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CLITOREA TERNATEA (APARIJITA) FLOWER USE AS AN ANTIARRHYTHMIA

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Abstract : Butterfly pea or Asian Pigeon Wing which has scientific name – ***Clitoria Ternatea***. It is a Ayurvedic plant that is been used traditionally to fight many disease. It has been used to treat health issues such as Indigestion, Constipation, Arthritis, Skin disease, Liver and Intestinal problems. *Clitoria Ternatea* are used as an ornamental flowers and also commonly as food colourant.

Keywords : Tachycardia, Bradycardia, Anthocyanin, Flavonoids, Anti-Bacterial, Anti-Inflammatory.

Introduction : Traditionally aromatic and medicinal plants have been used for therapeutic, religious, cosmetic, nutritional, and beautifying purpose[1][2][3][4]. One of these is *Clitoria ternatea* commonly known as ***ButterflyPea*** belonging to the Kingdom ***Plantae***, Phylum ***Tracheophyta***, class ***Magnoliopside***, Family ***Fabaceae*** and sub-family –***Papilionaceae***[5]. It is a perennial leguminous twiner which comprises **60 species** distributed mostly in the topical belt while some them are found in temperate areas and are well adapted to various climate[6]. *Clitoria Ternatea* is widely distributed in India, Philipines, tropical Asian countries, South and Central America, the Caribbean, Madagascar and is native to the island of Ternate in the Molluca archipelago[7]. It is commonly grown as ornamental plant or fodder also been used as **food colourant**[8][9]. *C. Ternatea* is commonly also called blue-pea, kordofan pea(Sudan), cunha(Brazil), pokindong(Philippines)[10]. In Indian traditional medicines (Ayurvedic) also it has different names- Aparajit(Hindi), Aparajita(Bengali), Kokkattan (Tamil), Sanskrit names- Girikarnu, Asphota, Vishnukranta[12]. It grows well in full sunlight/ partially shaded area for which seed germination takes one to two weeks and for flowering it takes four weeks. It is present in different color such as blue, dark blue, white and mauve which are 4-5 cm long. *C. Ternatea* has a twining fine stems 0.5-3 m long. Leaves are pinnate 3-5 cm long and shortly pubescent underneath. Pods are

flat, linear, beaked, 6-12 cm long, 0.7-1.2 ml wide. The seeds are olive, brown or black in colour, oftenly mottled 4.5-7 mm long and 3-4 mm wide[11]. It is considered as **"*Medhya-Rasayana*"** and to treat **"*MasasikaRoga*"** (mental illness). It comprises of following botanicals viz[14][12].

- Convolvulus pluricaulis (Convolvulaceae)
- Evolvulus alsinoides (Convolvulaceae)
- Conscora decusata (Gentianaceae)

It also shows its action on CNS (Central Nervous System) especially for boosting memory and improving Intellect[14].

Extraction process:- Take a required amount of *C. ternatea flower*and shade dry them properly to remove the moisture from it. The maceration is the better procedure to get flavonoids and anthocyanides to give anti-arrhythmic activity. Macerate the dried flowers into 50% of ethanol (95 %) for 7 to 8 days without agitation[15]. After than filter it using funnel and filter paper then remove ethanol by giving heat with the help of **ROTA EVAPORATOR** and **SOXHLET APPRTUS**.

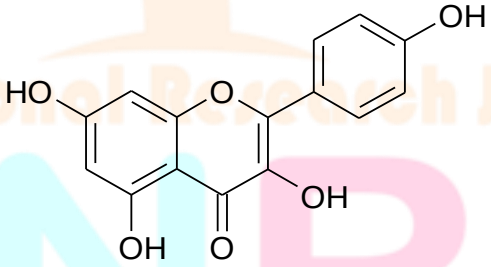
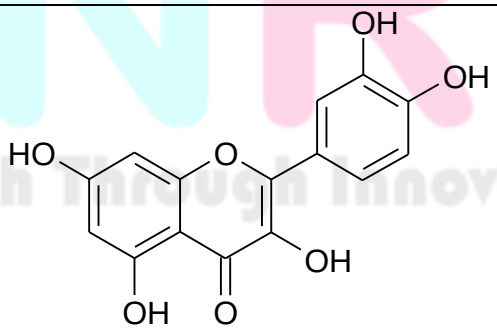
Arrhythmia

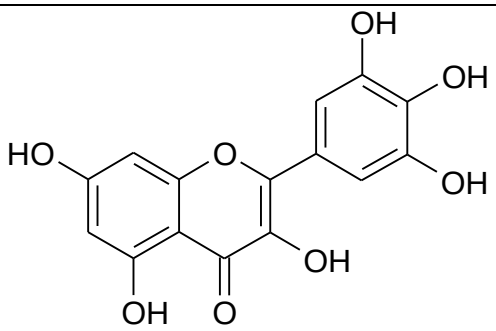
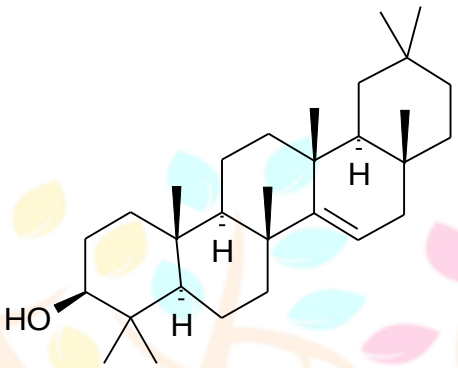
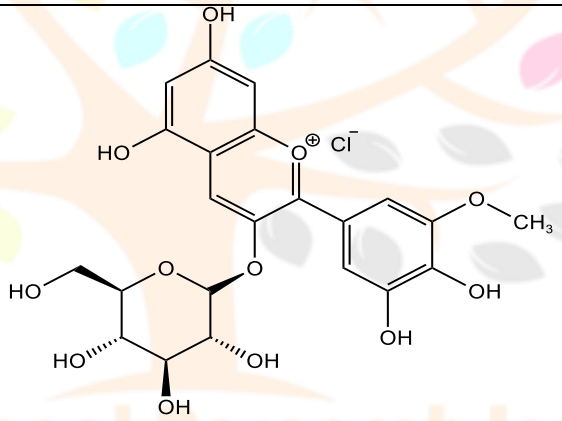
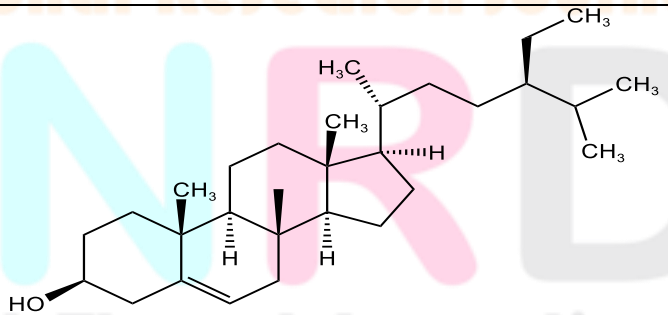
In normal heartbeat, special heart cells generate na^+ electrical signals that travels through the heart. This electricity causes the heart's muscles to contract, and this is how a heartbeat is made. An arrhythmia means irregular rhythm or heart is not beating in the proper rhythm. This can cause from minor symptoms to the major symptoms such as cardiac arrest and death.

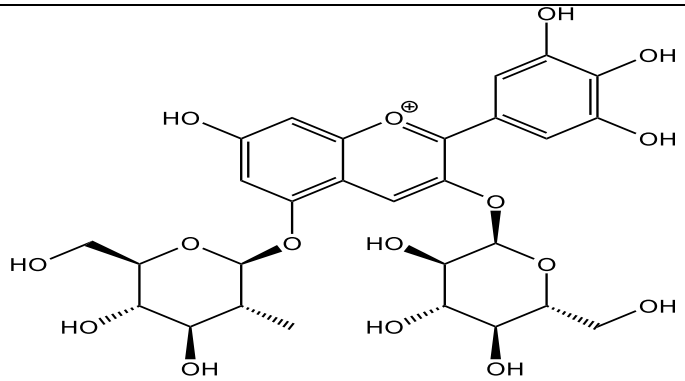
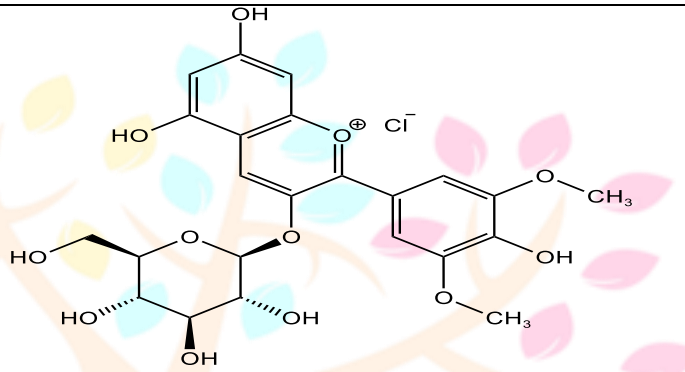
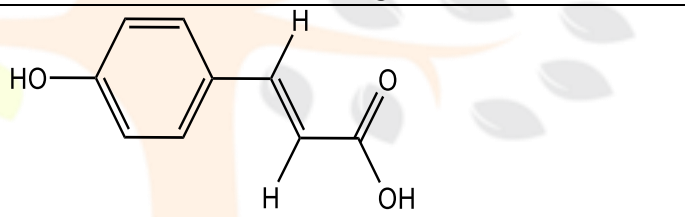
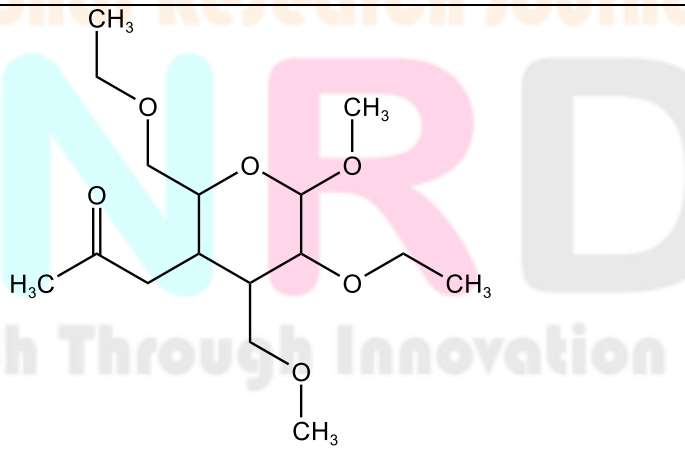
- **Types**:-

Types	Occurrence	Beats
Atrial Fibrillation	It is one of the most common type where the heart beats irregularly and faster than normal.	500
Ventricular Tachycardia	It occurs when the heart muscles damaged and scar tissue create abnormal electrical pathway in ventricles.	150-250
Atrial Flutter	It occurs when a short circuit in the heart causes the upper chambers(atria) to pump very rapidly.	350
Supraventricular Tachycardia	Also called as SVT, is usually caused by either an abnormal electrical circuits or by rapidly firing cells in the upper chambers.	140-180
Ventricular Fibrillation	It happens in patients with some sort of underlying heart conditions.	60-100
Bradycardia	Its decrease in heartrate. Which happens when the electrical impules that signals the heart to contract is not formed in SA node .	<60
Tachycardia	It occurs due to increase in heartrate.	>100
Sinus Bradycardia	It actually looks like a normal rhythm, but it is slower than normal rate for SA node.	<60
Premature Atrial contractions	It involves heartbeat that occurs alone on in series.	>100
Sinus Arrhythmia	It is name for changes in heart rate that occur during breathing.	>100
Premature Ventricular contraction	It happens when the ventricle contract too early, out of sequence with a normal heartbeat.	5
Ventricular Arrhythmia	A condition which originates in the lower chamber of the heart (ventricles) where there is three or more.	60 -100
Atrial Tachycardia	It is a type of SVT that is caused due to abnormal firing of group of cells in one of the top chamber of heart.	100 or >100
Sick sinus syndrome	It's a condition where the normal pacemaker of the heart(SA node) doesn't works properly giving irregular heartbeat	<40
Wolff-Parkinson-White syndrome	Its a syndrome where people are born with an extra electrical pathway between top and bottom chambers of heart	>100
Supraventricular Arrhythmia	It's a rapid heartbeat which develops when the normal electrical impulses of heart are disrupted.	150-220

- **Phytoconstituents:-** The different parts of *C. Ternatea* consist of different phytoconstituents. The major phytoconstituents are the pentacyclic triterpenoids, such as **taraxerol and taraxerone**[17][18]**.** The roots of this plant consist ternatins, alkaloids, flavonoids, saponins, tannins, carbohydrates, proteins, resins, starch[36]. The taraxerol in *C. Ternatea* can be determined with the method of High Performance Thin Layer Chromatography(HPTLC) which is being performed on Thin Layer Chromatography aluminium plates[13]. The leaves *C. Ternatea* includes Kaempferol-3-glucoside (1), Kaempferol-3-rutinoside (2), Kaempferol-3-neohesperidosite (3). These are identified by Ultra Violet, Protein Magnetic Resonance[20][12]. The seeds contain nucleoprotein where its amino acid sequence is similar to Insulin, Delphinidin-3,3,5-triglucoside[21]. It also contains g-sitosterol, Beta-sitosterol, Hexacosanol and Anthocynin glucoside[19].Recently it has been studied that the petals of it consist malonylated flavonol glycosides[16]. Another study determined the presence of minor delphinidin glycosides, 8 anthocynins (ternatins C1, C2, C3, C4, C5, D3 and preternatins A3 and C4) can be isolated from the young flowers of it[23]. The new anthocynins such as A3, B2, B3, B4 and D2 are also isolated from flowers[23]. A large range of secondary metabolites like triterpenoids, flavonol glycosides, anthocynins and steroids are also found in *C. Ternatea*[36]. It also includes essential amino acids, pentosan, water soluble mucilage, adenosine, anthoxanthin glucosides, greenish yellow fixed oil, a phenol glycosides, 3,5,7,4- tetrahydroxy-flavone-3-rhamoglycoside, ethyl D-galactopyranoside, p-hydroxycinnamic acid polypeptide, basic protein- finotin, beta acid resin, tannic acid, 6% ash and toxic alkaloid[20]. This flowers also found to have high content of calcium(3.09 mg / g), magnesium(2.2 3 mg/
g), potassium(1.25 mg/g), zinc(0.59 mg/g), sodium(0.14 mg/g) and iron(0.14 mg/g)[41].

Sr.no.	Name of Compound	Structures	Reference
1.	Kaempferol		Pendbhaje,2011
2.	Quercetin		

3.	Myricetin		
4.	Taxaxerol		
5.	3-monoglucoside	 3- Monoglucoside	
6.	Beta-sitosterol	 BETA- SITOSTEROL	

7.	Delphinidin-3,5-diglucoside	 Delphinidin-3,5-diglucoside
8.	Malvidin-3 beta-glucoside	 Malvidin-3-beta-glucoside
9.	p-hydroxycinnamic acid	 P-Hydroxycinnamic acid
10.	Ethyl-alpha-D-galactopyranoside	 Ethyl-alpha-D- galactopyranoside

Antiarrhythmic agents:- These are those agents which are used in the treatment of arrhythmia. There are some different types of anti - arrhythmic drugs which are as follows.

Class	Mechanism	Examples	Comments	Side Effects
Class Ia	Na+ channel block (intermediate association/ dissociation) and K+ channel blocking effect	Quinidine	Affect QRS morphology, prolongs QT interval	Colic diarrhoea, arrhythmia, stridor, ataxia, seizures
		Procainamide		Arrhythmia, vasodilation
Class Ib	Na^+ channel block (fast association/dissociation)	Lidocaine	Overdose prolongs QRS complex	Central nervous system excitement
		Phenytoin		Lethargy, colic, seizures, arrhythmia
Class Ic	Na+ channel block (slow association/dissociation)	Flecainide		Arrhythmia, depression, hypotension, agitation, sudden death
		Propafenone		Arrhythmia, bronchospasms
Class II	β – blocker	Propanolol	Non-selective(β1 and β2), also some class I action	Weakness, lethargy, may worse heart failure and bronchospasms
		Esmolol	β2-selective	
		Atenolol	β 2-selective	
Class III	K+ channel blockers	Sotalol	Also non-selective β block, prolongs QT interval	Weaknes, lethargy
		Amiodarone	Also class I, II and IV activity, prolongs QT int	Diarrhea, colic
Class IV	Ca2+ channel blocker	Diltiazem		Weakness, lethargy
Class V	Other, unknown mechanism(direct nodal inhibition ?)	Magnesium sulphate		Rare
		Digoxin		Anorexia, depression, colic, arrhythmia

- **Biological activities of C.ternatea :**

1) **Anticancer activities*:*** Since, there is no proper treatment of cancer yet has been found. The treatment usually done is chemotherapy, radiation therapy and targeted therapy for the management of cancer but, they are not able to provide permanent cure as well as associates with various side effects and toxicity[45].Thus, new agents that are safe, effective ,and less toxic are needed as early as possible. Several studies has investigated the anticancer potential of C. ternatea extracted using various solvents.It was found that 100% ethanaol extract (IC50 value of 57 µg/ml) is less potent that the 100% petroleum ether extract (IC50= 36 µg/ml) in in-vitro cytotoxic assay against Daltons lymphoma ascites (DLA) cells at 3 h which is presumed to be due to different phytochemical compositions in both extracts.The petroleum ether found to consist of saponins, tannins, steroids and triterpenoids where as the ethanol extract consist of flavonoids only. While in another studies , the water extract was found to be more potent than the methanol extract that having much lower IC50 values with activity against hormone dependent breast cancer cell line (MCF-7), non-hormone-dependent breast cancer cell line (MCF-MB-231), human ovary cancer cell line (Caov-3), and human liver cancer cell line (HepG2) at 72 h. The overall study suggested that aqueous extract have more significant anticancer activity than methanol extract as it an have more active compound present (flavonoids) present[44] .The potent active compounds found in hydrophilic extract were namely tertatins, kaempferol, quercitin that are responsible for anticancer activity as it opposed lipophiic extract which constitutes of fatty acids, phytosterols and tocopherols[4].

2) **Anti-diabetic activity*:*** Oral antidiabetic medicines such as biguanides, meglitinide, thioazolidinedione, sulfonylureas and dipeptidyl peptidase 4 are known to have various side effect[24]. Nowadays, Herabal based medications are worthy and potential in management of diabetes as they have less side-effects and toxicity[25]. After several studies the in vitro and in vivo potential lof C.ternatea flower extract for anti-diabetic activity has been found. The water extract reduce the formation of fluorescent advance glycation end products that having activity at day 28 (49.4% at 1 mg/Ml) as well as reduces **fructosamine** level (14.47-36.66%) in glycated bovine serum albumin. The had suggested that potential of the extract that prevents formation of advance glycation end products is mainly attributed by active compounds present as anthocynins, delphinidin derivatives, and kaempferol[26]. The in vivo study for antidiabetic activity in alloxan- induced diabetic rats (wister albino) by utilized 95% methanol, ethyl acetate and chloroform extract was found to have significant reduction in the serum urea, creatinine, cholesterol and triglyceride levels as compared to control untreated diabetic rats. Similar trend was also found in vivo studies by[27] using 100% methanol extract and water in the study of Daisy and. In a randomized study it was found that acute ingestion of C.ternatea flower extract/beverage suppresses postprandial plasma gluose and insulin levels on consumption with sucrose in healthy men[46]. Over learning all this studies it suggest that hypoglycemic activity maybe exerted by flavonoid principles and alkaloids present in extract which involves potentiation of insulin secretion from the β-cells of pancreas.

3) **Anti-oxidant activity:** Oxidative stress is a major part for development of chronic and degenerative illness such as cancer, autoimmune diseases, cardiovascular and neurodegenerative diseases[28][29]. The discovery of antioxidants was very beneficial for human health. Various studies investigated the antioxidant property of C.ternatea flowers utilizing antioxidant assays such as 2,2 diphenylhydrazyl radical (DPPH) radical scavenging, ferric reducing antioxidant power (FRAP) ,hydroxyl radical scavenging activity (HRSA),

hydrogen peroxide scavenging, oxygen radical absorbance capacity (ORAC), Superoxide radical scavenging activity (SRSA), ferrous ion chelating power, 2,2'- azino- bis(3-ethylbenzthiazoline-6-sulphonic acid) (ABTS) radical scavenging and cuprous reducing powers. In the DPPH assay the vitamin E was found to be less potent than 100% methanol extract of C.ternatea as well as the water extract was found to beloer than ascorbic acid (vitamin C)[43][26]. After long studies and comparing the antioxidant activity (DPPHcassay) of extract using different solvents it has been identified that water extract was found to be more potent than 100% ethanol extract at 15 min extraction time. The in vitro chemical assay that measures antioxidant activity needs to be carefully analysed as they bear no similarity to biological systems with inclusion of absorption of antioxidants by the human body[31]. Whereas in other studies it was found that the pre-treatment of human HaCaT keratinocytes with water extract cause reduction of UV- induced mitochondrial DNA damage[32]. The overall studies attributes the flavonols and anthocynins for the antioxidant activity.

4) **Anti-bacterial activity:** The several antibiotics resistance microbes brings limits to the effectiveness of current drugs that significantly causes failure of treatment of various infections[33]. With this challenge, there is need to develop an alternative option with exploring for new antibacterial compounds. The in vitro methods to identify the activity antibacterial agents can be tested using various methods such as broth or agar dilution and disc diffusion methods[34]. There has been done several studies on potency of C.ternatea flowers antibacterial activity. The methanolic extract of C.ternatea flower was tested against 12 bacterial species namely :

a) Bacillus cereus
b) Bacillus subtilis
c) Bacillus thuringiensis
d) Staphylococcus aureus
e) Streptococcus faecalis
f) Escherichi coli
g) Klebsiella pneumonia
h) Psuedomona eruginosa
i) Salmonella typhi
j) Enterobacter aerogens
k) Proteus mirabilis
l) Herbaspirillum spp

Whereas it shows more potent activity against Bacillus thuringiensis with a minimum inhibition concentration (MIC) of 12.5 mg/mL and shows minimum bactericidal concentration (MBC) of 25 mg/mL with an inhibition zone 0f 15.7 mm utilizing agar disc diffusion technique[35]. While in other studies the water, methanol, petroleum ether, hexane and chloroform extract of C.ternatea flowers (4 mg) was tested against E.coli ,K. pneumonia, S. enteritidis, S.typhimurium and P. aeruginosa to determine the antibacterial activity. On the other side methanolic extract was identified to have highest activity when tested utilizing agar disc diffusion technique with an inhibitory zone range of 16- 26 mm in E.colli, K. pneumonia and P. aeruginosa but it didn't show any activity against S.typhi and S. enteritidis. The highest zone of inhibition 26 mm was found against K.pneumonia and P.aeruginosa (Uma et al. 2009)[36]. Leong et al. 2017 explained

antibacterial activity of anthocynins of C.ternatea flower ethanolic extract paste against B.cereus, B.subtilis, S.aureus, B.subtiis subsp, spizizenii, Proteus mirabilis, K. pneumonia, Yersinia enterocolitica and E.coli. From above all the finding it concludes the potential of the anthocyanins for its antibacterial activity.

5) **Antifungal activity:** Recently it has been found that there is increase in the resistance towards antifungal agents with diverse pathogens which brings about a need to identify new therepeutic agents[37]. After experimenting the methanolic extract of C.ternatea flower (100 mg/mL) against Candida albicans, Rhizopus and Penicillium spp. It showed maximum activity against Candida albicans with an inhibitory zone of 19 mm in agar disc diffusion. Where in case of broth dilution method ,it showed its activity against only Penicillium spp and Rhizopus with same MIC value of 0.8 mg/mL and MFC value of 1.6 mg/mL[35]. The fraction of anthocynins obtained from ethanolic extract of C.ternatea flowers was tested against Fusarium sp. , Aspergillus niger and Trichoderma sp. Which resulted in showing highest activity against Fusarium sp. With an inhibitory zone of 10 mm in agar disc diffusion technique[38]. The anthocynins of C. ternatea flower ethanolic extract paste (50 mg/mL) was tested against Aspergillus niger, P. expansum that showed inhibition zone of 15.5 mm in agar disc diffusion where it had an MIC value of 12.5 mg/Ml and MLC value of 25 mg/mL. The mechanism of action for the antifungal activity showed against P.expansum was identified and it was found to be mediated due to alteration in morphology of P. expansum fungal hyphae, which contains flattened empty hyphae caused from cell wall disruption and damage of conidiophores. The C. ternatea flower has a history of use in **Ayurveda** and Indian traditional medicines, for treating the eye ailments. The study investigated the antifungal and antibiofilm effects of C. ternatea flower etracts on the Fungal keratitis (FK) which is a disease that cause severe threat to vision, leading to blindness if not addressed properly[46].

6) **Anti-convulsant activity:** From recent studies it has been scientifically found that medicinal herbs that have been used from ancient time for the treatment of epilepsy consist of promising anticonvulsant properties and now can be renowned as a newer source of anticonvulsant agents. The main objective is to evaluate the ethanolic root extract of C.ternatea for its phytocemical components, anticonvulsant, and anxiolytic effects. In this the anticonvulsant activity was evaluated against Maximum electricshock (MES) induced convulsions and pentylenetetrazole (PTZ) Iinduced convulsions model in rats . By utilizing phenytoin (25 mg/kg) as a standard drug , the efficacy of the extract of oral dose levels of 200 and 400 mg/kg was evaluated in the experimental rat model. Then the marble bury test was utilize to assess the mice for its anxiolytic activity, and the lorazepam dose of 0.005 mg/kg was taken as standard drug. After the proper screening of phytochemicals of C.ternatea etract it revealed that it contains carbhohydrates, flavonoids, alkaloids, proteins, triterpenoids, phenols, and steroids. In the MES induced model ($p<0.05$) ,the ethanolic extract significantly reduced the duration of tonic flexion and tonic extension. Whereas in case of PTZ induced model ($p<0.05$) this ethanolic extract significantly increased the latency of convulsion and decreased the duration of convulsions. The methanolic extract shows anxiolytic activity as it significantly decrease the number of marbles buried in the treated groups as compared to the control group. According to the some specific studies, terpenes and steroids exhibited anticonvulsant effects in some experimental seizures models, with incusion of MES and PTZ . It is assumed that the alkaloids and triterpenes which are the phytoconstituents of ethanolic extract of C.ternatea might be the basis of its anxiolytic actions. From overall studies it has been observed that C.ternatea ethanolic root extract has anticonvulsant and anxiolytic effects on animals, with which we can presumed it might can also be used in humans with convulsions[12].

7) ***Anti – depressant activity:*** C. ternatea is one of the oldest plant of the ayurveda with various benefits within it and has been use over centuries for various treatments. In this study we investigate the antidepressant activity of the C.ternatea by Tail suspension test and Forced swimming test , motor coordination by Rota rod method and locomotion with an actophotometer using ethanolic extrct of C.ternatea. After the study it revealed that the extracts (150 and 300 mg/kg po) was able to reduce the immobility time with dose dependant manner with subjecting to both Tail suspension and Forced swim tests and the result were found to be similar to the standard drug imipramine (15 mg/kg po)in rats. The (300 mg/kg) ethanolic root extract results in mild reduction in locomotor and motor coordination activity. The final results indicated that ethanolic extract of C.ternatea shows significant antidepressant activity with mild sedative effect which maybe be due to higher dose. Hence the study suggests that the C. ternatea can be used as a natural source of psychotherapeutic agent against depression and mood disorders.

8) **Anti –inflammatory activity*:*** The recently available Non-steroidal anti-inflammatory drugs (NSAID's) , includes parcetamol, acetaminophen and aspirin which are mainly associated with various side effects, paticurarly GIT effecta, cardiovascular effects as they knowingly effects both COX-1 and COX-2 . Hence there is rising need for new discovery or alternate strategies to reduce the risks coming with NSAID's with achieving sufficient pain relief[39]. For the evaluation of anti-inflammatory activity the petroleum ether extract of C.ternatea flower was taken using carrageenan paw edema method with healthy albino rats of both sex. In control untreated group the extract (200 and 400 mg/kg) showed significant inhibition as compared to paw edema. While in Eddy's hot plate method, as compared to control untreated group the treatment group (400 mg/kg) had shown significant increased reaction time. The study suggested that there is possibilities of the extract to have a protective effect against the release of prostaglandins, kinnins and other substances in carrageenan induced edema [40].

- **Conclusion :** ***Clitorea ternatea*** is found to be a very versatile and sophisticated plant very well knowned for its various traditional applications in ayurveda medicines, as a food colourant , and cover crop among others. Various beneficial results from studies have been done and it has been found out with many health benefits thus gives better insights on its potential uses. The extraction procedure is very important point where the different phytoconstituents have been observed which has several medical benefits. The extraction is done using ethanol as a solvent also other extraction methods includes conventional methods & non-conventional methods etc. Hence the future studies has been geared with this new extractions methods to widely investigate the constituents of the flower as well as gives wide exploration towards environment friendly methods. The study showed the availability of various phytoconstituents with its wide range of health benefits . Most of the studies have shown that the *C. ternatea* flowers phytoconstituents mainly the anthocyanins, quercetin and kaemferol glycosides are probably responsible for the beneficial effects. Numerous studies have been showed its antioxidant activity along with in vivo studies. The consumption of C.ternatea beverage/extract has been shown to have potential antidiabetic effect in human body but whch may not be generalised to overall population. It also shows its remarkable effects as anti-arrhythmic agent hence further deep study and sophisticated research can help more to find it out as a new agent to treat arrhythmia. Moreover, it has been showed its effects as a anti-depressant , anti-inflammatory for reducing edema, and also anti-bacterial and anti-fungal activity to redue the causes that have been cused by the fungus and certin microbes. From overall research it has been investigated that ***Clitorea ternatea (butterfly pea)*** is one of the most health promising plant in nature which has numerous medicinal benefits hidden within itself which can be proved to significantly promote human health and wellbeing.**s:**

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