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RESEARCH ARTICLE

Flavonoids from *Clitoria ternatea* as Promising Therapeutic Agents against Ovarian Cancer

[version 1; peer review: awaiting peer review]

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Abstract

Background

Flavonoid-based natural products have shown promising anti-cancer potential through dual-pathway inhibition. The PI3K/AKT/mTOR signaling pathway is the most frequently altered pathway in ovarian cancer, making it a critical therapeutic target.

Methods

Extensive computational studies including molecular docking and 200 nanosecond molecular dynamics simulations were conducted to evaluate the binding affinity, interaction stability, and conformational dynamics of the PI3K (5DXT) and mTOR (5GPG) proteins. Following *in-silico* validation, naringin-coated zinc oxide nanoparticles incorporating *Clitoria ternatea* flower extract were formulated to enhance bioavailability and therapeutic efficacy. Additionally, cytotoxic evaluation against SKOV3 ovarian cancer cell lines using MTT assay was performed.

Results

This study investigated the efficacy of major flavonoid components

from *Clitoria ternatea* flowers, specifically quercetin-3-rutinoside and quercetin-3,7-glucoside, as dual PI3K/mTOR inhibitors. Molecular dynamics analysis revealed that quercetin-3-rutinoside and quercetin-3,7-glucoside exhibited stable interactions with critical amino acid residues throughout the simulation period, promising enhanced stability compared with the standard dual inhibitor gedatolisib. Absorption, Distribution, Metabolism, and Excretion (ADME) profiling identified quercetin derivatives as promising lead hits, despite minor violations of Lipinski's Rule of Five. Cytotoxic evaluation against SKOV3 ovarian cancer cell lines using MTT assay demonstrated the superior performance of naringin-coated nanoparticles (NC1) with an IC_{50} value of $144 \pm 2.43 \mu\text{g/mL}$.

Conclusion

This synergistic approach, combining natural flavonoids with nanotechnology, provides a novel therapeutic strategy for targeting the dysregulated PI3K/mTOR pathway in ovarian cancer. These findings establish *Clitoria ternatea* flavonoids as superior candidates for the development of enhanced nanoformulations for anti-cancer therapeutics against ovarian cancer.

Keywords

Flavonoids, quercetin derivatives, dual PI3K/mTOR inhibitors, *Clitoria ternatea*, naringin-coated nanoparticles, ovarian cancer, molecular dynamics, SKOV3 cells.



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1. Introduction

Ovarian cancer is one of the most common gynecological cancers observed in women worldwide.¹ Due to its late recognition of symptoms, it is also called as the “silent killer” which makes it one of the deadliest cancers known till date.² According to epidemiological data from the American Cancer Society, the lifetime risk of ovarian cancer in women is approximately 1 in 78, with mortality rates approaching 1 in 108 cases. OC is usually diagnosed in elderly women.³ Almost half of the cases reported to date have been found in women aged 63–64 years.⁴ Even though few treatments are available, the recurrence rate is still high, which threatens the life of patients. The Global Cancer Observatory (GLOBOCAN 2020) reported a 42% increase in ovarian cancer incidence by 2040, underscoring the urgent need for novel therapeutic strategies and effective preventative approaches.⁵

Currently, many treatment methods are available for cancer, including chemotherapy and surgery.^{6,7} Chemotherapy is known to have undesirable effects, forcing people to look at alternatives to natural products, including traditional practices such as Ayurveda, a traditional Chinese medicine that provides relief. Nature provides us with many natural remedies for most diseases. One such miracle plant is *Clitoria ternatea* (CT). Gaining its importance from the age old ayurvedic “Medhya Rasayana” this plant which comes from Fabaceae family, is a nootropic perennial herb.^{8,9} It is also commonly known as Aparajita, Shankapushpa, butterfly pea, blue pea, Asian pigeonwings, or Darwin pea, but because of the resemblance of the flower to the human female genitals, it was named *Clitoria ternatea*.¹⁰ A study conducted by Anita et al. proved that the flower extract contains compounds such as kaempferol, quercetin, and ternatins, which are responsible for anti-cancer studies. This led us to the idea of using flower extracts for OC.¹¹ Another study by Vyshnavi et al., proved that the silver nanoparticles using the CT plant extract showed anti-cancer activity of lung cancer cell lines with an IC₅₀ value of 50.92 ± 0.05 µg/mL and 51.35 ± 0.05 µg/mL.¹² Studies have shown that compared to compounds in their original form, nanoparticles provide a high surface-to-volume ratio, thus making them ideal anti-cancer agents. A study on MCF-7 and EAC cell lines using CT-silver nanoparticles showed potential effects as tumor inhibitors through apoptosis.¹³

To enhance the bioavailability, cellular internalization, and therapeutic potency of blue-variant CT-derived flavonoids, we formulated naringin-coated zinc oxide nanoparticles. Naringin, a citrus-derived bioflavonoid, possesses intrinsic anti-inflammatory and anti-cancer properties and has been shown to enhance therapeutic outcomes through synergistic interactions with other bioactive compounds. Zinc oxide nanoparticles are well-established biocompatible nanomaterials with established cytotoxic properties against cancer cells through the generation of reactive oxygen species and induction of apoptosis.¹⁴

1.1 Plant description and Habitat.

The first reference to the CT plant can be found in history during 1678 by a Polish naturalist. This plant was then referred to as “Flos clitoridis ternatensis” which can be translated as “ternatean flower of the clitoris.”¹⁵ Ternatea, the species name, originated from the name of the Island Tenate, which is located in the northern part of the Maluku Islands where Carl Linnaeus’s species originated.¹⁶ The plant has a vine wildflower type with stalked leaves that are divided into 1–2 inches with egg- or lance-shaped leaflets.¹⁰ This plant consists of flowers that have many colors such as blue, white, dark blue, mauve, and pink. Usually, the flowers are seen to be somewhere between 1 to 2 inches with one to three flowers per stalk. These flowers are small buds that arise from leaf axils. A normal CT flower consists of five petals, one of which is a large standard petal, two wings, and two keel petals (Figure 1).

1.2 Historical and current applications.

As for Aparajita, by the name itself one can tell that this plant can be used as a cure for many diseases. This plant, which cannot be defeated by any disease, has many medicinal uses in the past. All the evidence and research regarding this plant indicates that all parts of this plant have one or the other medicinal properties. Researchers worldwide have found antibacterial, antidiarrheal, antifungal, anticarcinogenic, antidiabetic, anticonvulsant, antidepressant, antimicrobial, antitumor, anti-inflammatory, wound healing, and nootropic properties in different parts of the CT plant (Figure 2).^{8,16–19} A study by Manokari et al. showed that zinc oxide nanoparticles from different parts of the CT plant, using a green approach, are effective in treating different illnesses.²⁰ Nanoparticles, compared to other compounds, have shown greater efficacy in treating diseases. A review article reported the cytotoxic effects of different combinations of *Clitoria ternatea* extract. A study using the Trypan blue dye exclusion method revealed the *in-vitro* cytotoxic effects of petroleum and ethanolic flower extract. The petroleum extract showed a 100% reduction in the cell count at 500 µg/mL, and the ethanolic extract showed an 80% reduction in the cell count at 500 µg/mL.^{21,22} Another study demonstrated the cytotoxicity of aqueous and methanol extracts of CT flowers on six types of normal and cancer cell lines, in which CaOV-3 was involved. The work revealed greater inhibitory action against MCF-7 with an IC₅₀ value of 175.35 µg/mL.²³ A recent study also noted that CT root extract is a promising anti-cancer agent with antioxidant, apoptotic, and cell cycle arrest activities.²⁴ Therefore, in our approach, we used the green synthesis method of preparing ZnO nanoparticles with naringin to observe its effects on the SKOV-3 cell line.

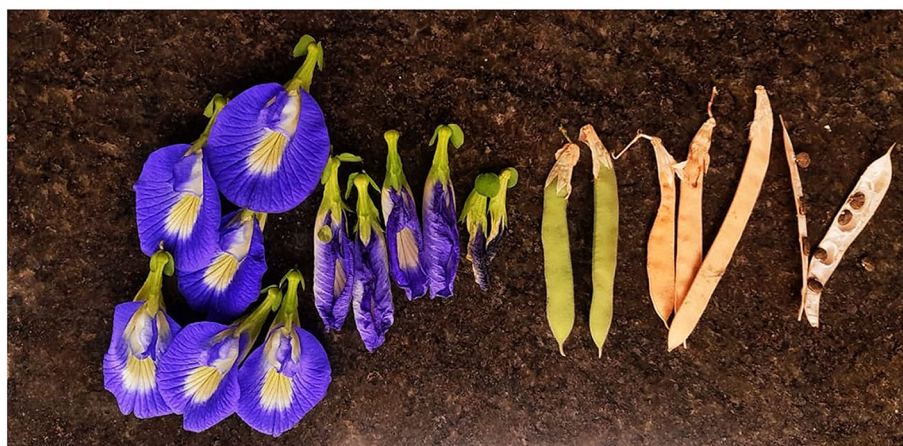


Figure 1. *Clitoria ternatea* flowers, pods, and seeds.

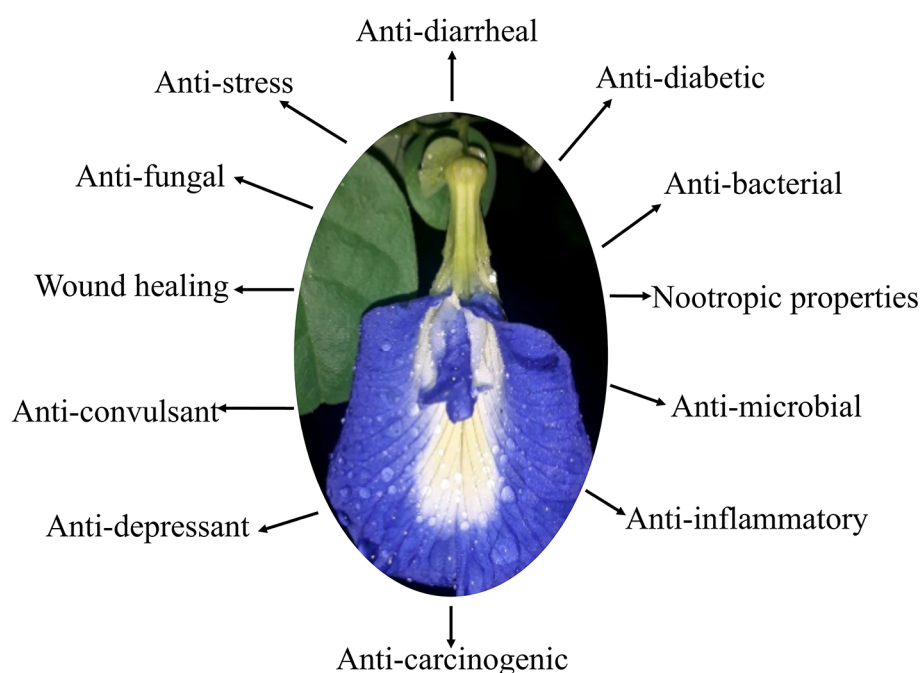


Figure 2. Uses of CT flower.

1.3. PI3K/Akt/mTOR Pathway

Various pathways are involved in cancer development. Among these pathways, the PI3K/mTOR pathway is considered to be one of the most important pathways that undergo alterations and lead to ovarian cancer.^{25–27} The phosphoinositide 3-kinase pathway is one of the most significant pathways that plays a major role in regulating cell growth, proliferation, survival, and angiogenesis. This pathway is driven by three important factors, PI3K, AKT, and mTOR. PI3K is a family of lipid kinases that comprises three classes: class I, class II, and class III. Once PI3K is fully activated, PIP2 is converted to PIP3, which allows the activation of AKT. AKT can also be activated through MTORC2, which is present in the helical domain of AKT. Constitutive activation of the PI3K/mTOR pathway due to PIK3CA mutations or PTEN loss has been shown to initiate ovarian cancer in mice.²⁸ Inhibition of this pathway has shown a significant delay in tumor progression and extended survival rate, offering strong proof of concept for its oncogenic role in OC and supporting its potential as a viable therapeutic target. A growing body of research has focused on inhibiting PI3K, Akt, and mTOR separately. However, only a few studies have succeeded in simultaneously targeting PI3K and mTOR at the same time. At the same time, inhibiting this pathway through PI3K or mTOR alone fails to serve this purpose. The PI3K pathway can also be

activated via phosphorylation of AKT. Owing to the presence of multiple pathways for the upregulation of this pathway, the inhibition of PI3K or mTOR alone will activate the pathway again.^{28,29} Therefore, we aimed to target both PI3K and mTOR together to inhibit this pathway. Targeting both these targets together is essential and crucial because targeting any one of them might lead to negative feedback and the whole pathway might be reactivated, which we do not want. Therefore, this method will be a boon in the future.

2. Materials and methods

2.1 Materials

We selected components that have already been proven to be present in the flowers of the CT plant for *in-silico* studies. They were docked using Maestro 11.8 Schrodinger software, and the selected leads were used for Molecular Dynamics (MD) studies. Interpreting the results of the MD potent component was selected as a dual PI3K/mTOR inhibitor for ovarian cancer. The blue variant of *Clitoria ternatea* flowers were grown under economic conditions near DC office, Manipal, Karnataka, were selected for the study. The plant was authenticated by Dr. Gayathri Pai, HOD, Department of Botany, Mahatma Gandhi Memorial College, Udupi. A voucher specimen PP596A has been deposited in the herbarium at Department of Pharmacognosy, Manipal College of Pharmaceutical Sciences, MAHE, Manipal for future reference. Analytical grade zinc acetate dihydrate was purchased from Merck, India, sodium hydroxide was procured from Molychem, Mumbai, India, *Clitoria ternatea* flower extract was freshly prepared, and naringin was purchased from TCI Chemicals, India.

2.2 Methods

2.2.1 Preparation of protein:

The X-ray crystal structures of PI3K and mTOR proteins, 5DXT and 5GPG (resolution 2.25 Å⁰ and 1.67 Å⁰ respectively), were retrieved from the RCSB Protein Data Bank. The retrieved protein was prepared using the protein preparation wizard tool from the Maestro 11.8 Schrodinger software at 7.5 pH. Protein preparation started with preprocesses where the missing side loops were filled and then the optimization was done. This was followed by minimization of proteins at 7.5 pH. The minimized proteins were further docked with the prepared ligands.

2.2.2 Preparation of ligands:

All ligand structures were retrieved from PubChem.sdf format. These ligands were further prepared at 7.5, and the grid was developed using the grid generation tool around both PI3K and mTOR PDB separately.

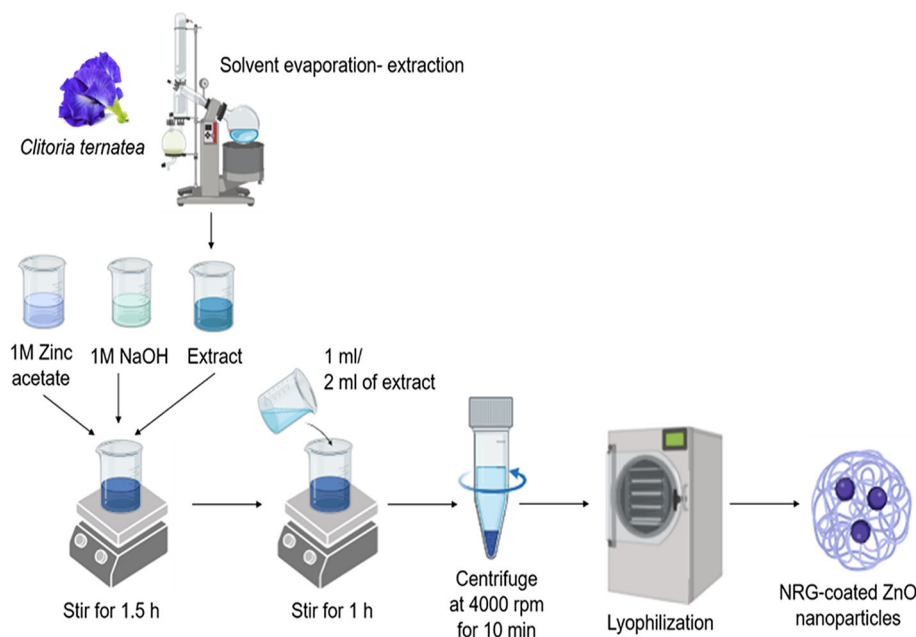


Figure 3. Preparation of NRG-coated zinc oxide nanoparticles by green synthesis mediated by *Clitoria ternatea* flower extract.

Table 1. Selected 24 compounds with CAS number.

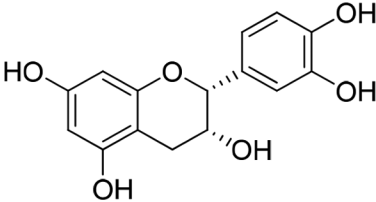
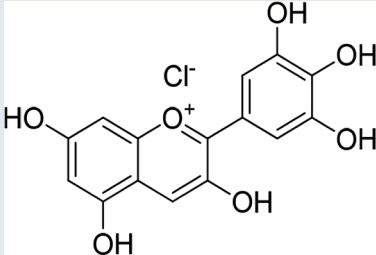
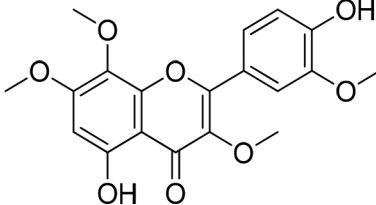
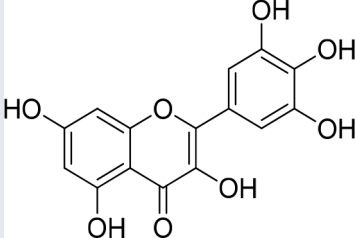
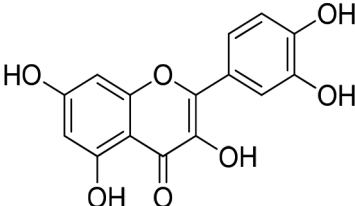
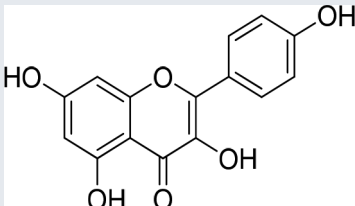
Sl. No	Compound Name	CAS number
1	Epicatechin 	72276
2	Delphinidin chloride 	68245
3	Ternatin 	5459184
4	Mvricetin 	5281672
5	Quercetin 	5280343
6	Kaempferol 	5280863

Table 1. Continued

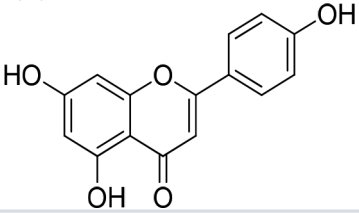
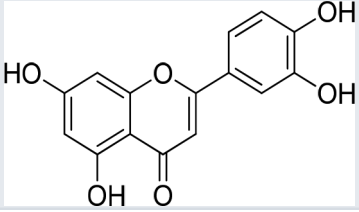
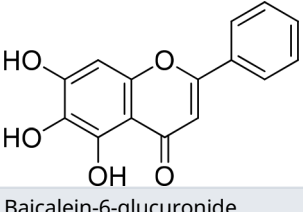
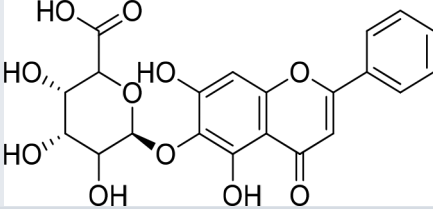
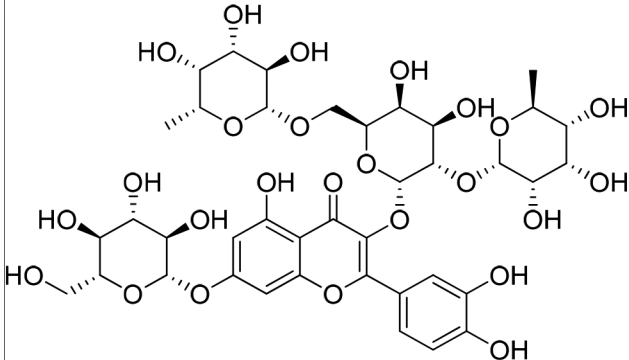
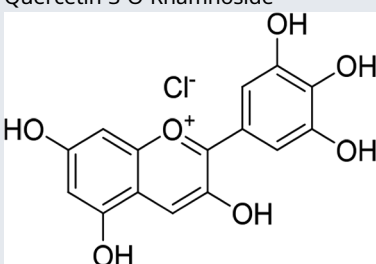
Sl. No	Compound Name	CAS number
7	Apigenin 	5280443
8	Luteolin 	5280445
9	Baicalein 	5281605
10	Baicalein-6-glucuronide 	156595888
11	Quercetin-3,7-glucoside 	44259185
12	Quercetin-3-O-Rhamnoside 	15939939

Table 1. Continued

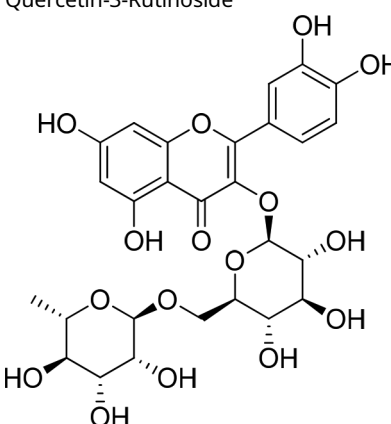
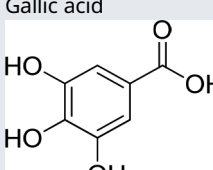
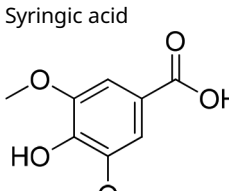
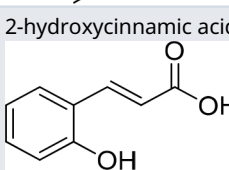
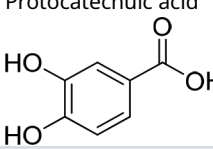
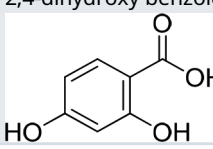
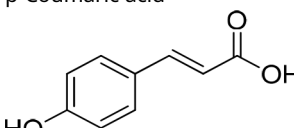
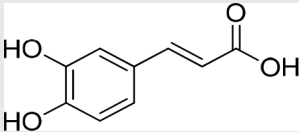
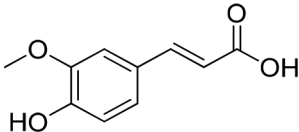
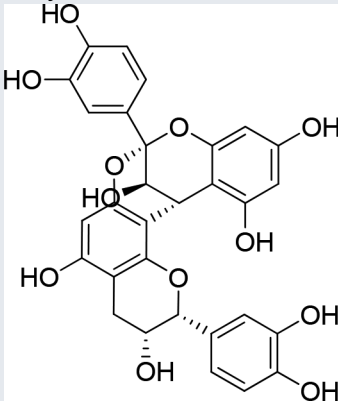
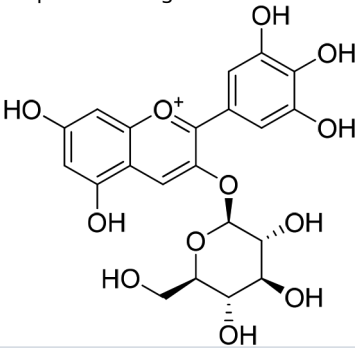
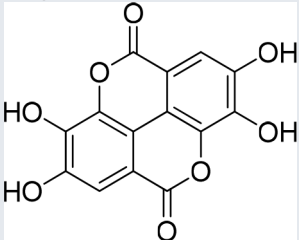
Sl. No	Compound Name	CAS number
13	Quercetin-3-Rutinoside 	5280805
14	Gallic acid 	370
15	Syringic acid 	10742
16	2-hydroxycinnamic acid 	637540
17	Protocatechuic acid 	72
18	2,4-dihydroxy benzoic acid 	1491
19	p-Coumaric acid 	637542

Table 1. Continued

Sl. No	Compound Name	CAS number
20	Caffeic acid 	689043
21	Ferulic acid 	445858
22	Procyanidin A2 	124025
23	Delphinidin-3-O-glucoside 	443650
24	Ellagic acid 	5281855

2.2.3 Ligand docking

The prepared ligands were docked with minimized proteins by ligand docking of glide in the Schrodinger software. The results were analyzed using the docking score and interactions that were retained. Based on these criteria, the selected potent compounds were used for molecular dynamics simulation studies.

Table 2. Interactions and dock score of the compounds with 5DXT.

Sl. No	Compound name	Hydrogen interactions	Hydrophobic interactions	Dock score (kcal/mol)
PDB ID: 5DXT (PI3K)				
1	Epicatechin	VAL851, GLU849, ARG770.	VAL851, VAL850, ILE848, PHE930, ILE932, MET772, TRP780, ILE800.	−8.888
2	Delphinidin chloride	VAL851, EDO1102, GLU849, TYR836, GLU2041, ASP810, LYS802, EDO1102.	VAL851, VAL850, ILE848, TYR836, LEU807, ILE800, PRO778, TRP780.	−9.715
3	Ternatin	VAL851, LYS802.	VAL851, VAL850, ILE848, TYR836, TRP780, PRO778, ALA775, MET772.	−10.112
4	Myricetin	GLU849, ASP933, PHE934, TYR 836, ASP810, GLU2041, LYS802, TRP780, VAL851.	PHE934, ILE932, PHE930, ILE848, VAL850, MET922, TRP780, PRO778, ILE800.	−14.129
5	Quercetin	VAL 851, GLU849, ASP810, TYR836, GLU2041, LYS802, EDO1102.	VAL851, ILE848, TYR836, LEU807, PHE934, ILE932, PHE930, MET772.	−14.295
6	Kaempferol	VAL851, LYS802, ASP933, EDO1102.	VAL851, VAL850, ILE848, PHE930, ILE932, ILE800, PRO778, TRP780.	−11.832
7	Apigenin	VAL851, ASP933, LYS802, EDO1102.	VAL851, VAL850, ILE848, PHE930, ILE932, PHE934, MET772, ILE800.	−11.222
8	Luteolin	VAL851, ASP810, TYR836, GLU2041, SER774, LYS802.	VAL851, VAL850, ILE848, LEY807, ILE800, MET772, PRO778, TRP780	−13.258
9	Baicalein	VAL851, EDO1102	VAL851, VAL850, ILE848, PHE930, ILE932, PHE934, ILE800, MET772.	−11.563
10	Baicalein-6-glucuronide	HIS855, SER854, VAL851, EDO1102, GLN859.	TRP780, VAL851, VAL850, ILE848, PHE930, ILE932, MET772.	−13.396
11	Quercetin-3,7-glucoside	GLU798, ASN853, EDO1102, GLU849, GLN859.	CYS862, VAL851, VAL850, ILE848, TRP780, MET922, PHE930, ILE932, TYR836.	−14.708
12	Quercetin-3-O-Rhamnoside	GLU798, GLN859.	ILE800, TRP780, VAL851, VAL850, PHE930, ILE932, MET922, MET772.	−8.028
13	Quercetin-3-Rutinoside	SER774, VAL851, TYR836, ASP810, ASP933.	VAL851, VAL850, ILE848, ILE800, ALA775, MET772, TRP780, MET858, MET922, PHE932, PHE930, LEU807, TYR836, PHE934.	−15.849
14	Gallic acid	VAL851, GLU849.	VAL851, VAL850, ILE848, PHE930, ILE932, ILE800, TYR836, MET772, TRP780, MET922.	−7.147
15	Syringic acid	VAL851.	VAL851, VAL850, ILE848, ILE932, MET922, MET772, TRP780, TYR836, ILE800.	−6.553
16	2-hydroxycinnamic acid	VAL851.	MET922, VAL851, VAL850, PHE930, ILE848, ILE932, ILE800, TYR836, MET772, TRP780.	−5.716

Table 2. *Continued*

Sl. No	Compound name	Hydrogen interactions	Hydrophobic interactions	Dock score (kcal/mol)
17	Protocatechuic acid	VAL851.	VAL851, VAL850, ILE848, ILE932, PHE930, TYR836, TRP780, MET772, ILE800.	−6.531
18	2,4-dihydroxy benzoic acid	VAL851.	VAL851, VAL850, PHE930, TYR836, ILE848, TYR836, ILE932, TRP780, MET922, MET772, ILE800.	−5.829
19	p-Coumaric acid	VAL851, SER774.	VAL851, VAL850, ILE848, TYR836, ILE800, ILE932, PHE930, MET922, TRP780, PRO778, MET772	−6.508
20	Caffeic acid	VAL851, GLU849, ASP933, TYR836.	VAL851, VAL850, PHE930, ILE932, ILE848, TYR836, ILE800, MET772, TRP780, MET922.	−8.139
21	Ferulic acid	VAL851, GLU849, SER774.	VAL850, VAL851, MET922, TRP780, PRO778, MET772, ILE800, TYR836, ILE932, PHE930, ILE848.	−7.508
22	Procyanidin A2	VAL851, ASP810, TYR836, ASP933.	VAL851, VAL850, ILE848, LEU807, TYR836, CYS838, MET922, ILE932, PHE930, TRP780, ILE800.	−9.925
23	Delphinidin-3-O-glucoside	VAL851, ASP933, ASP810, TYR836.	VAL850, VAL851, PHE930, TRP780, MET922, PHE934, MET772, LEU807, TYR836, CYS838.	−10.663
24	Ellagic acid	VAL851.	VAL851, VAL850, MET922, TRP780, ILE848, TYR836, PHE930, ILE932, ILE800, MET772.	−10.794
25	Gedatolisib	HIS936	ARG770, MET772, SER774, ALA775, ASP810, GLN809, LEU807, ASP806.	−6.910

2.2.4 Molecular dynamics

Of the selected ligands, four potent compounds were studied using molecular dynamics. This was performed using the Desmond tool of the 11.8 Maestro Schrodinger software. Molecular dynamics simulation is a three-step process. The first step was the system builder step, where for the XP docked complexes, a predefined SPC solvent model was used under the orthorhombic boundary condition. In the second step, minimization was performed. Subsequently, a simulation study was performed for the minimized model via the NPT ensemble class at 300 K and 1 bar pressure for 200 ns.

2.2.5 ADME analysis

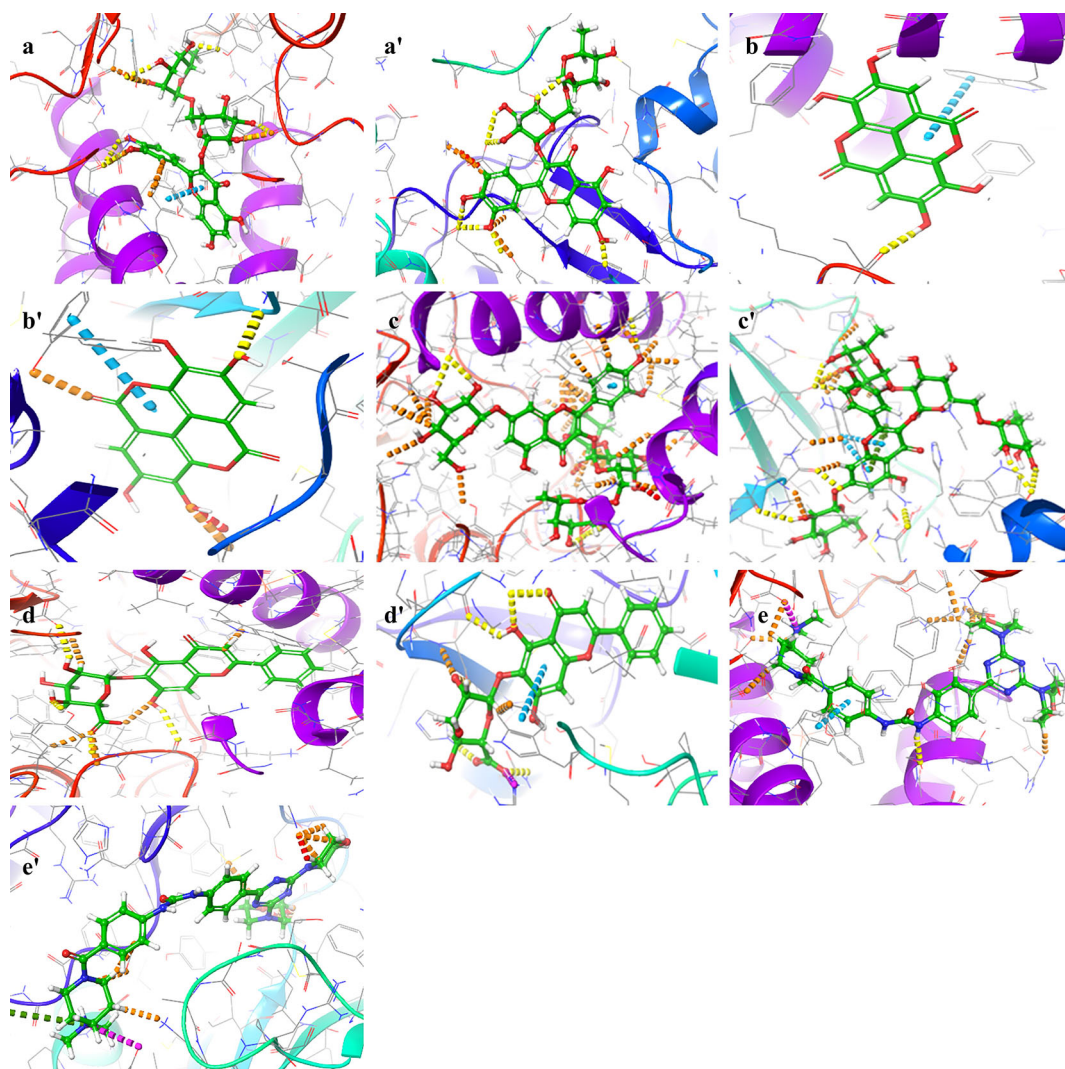
The selected 24 compounds were further used for ADME analysis. ADME analysis was performed using the QuikProp tool of the 11.8 Schrodinger software. Furthermore, the compounds were classified according to Lipinski's rule of five. Four criteria, molecular weight, lipophilicity, hydrogen bond donors, and hydrogen bond acceptors, are considered to identify drug candidates that are more likely to be absorbed and possess pharmacokinetic properties for oral administration. According to this rule, a molecule may be a better drug if its molecular weight is less than 500 Da, LogP is less than 5, the number of hydrogen bond donors is less than 5, and the number of hydrogen bond acceptors is less than 10. Considering these criteria, the selected 24 compounds were classified for further study.

Table 3. Interactions and dock score of the compounds with 5GPG.

Sl. No	Compound name	Hydrogen interactions	Hydrophobic interactions	Dock score (kcal/mol)
PDB ID: 5GPG (mTOR)				
1	Epicatechin	SER2035, SER163, LYS170.	TRP2101, TYR2104, PHE2039, LEU2031, PHE2108, PHE164, PHE2108.	−8.131
2	Delphinidin chloride	THR2098, ILE172, TYR198, ASP2102.	VAL171, ILE172, TRP175, LEU162, TYR135, PHE145, TYR2105, TRP2101, LEU2097, ALA206, TYR198.	−6.315
3	Ternatin	-	PHE2039, TRP2101, TYR2105, TYR2104, LEU2031, PHE2103, LEU162, TYR198, ILE172, VAL171.	−7.057
4	Myricetin	TYR135, ASP146, ASP2102.	TYR2104, TYR2105, LEU2031, LEU162, TYR135, TRP2101.	−9.121
5	Quercetin	SER2035, ASP2102, TYR2104.	TYR135, LEU162, PHE2108, LEU2031, TYR2105, TYR2104, TRP2101.	−9.116
6	Kaempferol	ASP2102.	TYR135, LEU162, PHE2039, LEU2031, PHE2108, TYR2105, TYR2104, TRP2101.	−7.587
7	Apigenin	ASP2102.	TYR135, LEU162, PHE2039, LEU2031, TYR2105, TYR2104, TRP2101.	−7.291
8	Luteolin	ASP2102.	TYR135, LEU162, PHE2039, TYR2104, TYR2105, TRP2101, PHE2108, LEU2031.	−8.371
9	Baicalein	-	TYR2104, PHE2089, TRP2101, TYR2105, LEU2081, PHE2108.	−8.468
10	Baicalein-6-glucuronide	TYR198, ILE172, LYS170, ASP146.	TYR135, TYR198, TRP175, ILE172, PHE145, LEU162, TRP2101, TYR2104, TYR2105, PHE2039, PHE2108, LEU2031.	−10.911
11	Quercetin-3,7-glucoside	THR2098, TYR2104, LYS170, GLY169.	TYR198, PHE216, TYR135, PHE145, ALA206, ILE208, VAL171, ILE172, VAL2094, PHE2039, TYR2106, TYR2104, PHE2108, LEU162, LEU2031.	−18.892
12	Quercetin-3-O-Rhamnoside	SER2035, ASP2102, LYS170.	VAL171, PHE2039, TRP2101, TYR2104, TYR2105, PHE2108, LEU2031.	−10.615
13	Quercetin-3-Rutinoside	LYS170, ASP2120, ASP146, TYR198.	LEU162, VAL171, TRP2101, TYR2105, TYR2104, PHE2108, LEU2031, ALA206, ILE208, TYR198, PHE216, TYR135, PHE145.	−14.566
14	Gallic acid	SER2035.	PHE2039, TRP2101, TYR2104, TYR2105, LEU2031, PHE2108.	−4.993
15	Syringic acid	-	TRP2101, PHE2039, TYR2104, TYR2105, PHE2108, LEU2031, PHE164, LEU162.	−4.556
16	2-hydroxycinnamic acid	-	PHE145, ILE208, ALA206, TYR198, LEU162, TRP175, ILE172, VAL171, TYR135, PHE216.	−4.896
17	Protocatechuic acid	-	PHE2039, TRP2101, TYR2104, TYR2105, PHE2108, LEU2031.	−5.060
18	2,4-dihydroxy benzoic acid	TYR198.	TYR198, LEU214, ILE208, TYR135, PHE216, VAL171, ILE172, TRP175, LEU162, PHE145.	−4.773
19	p-Coumaric acid	LEU2031.	LEU2031, PHE2108, TYR2105, TYR2104, TRP2101, PHE164.	−4.632
20	Caffeic acid	-	PHE2039, TRP2101, TYR2104, TYR2105, PHE2108, LEU2031.	−5.491
21	Ferulic acid	-	LEU162, PHE2039, TRP2101, TYR2104, TYR2105, PHE2108, LEU2031.	−4.912
22	Procyanidin A2	ASP146, ASP2102.	TYR198, TRP175, TYR135, PHE216, LEU162, PHE164, VAL171, LEU2031, PHE2108, TYR2105, TYR2104, PHE2039, TRP2101, ALA206.	−12.307

Table 3. Continued

Sl. No	Compound name	Hydrogen interactions	Hydrophobic interactions	Dock score (kcal/mol)
23	Delphinidin-3-O-glucoside	ASP146, TYR198, ILE172, LYS170, SER2035, ASP2102.	ALA206, PHE145, TYR135, PHE216, TYR198, ILE172, VAL171, LEU162, PHE164, PHE2039, TYR2105, TRP2101, LEU2097.	−11.054
24	Ellagic acid	LYS170.	PHE2039, VAL171, TYR2104, TYR2105, PHE2108, LEU2031, TRP2101.	−8.386
25	Gedatolisib	SER2035, TYR2105, ASP146, ARG2042.	GLU2032, ASP2102, TRP2102, THR2098, LEU2097, VAL2094, ARG2036, GLU2041.	−6.172

**Figure 4.** 3D interactions of (a) - (a') Quercetin-3-rutinoside, (b) - (b') Ellagic acid, (c) - (c') Quercetin-3-7-glucoside, (d) - (d') Baicalein-6-glucuronide and (e) - (e') gedatolisib with 5DXT and 5GPG respectively.

2.2.6 Preparation of the *Clitoria ternatea* flower extract:

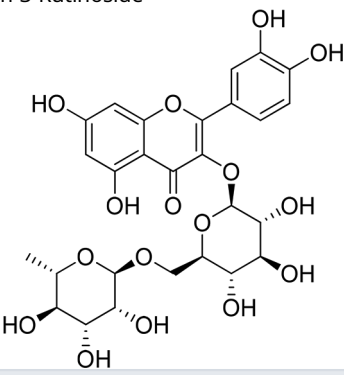
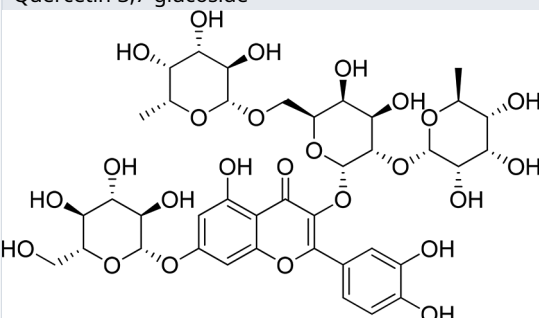
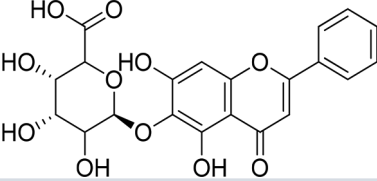
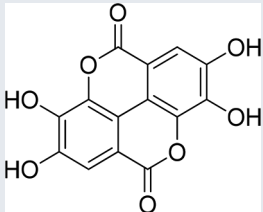
The CT flowers were dried under shade for 2 days and powdered using a mortar and pestle. Powdered flowers (0.1 g) were dissolved in a solvent mixture of 5:4:1 methanol/acetone/water and stirred at room temperature for 24 h. The obtained, blue-colored extract was centrifuged at 4000 rpm, and excess volatile solvents were removed using a

rotary evaporator. Further, an 8:2 ratio of methanol to water was added to the concentrated mixture and used for the preparation of nanoparticles. The prepared extract was analyzed using Liquid Chromatography-Mass Spectroscopy (LCMS) for a time period of 30 min with a sampler temperature of 25 °C, column temperature of 4 °C and probe temperature of 250 °C.

2.2.7 Preparation of the Naringin-coated Zinc oxide nanoparticle:

Naringin is a bioflavonoid present in grapefruit. Previous studies have shown that naringin has many pharmacological effects, including anti-inflammation, anti-cancer, anti-oxidative stress, and lipid metabolism. Studies have shown that

Table 4. Dock score and the interactions of 4 potent compounds.

Compounds	PI3K		mTOR	
	Dock score	Hydrogen bond interactions	Dock score	Hydrogen bond interactions
Quercetin-3-Rutinoside 	−15.849	SER774, VAL851, TYR836, ASP810, ASP933.	−14.566	LYS170, ASP2120, ASP146, TYR198.
Quercetin-3,7-glucoside 	−14.708	GLU798, ASN853, EDO1102, GLU849, GLN859.	−18.892	THR2098, TYR2104, LYS170, GLY169.
Baicalein-6-glucuronide 	−13.396	HIS855, SER854, VAL851, EDO1102, GLN859.	−10.911	TYR198, ILE172, LYS170, ASP146.
Ellagic acid 	−10.794	VAL851.	−8.386	LYS170.

naringin induces apoptosis in cancer cells. Additionally, Liping et al. studied the in vivo activity of naringin on ovarian tumor growth. Therefore, we chose naringin as a potential candidate for the preparation of the formulation using ZnO nanoparticles.

Naringin (NRG)-coated zinc oxide (ZnO) nanoparticles were prepared by a coating method reported by Poojary et al. with slight modifications.³² 1 M zinc acetate in 1.5 ml water, 1 M sodium hydroxide in 1.5 ml water, and 1 ml of prepared *Clitoria ternatea* extract were stirred at room temperature for 1.5 h. 50 mg of NRG dissolved in 1 ml of water was added and stirred for 1 h. A blank formulation was prepared without NRG loading (NB1). The resultant mixture was centrifuged for 10 min at 4000 rpm, and the supernatant was stored for further analysis. The pellets obtained were washed with water and lyophilized at 1.2 mbar pressure for 3 h (NC1 and NB1) (Figure 3). The nanoparticles were characterized by UV spectrophotometry and in-vitro analysis. The same method was applied to prepare ZnO nanoparticles using 2 ml of extract with and without NRG (NC2 and NB2, respectively).

2.2.8 Characterization of naringin-coated ZnO nanoparticles-UV analysis:

The naringin-coated ZnO nanoparticles were dispersed in water, and spectrophotometric analysis was carried out in the range of 200–400 nm by UV spectrophotometry.

2.2.9 MTT assay of the synthesized formulation:

SKOV3 Cells were seeded in a 96-well plate at a density of 10,000 cells/well and incubated overnight. After 24 h of culture, a cytotoxicity assay was performed. Cells were treated with varying concentrations (15–1000 µg) of the newly synthesized compounds for 48 h, with two replicates. Following treatment, the media was removed, and cells were incubated with MTT solution (final concentration: 0.5 mg/mL) for 4 h at 37 °C. The resulting MTT crystals

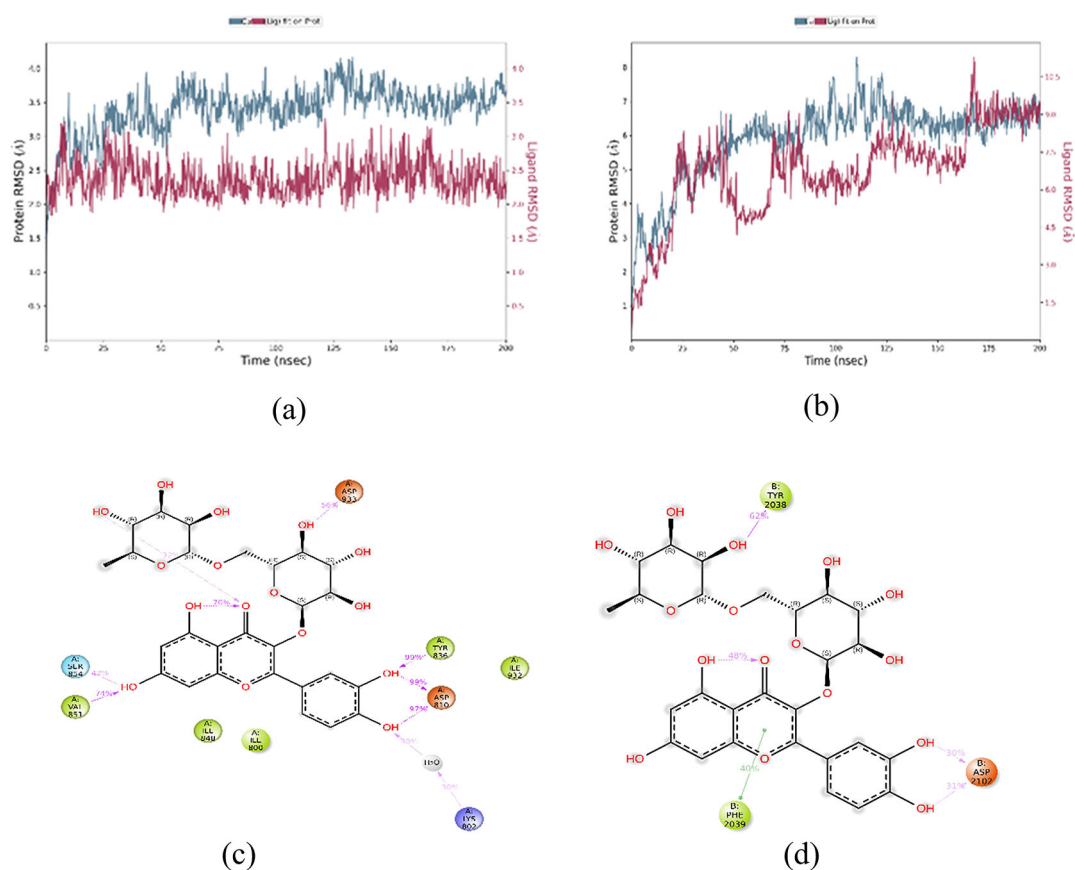


Figure 5. MD results of Quercetin-3-rutinoside: (a) RMSD and (c) protein ligand interaction of Quercetin-3-rutinoside with 5DXT (PI3K); (b) RMSD and (d) protein ligand interaction of Quercetin-3-rutinoside with 5GPG (mTOR).

were dissolved in 100 μ L DMSO, and the plates were placed on a shaker for 30 min. Absorbance was measured at 570 nm using a Multiscan Sky reader (Thermo Scientific), and the data were used to generate graphs and calculate the IC_{50} values.

3. Results

24 compounds were selected (Safira et al) that have already been shown to be present in the *Clitoria ternatea*.^{30,32} The selected compounds and their CAS numbers are listed in Table 1.

3.1 Molecular docking

Based on molecular docking studies, the docking score and interactions are depicted in Table 2 and 3 for PI3K and mTOR, respectively. Along with the selected compounds, gedatolisib, a compound currently in trials as a PI3K/mTOR inhibitor, was selected to compare the results.

After interpreting the docking results, based on the interactions and docking score, four potent compounds were selected for the MD studies. The 3D interactions of selected 4 compounds (Quercetin-3-rutinoside, Ellagic acid, Quercetin-3-7-glucoside, Baicalein-3-7-glucuronide) with both 5DXT and 5GPG PDB are shown in Figure 4. Among the four potent compounds, Quercetin-3-rutinoside showed a good docking score of -15.849 kcal/mol against 5DXT and Quercetin-3,7-glucoside showed -18.892 kcal/mol against 5GPG.

3.2 Molecular dynamic simulation

Based on the interactions and docking scores, four potent compounds were selected and used for molecular dynamics studies. Table 4 presents the docking scores and interactions of the four selected compounds.

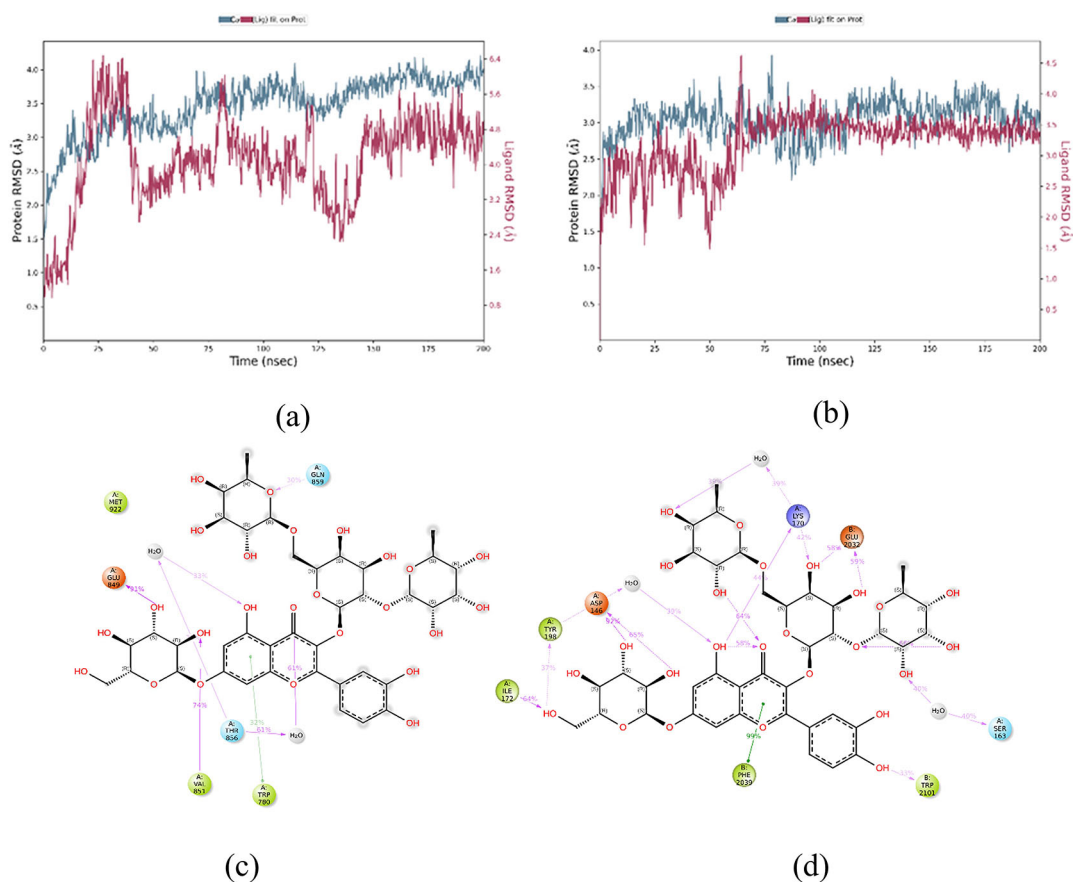


Figure 6. MD results of Quercetin-3,7-glucoside: (a) RMSD and (c) protein ligand interaction of Quercetin-3,7-glucoside with 5DXT(PI3K); (b) RMSD and (d) protein ligand interaction of Quercetin-3,7-glucoside with 5GPG (mTOR).

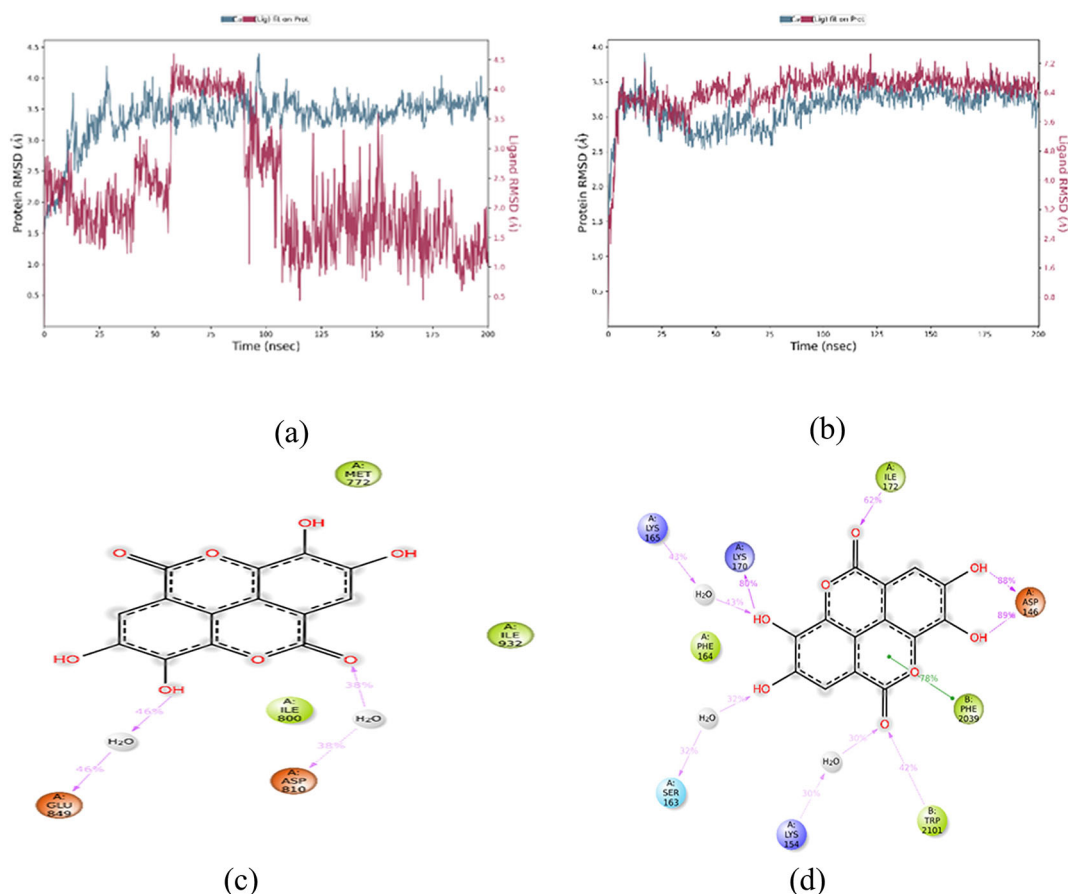


Figure 7. MD results of Ellagic acid: (a) RMSD and (c) protein ligand interaction of Ellagic acid with 5DXT(PI3K); (b) RMSD and (d) protein ligand interaction of Ellagic acid with 5GPG (mTOR).

By performing molecular dynamics simulation studies, we can observe the changes in the structure and parts of the structure over time. Figure 5-8 represents the MD results of all four potent compounds with both PI3K and mTOR PDB, and Figure 9 shows the MD results of gedatolisib. Each MD result contains the Root Mean Square Deviation (RMSD) graph, protein-ligand contact 2D diagram, and protein-ligand interaction histogram.

3.3 ADME studies

Toxicity studies were performed using the QikProp tool in Schrödinger, and the results are listed in Table 5. Based on the rule of five, the compounds are classified as shown by the number of violations (such as molecular weight more than 500) are seen in them.

3.4: Liquid Chromatography- Mass Spectrometry (LCMS)

Liquid Chromatography-Mass Spectrometry was used to analyze the components present in the prepared CT samples. Figure 10 shows the LC-MS spectra of the prepared extracts. Plant parts are often used as phytochemicals. In LCMS, the LC component separates the physicochemical components of the sample, whereas MS analyzes the mass of the component present in the sample. Figure 10 shows that certain components that are reported to be present in the sample such as Baicalein-6-glucuronide can be seen in the spectra. We restricted our study to CT flowers, but, as reported earlier, other parts of the plant, such as leaves and roots, also have medicinal importance. Other medically important phytochemicals may be present in different parts of the plant, which will be explored in the future.

3.5: UV analysis results of naringin-coated ZnO nanoparticles

The absorbance maxima of the naringin and *Clitoria ternatea* flower extracts were observed at 540 nm. The UV spectrum of NRG-coated ZnO nanoparticles in water is shown in Figure 11. The spectrum revealed a peak at 360 nm, which is the characteristic peak of ZnO nanoparticles (Figure 11).

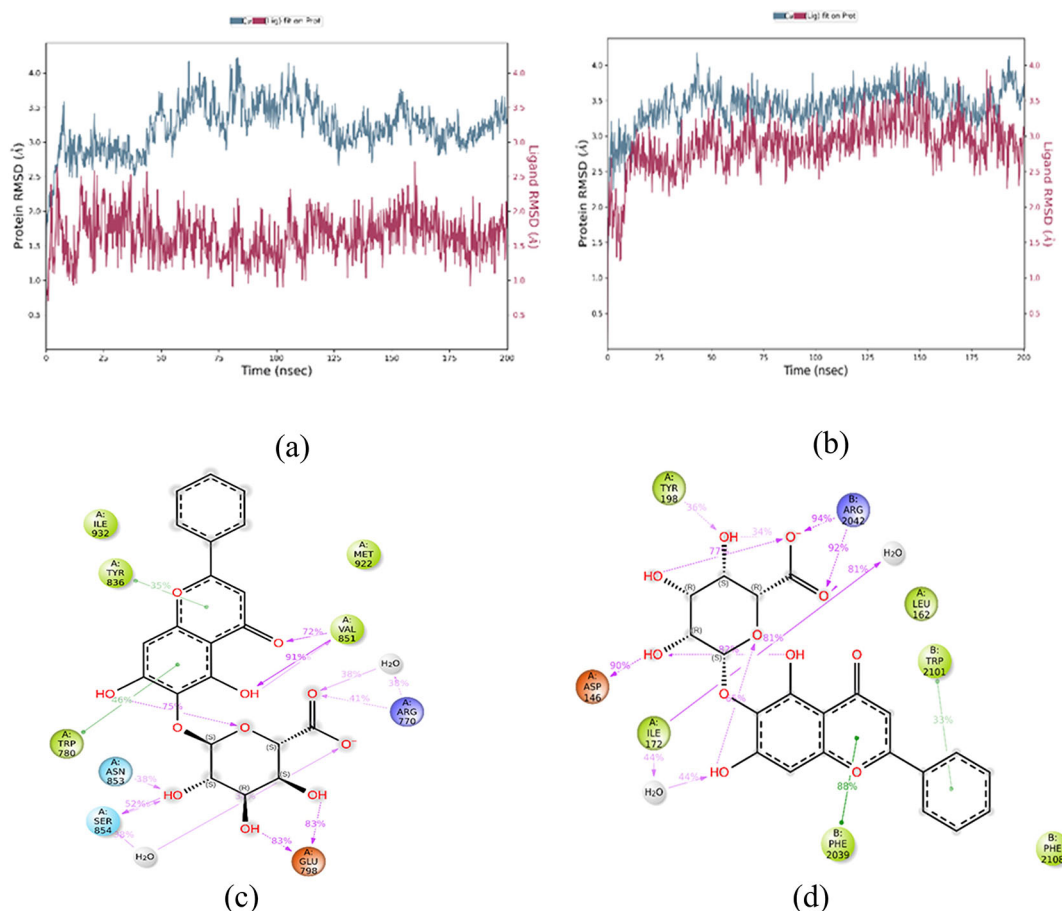


Figure 8. MD results of Baicalein-6-glucuronide: (a) RMSD and (c) protein ligand interaction of Baicalein-6-glucuronide with 5DXT(PI3K), (b) RMSD and (d) protein ligand interaction of Baicalein-6-glucuronide with 5GPG (mTOR).

3.6 MTT cytotoxicity assay

The data obtained after the MTT assay were analyzed to evaluate the cytotoxicity of the developed formulations. Based on these values, five graphs were plotted, and the IC₅₀ values were calculated. Figure 12 shows the graphs obtained after MTT analysis. In all five graphs, concentrations were taken along the X-axis and the average cell count was plotted against the Y-axis. From the five graphs, we can see that there is a significant decrease in the cell count with an increase in the concentration of the formulation. This decrease in cell count indicates cell death due to the formulation being treated. Based on this, IC₅₀ values were calculated and are listed in table 6. From this study, we can conclude that both the formulation and blank showed significant cytotoxicity, paving the way for further *in-vitro* and *in-vivo* studies to use this formulation against ovarian cancer. Figure 13 illustrates the concentration-dependent cytotoxicity profile obtained from the MTT assay, where the percentage cell viability was plotted against concentration. Among the prepared formulations, NC1 demonstrated a marked reduction in cell viability with increasing concentrations.

4. Discussions

When compared with the standard inhibitor gedatolisib (Tables 2 and 3), the docking scores of the compounds identified from *Clitoria ternatea* (CT) flowers exhibited more negative values, indicating stronger binding affinity and potentially higher potency. All four selected compounds (Quercetin-3-rutinoside, Ellagic acid, Quercetin-3-7-glucoside, Baicalein-3-7-glucuronide) demonstrated favorable interactions with the key amino acid residues of the target proteins.

The root mean square deviation (RMSD) is a quantitative measure used to evaluate structural deviations of a protein–ligand complex with respect to a reference structure over the simulation time. RMSD plots provide insights

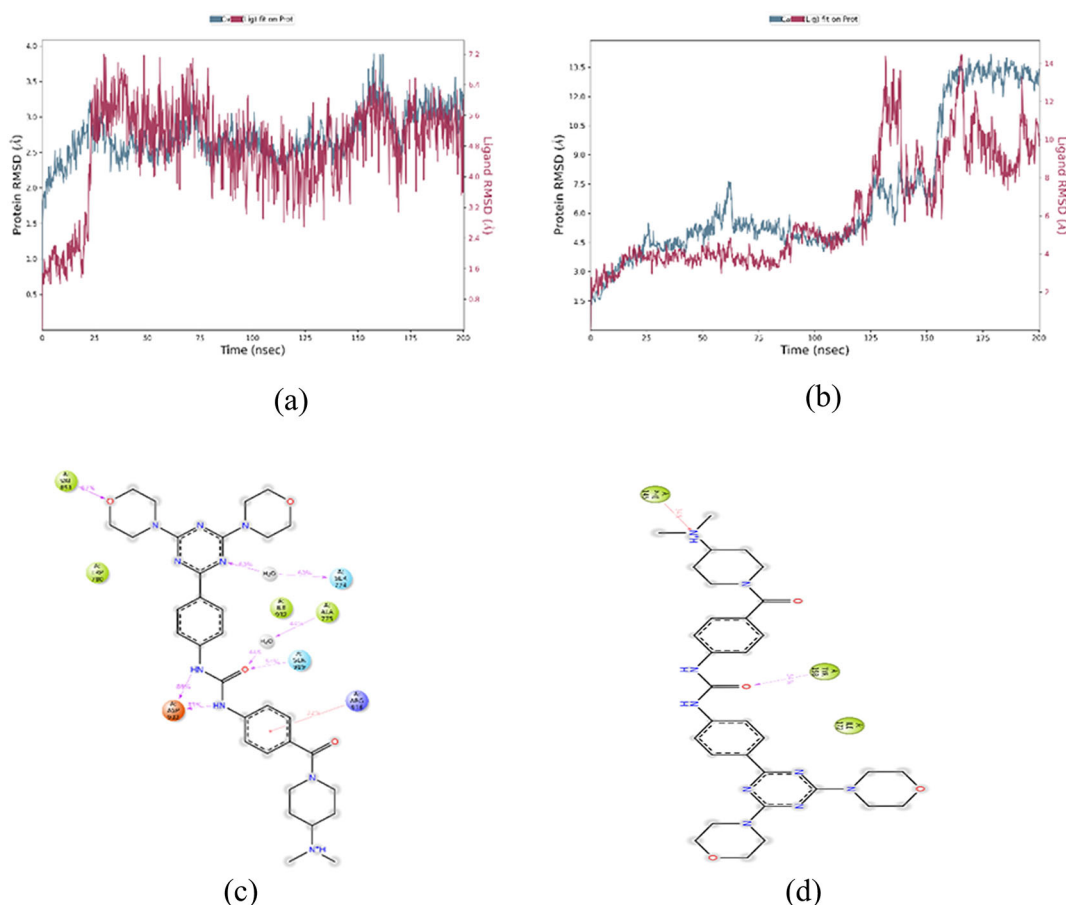


Figure 9. MD results of gedatolisib: (a) RMSD and (c) protein ligand interaction of gedatolisib with 5DXT(PI3K); (b) RMSD and (d) protein ligand interaction of gedatolisib with 5GPG (mTOR).

into protein stability and equilibration, where a plateau in the curve indicates the attainment of equilibrium. Upon comparison of the RMSD profiles, the complexes of quercetin-3-rutinoside with 5GPG and 5DXT reached equilibrium toward the end of the simulation period, as depicted in Figure 5. The RMSD plots of ellagic acid with 5GPG and baicalein-6-glucuronide with 5GPG Figures 7 and 8 showed similar behavior, with equilibrium attained at the initial stages and maintained throughout the 200 ns simulation. In contrast, the quercetin-3,7-glucoside with 5GPG complex achieved equilibrium after 75 ns and remained stable until the end of the simulation, as shown in Figure 6.

RMSD, along with docking scores and retention of crucial interactions, is an important criterion for selecting potent lead molecules. Histogram analysis confirmed that key interactions were consistently retained throughout the molecular dynamics (MD) simulations for both PI3K and mTOR proteins (Figures 5 and 6), with all four compounds exhibiting conserved interactions. Notably, ellagic acid also demonstrates essential interactions with PI3K.

Among the eight MD simulations performed, quercetin-3-rutinoside and quercetin-3,7-glucoside emerged as the most promising candidates (Figures 5 and 6). Both compounds exhibited stable binding and conformational integrity throughout the 200 ns MD simulations. Additionally, MD simulations were conducted for the standard compound gedatolisib (Figure 9), and comparative analysis revealed that CT-derived flavonoids displayed superior stability relative to gedatolisib.

The ADME profiles of the selected 24 compounds are summarized in Table 5. Several compounds complied with Lipinski's rule of five; however, they did not consistently exhibit the crucial molecular interactions observed for some compounds that violated the rule. Notably, quercetin-3-rutinoside and quercetin-3,7-glucoside demonstrated superior

Table 5. ADME results of 24 compounds.

Compound	MW	Donor HB	Acceptor HB	SASA	QLogPo/w	QLogBB	QLogS	%human oral absorption	Obeded rule of five
Epicatechin	290.272	2	2	495.637	1.393	-1.879	-3.678	58.492	No
Delphinidin chloride	338.701	2	1.5	490.289	1.309	-2.359	-3.486	51.222	No
Ternatin	374.346	1	6	595.168	2.909	-0.927	-3.983	94.396	Yes
Myricetin	318.239	1	3.5	485.767	0.584	-2.473	-2.932	46.038	No
Quercetin	302.24	1	3.75	455.795	0.409	-2.074	-2.498	61.013	Yes
Kaempferol	286.24	1	4	427.511	0.41	-1.502	-2.107	67.543	Yes
Apigenin	270.241	1	4.25	376.34	0.095	-1.077	-1.362	69.072	Yes
Luteolin	286.24	1	4	385.296	0.017	-1.473	-1.409	62.092	Yes
Baicalein	270.241	1	3	389.463	0.537	-1.167	-1.907	71.076	Yes
Baicalein-6-glucuronide	446.367	4	11.25	512.604	-1.783	-2.064	-2.496	17.248	No
Quercetin-3,7-glucoside	918.809	14	35.850	1157.591	-5.571	-7.564	-1.273	0.000	No
Quercetin-3-O-Rhamnoside	-	-	-	-	-	-	-	-	-
Quercetin-3-Rutinoside ¹⁸	611	10	16	240.90	-1.69	-1.90	-2.89	23.45	No
Gallic acid	170.121	1	2	268.398	-0.545	-1.177	0.052	60.041	Yes
Syringic acid	198.175	2	3.5	391.551	0.453	-0.66	-1.939	67.833	No
2-hydroxycinnamic acid	164.16	2	2.25	347.293	0.284	-0.74	-1.407	77.558	Yes
Protocatechuic acid	154.122	1	2.25	259.441	-0.453	-0.826	0.068	67.101	Yes
2,4-dihydroxy benzoic acid	154.122	1	2.25	258.553	-0.387	-0.745	0.081	69.485	Yes
p-Coumaric acid	164.16	2	2.25	292.216	-0.125	-0.645	-0.536	73.312	Yes
Caffeic acid	180.16	3	3	301.155	-0.667	-1.01	-0.385	63.614	Yes
Ferulic acid	194.187	2	2.25	318.714	0.184	-0.648	-0.948	75.686	Yes

Table 5. *Continued*

Compound	MW	Donor HB	Acceptor HB	SASA	QPlogPo/w	QPlogBB	QPlogS	%human oral absorption	Obeded rule of five
Procyanidin A2 ¹⁸	576.51	9	12	236.26	2.79	-1.77	-2.89	69.46	No
Delphinidin-3-O-glucoside	465.39	9	11	184.53	0.088	-2.16	-2.89	32.50	No
Ellagic acid	302.197	0	6	349.905	-1.811	-1.673	0.945	43.621	Yes

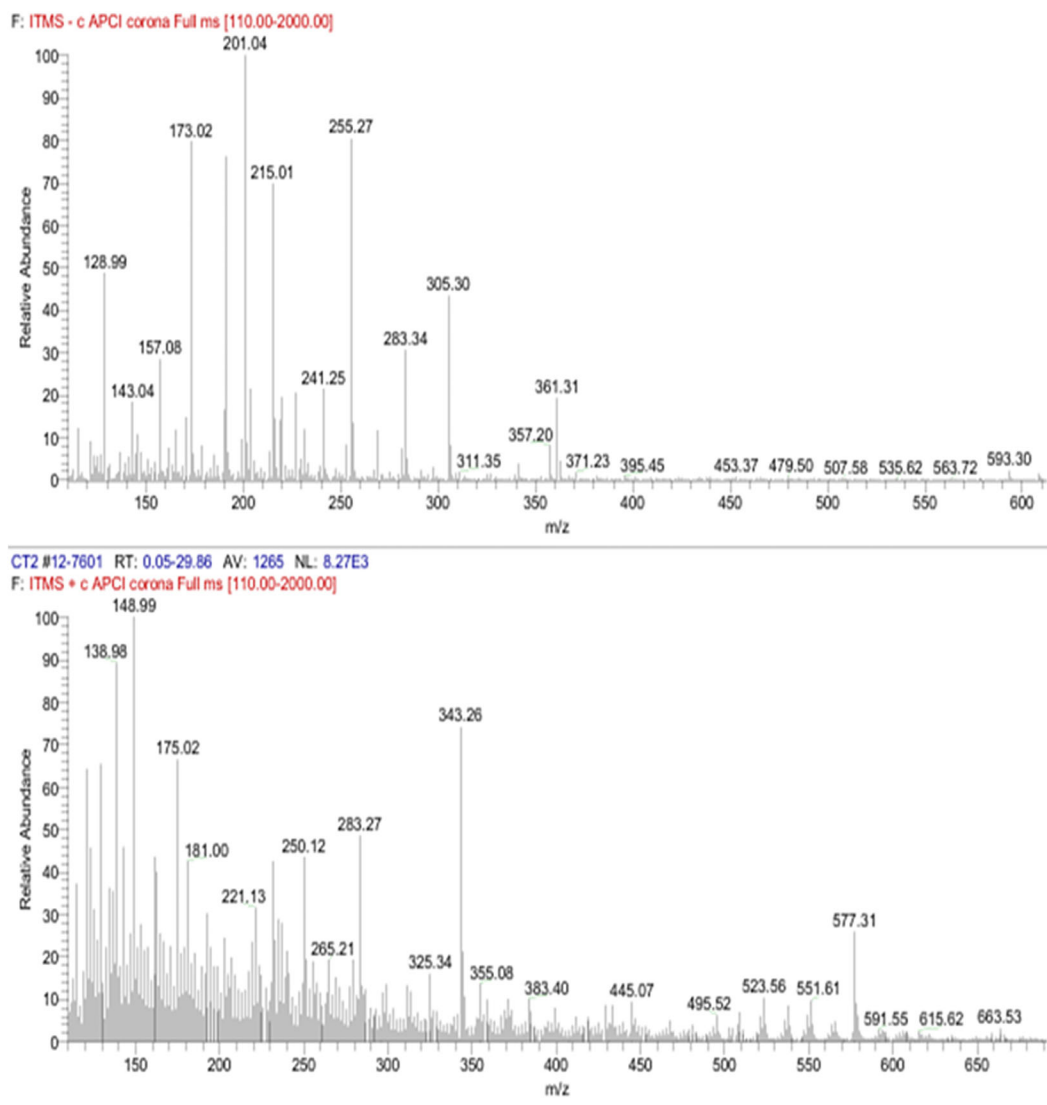


Figure 10. LCMS spectra of the prepared flower extract.

docking and MD performance, despite violating Lipinski's criteria. Because Lipinski's rule primarily applies to small molecules with molecular weights below 500 Da, it may not fully encompass the drug-likeness of natural products. Importantly, the core scaffold of both compounds was quercetin, which satisfied Lipinski's rule. Therefore, considering their strong binding affinity and stable interactions, these compounds are promising candidates for further experimental validation, including enzyme inhibition and cell-based assays.³¹

From Table 6 it is observed that the formulation NC1 showed an IC_{50} value of $144 \pm 2.43 \mu\text{g/mL}$ and NC2 was $251.4 \pm 3.00 \mu\text{g/mL}$. Among the four naringin-coated ZnO formulations prepared using CT flower extracts (NB1, NC1, NB2, and NC2), NC1 exhibited enhanced cytotoxic activity, achieving lower cell viability at reduced concentrations. Although all formulations showed comparable cell viability at the highest concentration ($500 \mu\text{g/mL}$), NC1 showed the lowest viability at lower doses, indicating improved efficacy. The synergistic effect of naringin and CT extracts in the NC1 formulation resulted in a significant decrease in cell viability, with a lower IC_{50} value of $144 \pm 2.43 \mu\text{g/mL}$. Therefore, from this study, we can conclude that among the two prepared formulations, NC1 showed better cytotoxicity; however, there is scope for further superior IC_{50} values using different sets of formulations with CT flower extract. In the future, different concentrations of CT flower extract can be used to prepare formulations to obtain better cytotoxicity and IC_{50} values.

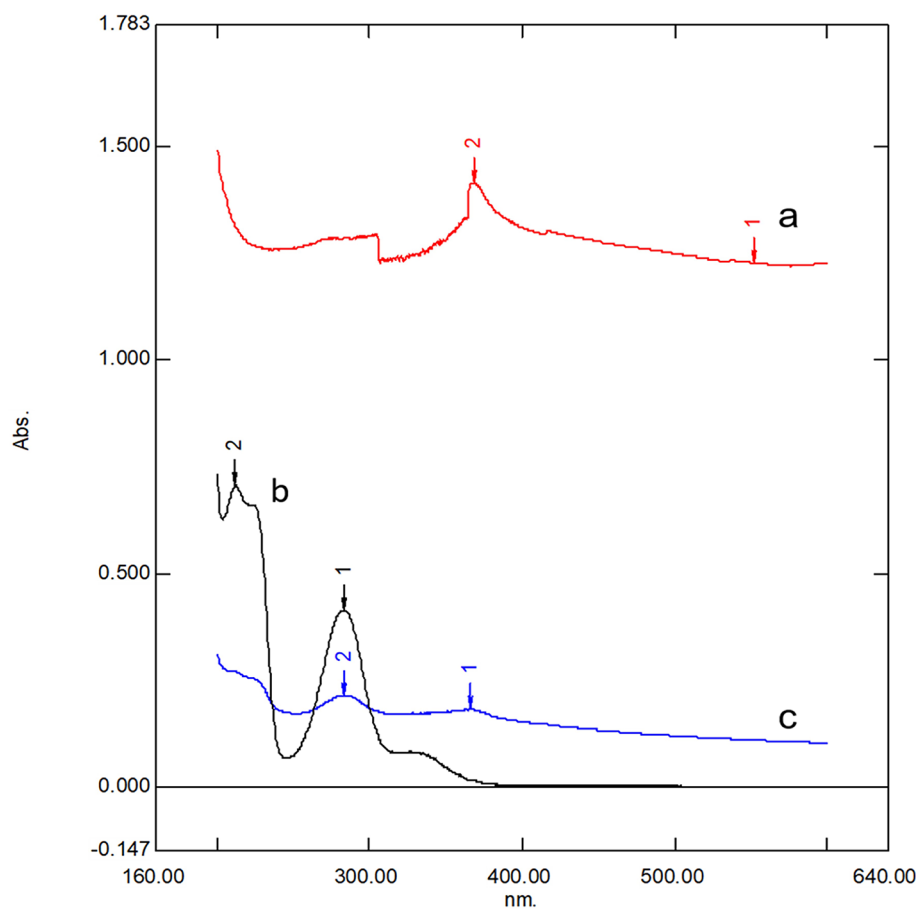


Figure 11. UV spectra of a) blank formulation, b) NRG (50 mg), and c) Formulation (equivalent to 50 mg NRG) indicating the presence of Extract and the formation of Zinc oxide nanoparticles.

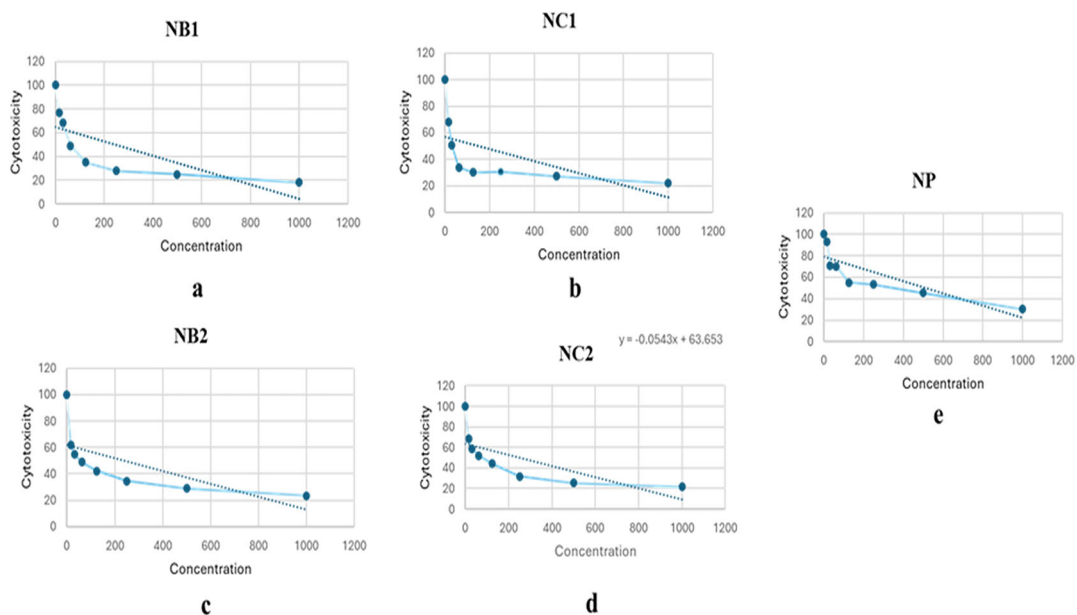
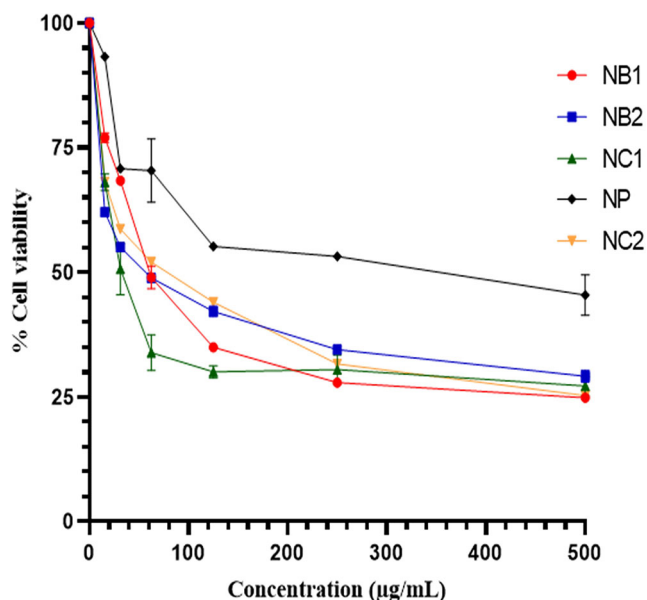


Figure 12. Plots obtained from MTT assay.

Table 6. IC50 values of the formulations and standard.

Formulation	CT flower extract (mL)	NRG (50 mg/MI)	IC50 ($\mu\text{g/mL}$)
NB1	1 mL	0 mL	248.8 ± 1.48
NC1	1 mL	1 mL	144 ± 2.43
NB2	2 mL	0 mL	235.5 ± 2.28
NC2	2 mL	1 mL	251.4 ± 3.00
NP	0 mL	1 mL	509.6 ± 2.44

**Figure 13.** Cell viability v/s concentration plot for prepared formulations against SKOV3 ovarian cancer cell lines using MTT assay method.

5. Conclusion

Natural compounds are part of the human world. In recent years, several studies have focused on the chemistry of natural products. In our study, using the reported compounds that are present in *Clitoria ternatea* flowers, we found that there are four potent compounds that strongly inhibit both PI3K and mTOR proteins. Furthermore, after the docking and MD studies, we found that of the four compounds, Quercetin-3-rutinoside and Quercetin-3,7-glucoside were quite stable throughout the MD and had all the crucial interactions. To enhance efficacy, we developed a nanoformulation incorporating naringin, which is reported to be effective against ovarian cancer. Naringin-coated zinc oxide nanoparticles were prepared using *Clitoria ternatea* flower extract. The formulation was evaluated for cytotoxicity in the SKOV3 ovarian cancer cell line. The MTT assay for cytotoxicity revealed that the naringin-coated ZnO nanoparticle formulations caused cancer cell death. The results of this study demonstrate the potential of the natural compounds present in *Clitoria ternatea* flowers to inhibit the growth of ovarian cancer cells SKOV3. These findings are also supported by in silico studies, wherein it is evident that the compounds present in the CT flower can inhibit the PI3K/mTOR pathway in ovarian cancer. From this study, it can be concluded that *Clitoria ternatea* flowers can be used to prepare different sets of formulations with varied concentrations to further validate the findings against ovarian cancer. Due to current limitations, in vivo experiments involving different animal models were not included in this study but are intended to be explored in future research.

Abbreviations

OC: Ovarian Cancer

PI3K: Phosphoinositide 3-Kinase

mTOR: Mammalian Target of Rapamycin

CT: *Clitoria Ternatea*
MD: Molecular Dynamics
PDB: Protein Data Bank

Human ethics approval and consent to participate

Not applicable.

Data availability

All the data generated in this study are presented in this article.

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