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Review Article

The Traditional Uses, Phytochemistry, and Pharmacological Effects of *Clitoria ternatea*: A Review

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ABSTRACT

Clitoria ternatea (Family: Fabaceae) is an important medicinal plant in traditional folk medicine. This plant was found to contain various types of metabolites. Many different pharmacological effects, including antioxidant protection from illness, have been attributed to the plant's wide range of phytochemical constituents. This article provides an overview of the current phytochemical and pharmacological research as well as the traditional and medical applications of this plant. The significant and varied experimental findings have been addressed. Since *C. ternatea* has several conventional and pharmacological benefits in treating many illnesses. This makes it an appealing subject for future experimental and clinical investigations.

Keywords: *Clitoria ternatea*, Butter pea flower, Extract, Biological activity.

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INTRODUCTION

Clitoria ternatea (CT) commonly known as butterfly pea or Asian pigeon wings is a plant species that belongs to the Fabaceae family. It is an elliptic, obtuse perennial herbaceous plant that thrives in damp, neutral soil and grows as a vine or creeper.[1] *C. ternatea* is a widely cultivated plant in the Asian region, including India, Malaysia, Burma, Sri Lanka, and the Philippines.[2-4] It is a perennial twining herb with seven elliptic and obtuse leaflets, terete and pubescent stems, spectacular flowers with uneven blue or white petals, and a bearded style below the stigma. The fruit pods are compressed and linear. Each pod is 5-7 cm long, flat, and contains 6 to 10 seeds. The seeds range in size from 6 to 10 and are black in appearance. In the rainy season, the plant produces flowers, whereas it produces fruit in the winter.[5] The color of this plant's petals, which are a vibrant deep blue, is its most remarkable feature, and they are generally 4-5 cm long.[5,6]

This plant is known by different names in different regions. The other names of the plant are butterfly pea, blue pea vine, mussel-shell climber, or pigeon wings, whereas this is also known by different names in different countries, like honte (French), blaue Klitorie (German), Clitoriaazul (Portuguese), Cunha (Brazil), Pokindang (Philippines), or Kordofan pea (Sudan). In Malaysia, the flowers are commercially known as Bunga telang by the locals and are frequently used as food colors in Nasi kerabu (a traditional Kelantan meal) and kueh tekan (a Baba and Nyonya kueh).[5] Currently, *C. ternatea* has sparked a lot of attention due to its agricultural and medical uses, which vary from fodder and nitrogen fixation to culinary coloring and cosmetics, traditional medicine, and as a source of an eco-friendly insecticide.[7] *C. ternatea* has also been widely used in traditional medicine, especially Ayurvedic medicine, particularly as a supplement to improve cognitive functions and relieve the symptoms of a variety of ailments, such as fever, inflammation, pain, and diabetes.[8] To stimulate menstruation, produce uterine contractions, and heal the liver and intestinal issues, traditional Cuban culture employs a decoction of the roots alone or in combination with flowers.[6] Meanwhile, many studies showed that the flower extract of *C. ternatea* can be used as antidiabetic,[9] antioxidant, an antimicrobial, and an anti-proliferative agent.[12]

In this review, we consistently organize the data on botanical features, traditional applications, phytochemical characteristics, and pharmacological actions of this plant, which contain different types of metabolites.

PHYTOCHEMISTRY

The plant is found to possess various kinds of metabolites, including pentacyclic triterpenoids like taraxerol, taraxerone, ternatins, alkaloids, flavonoids, saponins, tannins, and anthocyanins.[13] The previous studies showed that different parts of plants contain different types of metabolites.

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Seeds

The seed of *C. ternatea* contains a variety of metabolites, such as three unidentified trypsin inhibitors, water-soluble mucilage, delphinidin 3,3,5-triglucoside, which can be used as a food dye, p-hydroxycinnamic acid, flavonol-3-glycoside, ethyl-α-D-galactopyranoside, adenosine, 3,5,7,4'-tetrahydroxyflavone, 3-rhamnoglucoside, a polypeptide, hexacosanol, β-sitosterol, γ-sitosterol, and anthoxanthin glucoside, as oligosaccharides and anthoxanthin are reported.[8,14] Another study also showed the presence of sterols, alkaloids, glycosides, saponins, tannins, carbohydrates, protein, flavonoids, and phenolic compounds in the seeds of *C. ternatea*.[15]

Root

The root contains various phytochemicals. Several researchers investigated and identified the different bioactive constituents in the roots of *C. ternatea*. The studies showed that the root contains ternatins, alkaloids, flavonoids, saponins, tannins, carbohydrates, proteins, resins, starch, taraxerol, and taraxerone.[5] A study showed the presence of resin, tannin, starch, and flavonol glycosides in the bark of roots, whereas glycine, alanine, valine, leucine, aminobutyric acid, aspartic acid, glutamic acid, arginine, ornithine, histadine, and Gama-aminobutyric acid are reported in the root nodule.[16] Kumar *et al.*[17] also determined taraxerol from the root of *C. ternatea* using a hydroalcoholic extract. Other preliminary phytochemical screening also confirmed the presence of moderate amounts of alkaloids, terpenoids, small amounts of tannins, flavonoids, reducing sugars, steroids, and phenol in the methanolic extract.[18] A study showed the presence of phenolics, flavonoids, alkaloids, glycosides, and tannins in the ethanolic root extract of *C. ternatea* obtained from the Soxhlet extraction method.[19]

Almeida and co-workers reported many phytoconstituents such as alkaloids, flavonoids, steroids, carbohydrates, coumarins, and resin in preliminary phytochemical screening tests of aqueous extracts of *C. ternatea*'s root.[20] Another preliminary phytochemical analysis shows the presence of tannins, alkaloids, saponins, steroids, carbohydrates, protein, flavonoids, and triterpenoids in the ethanolic root extract of *C. ternatea*.[21] A phytochemical study conducted by Swathi *et al.*[22] on an ethanolic extract of *C. ternatea* seeds showed the presence of several compounds, including phenolics, alkaloids, flavonoids, and terpenoids. Furthermore, Lee *et al.*[23] also carried out phytochemical profiling of the ethanolic extracts of *C. ternatea* root using GC-MS and reported several compounds, including campesterol, taraxasterol, n-hexadecanoic acid, vitamin E, and 12-oleanen-3-yl acetate.

Leaves

The leaves of *C. ternatea* also contain various secondary metabolites such as alkaloids, flavonoids, phenols, terpenoids, glycosides, coumarins, catechol, quinines, gum, mucilage, and protein.[24] Most of the constituents were discovered in aqueous extracts as compared to other solvents like acetone. In another experiment, alkaloids, flavonoids, phenols, terpenoids, glycosides, coumarins, catechol, quinines, gum, and mucilage were identified in blue-flowered leaves, while alkaloids, glycosides, catechol, quinines, gum, and mucilage were also identified in white-flowered leaves.[25] Thakur *et al.*[26] reported the presence of protein, carbohydrates, resins, tannins, saponins, flavonoids, alkaloids, steroids, phenols, and glycosides in the hydromethanolic extract of the leaf extract of *C. ternatea*. They have also reported the presence of antioxidant compounds such as β-sitosterol, kaempferol-3-monoglucoside, kaempferol-3-rutinoside, kaempferol-3 neohesperiodoside, kaempferol-3-O-rhamnosyl-(1,6)-glucoside, kaempferol-3-O-rhamnosyl-(1,6)-galactoside and kaempferol-3-O-rhamlnosyl-(1,2)-O-chalmnosyl-(1,2)-O-[rhamnosyl-(1,6)]-glucoside. Another preliminary phytochemical screening study reported the presence of tannin and glycosides, as well as small amounts of alkaloids, terpenoids, and phenols, in the methanolic extract of the leaf of *C. ternatea*.[18] Chandra *et al.*[27] also showed the presence of flavonoids, alkaloids, glycosides, terpenes, carbohydrates, saponins, and sterols in the methanolic leaves extract of *C. ternatea*. A previous study on hydroalcoholic (10:90) leaves extract by Kaur *et al.*[28] identified and reported the presence of alkaloids, flavanol glycosides, steroids, saponins, tannins, volatile oils, and carbohydrates.

Flowers

The flowers of *C. ternatea* are a very important part of the plant, which contains many valuable phytoconstituents. These phytoconstituents exhibited various biological effects such as antioxidant activity, anti-diabetic activity, antimicrobial activity, larvicidal activity, antipyretic activity, hepatoprotective activity, and anticytotoxicity activity.[16] Kazuma *et al.*[29] have identified flavonoids in the petals of *C. ternatea* with different petal colours. These are delphinidin 3-O-(2''-O-α-rhamnosyl-6' '-O-malonyl)-β-glucoside, delphinidin 3-O-(6''-O-malonyl)-α-glucoside, delphinidin 3-neohesperidoside, and delphinidin 3-O-glucoside, as well as three other anthocyanins. *C. ternatea* petals produced three flavonol glycosides, including kaempferol 3-O-(2''-O-α-rhamnosyl-6''-O-malonyl)-β-glucoside, quercetin 3-O-(2''-O-α-rhamnosyl-6''-O-malonyl)-β-glucoside, and myricetin 3-3-O-(2''-O-α-rhamnosyl-6''-O-malonyl)-β-glucoside as well as eleven additional flavonol.[30] Ternatins, the blue acylated anthocyanins found in flowers, are derivatives of delphinidin. A total of 15 (poly) acylated delphinidin glucosides, including ternatins A1, A3, B1, B2, C1, C2, and D1, D3, were found in all blue petal lines. Their structures were determined to be malonylated delphinidin 3,3′,5′-triglucosides with 3′,5′-side chains and alternate D-glucose and p-coumaric acid units.[31] Researchers found that the transition from blue to mauve flower color is due to a lack of (poly) acylated glucosyl group substitutions at both

the 3′ and 5′ positions of ternatins, rather than a change in the structure of an anthocyanidin from delphinidin. This showed that flavonoids were found in a variety of *C. ternatea* with different petal types. This is because the chemical structure of different anthocyanins present in the flower is primarily responsible for the variety of petal colours. For example, the 'double blue' line flower was found to contain numerous (poly) acylated anthocyanins and ternatins, whereas the white petal line appeared to be devoid of anthocyanins.[32] Because the anthocyanins accumulated in the petals of *C. ternatea's* flower produce a vivid blue colour, it is widely used as a food colourant.[33]

Shen *et al.*[12] identified compounds that are lipophilic such as fatty acids (palmitic acid, stearic acids, petroselinic acids, linoleic acid, arachidic acid, behenic acid, and phytanic acid), phytosterols (campesterol, stigmasterol, β-sitosterol, and sitostanol), and tocols (α-tocopherol and β-tocopherol). Meanwhile, Zakaria *et al.*[31] showed the presence of other components such as 6″-malonylastragalin, phenylalanine, coumaroyl sucrose, tryptophan, and coumaroyl glucose in addition to anthocyanins and flavonol glycosides. Escher *et al.*[34] reported the presence of phenolic acids (gallic acid, syringic acid, 2-hydroxycinnamic acid, protocatechuic acid, 2,4-Dihydrobenzoic acid, p-Coumaric acid, caffeic acid, ferulic acid, total phenolic acid), flavonoids (quercetin-3-rutinoside, procyanidin A2, (-)-Epicatechin, total flavonoids), anthocyanins (delphinidin-3-O-glucoside, total anthocyanins), and others ellagic acid in flower petals.

Previous studies by Jaafar *et al.*[35] determined the total amount of specific constituents like phenolics, flavonoids, and anthocyanins from the ethanolic flower extract. of *C. ternatea*. A study reported the highest anthocyanin yield at 46 min and at 60.6°C using ethanol as the solvent of extraction.[36] Chayaratanasin *et al.*[10] have also investigated and analyzed the flower extract by using liquid chromatography and tandem mass spectrometry (LC-MS/MS). According to the study, important compounds such as quercetin-3-rutinoside, kaempferol-3-O-(2-rhamnosyl) rutinoside, delphinidine-3-glucoside, syringentin-3-O-glucoside, and preternatin A3 were identified. As per a study, at 50°C for 150 min, water-based ultrasonication extraction produced a higher anthocyanin extraction yield.[37] The phytochemicals reported in various *C. ternatea* extracts are given in Table 1. Figure 1 shows the structures of different phytochemicals reported in *C. ternatea*. Table 2 shows different phytochemical analyses reported for *C. ternatea*.

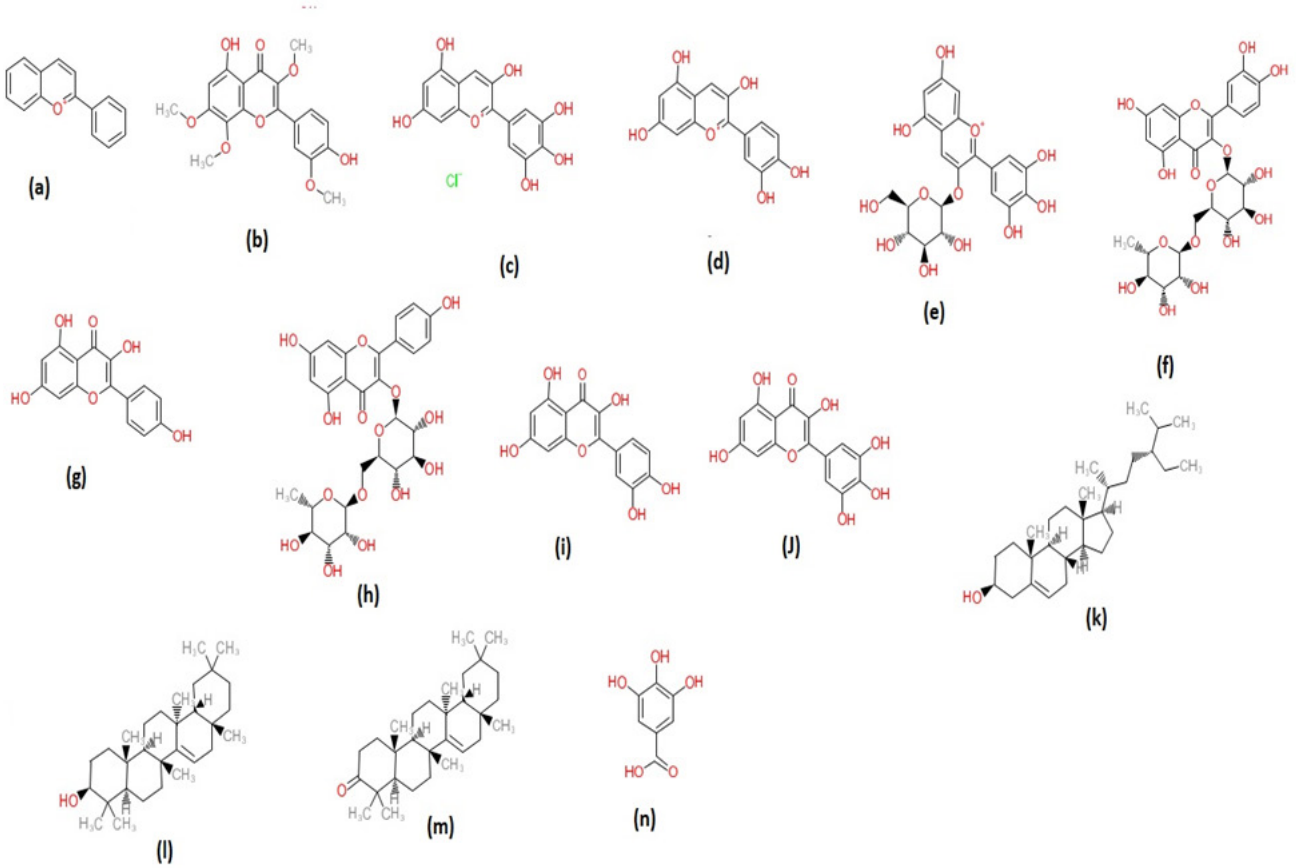

Figure 1: Some phytoconstituents reported in *C. ternatea.* (a). Anthocyanins, (b). Ternatin, (c). Delphinidin, (d). Cyanidin, (e). Delphinidin 3-O-β-glycoside, (f). Rutin, (g). Kaempferol, (h). Kaempferol-3-O-rutinoside, (i). Quercetin, (j). Myricetin, (k). β-sitosterol, (l). Taraxerol, (m). Taraxerone, (n). Gallic acid.

Table 1: Different phytochemicals reported in different extracts of *C. ternatea*.

Plant parts	Extraction method	Extraction solvent	Phytochemicals reported	References
Flowers	Maceration	Water	Phenolics, flavonoids, anthocyanins.	3
	Ultrasonic	Water	Phenolics and flavonoids.	38
	Maceration	70% ethanol:30% water	Anthocyanins.	39
	Ultrasonic	50% ethanol: 50% water	Phenolics.	40
	Maceration	40% ethanol: 60% water	Flavonoids.	40
	Maceration	Methanol	Anthocyanins (Ternatin and delphinidin derivatives), kaempferol.	12
	Maceration	Methanol: Chloroform	dl-Glyceraldehyde dimer, 1,2-Dioxolan-3-one, 5-ethyl-5-methyl-4-methylene.	41
	Maceration	Dichloromethane: cyclohexane: ethyl acetate (2:3:0.5)	Phenols, flavonoids, tannins, alkaloids, terpenoids, cardiac glycosides, and steroids.	42
Leaves	Maceration	50% methanol: 50% water	Tannins, saponins, flavonoids, alkaloids, glycosides, phenols.	26
	Maceration	Acetone	Carbohydrate, terpenoids, alkaloids, tannin, saponin, phenols.	43
	Maceration	Water	Carbohydrate, alkaloids, tannin, saponin, phenols, flavonoid.	43
	Maceration	60% methanol: 40% water	Alkaloids, flavonoid, resins, tannin, saponin, steroid, phenol, glycosides.	44
	Soxhlet	70% ethanol: 30% water	Alkaloids, flavonoids, glycosides, tannins, steroids, phenol.	45
Roots	Soxhlet	Ethanol	Phenolic, flavonoids, alkaloids, glycosides, tannins.	19
	Maceration	Water	Carbohydrate, terpenoids, alkaloids, steroids, phenol.	43
	Maceration	Acetone	Carbohydrate, terpenoids, alkaloids, saponin, flavonoid, phenol.	43
	Maceration	Chloroform: Methanol (15:1)	Alkaloids.	46
	Maceration	Hexane: ethyl acetate (80:20)	Taraxerol.	17
	Maceration	Toluene: ethyl acetate (7:1)	Alkaloids, flavonoids, steroid, carbohydrates, coumarins, and resin.	20

BIOLOGICAL ACTIVITIES

C. ternatea contains various types of phytochemicals that could exhibit different types of biological activities, including antioxidant, anti-cancer, anti-inflammatory, anti-diabetic, anti-microbial, anti-diuretic, and anthelminthic effects.[8]

Antioxidant

C. ternatea possesses a range of phytochemicals, including phenolic acids, flavonoids, anthocyanins, and polyphenols, which contribute to its natural antioxidant properties that are beneficial in the battle against reactive oxygen species. These natural antioxidants can prevent oxidative stress, which in turn protects against a number of ailments.[47] This is due to the fact that oxidative stress is a key contributor to many chronic and degenerative diseases, such as cancer, autoimmune disorders, cardiovascular disease, and neurological disorders.[6] Since it has been established that antioxidants derived from natural sources are beneficial to human health, many studies have been conducted to investigate the antioxidant activity of *C. ternatea* using various antioxidant assays, including 2,2 -diphenyl-1-picrylhydrazil radical (DPPH), ferric reducing antioxidant power (FRAP), 2,2'-azino-bis(3-e thylbenzthiazoline-6-sulfonic acid) (ABTS)[6] The IC_{50} value is a widely used parameter to determine the antioxidant activity of the plant sample, where a lower IC_{50} value indicates a higher antioxidant activity.[53] Table 3 shows the different antioxidant activities of *C. ternatea*.

Anti-cancer Activity

Chemotherapy is used for the treatment of various types of cancer. However, these treatments do not offer a permanent cure and have been associated with a number of toxicities and side effects. Therefore, new, safe, and efficacious agents are highly needed. Generally, there are four mechanisms for a component of an

Table 2: Phytochemical analysis reported for *C. ternatea*.

Sl. No.	Plant part/solvent extracts	Analytical method	Identified compounds	References
1	Leaves (80% aqueous methanol extract).	RP-HPLC	Quercetin, and kaempferol.	47
2	Leaves (80% methanol extract).	RP-HPLC	Quercetin and kaempferol.	48
3	Flower (80% aqueous extract).	RP-HPLC	Phenolic acids (Gallic acid, protocatechuic acid, chlorogenic acid), Anthocyanidin (Delphinidin), Flavonoids (kaempferol, quercetin, myricetin, rutin, epicatechin.	49
4	Flower (ethanol extract).	RP-HPLC	Phenolics, gallic acid and rutin.	40
5	Flower petals (aqueous methanol).	RP- HPLC	Anthocyanins.	50
6	Flower petals (100% methanol extract.	RP-HPLC	Phenol acids: gallic acid syringic acid, 2-Hydroxycinnamic acid protocatechuic acid 2,4-Dihydrobenzoic acid, *p*-Coumaric acid, caffeic acid, ferulic acid. Flavonoids: quercetin-3-rutinoside procyanidin A2 (-)-Epicatechin, Anthocyanins, delphinidin-3-Oglucoside others (ellagic acid).	34
7	Leaves (100% methanol extract).	RP-HPLC	Gallic acid, ferulic acid and caffeic acid.	51
8	Flower	RP-HPLC	Gallic acid, protocatechuic acid, chlorogenic acid, and delphinidin.	49
9	Flower	LCMS/MS	Flavonoids.	29
10	Flower	LC-MS/MS	Preternatin A3, ternatin B2, ternatin D2, quercetin-3-rutinoside, ternatin D1, kaemferol-3-O-(2-rhamnosyl) rutinoside, delphinidin-3-glucoside, kaemferol-3-O-rutinoside, delphinidin-3-O-(6-O-*p*-coumaryl) glucoside-pyruvic acid, (+)-catechin 7-O-β-glucoside, syringetin-3-O-glucoside, quercetin triglycoside, and delphinidin derivatives.	10
11	Root	LCMS	Tannins, alkaloids, saponins, steroids, carbohydrate, protein, flavonoids, and triterpenoids.	21
12	Root	HPTLC	β-sitosterol and taraxerol.	48
13	Leaves	GCMS	n-Hexadecanoic acid, 1-butanol, 3-methyl-acetate, propane, 1,1,3-triethoxy, Z, Z, Z-1, 4, 6, 9-nonadecatetraene, undecanoic acid, 3-trifluoroacetoxy pentadecane, and 4- ethyl - 5-octyl- 2, 2- bis(trifluoromethyl) - cis 1, 3 – dioxalone.	52

Table 3: Antioxidant activities of *C. ternatea* reported in different extracts.

Antioxidant assays	Plant parts	Extraction method	Solvent extractions	Results	References
DPPH radical scavenging	Flower	(a) Ultrasonication (b) Conventional	(a) Water extract with Ultrasound assistance (b) Water extract with heat assistance at 50°C.	(a) 931.5µg Trolox equivalent/g extract. (b) 764.3µg Trolox equivalent/g extract. (Ultrasonication showed higher scavenging activity).	38
		Maceration	Water	Flower extract: IC_{50}= 195.5 µg/mL. Trolox standard: IC_{50}= 3.32 µg/mL. (Flower extract shows less potency than Trolox standard).	31
		Maceration	100% methanol.	IC_{50}= 327 µg/mL, (Flower extract shows more potency than vitamin E).	54
	Leaves	Soxhlet	(a)100% methanol (b)100% chloroform (c) Water.	(a)100% methanol: IC_{50}= 35.5 µg/mL (b)100% chloroform: IC_{50}= 45.3 µg/mL (c) Water: IC_{50}= 41.1 µg/mL Standard (Vitamin C): IC_{50}= 21.01 µg/mL (Methanol extract shows higher antioxidant activity among all extracts).	47
		Soxhlet	(a) Ethyl acetate (b) Methanol.	(a) Ethyl acetate: IC_{50}= 8.53 µg/mL (b) Methanol: IC_{50}= 93.43 µg/mL. (Ethyl acetate extract exhibited good scavenging activity).	25
	Leaves	Maceration	(a)100% methanol (b) 80% methanol.	(a)100% methanol: IC_{50}= 89.70 µg/mL. (b) 80% methanol: IC_{50}= 103.46 µg/mL (100% methanol extract has higher scavenging ability).	55
Ferric ion Reducing Antioxidant Power (FRAP)	Flower	Ultrasonication and conventional	(a) Water extract with ultrasound assistance (b) Water extract with heat assistance at 50°C.	(a) 5834.6µg Trolox equivalent/g extract. (b) 4195.3µg Trolox equivalent/g extract. (Ultrasonication showed higher FRAP capacity).	38
		Sonication	Water	(a) *G. mangostana* peel=75.37mM Trolox equivalent/g extract. (b) *C. ternatea* flower=10.9 mM Trolox equivalent/g extract. (c) *A. colorata* fruit=16.57mM trolox equivalent/g extract. (d) *S. cumini* fruit=20.84mM trolox equivalent/g extract. (*C. ternatea* flower has lowest FRAP value).	49

Antioxidant assays	Plant parts	Extraction method	Solvent extractions	Results	References
	Leaves	Soxhlet	(a)100% methanol (b)100% chloroform (c) Water	100% methanol extract shows better reduction of ferric ion capacity.	47
ABTS radical scavenging	Flower	(a)Ultrasonication extraction (b)Conventional extraction	(a) Water extract with ultrasound assistance (b)Water extraction with heat assistance at 50°C	(a)13.488 µg Trolox equivalent/g extract. (b) 4195.3 µg Trolox equivalent/g extract. (Ultrasonication showed highest scavenging activity).	38
		Maceration	Water	IC_{50}=42.9 µg/mL. extract Trolox standard: IC_{50}= 6.51 µg/mL. (Flower extract shows less potency).	31
	Leaves	Maceration	(a)100% methanol (b) 80% methanol	(a)100% methanol: IC_{50}=1205.91 µg/mL. (b)80% methanol: IC_{50}= 1160.95 µg/mL. (80% methanol extract showed higher scavenging activity).	55
Oxygen Radical Absorbance Capacity, (ORAC)	Flower	Sonication	Water	(a) *G. mangostana* peel=20.2 µmol Trolox equivalent/g extract. (b). *C. ternatea* flower=15.8 µmol Trolox equivalent/g extract. (c) *A. colorata* fruit=11.8 µmol. Trolox equivalent/g extract. *S. cumini* fruit=14.5µ of Trolox equivalent/g extract. (*C. ternatea* flower extract showed second highest ORAC value).	49
		Decoction	Water	17.54 g Trolox equivalent/mg extract which is enough to protect erythrocytes from oxidative damage.	56
Hydrogen peroxide (H_2O_2) scavenging activity	Flower	Maceration	Methanol	Flower extract: IC_{50}= 297 µg/mL Ascorbic acid: IC_{50}= 439 µg/mL) (Flower extract shows more potency)	57
	Leaves	Soxhlet	(a) Ethyl acetate (b) Methanol	(a) Ethyl acetate: IC_{50}=14.60 µg/mL. (b)Methanol: IC_{50}=31.91 µg/mL (Ethyl acetate showed more potency than methanol extract).	25

Antioxidant assays	Plant parts	Extraction method	Solvent extractions	Results	References
Hydroxyl radical scavenging activity	Flower	Decoction	Water	Flower extract: IC_{50}= 19.2 mg/mL Trolox standard: IC_{50}= 2 mg/mL (Flower extract shows less potency than standard).	58
		Maceration	Methanol	Flower extract: IC_{50}= 285 µg/mL Ascorbic acid: IC_{50}=453 µg/mL (Flower extract showed more potency than standard Ascorbic acid).	57
	Leaves	Maceration	Methanol	Leaf extract: IC_{50}= 263 µg/mL Ascorbic acid: IC_{50}= 453 µg/mL (Leaf extract showed more potency than standard Ascorbic acid).	57

active substance to fight cancer: antiproliferative activity (prevent or slow the spread of cancer cells), inhibition of angiogenesis (formation of new blood vessels), induction of apoptosis, and prevention of metastasis.

Shen *et al.*[12] investigated the anti-proliferative activity of lipophilic and hydrophilic flower extracts of *C. ternatea* against laryngeal cancer cell lines (Hep-2: human epithelial type 2). According to the study, the hydrophilic fraction of *C. ternatea* is more effective than the lipophilic fraction. Angiogenesis is the development of new blood vessels by cancer cells to aid in the delivery of nutrients for cancer cell proliferation. Angiogenesis is also responsible for the progression of malignancies from a dormant stage to a malignant stage. VEGF (vascular endothelial growth factor) is a protein involved in angiogenesis. According to Shivaprakash *et al.*[59]*C. ternatea* flower methanol extract has been shown to inhibit angiogenesis in the EAC (Ehrlich ascites carcinoma) cell line by controlling VEGF secretion. HIF-1 (Hypoxia Inducible Factor-1) activity also appears to be suppressed by *C. ternatea* flower methanol extract. This is assumed to be a technique for suppressing cancer cell proliferation.[59] The methanolic extract showed anti-cancer activity when tested on the MCF-7 breast cancer cell line through the induction of apoptosis.[59] The apoptosis induction pathway is characterized by DNA fragmentation and the activation of the Caspase-3 enzyme. *C. ternatea* flower ethanolic extract has shown downregulation of the cell cycle at the pre-G0, G1, and S phases associated with apoptotic induction.[60] An aqueous extract of *C. ternatea* blue petals was investigated via an *in vivo* animal mouse model. The extract mainly contained flavonoids, which were identified by LCMS. Results showed that the aqueous extract ameliorated oxidative stress and inflammation mediators.[61] Jeyaraj *et al.* have carried out bioactivities of the anthocyanin-rich fraction of *C. ternatea* flower via *in vitro* cytotoxicity assay using the human embryonic kidney HEK-293 cell line. Results showed that the anthocyanin-rich fraction was more toxic than the crude extracts.[62] According to another research, luteolin and flavonoids may also stop the regulation of VEGF and HIF-1 release.[63] According to Hussain *et al.*, Nrf2 regulation prevented pro-metastatic transcription in breast cancer and lung cancer cell lines. It is also said to encourage the reprogramming of cancer cells by knocking down the Nrf2 gene.[64] Some anti-cancer activities of *C. ternatea* extracts are also given in Table 4.

Anti-inflammatory Activity

Non-steroidal anti-inflammatory drugs (NSAIDs) are now frequently used to treat inflammation, but they are associated with a number of undesirable side effects. For example, acetaminophen and aspirin, can affect both COX-1 and COX-2 and are linked to negative effects (mostly gastrointestinal and cardiovascular repercussions). Consequently, researchers are now focusing on plant-based therapy for the treatment of inflammatory diseases and also to lessen the risks associated with NSAIDs while delivering adequate pain management. In a recent study, Swathi *et al.*[22] carried out two experimental models of carrageenan-induced paw oedema and histamine-induced paw oedema to assess the anti-inflammatory effect of an ethanolic extract of *C. ternatea* roots. A study showed that a histamine-induced paw oedema model at two doses of extract (200 mg/kg and 400 mg/kg) inhibited the synthesis, release, or action of histamine by 41.66% and 54.16% at 90 min and 69.76% and 81.39% at 180 min, respectively. This could be due to the effectiveness of the ethanolic root extract of *C. ternatea* for oedema suppression. Thus, inhibit the synthesis, release, or action of histamine involved in inflammation. According to a study, Cyclooxygenase-2 (COX-2) activity, Reactive Oxygen Species (ROS), nuclear NF-kB translocation, inducible Nitric Oxide Synthase (iNOS) protein expression, and Nitric Oxide (NO) production were all reduced by a methanolic flower extract of blue *C. ternatea*.

Devi *et al.*[66] studied the root methanolic extract of *C. ternatea* on rats. The extract was administered orally, and it was discovered to decrease both the vascular permeability of acetic acid and

Table 4: Some important different biological activities of *C. ternatea*.

Biological Activity	Plant Parts	Extraction Solvents	Results	References
Anti-cancer	Flowers	Petroleum ether	Flower extract at 500 µg/mL, showed cytotoxic effect by 100% reduction in cell count using trypan blue dye exclusion method.	32
	Flowers	Ethanol	Cytotoxic effect of *C. ternatea* flower extract was observed at 500 µg/mL by 80% reduction in cell count using trypan blue dye exclusion method.	32
	Flowers	-	*p*-hydroxycinnamic acid showed the best inhibitor against Cyclin Dependent Kinase-2 (CDK-2) and Cyclin Dependent Kinase-6 (CDK-6).	82
	Flowers	Aqueous	It showed cytotoxicity at dose 40 µg/mL, (50.33±1.52%) reduction against Human peripheral B-lymphoblast DAUDI cancerous cell lines using trypan blue dye exclusion method.	83
	Flower	Ethanol	Inhibition of the spread of MCF-7 HER2-positive breast cancer cells IC_{50} = 862 µg/mL (MTT assay).	84
	Leaves	Methanol	Highest cytotoxicity (79.93%) at 250 µg/mL (MTT assay) against human promyelocytic leukemia cells (HL60).	85
	Stems	Methanol	Clitorternalactone was found cytotoxic to DLD-1, CCRF-CEM, and IMR-32 cell lines, with IC_{50} values of 2.54±0.23, 3.68±0.17, and 4.05±0.43 µM, respectively.	86
Anti-inflammatory	Flowers	Ethanol	It showed 84% inhibition of anti-inflammatory activity at dose of 400 mg/kg compared to diclofenac sodium (75%).	87
	Flowers	Methanol: acetone: water (5:4:1)	Blue-flower *C. ternatea* alleviated LPS-induced inflammation in machrophase cells by an inhibition of cyclooxygenase-2 (COX-2) activity, reducing reactive oxygen species (ROS), preventing nuclear NF-kB translocation, decreasing inducible Nitric Oxide Synthase (iNOS) protein expression, and decreasing Nitric Oxide (NO) production.	65
	Flowers	Ethanol	Ethanolic extract of *C. ternatea* flower showed highest percent of inhibition (80±5.60%) anti-inflammatory activity compared to aspirin (73.3±5.13%).	88
	Leaves	Ethanol	Ethanolic extract of *C. ternatea* leaves showed highest percent inhibition (89.3±6.25%) anti-inflammatory activity compared to aspirin (73.3±5.13%).	88
Anti-diabetic	Flowers	Ethanol	*Wistar* albino rats showed 103.64±3.14 mg/dL glucose level at dose of 400 mg/kg after treatment with *C. ternatea* flower extract compared to glimenclamide (102.34±8.34).	87
	Leaves	Ethanol	Reduction of blood glucose, urea, creatinine and glycosylated haemoglobin levels as well as increase in insulin levels in streptozotocin-induced diabetic rats.	89

the carrageenan-induced swelling of rat paws. It demonstrates strong analgesic, anti-pyretic, and anti-inflammatory effects. At 200 and 400 mg/kg, the extract significantly reduced the oedema caused by carrageenan by 21.6% and 31.8%, respectively. additional anti-inflammatory properties of several extracts. Other anti-inflammatory activities of different extracts of *C. ternatea* are summarized in Table 4.

In a recent experiment, researchers tested the anti-inflammatory activity of selenium nanoparticles synthesized from *C. ternatea* and reported a dose-dependent reduction in inflammation at an

Biological Activity	Plant Parts	Extraction Solvents	Results	References
Anti-microbial	Flowers	Ethanol	Anti-microbial activity against: Gram (+) bacteria: *Bacillus cereus* showed Zone of inhibition (ZOI), 14.5±2.1 mm, *Bacillus subtilis* zone of inhibition 15.8±1.7 mm, *Staphylococcus aureus* ZOI,13.4±1.4 mm. Gram (-) bacteria: *Proteus mirabilis* showed ZOI,14.0±1.1 mm, *Klebsiella pneumoniae* showed ZOI, 12.0±0.4 mm. Filamentous fungi *Penicillium expansium* showed ZOI, 15.5±1.3 mm.	11
	Leaves	Ethyl acetate	Maximum zone of inhibition against *Aeromonas formicans* (18 mm), *Aeromonas hydrophila* (19 mm), *Bacillus subtilis* (19 mm), *Pseudomonas aeruginosa* (21 mm).	90
	Leaves	Ethanol	Maximum ZOI against *A. formicans* (18 mm) *Escherichia coli* (14 mm).	
	Leaves	Acetone	Maximum ZOI against *Streptococcus agalactiae* (19 mm) and *Klebsiella pneumonia* (17 mm).	
	Leaves	Methanol	ZOI against *Streptococcus agalactiae* (7 mm), *Salmonella typhi* (9 mm), *Staphylococcus aureus* (8 mm), *Enterobacter aerogenes* (5.8), *Escherichia coli* (6.5), *Bacillus subtilis* (7.5).	85
Anthelmintic	Roots	Aqueous	Significant toxicity on larvae of *Caenorhabditis elegans*	91

inhibition percentage of 85.5%, which was found to be higher than the control.[67] A study also showed that an aqueous extract of *C. ternatea* blue petals, which mainly contained flavonoids, ameliorated oxidative stress and inflammation mediators.[61,68]

Anti-diabetic Activity

Herbal-based drugs are worth exploring for prospective usage in diabetes control because they are thought to be safer and have fewer adverse effects. Biguanides, meglitinide, thiazolidinedione, sulfonylureas, and dipeptidyl peptidase oral antidiabetic drugs have been linked to a variety of side effects. In recent days, many anti-diabetic activities have been carried out to evaluate the potency of extracts of *C. ternatea*. According to a study, a short-term intake of *C. ternatea* flower extract or beverage, when consumed with sugar, was found to lower postprandial plasma glucose and insulin levels in healthy individuals.[62,69] The model postulates that flavonoid principles (flavonol glycosides and anthocyanins) and alkaloids, which may potentiate insulin production from the beta-cell or enhance blood glucose transfer from plasma to peripheral tissues, are responsible for the extract's hypoglycemic activity. An anti-diabetic effect can also be achieved by inhibiting the production of Advanced Glycation End products (AGEs). At dosages of 0.25–1.00 mg/mL, *C. ternatea* flower extract significantly inhibited AGE formation as well as decreased fructosamine levels and protein oxidation. This was accomplished by lowering protein carbonyl content and preventing free thiol depletion.[58] According to Chu *et al.*, *C. ternatea* flower water extract can suppress the function of the alpha-amylase enzyme *in vitro*. Another study showed that *C. ternatea* flower extract, at concentrations of 1% and 2% (w/v), reduced the activity of the pancreatic amylase enzyme when starch from potato, cassava, rice, corn, wheat, and glutinous rice flour was used as a substrate. A study found that treatment with an ethanolic extract of *C. ternatea* significantly reduced the serum sugar level in experimentally induced diabetes by inhibiting the galactosidase and glucosidase activities.[71] In another investigation, the 200 mg/kg dose of methanolic leaf extract was found to be most effective at lowering blood glucose levels when compared to the 400 mg/kg dose. Studies also revealed that the 200 mg/kg dose of extract is far more effective in controlling blood glucose levels over the long term than the 400 mg/kg dose in alloxan-induced diabetic rats. It showed a significant reduction in blood glucose levels twelve hours after administration.[32,72] Serum glucose, glycosylated hemoglobin, and activities of the gluconeogenic enzyme, glucose-6-phosphatase, were significantly decreased by a 400 mg/kg body weight dose of *C. ternatea* aqueous extract of leaves and flowers, while serum insulin, liver and skeletal muscle glycogen, and activities of the glycolytic enzyme, glucokinase,

were significantly increased.[73] The effects of a *C. ternatea* aerial ethanolic extract and its fractions on streptozotocin-induced diabetic rats were investigated in a separate investigation. Doses of 100-200 mg/kg were used to test the extract and its components for acute and sub-chronic antidiabetic activities. The results demonstrated that a dose of 200 mg/kg of either the ethanol extract or the butanol-soluble fractions was efficacious.[74] Rajamanickam *et al.*[75] reported that chloroform extract of *C. ternatea* flower had more effective hypoglycemic activity than ethyl acetate and methanol extract due to non-polar bioactive components contributing to the hypoglycemic activity. This was shown by the mechanism of elevated insulin secretion. A study also revealed that methanol leaf extract of *C. ternatea* had the best diuretic activity at a maximal dose of 450 mg/kg, followed by aqueous extract and then chloroform extract in a dose-dependent manner.[47]

Anti-microbial Activity

Most of the studies showed that the best solvents for extracting bioactive components of *C. ternatea* flowers as antimicrobials are methanol and ethanol. According to Mahmad *et al.*,[76] the ethanol extract inhibited the growth of several bacteria and fungi, but the aqueous extract had no antimicrobial effect. A study showed that anthocyanin in the ethanolic extracts from the blue flowers of *C. ternatea* had the best antibacterial activity *in vivo* and *in vitro* against *Bacillus subtilis*, with inhibition zones of 11 and 10 mm, respectively. *In vitro* ethanolic callus extract showed broad antifungal activity (ZOI: 12 mm) against *Trichoderma* sp., whereas ethanolic extract showed antifungal activity (ZOI: 10 mm) against *Fusarium sp.* In 2019, Dhanasekaran *et al.*[77] investigated the antimicrobial activity of crude extracts of *C. ternatea* against the pathogen *Proteus mirabilis*, which causes urinary tract infections. According to their findings, acetone had the maximum antibacterial action against *Proteus mirabilis*, whereas isopropyl alcohol and petroleum ether extracts had the lowest antibacterial activity. A study showed that various bacteria and fungi were resistant to an antibacterial flavanol glycoside isolated from the ethyl acetate-soluble fraction of *C. ternatea* roots.[78]

Anthelminthic Activity

Anthelmintic are medications that work locally to expel worms from the gastrointestinal tract while also eradicating adult worms and diseases that can harm organs and tissues on a systemic level. *C. ternatea* was tested for its anthelmintic properties using ethanol and aqueous leaf extracts at 100 mg/mL.[79] The anthelmintic activity of the ethanolic extract of *C. ternatea* was more effective than that of the aqueous extract, which was comparable to levamisole. In the case of the aqueous extract, the time of paralysis and death was 18±1.57 min and 53.33±0.33 min, respectively, and in the case of the ethanolic extract, 12.33±0.80 min and 32.33±0.71 min. According to Nirmal *et al.*[80] the roots of *C. ternatea* showed the highest anthelmintic content due to the short time it takes to kill the earthworm *Pheretima posthuma*. According to Kanthal *et al.*[81] the crude chloroform extract of *C. ternatea* showed significant anthelmintic activity against *Pheritima posthuman* at concentrations of 25, 50, and 150 mg/mL, demonstrating that the chloroform extract of *C. ternatea* had a death time of 97.02.0 min, 75.02.0 min, and 65.51.5 min (slowest), respectively. Different biological activities of *C. ternatea* are also mentioned in Table 4.

THERAPEUTIC AND TRADITIONAL USES

C. ternatea was found to be useful in the treatment of a wide range of ailments, such as infections, physical discomfort, and urogenital issues. The roots and leaves are also used in the treatment of infections and physical aches and pains. The roots of *C. ternatea* have purgative, laxative, and diuretic characteristics as well. It also helps in the treatment of different ailments, including dyspepsia, constipation, pain, fever, eye conditions, enlarged abdominal organs, and skin and throat irritation diseases.[8] It also serves as a tonic for the mind. It significantly enhances children's mental ability, physical strength, and mental wellness. The emmenagogue properties of roots and flowers have also been reported. The powder or decoction of roots is helpful for rheumatism and ear problems. Powdered seeds and ginger are used as laxatives, although the action is accompanied by lower abdominal gritting. The seeds are also utilized for swelling joints, colic, dropsy, and the expansion of the abdominal viscera.[8] It is reported that seeds have laxative, vermifugal, and mildly emetic properties. Examples include the use of seeds as an anti-helminthic,[92] a diuretic, an antidote for poisons, a refrigerant.[93] *C. ternatea* can also be utilized as green manure. It is often grown as an ornamental plant because of its lovely blossom colours.[94] In the Philippines, the young shoots, leaves, blossoms, and fragile pods are consumed as vegetables. In Malaysia, the leaves are used to give meals a green hue, and the flowers are used to give rice cakes a vivid blue hue. Throughout the year, the climber produces useful green fodder, especially during the dry season, as well as dry feed.[95,96]

CONCLUSION

The traditional plant *C. ternatea* has a long history of use as a memory booster and anxiolytic. Extracts of the *C. ternatea* flower, seeds, roots, and leaves have traditionally been used for many years. There have been reports of numerous secondary metabolites from this plant, including flavonoids, anthocyanin glycosides, pentacyclic triterpenoids, and phytosterols. This might be used as a memory booster and as a lead for the development of novel phytopharmaceuticals for the treatment of CNS illnesses. Despite having a large number of secondary metabolites, the flower part has not yet undergone a thorough clinical investigation. Hence, it is highly recommended that the flower part of *C. ternatea* be studied clinically in future research.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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