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REVIEW ARTICLE

Role of *Aparajita* (*Clitorea ternatea* Linn.) in Cancer Prevention and Therapy: Evidence from Ethnomedicine, Phytochemistry and Pharmacology

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Abstract

Clitorea ternatea Linn. (*C. ternatea*), native to tropical Asia, is commonly referred to as "*Aparajita,*" "blue pea," "darwin pea," "Asian pigeon wings," "cordofan pea," "conch flower," and "blue bellvine. "In the context of Ayurvedic practice, it is utilised to enhance intellectual capacity and memory, treat dermatological conditions, and exhibits both anti-inflammatory and detoxifying effects. *C. ternatea* is rich in various phytochemicals, such as quercetin, kaempferol, myricetin glycosides, and anthocyanins. Herbal medicines and their phytochemical constituents are increasingly recognised as complementary interventions in cancer therapy. Consequently, this study sought to examine the anticancer potential of *C. ternatea*. This detailed report investigates the ethnomedicinal applications, phytochemical composition, nutritional benefits, and pharmacotherapeutic potential of this plant by conducting an exhaustive review of databases such as Embase, PubMed, SinoMed, and the China National Knowledge Infrastructure. Encompassed within are essential nutrients, including calcium, iron, proteins, and vitamins, as well as a variety of antioxidants such as flavonoids, phenols, and carotenoids. In addition, it exhibits properties that are antibacterial, anti-inflammatory, antispasmodic, antioxidant, anticancer, and antidiabetic. In addition, studies have shown that the plant's bioactive constituents exhibit antioxidative, anti-inflammatory, and antiproliferative effects, which serve to impede the development of cancer cells. This literature review explores the mechanisms and signalling pathways linked to the diverse phytoconstituents of *C. ternatea*. It delves into safety issues, examines potential drug-drug interactions, and evaluates the influence of these phytoconstituents on the proliferation of cancer cells in various experimental settings.

Major Findings: *Clitorea ternatea* has been extensively studied for ethnomedicinal uses, pharmacological actions, phytochemistry, clinical studies, nutritional profile, toxicity and safety studies. It holds potential bioactive compounds for use as an anticancer drug by different pathways, like Phosphoinositide 3-Kinase (PI3K) Signalling Pathway, and NF-kB Signalling Pathway, *etc*.

Keywords: *Aparajita*, Anti-cancer, *Clitorea ternatea*, Ethnomedicinal, Pharmacological Action, Phytochemistry

1. Introduction

Cancer is the second major cause of death in the United States, which is considered one of the worst and most devastating diseases around the world[1,2]. In the United States, it was anticipated that there would be 1,958,310 new cases of cancer and 609,820 cancer deaths in 2023[2]. Between 2014 and 2019, a total of 99,000 new instances of prostate cancer were

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identified as a result of an increase of 3% annually[2]. Furthermore, there are projected to be roughly 55,720 new instances of ductal carcinoma in situ in women and 89,070 new cases of in situ skin melanoma[2]. Figure 1A illustrates the prevalence of cancer in different countries. Globally, rapid urbanisation, unhealthy lifestyles, population ageing, outdoor and indoor air pollution, and others are contributing factors to the growing cancer burden[3]. In humans, these elements may interact to cause cancer (Figure 1B). Cancer's impact on global health is unequally distributed with regard to Disability-Adjusted Life Years (DALYs), with high-income nations carrying a larger cost per person than low- and middle-income nations[4]. Cancer undoubtedly has a significant effect on the economy, resulting in unemployment, reduced productivity, reduced capital investments, as well as forced labour losses[5]. There are several characteristics of cancer, including ultra-fast proliferation, replicative immortality, evasion of growth suppressors, and immune evasion[6]. A major cause of cancer death is metastasis, which is the process of spreading from one cancerous site to another[7]. Besides cancer, neoplasms and malignant tumours are also common names[7]. Surgery, radiotherapy, or conventional chemotherapy were the most common treatments for cancer[8]. Several side effects may occur as a result of this systemic treatment, including nausea, vomiting, hair loss, fatigue, anaemia, bleeding, bruising and development of resistance to cancer treatment[8,9]. Currently, over half of all existing medical treatment trials are targeting cancer treatments across the world at this point, which is a major trend[10]. Although some efficient methods have been established to prevent or treat these side effects, they are not enough to accomplish the desired outcome[11]. Therefore, the development of novel therapeutic strategies is one of cancer biology's main goals[9].

Using plant products for treating disease has been a successful approach since ancient times[9]. Due to the multiple chemical compounds in herbal medicines, they are important for finding new cancer-fighting substances[12]. The use of plants with medicinal properties, such as anti-inflammatory, antioxidant compounds, and immunomodulators, can relieve and treat cancer by utilising the antioxidants and anticancer properties present in them that can prevent or eliminate cancer-causing cells. Numerous plants may have inherent qualities that reduce the chance of acquiring cancer or its spread[13]. One such plant is *Clitorea ternatea* Linn. (*C. ternatea*), also known as *Aparajita* in Sanskrit[14]. It bears white or blue flowers, and grows throughout India's tropical region, growing wild as well in gardens, as a perennial climber in the family Fabaceae[15]. In Hindi, it is called Aparajita or Koyal, and in English, Butterfly pea[16]. Every part (Figure 2A) of the plant has numerous traditional uses[15]. Various medicinal properties of *C. ternatea* have been identified, including antipyretic, antimicrobial, anti-inflammatory, anticancer, antioxidant, cardiovascular, hypolipidemic, respiratory, central nervous, analgesic, immunological, and many others[16]. Several phytoconstituents are found in *C. ternatea*, including ternatin anthocyanins, flavanol glycosides (quercetin, kaempferol, and myricetin), fatty acids (palmitic acid, linoleic acid, petroselinic acids, stearic acids, behenic acid, and arachidic acid), tocols (α-tocopherol and γ-tocopherol), and phytosterols (stigmasterol, campesterol, sitostanol, and β-sitosterol)[17].

Numerous reports confirm the diverse biological activities of its active phytoconstituents. This review aims to summarise the geographic distribution, ethnopharmacology, phytochemistry, different signalling pathways responsible for cancer mechanisms, preclinical and clinical claims relevant for cancer treatment in *C. ternatea*. As far as we are aware, no review is available on *C. ternatea* that describes the geographical presence, phytochemistry, ethnopharmacology, mechanism of action, signalling pathways and preclinical and clinical studies related to cancer management. Therefore, this study will investigate and gather information about the incidence and prevalence of cancer, epidemiology, phytochemicals, nutritional value, ethnomedicinal applications, and both *in vivo* and *in vitro* anti-inflammatory, antioxidant, and anti-cancer properties that involve implicated signalling pathways.

2. Materials and Methods

We have extended the availability of the search until 23 June 2025. The available classical literature in the field of Ayurveda, as well as online published articles from various reputable sources such as Scopus,

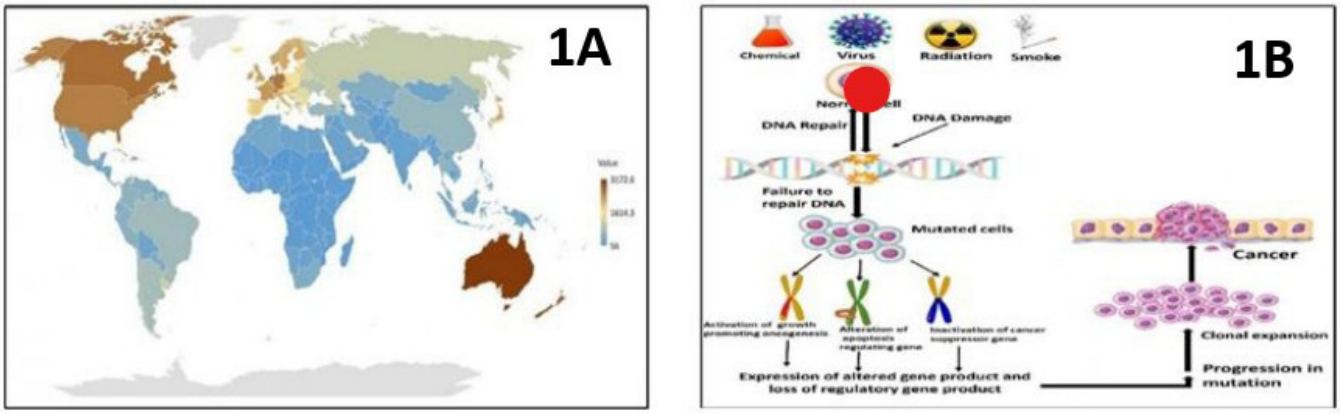


Figure 1. **(A).** The expected number of common cases (5 years). **(B).** Diagrammatic depiction of the pathophysiology of all cancers in both sexes and all age groups in 2020 cancer.

Web of Science, Google Scholar, and PubMed, were thoroughly investigated to obtain data on the epidemiology and prevalence of cancer, phytochemical properties, ethnomedicinal uses, nutritional value, industrial significance, antioxidant effects, anti-inflammatory properties, anti-cancer studies, *in vivo* research, clinical research, and *in vitro* research. This research was carried out by using specific keywords such as "*Aparajita*", "*Clitoria ternatea*", "cancer", "anti-inflammatory", "antioxidant", and "anti-proliferative". These keywords were combined with relevant Medical Subject Headings (MeSH) terms using conjunctions like "OR" and "AND". We restricted our search to English only. Review articles about cancer studies were included. Additionally, *in vivo*, *in vitro*, and clinical trials were included. Moreover, the review included studies describing extracts' anti-cancer effects, isolated compounds, and nanoparticles. Our review excluded letters to the editor, conference proceedings, newspaper articles, unpublished data, gray literature, unsupported ethnobotanical analyses, unavailable abstracts and full texts, studies irrelevant to the topic and written in another language.

3. Geographical Distribution

Globally, the *Clitoria* genus occurs in subtropical and tropical regions. In *Clitoria*, three subgenera are discussed and accepted as valid by the monograph[18,19]. Based on Linnaeus' description of specimens from the Indonesian archipelago, it is believed the species name derives from Ternate, on the island of the same name[18,19]. Rather than being located in the Indian Ocean, Ternate can be found in eastern Indonesia and the Molucca Sea, creating ambiguity regarding the species' native range[19].

The butterfly pea, botanically known as *C. ternatea*, is a perennial herbaceous plant belonging to the Fabaceae family[18,19]. Growing wild and in gardens, *C. ternatea* is a beautiful perennial climbing plant that resembles conch shells. It has twining, delicate branches that can reach a height of 2-3 m, and it bears blue and white flowers[20-22]. The root system has a large taproot, a few branches, and numerous thin lateral roots[20-22]. The thick horizontal root, which can reach a length of more than 2 m, gives rise to one or more purple, glaucous, and wiry stems[20-22]. There are pinnate leaves consisting of petioles 2-2.5 cm high; the stipules are sharp, linear, and 4 mm long[20-22]. The plant has 5(16)-7 elliptic-oblong, subcoriaceous leaflets with filiform stipules that are 2.5-5 by 2-3.2 cm in size[20-22]. Flowers have a deep blue, white or mauve core having an orange centre. It has 4-5 cm long, very short pedicellate[20-22]. A flat, linear, beaked pod with up to 10 seeds measures 6-12 cm in length, 0.7-1.2 mm broad, and has a mild pubescence[20-22]. There are yellowish brown or blackish colored seeds, shaped like sub-globoses or ovals, ranging from 4.5 mm to 7.0 mm in length, and 4.0 mm to 4.5 mm in width[20-22]. Plant flowers during rainy seasons and fruits during winter[23].

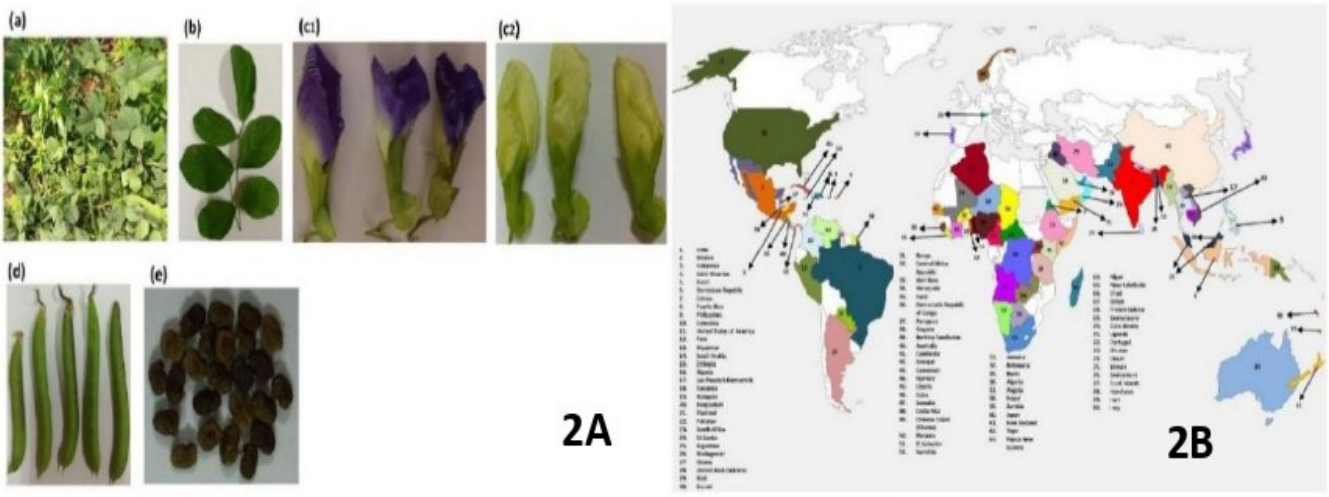


Figure 2. **(A).** Illustrating *C. ternatea*'s (a) natural habitat, (b) leaves, (c1 and c2) blue and white flowers, (d) legumes and (e) seeds of *C. ternatea*. **(B).** Geographical distribution of *C. ternatea* worldwide.

A common name for *C. ternatea* includes blue-pea, *Clitoria, cunha* (Brazil), pokindong (Philippines), or kordofan pea (Sudan)[24]. Indian traditional medicine calls this plant *Aparajit* (Hindi), *Kokkattan* (Tamil), and *Aparajita* (Bengali), *Gokarna* (Marathi), *Gorani* (Gujarathi), and *Buzrula* (Arabic)[24]. *Aparajita, Vishnukranta, Asphota*, and *Girikarnu* are some of its synonyms found in *Ayurvedic* texts[24]. Butterfly pea, Winged leaved Clitoria, and Mazerion are some common English names of the plant[24]. *C. ternatea* is originally from tropical Asia; the plant is now extensively scattered in Central and South America, Australia, China, Africa, India, and the East and West Indies[24,25]. There are two varieties of *C. ternatea* - a white variety and a blue variety (Figure 2A). It is widely distributed throughout India, and it is used as an ornamental plant[26].

Furthermore, Figure 2B shows the plant's global distribution, including India, utilising data from the Global Biodiversity Information Facility[25-27].

4. Ethnomedicinal Updates on *C. ternatea*

It is well known that *C. ternatea* could be used as an Ayurvedic medicine to cure a wide range of diseases. This herb has a long history of being used to increase memory and relieve anxiety. Table 1 lists a few of its various elements' ethnomedical applications.

5. Phytochemistry

Phytochemicals have been increasingly used for cancer therapeutics because of their wide range of pharmacological properties, promising therapeutic efficacy, minimal side effects, and low cost[34]. Bioactive substances, including alkaloids, tannins, glycosides, resins, saponins, steroids, phenols, and flavonoids, are found in the leaves, flowers, seeds, and roots of *C. ternatea*[35]. Liao *et al.*,[37] investigated the anti-proliferative activity of taraxerol (a triterpenoid anti-cancer drug) utilising clonogenic tests and the cell counting kit-8 (CCK8)[36]. Apoptosis resulted from the medication's reduction of the mitochondrial membrane potential in middle ear epithelial cholesteatoma cells. It also caused a sub-G1 cell cycle arrest[37]. Also, taraxerol inhibited Nf-kB expression[37]. Some significant phytoconstituents along with their chemical formula and structure that contribute to their anticancer activities are listed in Table 2, Figure 3.

6. Pharmacological Profile

Clitoria ternatea demonstrates a range of pharmacological characteristics, such as antioxidants, hypolipidemics, anti-inflammatory, nootropic, anticonvulsant, antistress, antianxiety, antidepressant, antiasthmatic, antidiabetic, anti-hypertensive, antimicrobial, CNS, analgesic, immunomodulatory, platelet aggregation inhibitory, cytotoxicity,

Table 1. Ethnomedicinal uses of various parts/dosage forms of *C. ternatea* worldwide

Country	Part used/dosage form	Route of administration	Uses	References
India	Root/tablet	Oral	Neurological disorders, treat headaches, eye diseases, and indigestion	28,29
	Leaves	Local application	In an earache, mixed juice with salt is applied around the ears to relieve pain, swelling of the adjacent gland, as an antidote to snake poison, dye food, and burns	20,28
	Flower	Oral	Used to give a blue tinge to boiled rice, rice cakes, eye infection, and headache	20-29
America	Root/Decoction	Oral	Use in uterine contractions, promote menstruation	20
		Local application	Vaginal douche	
	Flowers/infusion	Oral	Use in uterine contractions, promote menstruation	
		Local application	Vaginal douche	
	Flowers +roots	Oral	Address digestive issues, hepatic issues, and clorosis (a teenage disease characterised by "impoverishment of the blood," most likely anaemia).	
	Seeds	Oral	Antidiuretic, antihelminthic, refrigerant, antidote to poison, and used in reproductive problems.	
Iraq	Root	Oral	Useful in sore throat, ascetics, skin diseases, enlargement of the abdominal viscera, complexion tonics administered with honey and ghee, general tonic to children for muscular strength, improving mental faculties, insanity, epilepsy, brain tonic, promotes memory, intelligence	16
	Seed	Oral/crushed seeds with boiled or cold water	Uses to promote intelligence and memory, as a brain tonic, for swollen joints, and urinary problems	
	Flowers	Oral	Antidote for snake bite	
Sri Lanka	Whole plant	Oral	Use in liver problems, ascites, anasarca, hemicrania, enlargement of abdominal viscera, irritation of the urethra and bladder	30
Malaysia	Flower (Bunga Telang)	Oral	Use as food colouring in Nasi kerabu, a signature food called Kueh Tekan in Baba and Nyonya culture.	31
Indonesia	Flower	Oral/local	Boil's disease, eye medicine, fever, a symbol in traditional ceremonies, an ornamental plant, for cleaning baby eyes	32
	Roots	Oral	Fever, boil	
Bangladesh	Root	Oral	Use in Urinary problems- 32 ml decoction morning, evening for 7 days	33

gastroprotective, and hepatoprotective effects. and antiparasitic, and insecticidal (Figure 4)[16,69].

7. Anticancer Profile of *C. ternatea*

Anticancer drugs produced from plants are highly sought after due to their ability to efficiently suppress cancer cell lines[70]. Ethanolic extracts from *C. ternatea* leaves were tested for their ability to inhibit the growth of thyroid, breast, and colon cancer cells[71]. The ethanolic extract of *C. ternatea* inhibits the angiogenesis of fibroblasts and increases the apoptosis of cancer cells by upregulating the genes for GAX (growth arrest-specific homeobox) and Smac (Second mitochondria-derived activator of caspase)/DIABLO (direct inhibitor of apoptosis-binding protein with LOw pI)[71]. Ethanolic

Table 2. *C. ternatea* phytoconstituents with anticancer activity

Part	Constituents	Chemical formula	Medicinal profile	References
Leaves and flowers	Kaempferol	$C_{15}H_{10}O_6$	Anti-proliferative, potent colorectal cancer management, Pancreatic cancer adjuvant therapy that inhibits P-gp and CYP3A results in increased bioavailability of oral tamoxifen, anti-oxidant	38,39
	Quercetin	$C_{15}H_{10}O_7$	Anti-inflammatory, anti-oxidant, reduced p53 protein and p21-ras oncogene expression, anti-cancer, antineoplastic, and chemopreventive effects when combined with chemotherapeutic medicines, and synergistic impact in reversing the multidrug resistant phenotype *in vitro*	38,40
	Quercetin-3-Glucoside	$C_{21}H_{19}O_{12}$	Anti-inflammatory, anticancer agent	41-43
	Kaempferol	$C_{15}H_{10}O_6$	Anti-proliferative, potent colorectal cancer management, Pancreatic cancer adjuvant therapy that inhibits P-gp and CYP3A results in increased bioavailability of oral tamoxifen, anti-oxidant	38,39
	Quercetin	$C_{15}H_{10}O_7$	Anti-inflammatory, anti-oxidant, reduced p53 protein and p21-ras oncogene expression, anti-cancer, antineoplastic, and chemopreventive effects when combined with chemotherapeutic medicines, and synergistic impact in reversing the multidrug resistant phenotype *in vitro*	38,40
	Quercetin-3-Glucoside	$C_{21}H_{19}O_{12}$	Anti-inflammatory, anticancer agent	41-44
Leaves	Genistein	$C_{15}H_{10}O_5$	Antineoplastic activity, causes G2/M cell cycle arrest, antiangiogenic, antioxidant, and anti-inflammatory	45,46
	Myricetin	$C_{15}H_{10}O_8$	Antioxidant, antineoplastic agent, by preventing the activation of NF-kB, contributes to chemopreventive effects through inhibition of COX-2 expression, directly targets JAK1 to block cell transformation	47
	Genistein	$C_{15}H_{10}O_5$	Antineoplastic activity, causes G2/M cell cycle arrest, antiangiogenic, antioxidant, and anti-inflammatory	45,46
Root	Taraxerol	$C_{30}H_{50}O$	Inhibits the expression of NF-kB, which causes cell cycle arrest and apoptosis	48
Seeds	Rutin	$C_{27}H_{30}O_{16}$	Antioxidant, anti-hepatocellular carcinoma	49,50
	Apigenin	$C_{15}H_{10}O_5$	An antineoplastic agent induces autophagy in leukaemia cells	49,51
	p-Coumaric acid	$C_9H_8O_3$	Anticancer activity, suppresses the growth of HT-29 and SW480 colon cancer cells	49,52
	Cinnamic acid	$C_9H_8O_2$	Antiproliferative activity	53-55
	Rosmarinic acid	$C_{18}H_{16}O_8$	Antioxidant, anti-inflammatory	53,56,57
	Ferulic acid	$C_{10}H_{10}O_4$	Antioxidant, anti-inflammatory, apoptosis	53
Flower	Anthocyanin	-	Shows higher cytotoxic activity	58
Seeds and petals	Ellagic acid	$C_{14}H_6O_8$	Antioxidant, anti-proliferative effect, antimutagenic, anticarcinogenic	53,59
	β-Sitosterol	$C_{29}H_{50}O$	Reduces side-effects of radiation-induced toxicity, an antioxidant	60
	Quercetin-3β-D-glucoside	$C_{21}H_{20}O_{12}$	Reduce tumour necrosis factor α-receptor 1, matrix metalloproteinase-2 expression, toll-like receptor 2, inducible isoform of nitric oxide synthase, and COX-2	61,62
	Palmitic acid	$C_{16}H_{32}O_2$	Block metastasis and prostate cancer proliferation by inhibiting essential components of the Akt /PI3K pathway	63,64
	Caffeic Acid	$C_9H_8O_4$	Anti-oxidant, anti-inflammatory, and antineoplastic activities.	53,65
	Syringic acid	$C_9H_{10}O_5$	Antioxidant, inhibits cell proliferation, induces apoptosis	53,66,67
	Gallic acid	$C_7H_6O_5$	Antioxidant, apoptosis inducer, antineoplastic agent	53,68

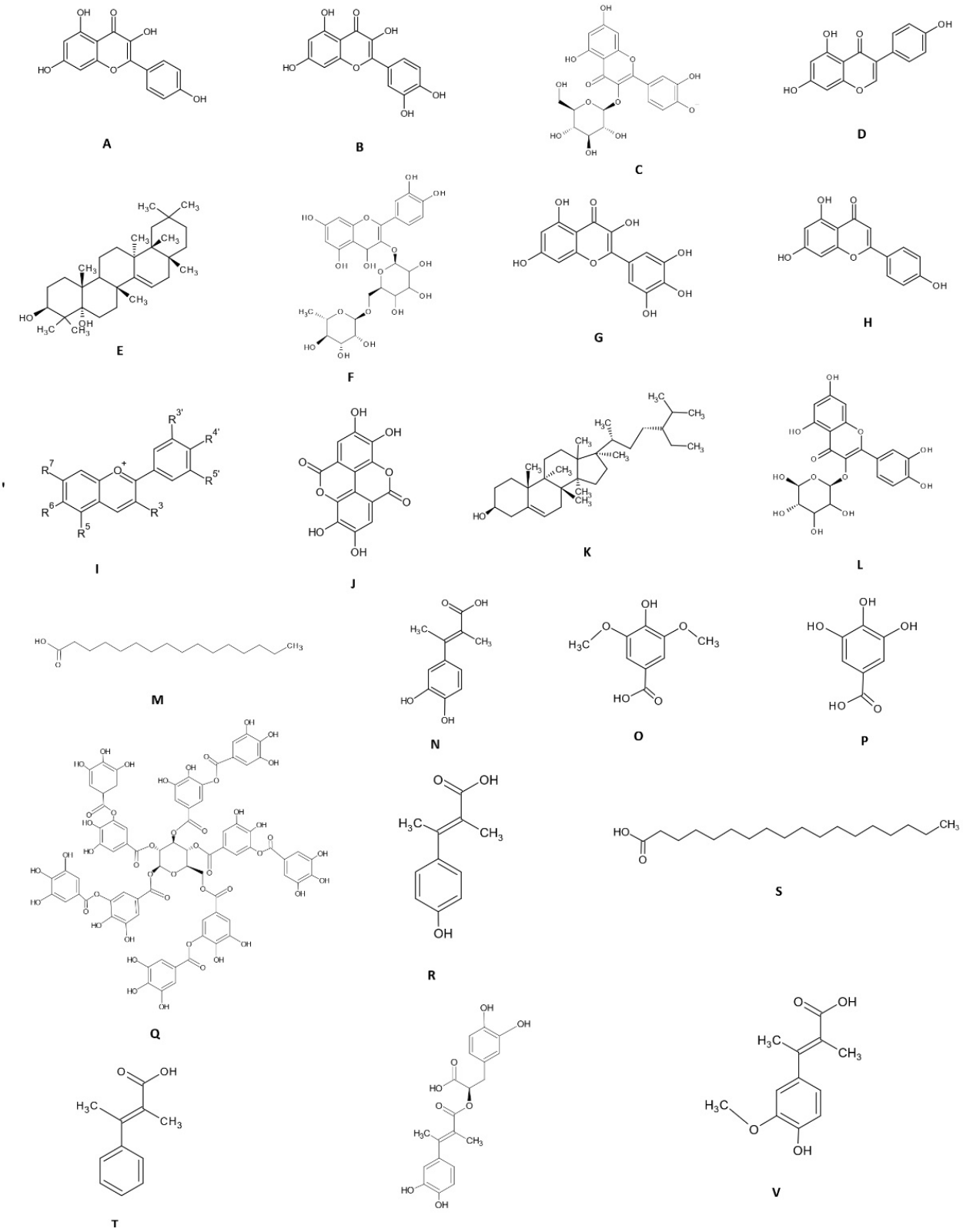


Figure 3. Chemical structure of *C. ternatea* phytoconstituents A=Kaemferol, B=Quercetin, C=Quercetin-O-glucoside, D=Genistein, E=Taraxerol, F=Rutin, G=Myricetin, H=Apigenin, I= Anthocyanin, J=Ellagic acid, K=β-Sitosterol, L=Querecetin 3-beta-D-glucoside, M=Palmitic acid, N=Caffeic acid, O=Syringic acid, P=Galic acid, Q=Tannic acid, R=P-Comaric acid, S=Stearic acid, T=Cinnamic acid, V=Ferulic acid.

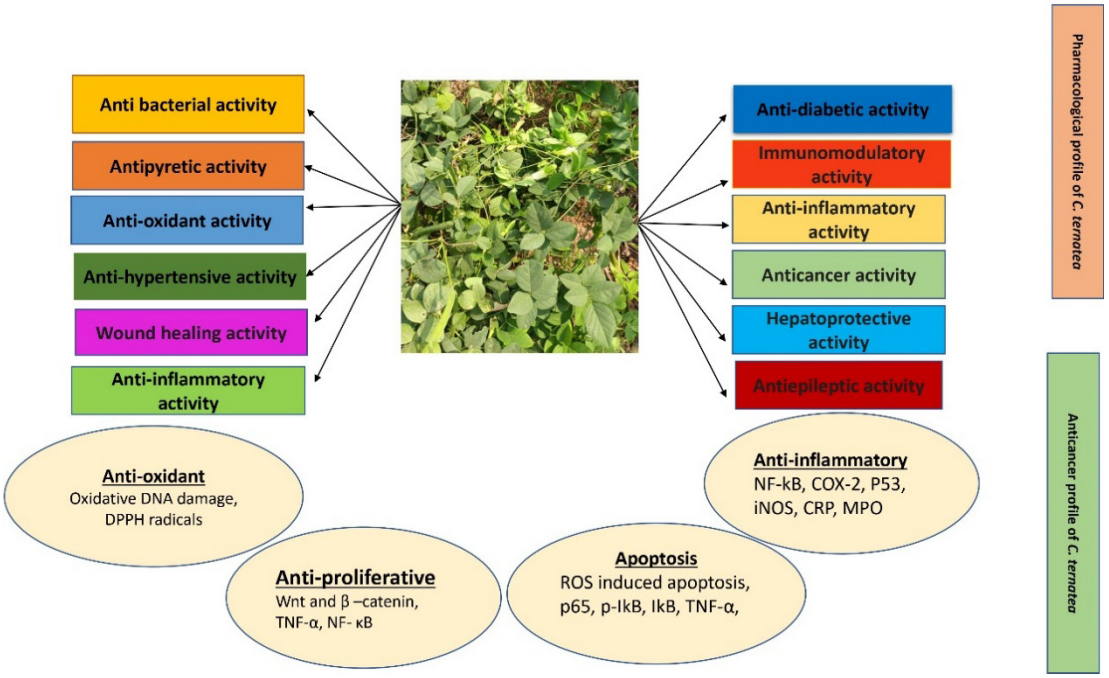


Figure 4. Pharmacological and anticancer profile of *C. ternatea*.

extract of *C. ternatea* downregulates NAIP1, triggering cancer cell apoptosis[71].

The anticancer properties of *C. ternatea*'s various parts, extracts, and isolated compounds were assessed both *in vivo* and *in vitro,* are stipulated in Tables 3 and 4.

7.1 Antioxidant Potential of *C. ternatea*

Cancer treatment still relies heavily on radiation therapy, chemotherapy, and immunotherapy despite current advances in systemic and local treatment options[94]. Chemotherapy employs chemically altered substances or naturally occurring compounds possessing cytotoxic qualities, whereas radiation therapy makes use of high-energy particles and waves, such as X-rays and Gamma Rays, to eradicate tumour cells[94]. As a result of chemotherapy and radiation therapy, ROS are generated[94]. ROS can damage tumour cells directly and indirectly, causing DNA damage or interfering with DNA replication[94]. Cell death occurs as a result of altered signalling pathways induced by chemotherapy or radiation[94]. Effectively eliminating cancer cells, minimising genotoxicity in healthy tissues, and detoxifying after therapy are the main goals of cancer treatment[95]. It is therefore recommended that antioxidant supplements be taken to minimise these effects[96]. There are several nutritional cancer chemopreventive compounds that are antioxidants that potentiate radiation therapy's cytotoxic effects and reduce cancer cell toxicity at the same time[94].

Jeyaraj *et al.*[58] assessed the anthocyanin-rich proportion of *C. ternatea* flowers using Ferric Reducing Power (FRP) and 2,2-diphenyl-1-picrylhydrazyl radical (DPPH) antioxidant tests. When comparing the anthocyanin-rich fraction to cellular antioxidants, the 1,1-diphenyl-2-picrylhydrazyl (DPPH) assay indicates increased antioxidant activity[58].

In another study, of *C. ternatea* flower 100% methanol extract was found to be more effective than vitamin E as assessed by the DPPH assay[62]. Authors found in their research that aqueous extracts were found to be more effective than ethanol extracts on DPPH scavenging activity, with IC_{50} values of approximately 1 mg/ml and 4 mg/ml, consequently[97]. 2,2-diphenyl-1-picrylhydrazyl (DPPH) and Ferric Reducing Antioxidant Power (FRAP) assays were used to assess *C. ternatea* flower extracts[98]. When measured for ferric reducing power using the FRAP assay in this work, *C. ternatea* aqueous extract was comparable to ascorbic acid[98].

According to a study by GOH Shu En *et al.*[99], *C. ternatea* showed DPPH scavenging activity with an

Table 3. Anti-cancer claims of *C. ternatea* based on *in vitro* reports

Dosage form	*In vitro* model/*in vivo* model	Dose	Standard	Activity	References
Petroleum ether and ethanolic extract of *C. ternatea* flower	Cytotoxic activity using DLA cell lines.	Petroleum ether: 10, 20, 50, 100, 200, 500 µg/ml ethanolic extract: 10, 20, 50, 100, 200, 500 µg/ml	Control (no treatment)	Both extract shows significant cell cytotoxic activity	[72]
Methanol extract of *C. ternatea* leaves	MTT Assay using HL60 cells	0.781, 1.562, 3.125, 6.25, 12.5, 25, 50, 100, 250 µg/ml	Control (no treatment)	Shows anticancer activity	[73]
Methanol extract	Cytotoxicity assay by the trypan blue method	25,50, 75, 100, 200 µg	Control (no treatment)	100% cell death at a concentration of 200 µg	[74]
Seven cliotide peptide molecules (CT2, CT4, CT7, CT10, CT12, CT19, CT20)	MTT assay (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) containing the A549 lung cancer cell line, its sub-line A549/paclitaxel	A549 cells: 7.59, 0.21, 0.73, 0.70, 0.78, 1.21 µM, A59/paclitaxel: 7.92,0.45, 1.76, 2.53, 1.6, >10 µM,	Control (no treatment)	Shows potent chemosensitisation, except CT19 and CT20; other cliotide has significant cytotoxicity.	[75]
Ethanolic extract of *C. ternatea* root	MTT assay against HCT116 (Colon), MCF-7 (breast), and TT (medullary thyroid) cell lines and staurosporine	0.4, 1.6, 6.3, 25, 100 µg/ml	Control (no treatment)	Decline in viable cell count with rising concentrations	[71]
	Apoptosis Detection			Shows a significant increase in apoptosis percentage, the highest induced apoptosis with HCT116 cells	
	Cell Cycle Analysis			In the S and pre-G1 cell cycle phases show statistically significantly higher percentage of cells with HCT116 and TT cells	
	Gene Expression Analysis			A concomitant decrease in the NAIP1 mRNA level and an apparent rise in the mRNA levels of DIABLO and GAX	
Ethanolic extract of *C. tertanea* flower	MTT assay on MCF-7	380, 500, 862 µg/ml	Control (no treatment)	Shows significant suppression in cancer cell migration	[76]

Table 3. Continued...

Dosage form	*In vitro* model/*in vivo model*	Dose	Standard	Activity	References
Water extract, ethanolic extract, anthocyanin-rich fraction of *C. ternatea* flower	Cytotoxicity assay using HEK-293 (human embryonic kidney) cell line	19.5, 39.1, 78.1, 156.3, 312.5, 625µg/ml	Control (no treatment)	In comparison to water and ethanolic extracts anthocyanin-rich fraction shows higher cytotoxic activity	[58]
C. ternatea methanolic extract	MTT colorimetric assay on HeLa (cervical cancer cell line)	75,100µg/ml	Cisplatin	Shows apoptosis	[77]
Aqueous extract of *C. ternatea* flower	MTS (3-(4, 5-dimethylthiazol-2-yl) -5-(3-carboxymethoxyphenyl) -2-(4-sulfophenyl) -2H-tetrazolium) assay on HaCaT (human keratinocytes cell line)	5, 10, 25, 50, 100, 150, 200, 250, 300 µM	Negative control (H_2O_2-hydrogen peroxide) Positive control (untreated HaCaT)	Shows significant cell viability reduction	[78]
Chloroform extract of C. ternatea whole	MTT assay using HeLa (Cervix carcinoma), HepG2 (Liver carcinoma) cell lines	62.5, 125, 250, 500, 1000 µg/ml	Control (no treatment)	Shows significant inhibition of cell growth	[79]
C. ternatea flowers: Methanol and aqueous extracts	MTT (3-(4,5-dimethylthiazol-2-yl) 2,5 diphenyltetrazolium bromide) assay against MDA-MB-231, MCF-7(breast cancer cell line), Hela, HepG2, Caov3, and Hs27	0.78, 1.56, 3.125, 6.25, 12.5, 25, 50 and 100 µg/ml	Control (no treatment)	Water extract showed stronger antiproliferation in comparison to the methanolic extract	[80]
Hydrophilic (100% methanol) and lipophilic ah (hexane: ethyl acetate, 1:1) extracts of *C. ternatea* seeds and petals ((HBP, HBS, LBP, LBS)	Hep-2 (human epithelial laryngeal carcinoma) cell line	Hydrophilic extract of seeds and petals (HBS, HB-lymphoblast. 4, 0.6, 0.8, 1.0 mg/ml Lipophilic extract of seeds and petals: 5, 10, 15mg/ml	Control (no treatment)	Hydrophilic (HBS) extract shows more potent anticancer activity	[53]
Aqueous extract of *C. ternatea* flower	Cell viability assay using Tryphan Blue Staining against DAUDI (Human peripheral B-lymphoblast) cells	5, 10, 20, 40, 50 µg/ml	Control (no treatment)	Shows apoptosis	[81]
	MTT Assay on DAUDI (Human peripheral B-lymphoblast) cells	5, 10, 20, 40 µg/ml			

Table 3. Continued...

Dosage form	*In vitro* model/*in vivo* model	Dose	Standard	Activity	References
C. *ternatea* ethanol, n-hexane, and ethyl acetate extracts	MTT Assay against T47D breast cancer cells	0,5 1 1, 5 2 2, 5 3 3.5 µg/ml	Positive control (doxorubicin)	Ethanol extract shows active cytotoxic activity	[82]
Ethanol extract of *C. ternatea*	Trypan Blue Dye Exclusion Method used to measure the cytotoxic activity of DLA cell lines	10,50, 100, 200, 500µg/ml	Control (no treatment)	Shows potent cytotoxic activity	[83]
	MTT assay using HeLa	0.0196, 0.0391, 0.078, 0.156, 0.312, 0.625, 1.25, 2.5, 5, 10 µg/ml			
Methanolic extract of *C. ternatea root*	MTT assay using N2a (Neuroblastoma) cell line	5, 10, 25, 50, 75, 100µg/ml	Positive control (Cisplatin)	Shows significant cytotoxic activity	[84]
Phenolic compounds extract of *C. ternatea* flower	MTT assay HeLa, HepG2, and NCI-H460 cells	0, 14.06, 28.12, 56.25, 112.50, 225.00, 450.00, and 900.00 µg/mL	Control (no treatment)	Reduction of proliferation is seen in a dose-dependent manner.	[85]
	Cell Morphology	0, 750, 900 µg/mL			
Methanolic extract of *C. ternatea* leaves, seed, stem-bark, Hexane, Oi-chloromethane fraction, Methanol fraction of *C. ternatea* leaves	Brine shrimp lethality bioassay	3.125, 6.25, 12.5, 25, 50, 100, 200, 400 µgm/ml	Control (no treatment)	Leaves' methanolic extract shows significantly higher cytotoxicity	[86]
Methanolic Extract of *C. ternatea* seeds	MTT assay against A549 (Lung Cancer cell line)	10,20, 40, 80, 160, 320 µg/ml	Control (no treatment)	Shows significant inhibition of the growth of A549	[87]
C. ternatea leaves chloroform and petroleum ether extracts	MTT assay against HeLa, K562 (myelogenous leukemia) MCF-7 cancer cells	12.5, 25, 50, 100, 200 µg/ml	Control (no treatment)	Both extracts show the maximum % of inhibition against MCF-7	[88]

Table 3. Continued...

Dosage form	*In vitro* model/*in vivo model*	Dose	Standard	Activity	References
Methanol extract of *C. ternatea* flowers	MTT assay against 8505C (Human anaplastic thyroid cancer), MCF-7 (Human breast adenocarcinoma), K562 (Human leukaemia cells), SK-BR-3 (Human breast carcinoma), Hep3b (Human hepatocellular carcinoma)	6.25, 12.5, 25 and 50 µg/ml	Control (no treatment)	Shows maximum anticancer effect on MCF-7	[89]
	Agarose gel electrophoresis (DNA laddering) against 8505C (Human anaplastic thyroid cancer), MCF-7 (Human breast adenocarcinoma), K562 (Human leukaemia cells), SK-BR-3 (Human breast carcinoma), Hep3b (Huthe man hepatocellular carcinoma)			Shows ladder pattern (key feature of apoptosis)	
	Caspase-3 activity against 8505C (Human anaplastic thyroid cancer), MCF-7 (Human breast adenocarcinoma), K562 (Human leukemia cells), SK-BR-3 (Human breast carcinoma), Hep3b (Human hepatocellular carcinoma)			Enhanced caspase-3 activity in MCF-7 cells	
C. ternatea flower water extract, ethanolic, and anthocyanin-rich fraction	MTT assay against the HEK-293 cell line (derived from the kidney of a human embryo)	19.5, 39.1, 78.1, 156.3, 312.5, 625 µg/mL	Control (no treatment)	Anthocyanin-rich fraction shows increased cytotoxic activity at 156.3 µg/mL	[58]
Flower and leaf methanol extract of *C. ternatea*	MTT colorimetric assay against AGS (gastric), MDA-MB-231, MCF-7 (breast), HT-29 (colon) cancer cells	-	Control (no treatment)	Demonstrated strong cytotoxic action against MDA-MB-231 (IC50 < 1.0 mg/mL).	[90]
Silver nanoparticles of *C. ternatea*	MTT assay L-132 cell lines, A549 cells	L-132 cell lines: 0, 10. 20. 30, 40, 50, 60 µg/mL A549 cells lines: 0, 5, 10, 30, 60, 100, 200	Control (no treatment)	A dose-dependent cytotoxic effect on A549 cells	[91]

Table 4. Based on *in vivo* studies, the anti-cancer claims of *C. ternatea*

Dosage form	*In vivo* model	Animal	Dose	Activity	References
Methanol extract of *C. ternatea* (MECT)	DLA (Dalton's Lymphoma ascites)	Male albino mice	Control group: Pair fed Standard group: Received 1×106 DLA cells (i.p) Test group 1: Received 1×106 DLA cells (i.p) +MECT 100mg/kg body weight Test group 2: Received 1×106 DLA cells (i.p) + MECT 200mg/kg body weight	Shows significant antitumour effects	74
Synthesized silver nanoparticles of *C. ternatea* flower aqueous extract	EAC (Ehrlich ascites carcinoma) model	Female Swiss albino Mice	Group 1: Untreated control Group 2: PBS (Phosphate buffered saline)10 mM Group 3: Synthesized silver nanoparticles (5 mg/kg b.w)	Shows potential tumor inhibition through anti-angiogenic mechanism and apoptosis	92
Methanol extract of *C. ternatea* flowers	EAC model	Swiss albino mice	Control group: untreated Test group: In 0.1% DMSO, 100 mg/kg body weight/i.p. alternate day in a week	Shows significant antiproliferative effect towards EAC cells in test group	93
Syringic acid	1,2-dimethylhydrazine (DMH)-induced colorectal cancer	Rats	Oral administration of syringic acid (50 mg/kg)	Inhibits cell proliferation, induces apoptosis	67

IC_{50} of 12.47 ± 2.96 mg/ml. The polar and non-polar *C. ternatea* seed extracts were investigated *in vitro* antioxidant activity using DPPH, FRAP assay[100]. The DPPH study revealed that methanolic extracts of *C. ternatea* had the strongest antioxidant activity, but the lowest concentration (20 g/ml) of ethyl acetate and chloroform also produced significant findings[100]. There were significant antioxidant activities observed for Crude Methanol Extract (365.16 ± 19.95), Ethyl Acetate Fraction (346.71 ± 25.18), n-Hexane Fraction (365.83 ± 9.24) and Crude Ethanol Extract (370.19 ± 20.50) by FRAP assay[100].

7.2 Anti-inflammatory Potential of *C. ternatea*

The bioactive and natural compounds included in medicinal plants and herbs have significant pharmacological effects and serve as a preventive measure against cancer[101]. Numerous pharmacological and epidemiological investigations have demonstrated that specific phytochemicals can lower the occurrence of a number of cancer forms[102,103]. It has also been demonstrated that inflammation is an important factor contributing to the development of several diseases[104]. Cancer formation and progression are strongly correlated with inflammation[105]. Inflammatory cells associated with cancer are genetically stable and do not rapidly develop drug resistance[105]. Targeting inflammation can therefore be used both as a cancer prevention strategy and a cancer treatment strategy[105]. Researchers discovered that *C. ternatea* ethanolic extract had anti-inflammatory properties *via* preventing albumin denaturation and membrane stabilisation *in vitro* activity[106]. In a different study, researchers used histamine-induced paw oedema and carrageenan models to find the anti-inflammatory efficacy of the ethanolic extract of *C. ternatea*[107]. In another research, authors found twelve phenolic metabolites from *C. ternatea* blue flowers[108]. In lipopolysaccharide (LPS)-induced inflammation in the TLR (Toll-like receptors) pathway, a polyphenol from *C. ternatea* demonstrated anti-inflammatory effects[108]. At a concentration of 50µl, the copper nanoparticles generated using *C. ternatea* extract at 660 nm demonstrated the maximum absorbance, as reported by Dhakshinya *et al*[109]. When copper nanoparticles made with *C. ternatea* extract were

compared to diclofenac sodium, the results showed potent anti-inflammatory effects[109].

7.3 Immunomodulatory Potential of *C. ternatea*

In immunotherapy, the immune system is stimulated or suppressed to treat disease without utilising cytotoxic agents[110]. In contrast to conventional cancer treatments, cancer immunotherapy aims to employ the immune system of the host to eliminate cancer cells in a manner that is non-invasive and has no negative side effects[110]. A growing number of researchers and clinicians are interested in developing novel therapies that target cancer cells with greater specificity and without causing significant side effects[111-113]. By immune modulation, it is possible to modify immune responses and the immune system[114]. Immune system adaptation may occur naturally as a component of homeostatic regulation or may be artificially stimulated for therapeutic purposes[114]. Furthermore, the immune response may be improved or diminished by this regulating mechanism depending on whether it is suppressive or helpful in nature[114]. Induced immunomodulation has become increasingly popular recently as a cancer treatment method[114]. Herbal treatments can also improve the efficacy of chemotherapy, and it has been widely utilised as an adjuvant therapy for cancer treatment[115]. Additionally, it has been proven that a range of naturally occurring bioactive substances derived from herbal medicines might alter immunological checkpoints in tumours and enhance anticancer immunity[115].

Solanki *et al.,*[116] investigated the immunomodulatory properties of the root and seed extracts of *C. ternatea*. Rats sensitised to SRBCs showed significant immunosuppressive effects, as seen by reduced DTH response paw thickness, neutrophil adherence, *in vitro* phagocytosis, and primary, along with secondary antibody titers[116]. It is possible to attribute *C. ternatea's* immunomodulatory effects on cell-mediated, humoral, and non-specific immune responses to a decrease in immune cell presentation, immune cell phagocytosis, and immune cell sensitisation[116].

Immunostimulatory properties were assessed in rats with alloxan-induced diabetes by giving them *C. ternatea* leaf and flower aqueous extract for the duration of 60 days[117]. The cholesterol levels and serum glucose of these rats significantly decreased as a result of the administration[117]. T-lymphocytes, B-lymphocytes, red blood cells, and white blood cells were all markedly increased in treated animals, whereas eosinophils and monocytes were reduced[117]. Plant extracts contain immunomodulatory qualities that boost immunity, as these findings showed[117]. In an *in vitro* study, the anthocyanin ternatin D1 isolated from the petals of *C. ternatea* inhibited rabbit platelet aggregation[117]. This is brought on by considerable platelet aggregation caused by ADP and suppression of platelet aggregation caused by collagen[117].

In vitro immunomodulatory assay authors evaluated the methanolic extract of *C. ternatea* for immunomodulatory activity[115]. Extract showed good immunomodulatory activity with QHS assay and Plaque-Forming Cell (PFC)[118]. As a test of *C. ternatea*'s immunomodulatory activity, antigen-antibody titers were assessed by measuring haemagglutination titers *in vivo*[118]. When compared to control and standard, *C. ternatea* extract produced significantly higher antibody titers[118]. The methanolic extract of *C. ternatea* exhibited noteworthy immunomodulatory action at 100, 200, and 400 mg/kg bd. Wt doses[118]. In spite of this, the most effective dose was discovered to be 100 mg/kg bd wt[118].

7.4 Regulation of Cell Proliferation

Cancer development and progression are dependent on proliferation[119]. The features of cancer cells enable them to live longer than usual and to multiply uncontrollably[119]. In cancer treatment, cytotoxic drugs are utilised to eliminate cells with a high rate of proliferating and regenerating[119].

Previous research has demonstrated that *C. ternatea* inhibits the proliferation of the cancer cell lines TT, MCF-7 and HCT116 at the cellular and molecular levels[71]. Studies showed that flowers from *C. ternatea* exhibited notable inhibitory effects on the growth of MCF-7 and MG-63 cells[120]. Research by Neda *et al.,* revealed that aqueous extracts from *C. ternatea* flowers exhibited growth-inhibiting effects on MCF-7 cell lines[80].

7.5 Cell Cycle Arrest and Apoptosis

As a result of abnormal cell cycle regulation, cancer cells that overexpress cyclins or lack CDKIs display uncontrolled proliferation[121]. The cell cycle is also

responsible for protecting DNA from damage[121]. Consequently, cell cycle arrest gives the tumour cell the chance to use a survival strategy to repair its damaged DNA[121]. Apoptosis can be activated by abrogating cell cycle checkpoints before DNA damage has been repaired[121]. Research indicates that *C. ternatea* extract has the ability to halt various stages of the cell cycle, including the pre-G1 and S phases, as well as other phases[122]. The research findings indicate that the extract from *C. ternatea* flower petals influences mRNA gene expression, hindering cell cycle progression by reversing the G2/M phase to the G0/G1 phase[123]. Studies suggest that kaempferol and quercetin may facilitate cancer cell reprogramming by suppressing the Nrf2 gene[124]. Hussain *et al.,* demonstrated that the modulation of Nrf2 suppressed pro-metastatic transcription in breast and lung cancer cell lines[124]. A primary goal of cancer treatment is to trigger programmed cell death in malignant cells[125]. In an *in vivo* study, Balaji *et al.,* discovered that aqueous extract of *C. ternatea* flower showed significant antiproliferative effects on EAC cells treated mice[93]. In the control group, cell viability was found to be higher (97%) than in the *C. ternatea* flower extract-treated group (42%)[93]. When tumour cells were treated with extract, they clearly showed apoptotic bodies and nuclear condensation, which is a hallmark of apoptosis, while in control EAC cells, very little apoptosis was observed[93].

7.6 *Clitoria ternatea* Anticancer Activity through Different Signalling Pathways

7.6.1 Phosphoinositide 3-Kinase (PI3K) Signaling Pathway

An infection, toxic compounds, irradiation, or damaged cells can trigger inflammation[126]. Through inflammation, harmful stimuli are eliminated and healing is accelerated[127]. Thus, inflammation is an essential defence mechanism for health[128]. Research has shown that both chronic and acute inflammation play a significant role in cancer development[129]. PI3K signalling regulates cell growth, survival, motility, angiogenesis, and metabolism, among other functions[130,131]. Tumours are developed when PI3K pathways are activated[122]. Many types of cancer can be effectively treated with the inhibition of PI3K signalling (Figure 5), which makes this an attractive therapeutic approach[132].

Yanti *et al.,*[133] found that when compared to a positive control, the anthocyanin extract from *C. ternatea* significantly suppressed inflammation in paw edema. The qPCR analysis showed that paw tissues treated with anthocyanin extract from *C. ternatea* significantly downregulated the expression of PI3Ks genes, such as p53, Ilk, Pdk2, PKB, Pik3Ca, and Akt1[133]. The PI3K signalling pathway plays a key role in regulating various essential processes involved in the body's inflammatory reaction to infections and injuries[133].

7.6.2 NF-kB Signalling Pathway

Inflammation occurs when the body reacts to infection or injury. Although it is normally beneficial and transient, it can also be harmful if not treated appropriately[134]. An excess of inflammation can lead to tissue damage as well as inflammation-related diseases[135]. As an important pro-inflammatory gene activator, NF-KB plays a significant role in both adaptive and inherent immunity[135]. There is a link between inflammation and infections, autoimmune diseases, and cancer, according to numerous studies[136].

Through inhibition of COX, iNOS, and LOX enzyme activity, quercetin glucosides exert long-term anti-inflammatory effects[137]. Nair *et al.* fractionated C. *ternatea* blue flowers extract in fractions containing ternatin anthocyanins and flavonols[138]. Flavonols inhibited COX-2 activity and partially suppressed ROS[138]. Through a non-ROS suppression mechanism, the ternatin anthocyanins prevent NO production, iNOS protein expression, and nuclear NF-κB translocation[138].

Therefore, *C. ternatea* may be useful for treating chronic inflammatory diseases such as cancer through inhibiting the NF-kB signalling pathway (Figure 5).

7.6.3 Phospho-ERK1/2 Signalling Pathway

Cancer development and progression depend on ERK1/2 activation[139]. BCL-2 proteins are regulated by the ERK1/2 pathway to promote tumour cell growth[140]. The activation of ERK1/2 inhibits apoptotic signalling by TNF, TRAIL, and Fas receptors[140]. This shows that recombinant, in addition to ERK1/2 inhibition, may be beneficial in treating cancers with deregulated ERK1/2 signaling[140]. It has been found that inhibition of signalling pathways such as ERK1/2 and Akt1 inhibits lipid accumulation in adipocytes, cell proliferation,

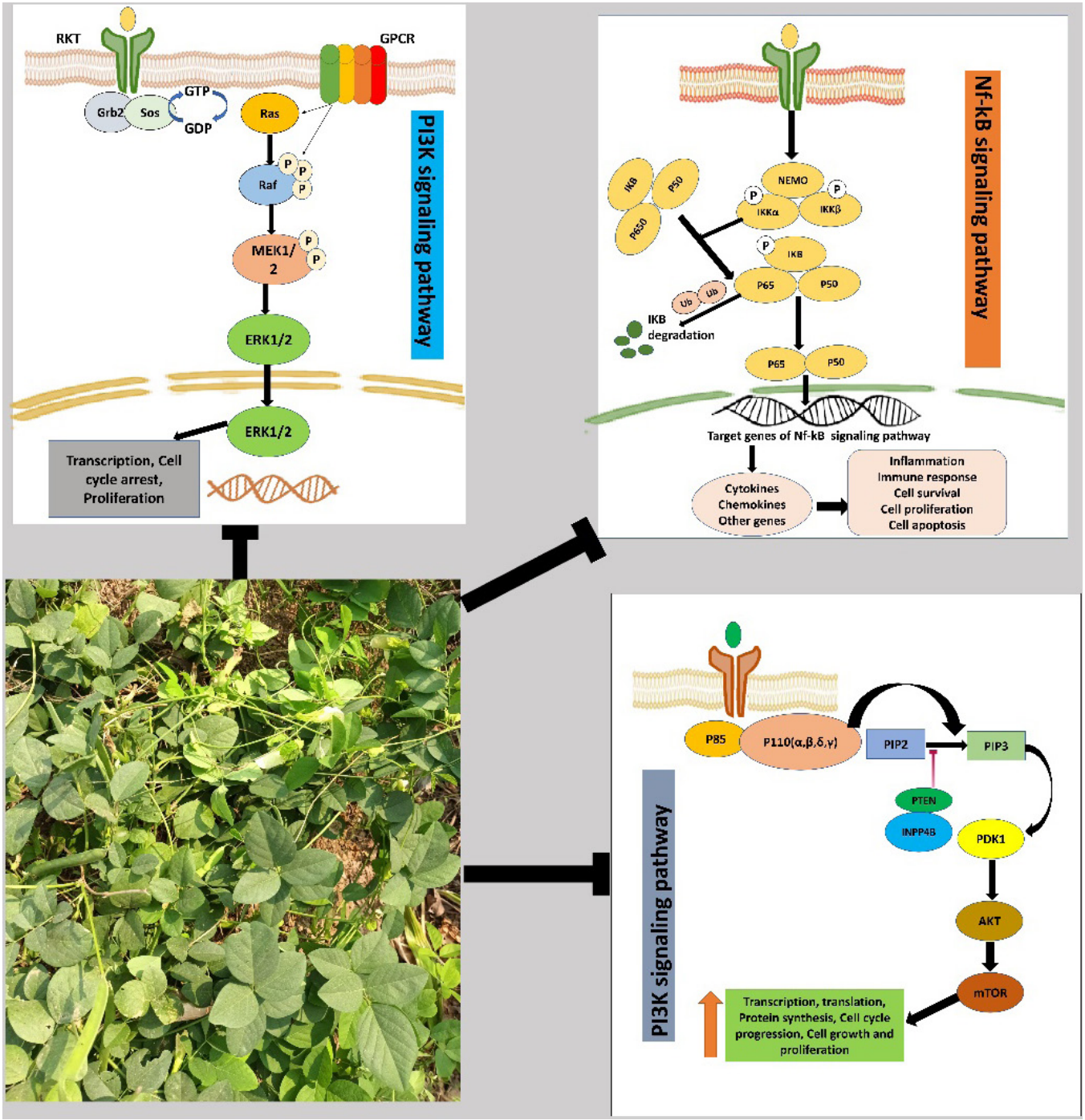


Figure 5. *C. ternatea* inhibiting different signalling pathways.

and adipogenic transcription factor expression[123]. By inverting cell cycle phases from G2/M to G0/G1, researchers discovered that flower petal extract of *C. ternatea* caused cell cycle arrest[123]. This might be related to the ERK1/2 signalling pathway suppression (Figure 5)[123].

7.7 Cell Cycle Protein Inhibition by *C. ternatea* - Molecular Docking

As a result of a molecular docking research utilising a computational approach, the phytocompounds Kaempferol, P-Hydroxycinnamic acid, Quercetin and Myricetin from *C. ternatea* suppress CDK-6 (Cyclin

Dependent Kinase-6) and CDK-2 (Cyclin Dependent Kinase-2) cell cycle checkpoint proteins. These proteins, known to be disease proteins involved in cancer proliferation[141].

By utilising the web-based ADMET-SAR, ADME/T system was conducted to predict the pharmacokinetics and pharmacodynamics of the drugs, including abdominal adsorption, blood-brain barrier permeability, Cytochrome P (CYP) inhibition, AMES toxicity, mutagenicity, carcinogenicity, and Caco-2 permeability[141]. In addition to targeting both target molecules, all the ligand molecules showed potential inhibition of both CDK-2 and CDK-6[141]. Compared to other ligand molecules, P-hydroxycinnamic acid has a slightly higher binding energy[141]. In this study, P-hydroxycinnamic acid docked efficiently with CDK-2 and CDK-6, but ADME/T results and its drug likeness property were satisfactory[141]. Therefore, P-Hydroxycinnamic acid blocks the Cyclin/CDK pathway in cancer cells by inhibiting CDK-2 and CDK-6[141].

8. Anti-cancer Claims of *C. ternatea* based on Clinical Studies

Although there is a considerable amount of clinical data available on various parts, extracts, and isolated compounds found in *C. ternatea*, only a few studies have focused on the anticancer potential of isolated compounds. This section discusses only clinical studies on the anticancer properties of isolated compounds. Clinical trials involving genistein for the treatment of cancer have been performed on humans[142]. There were 13 patients enrolled with histologically proven metastatic colorectal cancer and no prior treatment[143]. The researchers chose FOLFOX or FOLFOX-Bevacizumab as treatment[143]. Genistein was given orally every two weeks for seven days, starting four days before chemotherapy and continuing through the first three days of infusional chemotherapy[143]. The most typical side effects connected with genistein alone were headaches, nausea, and hot flashes[143]. Grade 3 hypertension was observed in one subject[143]. Genistein did not increase chemotherapy-related adverse events[143]. In addition, 11.5 months of progression-free survival were also achieved with 61.5% of the best overall response rates[143]. As genistein and FOLFOX were shown to be safe and tolerable in Phases I and II clinical studies for the treatment of colorectal cancer, further study is needed to determine whether genistein may be used as a cancer chemoprevention agent in combination with other drugs[143].

9. *Clitoria ternatea* as a Food and Nutritional Profile

Clitoria ternatea flower's bright, deep-blue blooms are due to the presence of delphinidin anthocyanins[144]. The rich anthocyanin pigment concentration of *C. ternatea* flowers makes them a popular choice for food and beverage coloring[144]. A natural blue colourant, *C. ternatea* flower is frequently utilised in food and beverages due to the high concentration of anthocyanin pigment[144]. This colourant is typically used in varied amounts in cakes, mocktails, ice cream, candies, and other classical desserts and meals[144].

In Asia, blue flower petals of *C. ternatea* are utilised for colouring tea, deserts, and clothing with a dark blue pigment[145]. The development of vibrant blue alcoholic gins that alter colour in response to pH levels when mixed with lime juice or tonic water is the result of recent research with *C. ternatea* extract[145]. In recent years, *C. ternatea* flowers have gained popularity over synthetic blue food colourants due to health concerns[145]. In studies, adding *C. ternatea* extract to sponge cakes boosted their polyphenolic and antioxidant content and decreased the projected glycemic index of wheat. and increased the oxidative stability of pork patties[146-148].

In recent years, there has been a consistent rise in the demand for anthocyanins, attributed to their perceived health benefits and their utility as a food colouring agent[149]. *C. ternatea* flower rice contains a large number of antioxidants. Inflammatory and cancer-fighting properties are found in this plant[149]. There is evidence that it may be helpful in heart disease, diabetes, and reducing obesity[149]. In addition, young shoots, fresh pods, and leaves can be served as a side dish or eaten as a vegetable[149]. A variety of meals use the leaves' natural green colour as a colorant[149].

Carbohydrates, proteins, fats, minerals, vitamins, and water are important components of a diet[150]. A food's quality is affected by its relative concentration of carbohydrates, fats, proteins, minerals, and vitamins[150]. Typically, proteins, carbohydrates, and fats make

up the bulk of our diets, whereas minerals play a critical role in regulating our metabolic activity[150]. A plant's nutritional status is influenced by its elemental content[150]. Nutritional and mineral profile is stipulated in Table 5[150,151].

10. Toxicity and Safety Concerns of *C. ternatea*

A number of preparations are in use as food and medicine around the world with no reported adverse effects. There have been no reports of adverse effects in humans till date. In the past, a number of studies have been conducted to determine the potential toxicity of *C. ternatea*. Table 6 summarises the results of different studies. No adverse effects have been observed up to 2000 mg/kg.

Table 5. Nutritional and mineral value in aerial portion (leaves, flowers, and stem together) of *C. ternatea*

Parameters	Aerial part	Leaves
Total protein (g)	11.5	-
Carbohydrate (g)	6.7	-
Beta carotene (g)	0.096	-
Iron (g)	0.02	-
Phosphorus (g)	0.2	-
Calcium (g)	0.2	-
Total fat (g)	Nil	-
Moisture (%)	-	74.51±0.38
Dry matter (%)	-	25.49±0.64
Crude fibre (%)	-	8.45±0.05
Total ash (%)	-	8.73±0.22
Crude protein (%)	-	14.99±0.43
Crude fat (%)	-	5.5±0.1
Total sugar(g/100g)	-	0.042±0.0001
Reducing sugar (g/100g)	-	0.036±0.001
Carbohydrate(g/100g)	-	0.080±0.002
Energy (KJ)	-	459.60±9.20
Starch(g/100g)	-	0.038±0.001
P(g/100g DW)	-	0.65±0.03
N (g/100g DW)	-	2.39±0.07
K (g/100g DW)	-	1.60±1.42
Na(g/100g DW)	-	0.27±0.006
Mg(g/100g DW)	-	0.58±0.02
Ca(g/100g DW)	-	0.78±0.025
Fe(mg/100g DW)	-	6.33±0.35
Mn(mg/100g DW)	-	3.24±0.13
Zn(mg/100g DW)	-	4.43±0.15
Cu(mg/100g DW)	-	2.23±0.12

11. Drug-drug Interaction

A drug-drug interaction occurs when medications interact pharmacokinetically or pharmacodynamically, which could lead to the intended outcomes, less effectiveness, or higher toxicity. This might lead to desirable effects, decreased efficacy, or higher toxicity[159]. It is possible that drug-drug interactions can cause adverse reactions that are severe enough to require hospitalisation[159]. The plant remedies cannot be used alone for the treatment. Therefore, it becomes essential to study whether they interact with any medications. Here, we discuss studies that utilise it as a combination therapy. Researchers investigated in ovariectomised athymic mice to study the impact of genistein, a soy isoflavone, and The Antiestrogen Tamoxifen (TAM) on the development of MCF-7 cells(estrogen-dependent breast cancer cells)[160]. Six groups were involved in this study[160]. In ovariectomised athymic mice, TAM therapy (2.5 TE and 5 TE) reduced the formation of MCF-7 tumours caused by E2[160]. Dietary genistein was shown to counteract the inhibitory effect of TAM on the growth of MCF-7 tumours, lower plasma E2 levels, and increase E-responsive genes (such as cyclin PR, D1, and pS2)[160]. Thus, it is wise to use caution when ingesting dietary genistein in postmenopausal women who are receiving TAM therapy for E-responsive breast cancer[160].

Through stomach intubation, rats in the control group were given an oral dose of 10 mg/kg of Nifedipine (NFP) in maize oil[161]. Three further groups were given oral kaempferol at doses of 5, 10, and 15 mg/kg, respectively, after receiving oral nifedipine at a dose of 10 mg/kg[161]. Neither the control nor the treated groups showed significant differences in plasma peak value times (Tmax) or elimination half-lives (t1/2(ke))[161]. In rats, kaempferol concomitantly used with NFP may influence its pharmacokinetics, suggesting that it might reduce NFP's first-pass metabolism[161].

Table 6. The results of various types of toxicity studies on *C. ternatea*

Dosage form	Type of Toxicity study	Animal	Standard	Dose	Observations	References
Roots extract	Acute oral toxicity	Male DDY-mice	1 cc Aquadest	2500, 5000, 10000 and 15000 mg/kg	LD_{50}: 32118.533 mg/kg, highest mortality rate at 15000 mg/kg body weight indicate nephrotoxicity, hepatotoxicity	[152]
Hydroalcoholic extract of *C. ternatea* leaves.	Acute oral toxicity	Female Wistar rats	-	Single dose: 2000 mg/kg	Shows no toxicity signs	[153]
Ethyl acetate fraction of the flower of *C. ternatea*	*In vivo* toxicity	Zebrafish embryos	0.1% DMSO	50 µg/ml 100 µg/ml and 200 µg/ml	No detectable changes in yolk expansion, body size, heart rate, blood circulation, pigment cell development, and the somite boundary of treated larvae	[154]
Alcoholic extracts of the white flower variety. *C. ternatea* root, aerial parts (leaves, stem, flowers)	Oral toxicity	Swiss Albino mice	Distilled water	200–3000 mg/kg	At 2000 mg/kg: lethargic, exhibited ptosis	[155]
C. ternatea leaf methanol extracts	Acute oral toxicity	Swiss albino mice (both male and female, nulliparous and non-pregnant)	2% aqueous Tween 80	50, 300, 2000 mg/kg	No significant changes in behaviour, skin effects, impairment in food, water consumption, breathing, hair loss, or posture issues	[156]
C. ternatea root decoction	Acute toxicity	Albino rat	-	2000 mg/kg bw	No mortality	[157]
C. ternatea flower methanolic extract	Acute toxicity	Swiss albino mice	Normal Saline	150, 300, 500, 1000, 2000, 3000mg/kg body weight	Up to 2000 mg/kg is non-toxic	[158]

12. Green Nanoparticles

The field of nanotechnology is rapidly growing for diagnosing and treating diseases[162]. There are a variety of applications for nanomaterials (NMs) in cancer therapy[162]. The integration of nanoscience with pharmaceutical science is potentially changing medical science, including the development of cancer-targeted drug delivery systems. A multitude of nanostructures, such as dendrimers, liposomes, micelles, gold nanoparticles, and carbon nanotubes, can be used to create drug delivery systems[163,164]. Alahmdi *et al.* synthesised zinc oxide nanoparticles (ZnO NPs) using *C. ternatea* flower extract[165]. ZnO NPs showed cytotoxicity against MCF-7. ZnO NPs promote apoptosis in MCF-7 cells via enhancing ROS generation, nuclear disintegration, and DNA damage[165]. *C. ternatea* flower aqueous extract was utilised by Srinivas *et al.*, to create synthetic silver nanoparticles[92]. Trypan blue

exclusion and MTT assays were used to evaluate the cytotoxicity of the nanoparticles against MCF-7 and EAC cells, yielding IC50 values of 19.37 g/ml and 24 g/ml, respectively[92]. Studies conducted in mice using the EAC model have confirmed silver nanoparticles' antitumor properties[92]. Nanoparticles showed anti-angiogenic properties when quantified by VEGF, CAM assays, and microvessel density counts[92]. An apoptotic-inducing activity of nanoparticles has been verified by fluorescent staining and DNA fragmentation studies[92]. Fatimah *et al.*[166] found in DPPH inhibition tests that silver and gold nanoparticles prepared from flower extracts of *C. ternatea* demonstrated more than 50% antioxidative activity. Researchers found that *C. ternatea* flower extracts synthesised into silver nanoparticles scavenged 43.08 % of DPPH radicals at 0.5 g/ml[167]. Researchers found that increasing drug concentrations significantly inhibited HeLa cancer cell proliferation *in vitro*[167]. The above studies show that synthesised nanoparticles are highly toxic to cancerous cells and have excellent biological activities.

13. Future Prospective

The *C. ternatea* has been used medicinally and therapeutically for centuries to treat a variety of diseases. We have outlined the large volume of scientific and medical research that has been done on its anticancer effects, including *in vitro* and *in vivo* trials, in this review. But still, there are many lacunas in this field because there aren't many *in vivo* studies and no clinical trials. And also, the studies available are also conducted mainly on extracts, not on the whole herb. As *Ayurvedic* medicines work on a holistic philosophy, so maybe they may show more potent results when used wholly. So, there is are need for well-established experimental trials along with clinical trials at large sample sizes and multiple centres in different types of cancer that present their mechanism, pharmacology and interactions with other treatments.

14. Conclusion

Clitoria ternatea has been extensively researched at present in order to identify and characterise its functions. In *C. ternatea*, phytoconstituents have been found that have nutritional value and can be converted into functional and nutraceutical foods. The treatment and prevention of a wide range of diseases can also be achieved with it. There is no proof of any negative effects associated with *C. ternatea* use at levels up to 2000 mg/kg based on numerous toxicity tests. In all parts of this plant, anticancer properties are present, including anti-inflammatory, cell cycle-arresting, antiproliferative, and antiapoptotic ones. Furthermore, it reduces the severity of the side effects caused by other available anticancer therapies. Researchers have conducted more *in vitro* studies on the potential of plant extracts and their separate phytoconstituents as anticancer agents. However, it is concerning that there are so few studies done in experimental models and clinical settings. So, there is a possibility that natural ingredients, such as *C. ternatea*, could facilitate the discovery of new drugs.

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16. Author Contribution

JS: Conceptualisation, Writing the Original draft; DNSG: Supervision; SS, Priyanka, and RS: Editing and proofreading. All authors have read and agreed to the published version of the manuscript.

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