to electroshocked control rats. The extract of CT root (300 mg/kg, p.o) also significantly increased ACh content. The AChE activity in midbrain and medulla oblongata was decreased but decrease in AChE activity was not significant. There was no change in the AChE activity in cerebral cortex and cerebellum. The root extract of CT at dose of 500 mg/kg, p.o. significantly increased the ACh content in whole rat's brain. It was found that root extract of CT at a dose of 500 mg/kg caused significant increase in AChE activity in cerebral cortex whereas in medulla oblongata, AChE activity was significantly decreased. Slightly decrease in AChE activity in midbrain and no change in AChE activity in cerebellum was observed at a dose of 500 mg/kg of root extract of CT. The results of this study suggest that roots of CT were found more beneficial in attenuating memory deficits as compared to aerials parts. The cathartic effect of root extract of CT was observed in mice.

In another study, Rai et al. [32] revealed the learning and memory enhancing effect of CT root extract during growth spurt period in rats. They administered 50 mg/kg and 100 mg/kg of aqueous root extract of CT to neonatal rat pups (7 day old) for 30 days. The rats were subjected to open field, two compartment passive avoidance and T-maze tests (spatial memory test). The study showed that aqueous extract of CT improved the retention in passive avoidance task and increased percentage correct response and total number of alterations and decreased percentage bias in T-maze test. They indicated permanent behavioral changes with CT. The aqueous extract of CT also enhances ACh content in rat's hippocampus when neonatal pups (7 days old) and young rat (60 days old) treated with aqueous extract of CT at dose of 100 mg/kg, p.o for 30 days. The root extract of CT increases the ACh content in rat's hippocampus [33] which may be one of the reasons for nootropic activity. The nootropic activity of methanolic extract of aerial parts of CT (100 mg/kg, p.o) was evaluated by using elevated plus maze and object recognition test in rats. Elevated plus maze test is used for long term memory and objection recognition test is recommended for short term memory. The results showed that CT significantly reduced the transfer latency and increased the inflexion ratio in elevated plus maze on ninth day of drug treatment. In object recognition test, CT significantly increased the discrimination index by reducing the time required for exploring the familiar object as compared to new object. The results in both tests show the nootropic activity of CT.

Rai et al. showed that the aqueous extract of CT root altered dendritic arborization of amygdala neurons in rats, which enhances their learning and memory [34]. The rats were treated with extract of CT at doses of 50 and 100 mg/kg, p.o for 30 days. The extract increases dentritic intersection, branching points and denritic processes arising from the soma of the amygdaloid neurons at both the doses. The aqueous extract of CT could contain substances similar to brain derived neurotrophic factor (BDNF) or nerve growth factor (NGF) which may be involved in neuronal survival and plasticity of dopaminergic, cholinergic and serotonergic neurons in the CNS. In another experimental study, the memory enhancing effect of aqueous-methanolic extract of CT was reported [35]. Jain et al. [36] also demonstrated the nootropic activity of CT using elevated plus maze and object recognition test. The results of the study revealed the memory enhancing effect of CT. Furthermore, the aqueous extract of CT root enhanced the proliferation and growth of neurospheres and increased the yield of differentiated neurons of anterior subventricular zone neural precursor cells, indicating the neurogenic effect of CT which may be responsible for learning and memory improvement [37]. The ethanolic extract of CT root (100 mg/kg, p.o) also protected the neurons of frontal cortex and dentate gyrus of young diabetic rats [38]. The aqueous and hydro-alcoholic extracts of CT showed the inhibitory effect on the enzymes involved in the pathophysiology of AD [39]. Moreover, the hydro-alcoholic extract of CT ameliorated the streptozotocin (STZ) induced Alzheimer like conditions in rats via cholinesterase inhibition, antioxidant effect and down-regulating the rho kinase expression in brain [39]. Additionally, alcoholic extracts of roots of the CT in combination with *Salacia reticulata* showed nootropic effect in rats with early-onset diabetes [40]. Furthermore, medhya rasayana prepared from CT showed neuroprotective effect and increased episodic memory in kainic acid induced brain injury in rats [41]. These results suggest that CT may be useful for the treatment of Alzheimer's disease.

Anticonvulsant activity: An imbalance between excitatory and inhibitory neurotransmitter caused seizures. The drugs which increase the GABA level in brain, may possess anticonvulsant activity in experimental model of seizures. The maximal electroshock (MES) is the validated model for screening of antiepileptic drugs in the generalized

tonic-clonic seizures [42]. The methanolic extract of aerial parts of CT has shown anticonvulsant activity at dose of 100 mg/kg, p.o in both pentylenetetrazole (PTZ) and MES induced seizures in mice [36] delaying the onset of convulsions and reducing the duration of tonic hind limb extension, respectively. These results suggest the potential of CT as an antiepileptic drug. However, in another experimental study, 230 and 460 mg/kg, p.o of ethanolic extract of aerial part of CT was not effective against PTZ and MES induced seizures in rats [43].

Antidepressant activity: The methanolic extract of CT at the doses of 100 and 400 mg/kg, p.o has shown antidepressant effect in tail suspension test in mice [36]. The extract of CT significantly decreased the duration of immobility at the doses of 100 and 400 mg/kg. The decrease in the duration of immobility was more at dose of 400 mg/kg of CT as compared to fluoxetine, 10 mg/kg, i.p. In another study, anti-depressant effect of ethanolic extract of CT root was also reported at the dose of 150 mg/kg and 300 mg/kg [44]. The results from previous study indicated that two compounds, (Z)-9,17-octadecadienal and n-hexadecanoic acid isolated from root of CT can serve as potential lead molecules for developing novel selective MAO-A inhibitors which can give herbal remedy for the treatment of psychiatric disorders including depression and anxiety [45].

Anti-anxiety effect: CT exhibited a weak anti-anxiety in the elevated plus maze and light/dark exploration test. The methanolic extract of CT has shown the dose (100-400 mg/kg, p.o) dependant anti-anxiety effect in mice when administered 60 min before the test [36]. The oral administration of CT (100-400 mg/kg) dose dependently increased the time spent in the open arm. In light/dark exploration test, higher doses of CT (100, 200 and 400 mg/kg, p.o) increased the time spent in the lit box. The duration of time spent in dark box decreased in dose dependant manner.

Anti-ulcer activity: The anti-stress activity of CT evaluated in cold restraint stress induced ulcer by measuring the ulcer index in rat's stomach. The ulcers were induced by strapping the rats on a wooden plank and keeping them for 2 h at 4°C. It was found that the methanolic extract of CT has shown the dose (100, 200 and 400 mg/kg, p.o) dependant anti-stress effect in mice when administered 60 min before the test [36]. The ethanolic and chloroform extracts of leaves of CT, alcoholic and aqueous extract of whole plant of CT also demonstrated the anti-ulcer effect in rats, which may be due to its antioxidant and anti-secretary effects [46,47].

Effect of CT on lithium induced head twitches: Lithium induced head twitches are due to increased level of serotonin in brain [48]. The extract of CT (100 mg/kg, p.o) was administered 60 min before the injection of lithium sulphate (3 mEq/kg, i.p). CT significantly decreased the numbers of head twitches over 60 min as compared to normal control [36].

Effect of CT on clonidine induced hypothermia: Clonidine is a presynaptic α-adrenoreceptors agonist which causes hypothermia by reducing nonadrenergic release [49]. Jain et al. [36] found that CT (100 mg/kg, i.p) did not prevent the hypothermia induced by clonidine. It indicates that CT does not affect the noradrenergic system in CNS.

Effect of CT on sodium nitrite induced respiratory arrest: Jain et al. used sodium nitrite (250 mg/kg, i.p) to induce chemical hypoxia. Sodium nitrite reduces the oxygen carrying capacity of blood by converting haemoglobin to methemoglobin. Drugs increasing cholinergic transmission delay or prevent the respiratory arrest. CT (100 mg/kg, i.p) was administered 60 min before injection of sodium nitrite [36]. The time between injection of sodium nitrite and death was recorded. The authors reported that CT did not decrease the effect of sodium nitrite induced respiratory arrest.

Effect of CT on haloperidol induced catalepsy: It is well reported that anti-psychotic induced catalepsy by blocking dopamine transmission in the striatum, ventrorostral region and the nucleus accumbens septi [50]. Jain et al. have given methanolic extract of CT (100 mg/kg) 60 min before the injection of haloperidol (1 mg/kg, i.p) and catalepsy was scored using "Bar test" at 0, 5, 15, 30, 45, 60, 90, 120, and 150 min [36]. They have found that CT did not significantly increase haloperidol induced catalepsy.

Tranquilizing effect-conditioned avoidance response: Kulkarni et al. revealed that ethanolic extract of CT at dose of 230 mg/kg, p.o did not affect conditioned avoidance response (CAR) whereas 460 mg/kg, p.o dose of CT inhibited CAR in 66% rats without affecting unconditioned response [43]. Rats were conditioned to avoid foot-shock by escaping on to a vertical pole.

Effect on spatial discrimination: The authors have evaluated the effect of ethanolic extract of CT at dose of 230 mg/kg and 460 mg/kg, p.o on spatial discrimination using Hebb William's maze in rats [43]. They found that CT (460 mg/kg, p.o) significantly increased the time taken to transverse the maze. The lower dose was not found effective.

Analgesic activity: Kulkarni et al. evaluated the analgesic activity of ethanolic extract of aerial parts of CT using radiant heat, tail clip in rats and acetic acid induced writhing in mice [43]. They found that CT at the doses of 230 mg/kg and 460 mg/kg, p.o possess significant analgesic activity from 30 min to 3 hrs post drug treatment by radiant heat method. In tail clip test, CT possessed to some extent analgesic activity and no significant analgesic activity was found in acetic acid induced writhing in mice. However, methanolic extract of CT root showed significant analgesic activity in acetic induced writhing at the doses of 200 and 400 mg/kg, p.o. They found that CT reduced the number of writhing by 50.1% and 63.8% at the doses of 200 mg/kg and 400 mg/kg of CT, respectively. Moreover, the methanolic extracts of CT root and leaves also demonstrated the antinociceptive effect in various experimental models of pain [51]. The analgesic activity of methanolic extract of CT leaves (200 mg/kg and 400 mg/kg, p.o) has also been demonstrated in acetic acid induced writhing test [52].

Potentiation of barbiturate induced sleeping time: The ethanolic extract of aerial parts of CT potentiates the barbiturate induced hypnosis in mice in dose (230 mg/kg and 460 mg/kg, p.o) dependant manner [43]. The higher dose of CT produced the effects similar to chlorpromazine (10 mg/kg) in mice. Moreover, decreased locomotor activity in whole cross and open field tests was observed with methanolic extract of CT leaves at doses of 200 mg/kg and 400 mg/kg, p.o [52].

Local anaesthetic effect: The local anaesthetic effect of the ethanolic extract of aerial parts of CT was evaluated by Kulkarni et al. using corneal anesthesia in rabbits and plexus anesthesia in frogs [43]. They found that 10% solution of CT extract produced abolition of the foot withdrawal reflex in frog but did not show any surface anesthetic effect on rabbit cornea.

Antipyretic effect: The ethanolic extract of aerial parts of CT at the doses of 230 mg/kg and 460 mg/kg, p.o. caused marked reduction in normal body temperature as recorded between 30 to 120 min which was almost similar to chlorpromazine [43]. The pyrexia was induced in rats by injecting subcutaneously 20% suspension of dried Brewer's yeast in 2% gum acacia. CT was administered at the doses of 230 mg/kg and 460 mg/kg, p.o in rats. The authors have found that CT produced dose dependant antipyretic effect in rats [43]. In another study, methanolic extract of CT root showed significant antipyretic effect in yeast induced

fever [53]. The ethanolic and acetone extracts of CT leaves at the dose of 400 mg/kg also showed the antipyretic effect in rats [54].

Anti-inflammatory activity: Parimala et al. has shown that methanolic extract of the root at the doses of 200 mg/kg and 400 mg/kg, p.o inhibited rat paw oedema caused by carrageenan and vascular permeability induced by acetic acid in rats [53]. The root extract of CT has shown 21.6% and 31.8% inhibition of the oedema at a dose of 200 mg/kg and 400 mg/kg, respectively. The dose of 400 mg/kg has shown inhibition comparable to that of 20 mg/kg of diclofenac. The extract also reduced the intensity of peritoneal inflammation by 35.9% and 55.1% at a dose of 200 mg/kg and 400 mg/kg, p.o, respectively. The ethanolic extract of leaves and flower of CT also showed the *in vitro* anti-inflammatory activity [55]. Additionally, quercetin glycosides and ternatin anthocyanins from the blue flower petals of CT ameliorated the lipopolysaccharide (LPS)-induced inflammation in macrophage cells via inhibiting cyclooxygenase-2 (COX-2) activity, reducing reactive oxygen species (ROS) production, preventing nuclear NF-κB translocation, decreasing inducible nitric oxide synthase (iNOS) protein expression and nitric oxide (NO) production [56]. These results indicate that CT may be beneficial in developing drugs or nutraceuticals for protection against chronic inflammatory diseases.

Anti-asthmatic activity: Anti-asthmatic activity of ethanolic extracts of CT roots was evaluated using the milk induced leucocytosis and eosinophilia in mice, egg albumin induced mast cell degranulations in rats and passive cutaneous anaphylaxis in rats [57]. Significant decreased in milk induced leucocytosis and eosinophilia, protection against egg albumin induced degranulations of mast cells in mice and inhibition of area of blue dye leakage in passive cutaneous anaphylaxis in rats were observed with treatment of ethanolic extracts of CT roots. Moreover, ethanolic extract of CT root showed the bronchodilator effect, indicating its potential for treatment of asthma [58].

Antihyperglycemic and antihyperlipidemic effects: Daisy et al. [59] studied the anti-hyperglycemic and anti-hyperlipidemic effects of aqueous extract of CT flowers and leaves at dose of 400 mg/kg, p.o. in alloxan induced diabetes in rats. The selected doses of the plant extracts were given every day till 84 days. They found that there is significant increase in blood glucose, glycosylated hemoglobin, cholesterol, triglyceride, urea, creatinine and a decrease in serum insulin, HDL-cholesterol, liver glycogen and skeletal muscle glycogen in diabetic control rats as compared to control rats. The aqueous extract of CT leaves and flower administered for 84 days to diabetic rats significantly decreased blood glucose, glycosylated hemoglobin, cholesterol, triglyceride, urea, creatinine and increased serum insulin, HDL-cholesterol, liver glycogen and skeletal muscle glycogen near to control rats. They have also evaluated the effect of extract of CT on the activities of glucokinase and glucose -6-phosphatase in the liver of control and alloxan-induced diabetic rats. The activity of glucokinase decreased in the liver of diabetic control animals, whereas, the activity of glucose -6-phosphatase was found to be increased in the liver of diabetic animals. Oral administration of CT leaves and flowers for 84 days resulted in an increase in the activity of glucokinase and a decrease in the activity of glucose-6-phosphatase enzyme in the liver of diabetic animals. The results of this study indicates that the aqueous extract of CT of leaf and flower have hypoglycemic effect on alloxan-induced diabetic rats. The extracts were highly effective in managing the complications associated with diabetes mellitus, such as hypercholesterolemia, hypertriglyceridemia and impaired renal function. Moreover, hydroalcoholic extract of the roots and seeds of CT exhibited the anti-hyperlipidemic activity, which may be due to increased biliary excretion and decreased absorption of dietary cholesterol [60]. Furthermore, single dose and 15 days treatment with methanolic extract of CT leaves showed the promising hypoglycemic effect in STZ induced diabetes in rats [61]. Kalyan et al. also reported the anti-diabetic activity of ethanolic extract of CT seed in STZ induced diabetes like conditions in rats [62].

Sharma and Majumdar [63] have also evaluated the anti-diabetic activity of ethanolic extract of flowers of CT in alloxan induced diabetes in rats. Rats fed with extracts for 3 weeks [63]. They found that the extract significantly lowered serum sugar level by 41.48% in alloxan induced diabetes in rats by inhibiting the ß-galactosidase and α-glucosidase enzymes activities. The results of this study showed that the extract of CT inhibits the activity of ß-galactosidase and α-glucosidase enzymes by 55.26% and 24.87% respectively. Moreover, administration of defatted alcoholic extract of CT root at the daily dose of 100 mg/kg for 30 days protected the hippocampal area CA3 and pancreatic tissue in juvenile diabetic rat experimental model [64]. The aqueous extract of CT flower petal showed the inhibitory effect on fructose-induced protein glycation to albumin, indicating its therapeutic potentials for reversing the glycation associated diabetic complications [65]. Moreover, 14 days treatment with aqueous extract of CT leaves (100 mg/kg, p.o) also showed the antidiabetic effect in alloxan induced diabetic like conditions in rats as indicated by decrease blood glucose level [66]. Suganya et al. also reported the *in vitro* antidiabetic activity of ethanolic extract of leaves and flower of CT [55].

Hepatoprotective activity: The methanolic extract of CT leaf at the dose of 200 mg/kg, p.o in mice showed the protective effect against paracetamol induced liver toxicity by decreasing the levels of aspartate aminotransferase, alanine aminotransferase and billirubin along with histopathological improvement [67]. In previous study, the hepatoprotective effect of white- and blue-flowered CT leave extract was evaluated in carbon tetrachloride induced hepatotoxicity in rats. They found that white-flowered CT leaves extract showed more hepato-protective effect than blue-flowered CT leaves, which may be attributed to its potential antioxidant effect [68].

Immunomodulatory activity: The alcoholic extract of CT root and hydroalcoholic extract of CT seed showed the immunomodulatory effect, which may be due to decreased immune cell sensitization, immune cell presentation and phagocytosis [60]. Cationic cliotides from CT reduced the secretion of various cytokines and chemokines in human monocytes at both resting and lipopolysaccharide-stimulated states suggesting CT as potential candidates for novel immunomodulating therapeutics [69]. The antioxidant and anti-inflammatory properties of CT may also be responsible for this immunomodulatory effect.

Platelet aggregation inhibitory activity: Honda et al. evaluated ternatin D1 (anthocyanin) isolated from CT flowers for its *in vitro* platelet inhibitory activity in rabbits [70]. The authors have mentioned that ternatin D1 showed significant inhibition of collegen and adenine diphosphate-induced platelet aggregation.

Antioxidant activity: Kamkaen and Wilkinson evaluated the antioxidant activity of extracts of flower of CT [71]. They found that aqueous extract shown to have stronger antioxidant activity (as measured by DPPH scavenging assay) than ethanol extract. *In vitro* study, methanolic extract of CT leaf also showed the antioxidant activity [67]. In various *in vitro* assays, the acetone and methanolic extract of CT also showed the antioxidant activity [72]. The free radical scavenging activity of aqueous extract of CT flower petal has also

been reported in previous study [65]. Moreover, aqueous extract of CT flower showed the protective effect against ketoconazole induced testicular damage in rats via its antioxidant effect [73]. The aqueous extract of flower petal demonstrated *in vitro* antioxidant activity and showed the protection against free radicals induced protein oxidation and lipid peroxidation in erythrocytes [74]. Sivaprabha et al. reported the presence of nonzymatic antioxidant namely ascorbic acid, reduced glutathione and total carotenoids in the leaves and flower of CT, which may be responsible for potential antioxidant effect of CT [75]. Furthermore, free radical scavenging activity of methanolic and aqueous extract of flowers and leaves of CT has also been reported in previous study, indicating the potential antioxidant effect of CT [76]. The ethanolic extract of leaves and flower of CT also showed the *in vitro* antioxidant activity [55]. The methanolic extract of CT leaves showed the protection against the aluminium induced oxidative stress in hippocampus of rats via restoring the activities of antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) in hippocampus [77].

Anti-cancer potential: In a previous study, it has been reported that CT possess promising cytotoxic activity. Rahman et al. [78] studied the cytotoxic activity of crude methanolic extract of leaves, seed and stem-bark of CT. They found that among the extracts of CT, only methanolic extract of leaves of CT possess significant higher cytotoxic activity as compared to seed and stem-bark of CT. The LC_{50} values of the crude methanol extract of leaves, seeds and stem-bark were found to be 25.82 µg/ml, 110.92 µg/ml, 179.89 µg/ml, respectively Then, they made sequential partition fraction of methanol crude extract of leaves by using different solvent systems (n-hexane, dichloromethane, methanol). The cytotoxic activity of all three fractions was evaluated by the researchers. Methanol fraction of leaves was found to have more potent cytotoxic activity with minimum LC_{50} (22.28 µg/ml) than the other extracts/fractions. Moreover, the cytotoxicity of methanolic of extract of leaves and flower of CT [79], and aqueous extract of CT flower [80] has also been demonstrated in various cancer cell lines. Sen et al. demonstrated the anticancer and chemosensitizing activities of cyclotides from CT in paclitaxel-resistant lung cancer cells [81]. Petroleum ether and ethanolic extracts of CT flower also showed the cytotoxic effect in trypan blue dye exclusion method [82]. The anticancer activity of methanolic extract of CT seed has been reported in previous study [83]. The anticancer activity of CT seed was also evidenced by decreased in tumour volume, packed cell volume, viable count and increased the life span of tumor bearing mice [83]. Therefore, the finding of this study indicates that CT plant can become a good option as an anticancer drug.

Toxicity

CT (ethanolic extract of aerial parts and root and methanolic extract of root) is reported to be non-lethal up to 3 g/kg, p.o in mice and 1 g/kg (hydroalcoholic extract of CT seed and alcoholic extract of CT root) in rats [31,60,84]. Ethanolic extract of aerials parts and root of CT led to lethargy in mice at the doses of 1500 mg/kg and above, orally [31]. Ptosis was seen above 2000 mg/kg dose in mice. Through intraperitoneal route, 2900 mg/kg dose was lethal within 6 hr due to severe CNS depression.

Anti-microbial activity

In previous studies, it is well documented that **e**fficiency of antibacterial chemotherapy is gradually more challenged by the emergence of pathogenic strains exhibiting high levels of antibiotic resistance and several mechanisms are involved in antibiotic resistance [85-95]. Therefore, there is urgent need of compounds/drugs which possess both antimicrobial activity and prevent emergence of antibiotic resistance. The anti-microbial activity of aqueous extract of flower of CT has been evaluated in agar well diffusion method and found effective against bacteria causing dental caries [96]. The anti-bacterial activity of petroleum ether, ethyl acetate and methanol extracts of the leaves of CT were measured against *Bacillus cereus, Staphylococcus aureus, Klebsiella pneumonia, Proteus vulgaris* and *Salmonella typhi* using agar disc and well diffusion methods. Among the extracts, methanolic extracts showed the promising antibacterial effect [97]. Finotin, a protein isolated from seeds of CT demonstrated the anti-microbial and insecticidal properties [15]. Uma et al. also reported the anti-microbial activity of aqueous, methanol and chloroform extracts of CT flower against uropathogenic *E. coli*, Enteropathogenic *E. coli*, Enterotoxigenic *E. coli*, *Klesiella pneumoniae* and *Pseudomonas aureginosa* in disc diffusion method [98]. *In vitro*, antibacterial activity of methanolic extract of CT has also been reported in previous study [99]. The various extract of CT leaves showed the antimicrobial activity by the agar well diffusion method against fish pathogen namely *P. aeruginosa*, *E. coli*, *K. pneumonia*, *B. subtilis*, *A. formicans*, *A. hydrophila* and *S. agalactiae* [100]. Furthermore, cyclotides derived from CT showed potential gram negative-specific antibacterial activity in previous study [69]. The hydroalcoholic extract of CT leaves showed the antifungal activity [101].

Anthelmintic activity

The ethanolic extract of CT leaves demonstrated the anthelmintic activity at 100 mg/ml [102]. In another study, anthelmintic activity was also observed with methanolic extract of CT leaves at 10 mg/ml and 25 mg/ml whereas at same concentration, no such activity was found with ethanolic extract [103].

Other Pharmacological Activities

The standardized leaf extract of CT showed the hyaluronidase and matrix-metalloproteinase-1 inhibitory activity, indicating its potential for skin wounds [104]. The larvicidal activity of methanolic extract of CT leaves, roots, flowers, and seeds has been reported against three major mosquito vectors in previous study. Among all methanolic extracts, seed extract showed the larvicidal activity against the larvae of *A. stephensi*, *A. aegypti*, and *C. quinquefasciatus* with IC_{50} 65.2, 154.5, and 54.4 ppm, respectively [105]. The ethanolic extract of aerial parts of CT showed the nephroprotective effect against the acetaminophen induced nephrotoxicity in rats [106]. This nephroprotective may be attributed to potential antioxidant activity of CT. The purgative effect of ethanolic and acetone extracts of CT leaves at the dose of 400 mg/ kg has also been reported in previous study [54]. However, methanolic extract of CT leaves showed the anti-diarrheal activity ate doses of 100 mg/kg, 200 mg/kg, 300 mg/kg, p.o in castor oil-induced diarrhea in mice [107]. The diuretic effect of CT root has been reported in dog [108].

Conclusion

Clitoria ternatea has been used since long as memory enhancing and anxiolytic agent in Ayurvedic system of medicine. Apart from this, CT has been reported to have nootropic, anti-stress, anxiolytic, antidepressant, tranqullizing, sedative, antipyretic, anti-inflammatory, analgesic, anti-diabetic ativities. However, there is need to conduct well planned studies to evaluate the true potential of CT in cognitive impairment. Therefore, it can be evaluated clinically for the efficacy and safety of CT in various types of dementia.

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