The 8th International Electronic Conference on Medicinal Chemistry (ECMC 2022)
01–30 NOVEMBER 2022 | ONLINE

EXPLORATORY STUDIES ON ANTICANCER POTENTIAL OF A VERNONIA SPECIES AGAINST COLORECTAL ADENOCARCINOMA: *IN VITRO* STUDIES AND *IN SILICO* MECHANISTIC INVESTIGATIONS

Chaired by DR. ALFREDO BERZAL-HERRANZ;
Co-Chaired by PROF. DR. MARIA EMÍLIA SOUSA

pharmaceuticals MDPI

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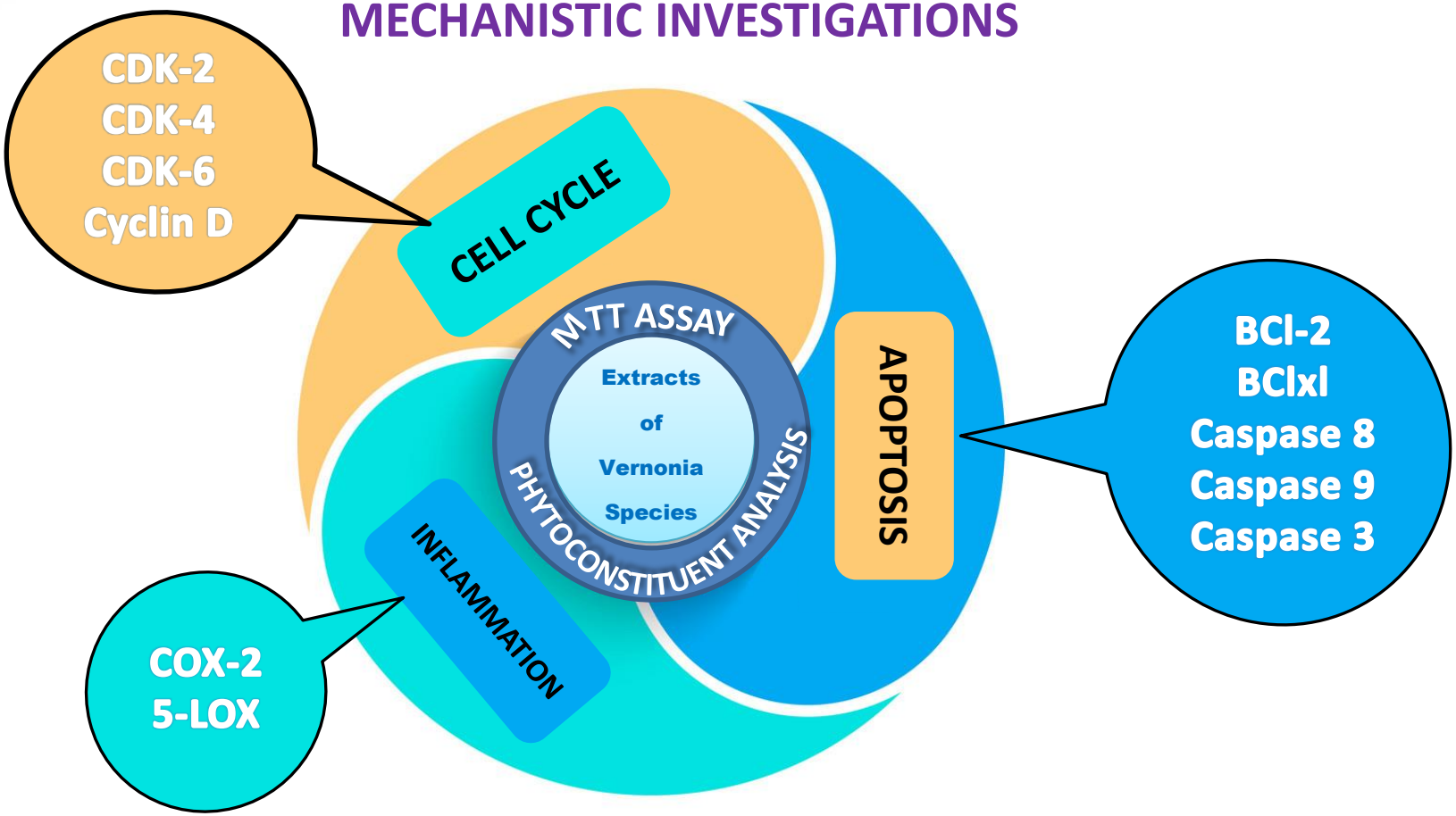
EXPLORATORY STUDIES ON ANTICANCER POTENTIAL OF A VERNONIA SPECIES AGAINST COLORECTAL ADENOCARCINOMA: IN VITRO STUDIES AND IN SILICO MECHANISTIC INVESTIGATIONS



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ABSTRACT

Globally, colorectal cancer (CRC) is amongst the top prevalent cancer incidences being the second most common amongst women and third most common amongst men as revealed by ‘GLOBOCAN 2022’ statistics. The projected morbidity for colorectal cancer is more than 3 million by the year 2040 according to the ‘WHO Cancer Tomorrow’’ predictions. Surgery, chemotherapy, and radiation therapy continue to remain the primary treatment options, each accompanied by their limitations. There is a growing need for identification of alternate therapies for treatment of the same to overcome the shortfalls of these treatment options. Phytoconstituents offer diverse pharmacophoric scaffolds with unique chemical features. Hence, in this work, phytoconstituents of a Vernonia species have been investigated wherein exploratory in vitro studies on successive extracts of aerial plant parts have been carried out. In vitro testing has been done on colorectal adenocarcinoma cell lines by MTT assay and compared with 5-Flurouracil as reference standard. In silico docking studies have been carried out on the plausible phytoconstituents of the active extracts against vital protein targets involved in the progression of CRCs. These studies will help in probing the mechanistic details of the anticancer activity and provide platform for development of novel multi-targeted small molecules.

Keywords: Colorectal cancer; Phytoconstituents; Docking; Proteins

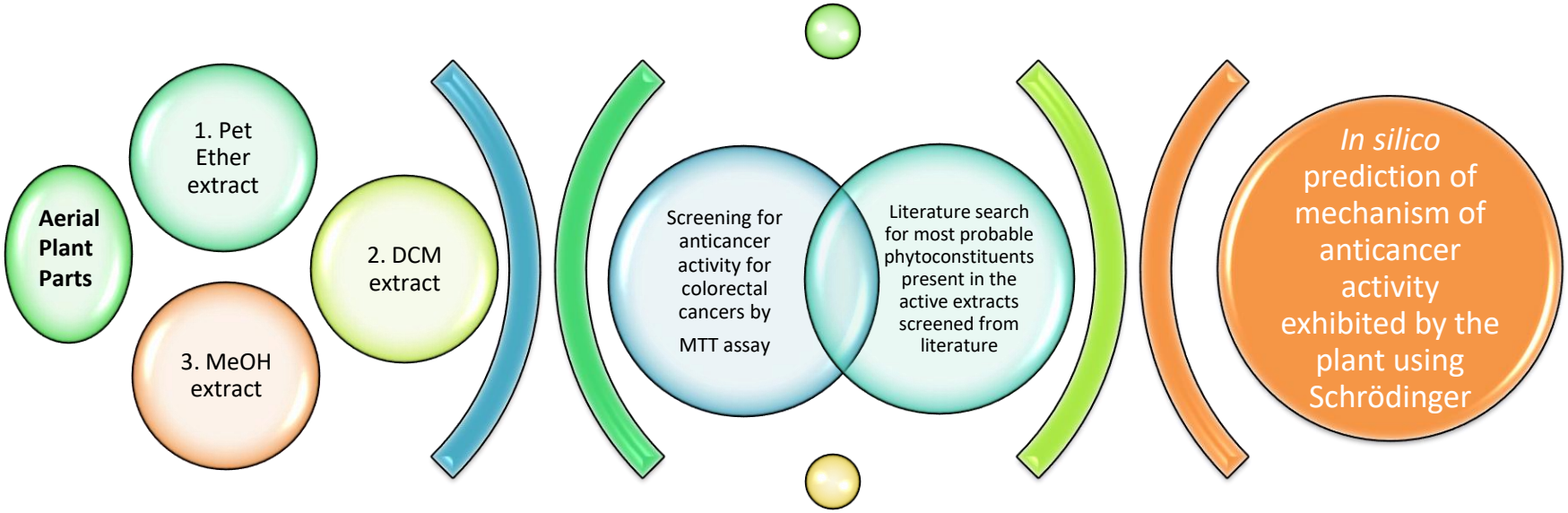
INTRODUCTION

- There is a rise in the global burden of colorectal cancers, with a prediction of over 3.2 million new cases by 2040.
- Death due to colorectal cancers accounts for 1.4% of the total deaths globally. The WHO statistics for the year 2020 depict 1.93 million new cases and about 9,00,000 deaths due to colorectal cancers.
- Surgery, chemotherapy and radiation therapy continue to be the frontline treatment modalities, each with well documented side effects.
- Medicinal plants offer lucrative alternative to synthetic drugs, since the isolated phytoconstituents not only offer unique structural features, but also offer selective toxicity towards the malignant cell masses.

INTRODUCTION

- Family Asteraceae comprises of about 1600 genera and 30,000 species of flowering plants. Important phytoconstituents such as flavonoids, alkaloids, terpenes and sesquiterpenes are known to be abundantly present in the plants of this family.
- In this work, we explored the anticancer potential of a Vernonia species of this family against colorectal adenocarcinomas.
- Using the in silico **SCHRÖDINGER RELEASE 2022-3**: GLIDE, SCHRÖDINGER, LLC, NEW YORK, NY, 2021 software, we attempted to propose the mechanism of anticancer activity exhibited by the phytoconstituents known to be present in this plant.

ROADMAP OF WORK UNDERTAKEN



STEP I

PREPARATION OF SUCCESSIVE EXTRACTS

STEP II

SCREENING FOR ANTICANCER ACTIVITY

STEP III

EXPLORATORY IN SILICO MECHANISTIC STUDIES USING **SCHRÖDINGER RELEASE 2022-3**: GLIDE, SCHRÖDINGER, LLC, NEW YORK, NY, 2021. SOFTWARE

EXPERIMENTAL

STEP I

PREPARATION OF SUCCESSIVE EXTRACTS

- The plant material was collected by Dr. Vinayak Naik (Piramal Life Sciences) and was authenticated at Botanical Survey of India, Pune.
- Successive extracts were prepared by treating the dried powdered aerial plant parts with solvents like petroleum ether (PE), dichloromethane (DCM) and methanol (MeOH), and evaporated in vacuo.

EXPERIMENTAL

STEP 2

SCREENING FOR ANTICANCER ACTIVITY

- The extracts were dispersed in cell culture grade DMSO, suitably diluted with nutrient medium and used for in vitro analysis.
- MTT assay was performed on two colorectal cancer cell lines: Colo205 and HT29 after 24 hrs exposure to varying concentrations of the above prepared extracts.

EXPERIMENTAL

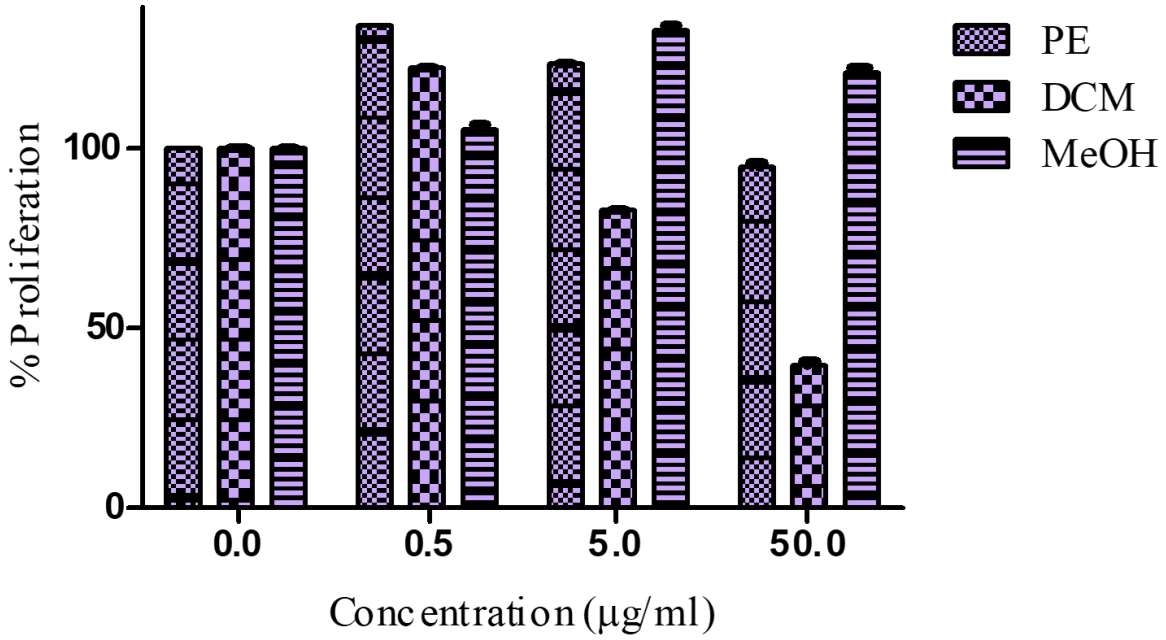
STEP III

EXPLORATORY IN SILICO MECHANISTIC STUDIES USING **SCHRÖDINGER RELEASE 2022-3**: GLIDE, SCHRÖDINGER, LLC, NEW YORK, NY, 2021. SOFTWARE

- The phytoconstituents known to be present in the plant were then screened *in silico* on key enzyme targets in pathways responsible for survival & growth of cells, and inflammation.
- Promising *in silico* predictions may be tested further experimentally to reinforce the mechanistic insights gained for the bioactive phytoconstituents.

RESULTS AND DISCUSSION

Screening of extracts of Vernonia species on Colo205 by MTT assay (24 hr exposure)



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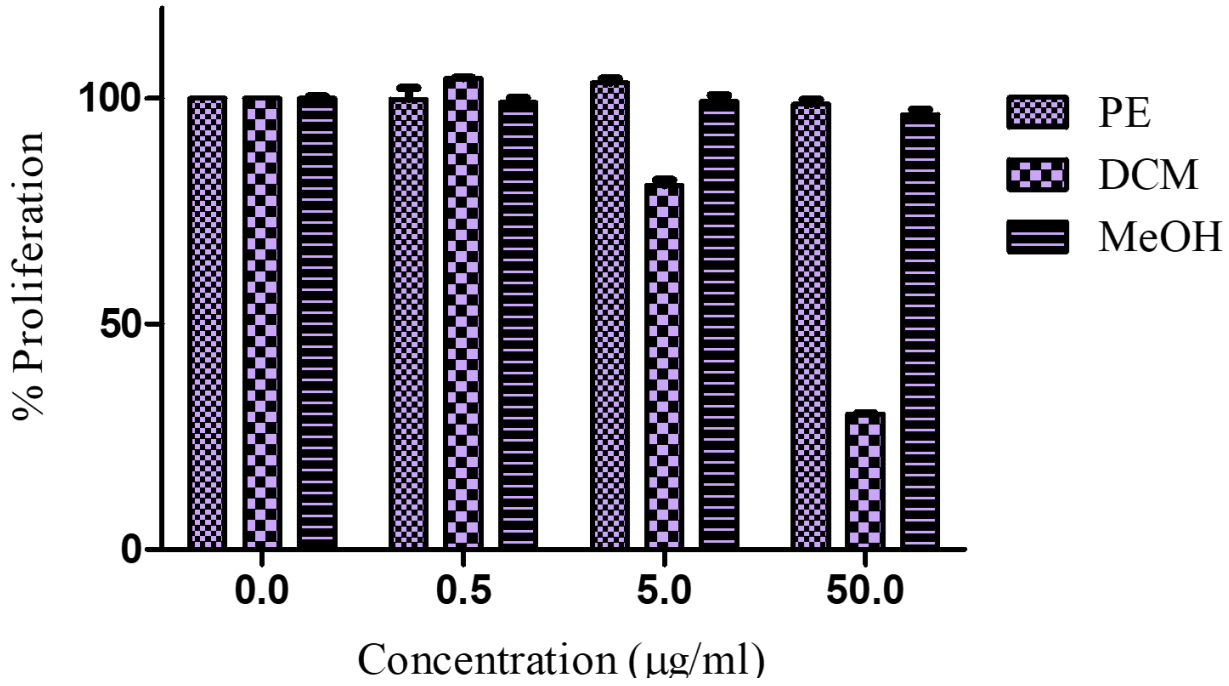
RESULTS AND DISCUSSION

Screening of extracts of Vernonia species on HT29 by MTT assay (24 hr exposure)



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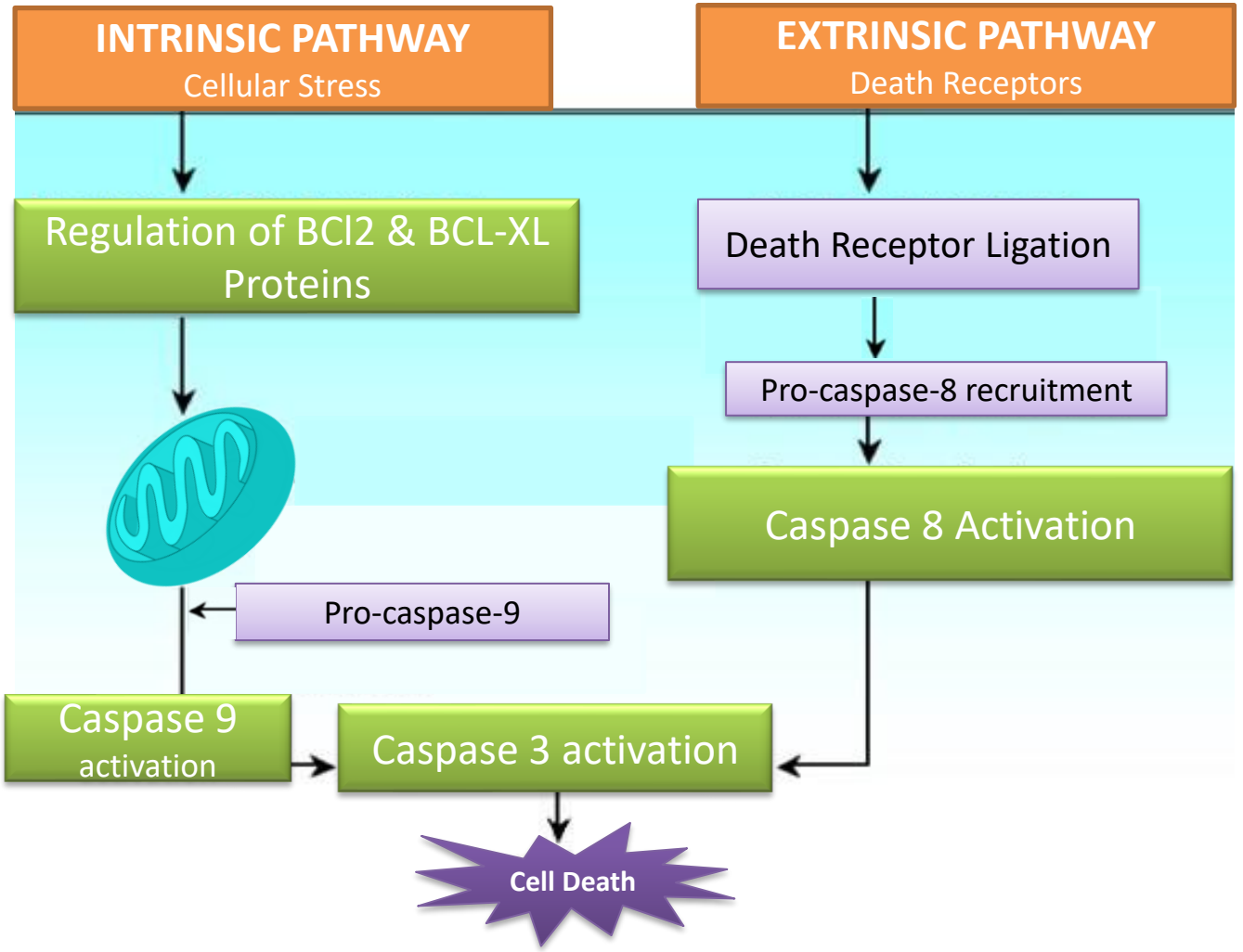
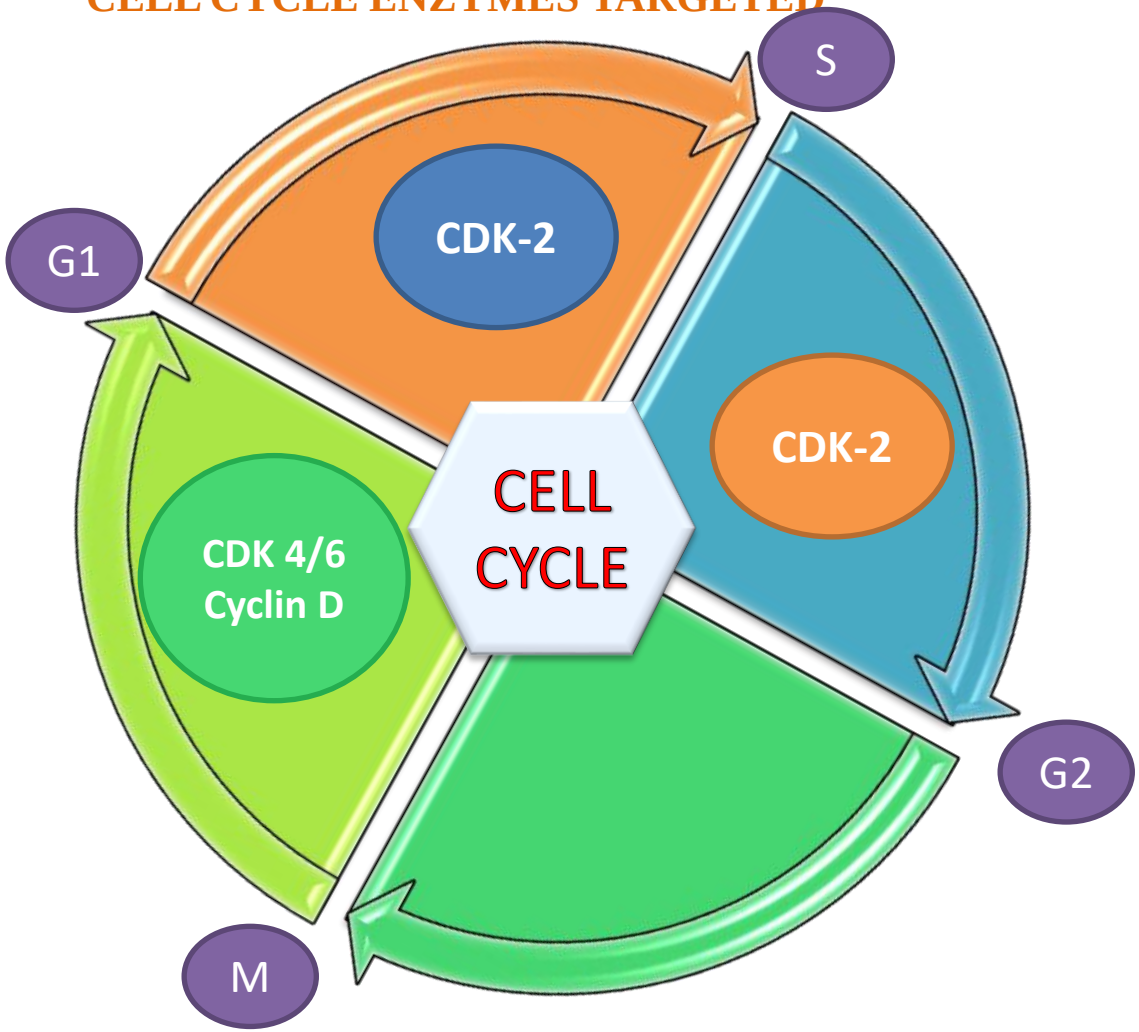
RESULTS AND DISCUSSION

APOPTOTIC PATHWAY

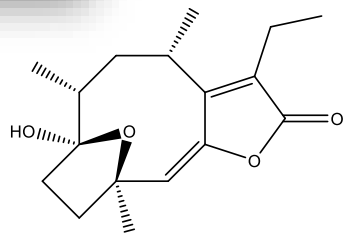


RESULTS AND DISCUSSION

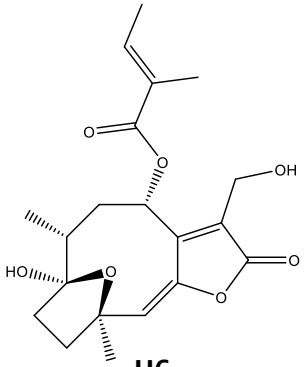
CELL CYCLE ENZYMES TARGETED



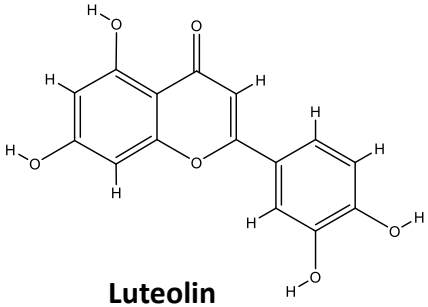
RESULTS AND DISCUSSION



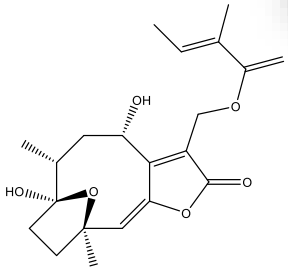
8-hydroxy-13-Otigloyl-hirsutinolide



H6

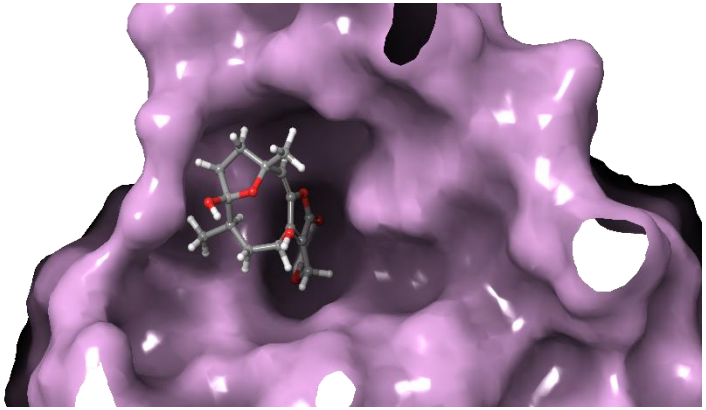


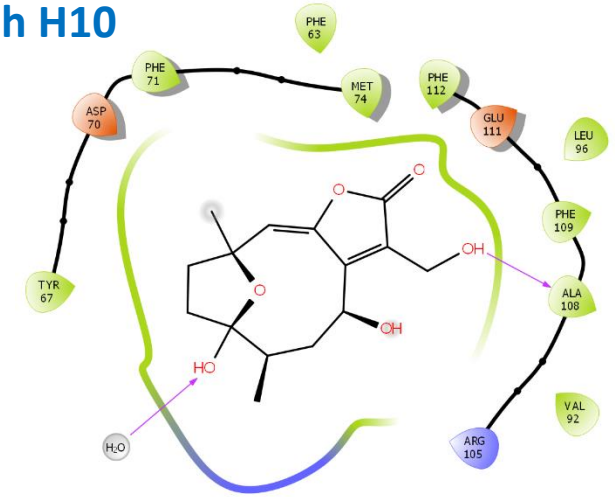
Luteolin



8-(4-hydroxytigloyloxy)hirsutinolide

BCl2 interactions with H10





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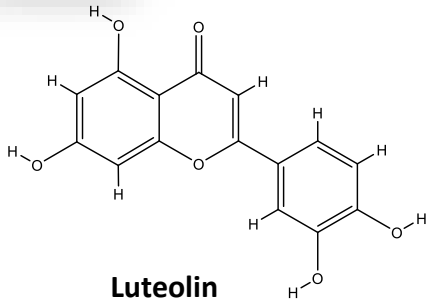
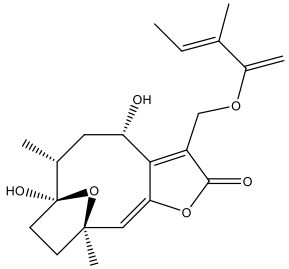
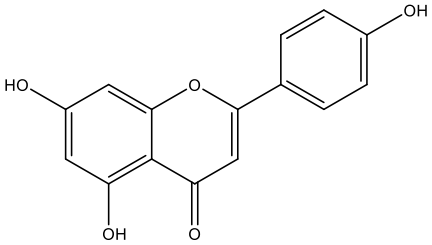


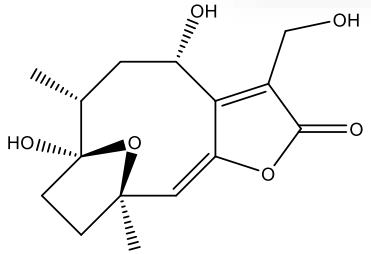
Luteolin



8-(4-hydroxytigloyloxy)hirsutinolide

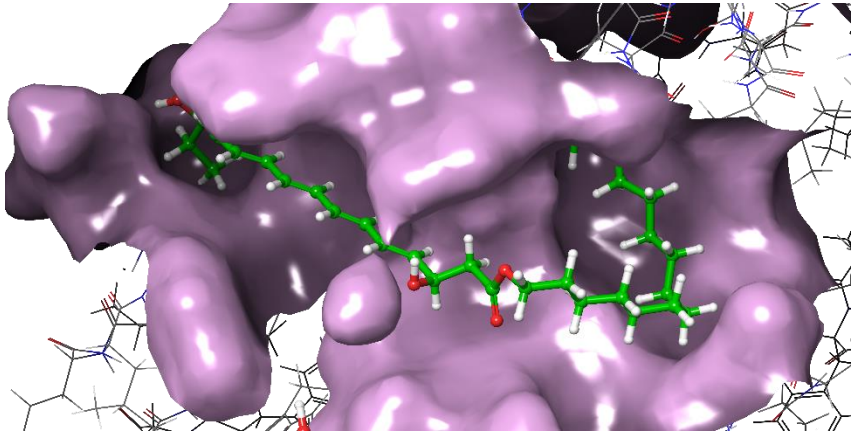


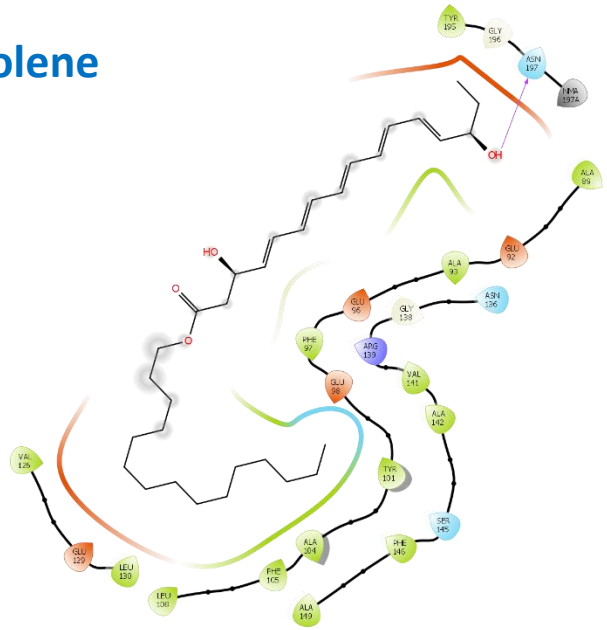
Hirsutinolide structure 15



H10

BClxl interactions with Urticofolene





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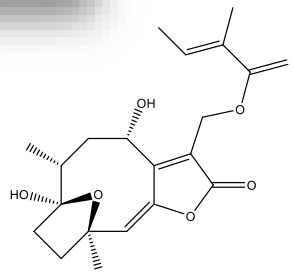
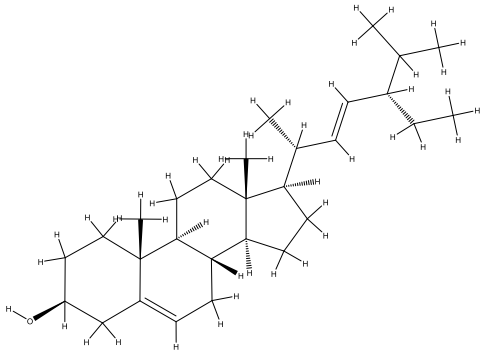
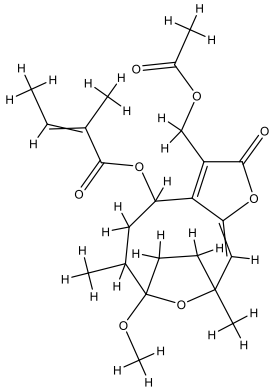


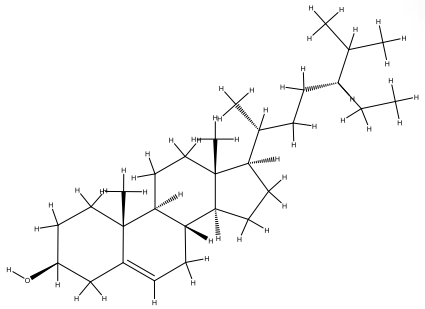
8-(4-hydroxytigloyloxy) hirsutinolide



Stigmasterol

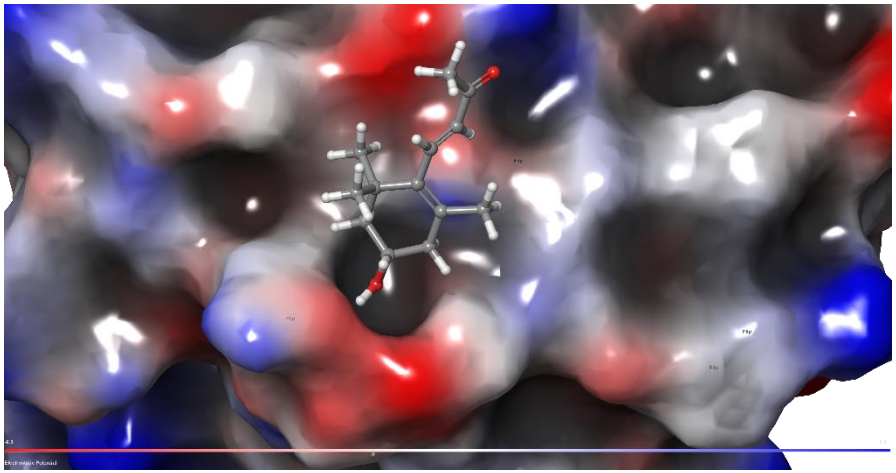


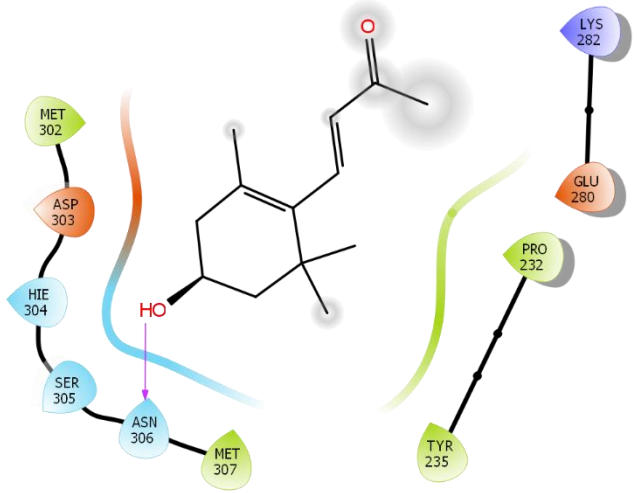
Vernolide B



β-Sitosterol

Caspase 8 interactions with H14





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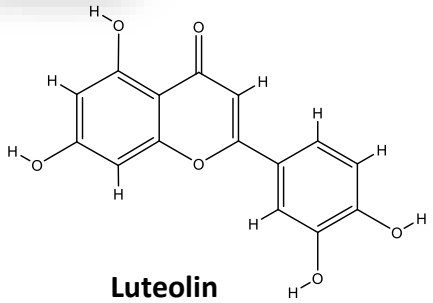
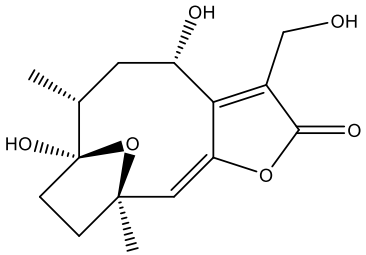
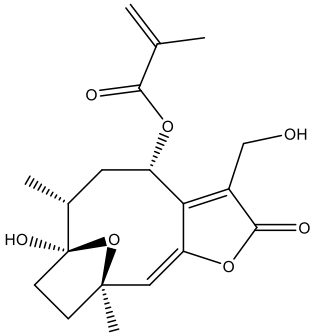


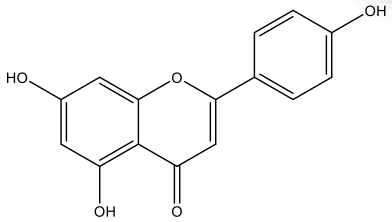
Luteolin



H10

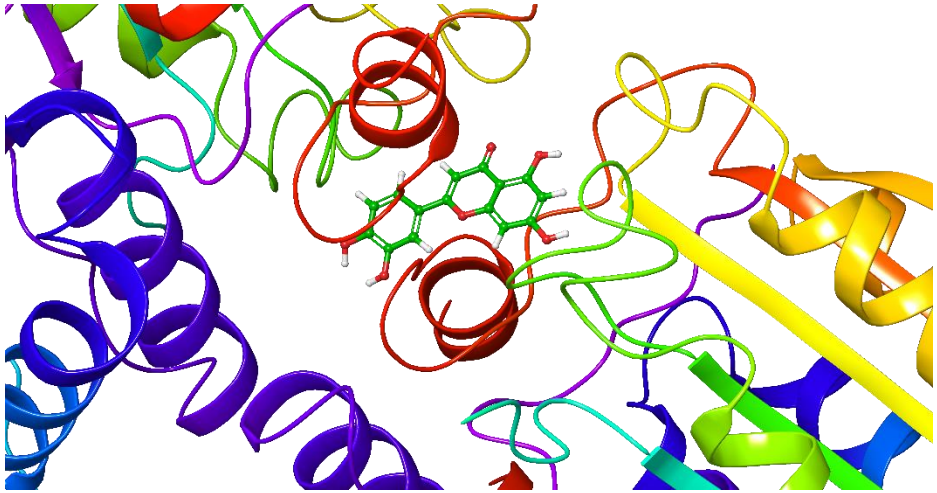


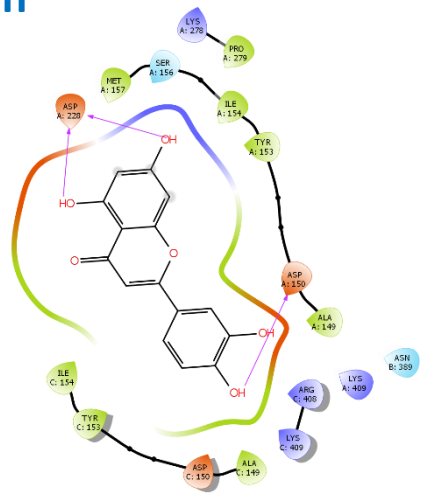
H5



Hirsutinolide structure 15

Caspase 9 interactions with Luteolin





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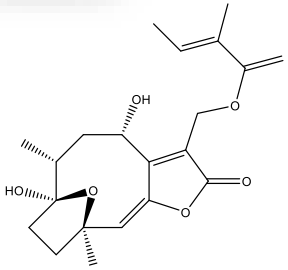
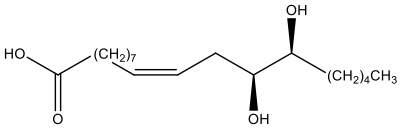
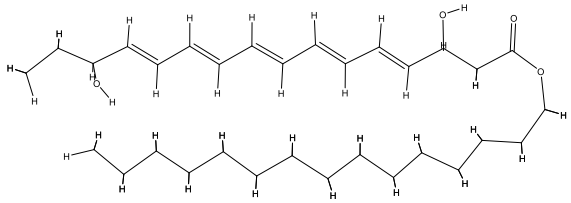


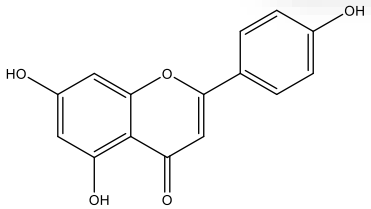
8-(4-hydroxytigloyloxy) hirsutinolide



Hirsutinolide structure 16

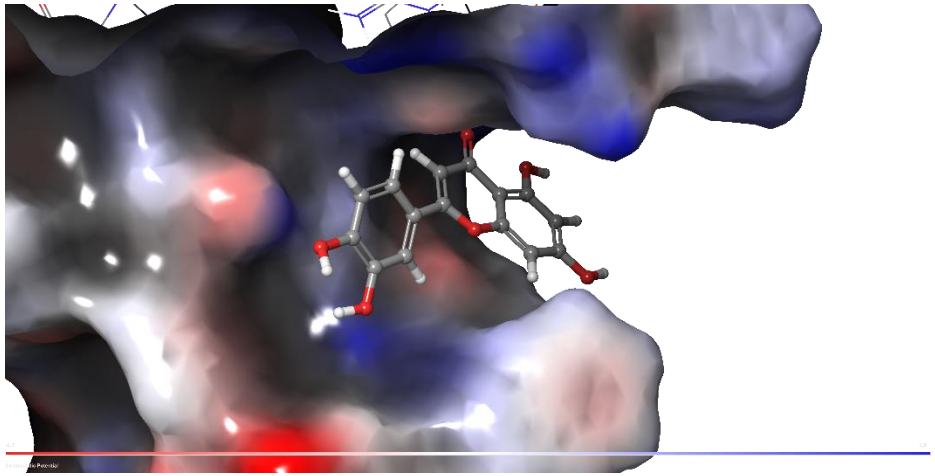


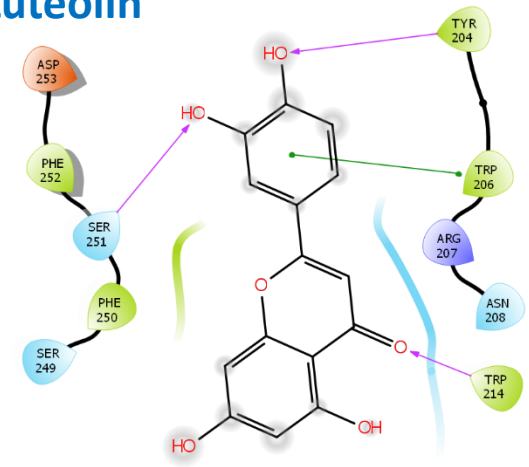
Urticifolene



Hirsutinolide structure 15

Caspase 3 interactions with Luteolin





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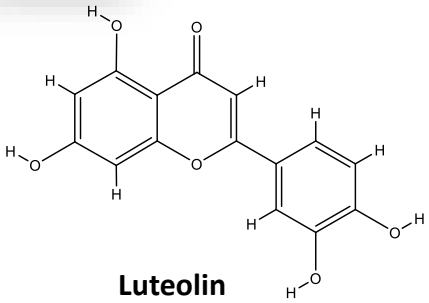
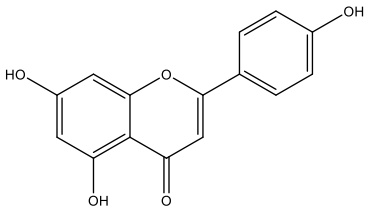
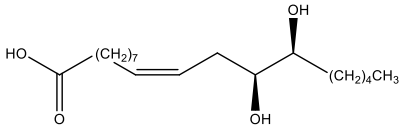


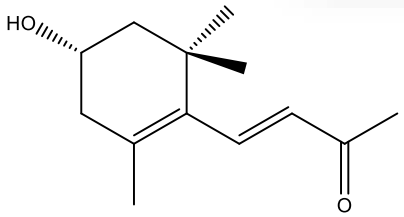
Luteolin



Hirsutinolide structure 15

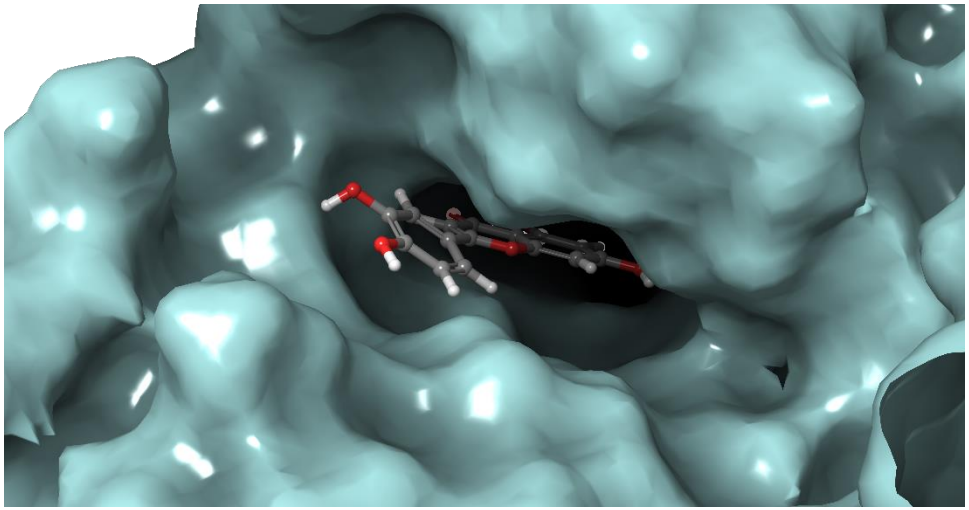


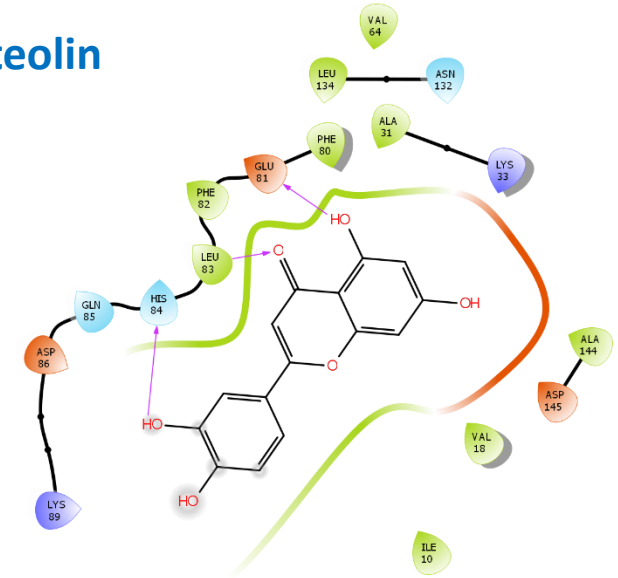
Hirsutinolide structure 16



H14

CDK-2 interactions with Luteolin





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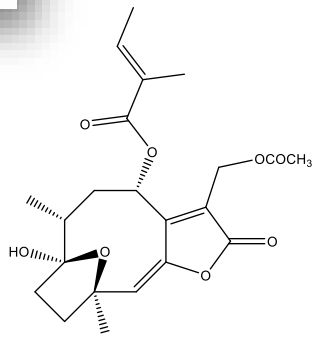
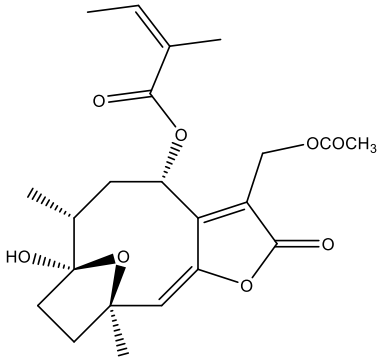
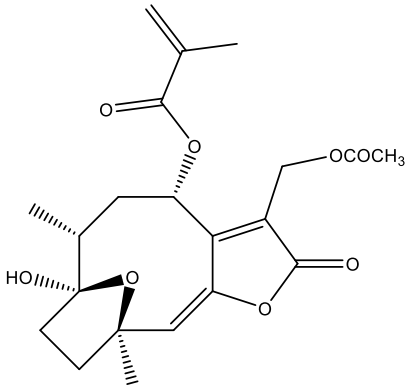


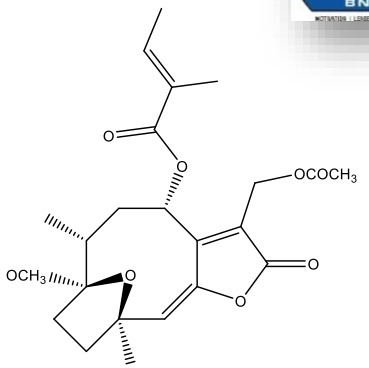
H7



8α-(2'Z-tigloyloxy)-hirsutinolide-13-O-Acetate

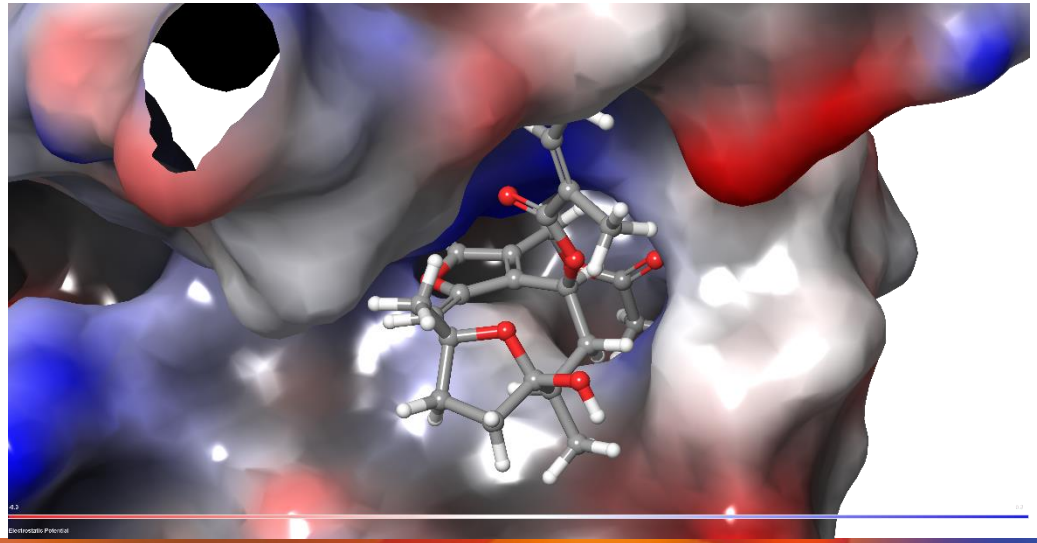


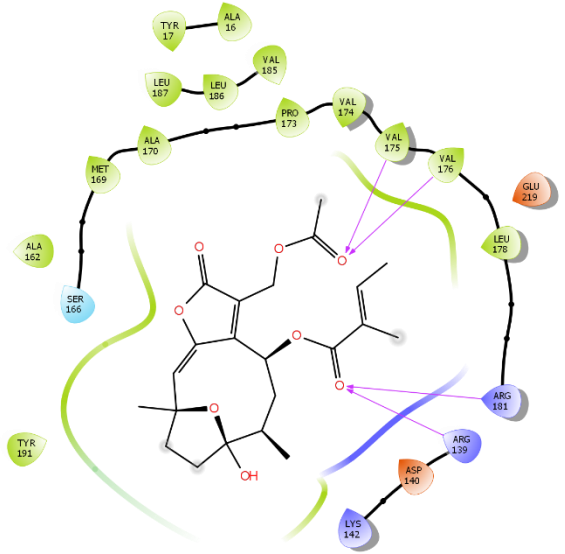
H8



H9

CDK-4 interactions with H7





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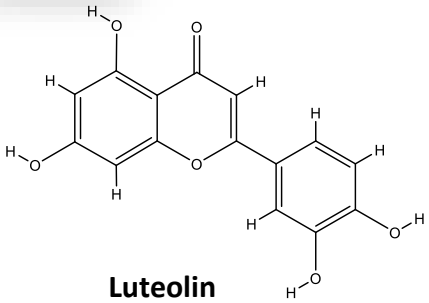
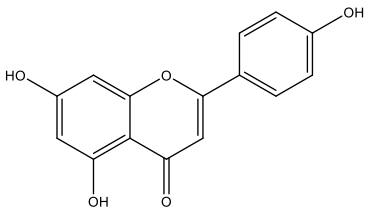
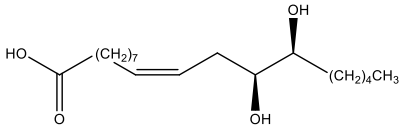


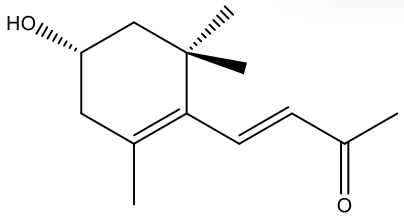
Luteolin



Hirsutinolide structure 15

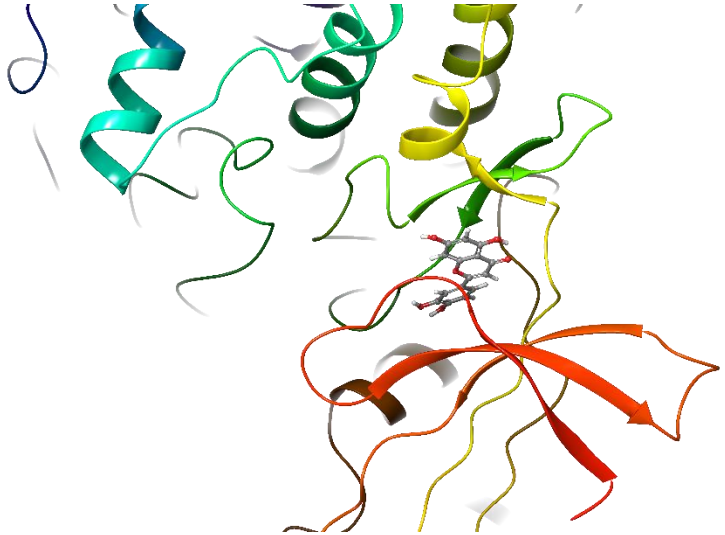


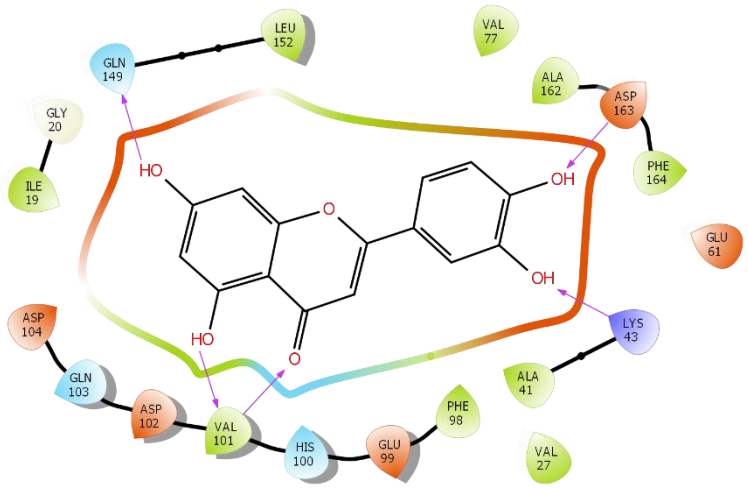
Hirsutinolide structure 16



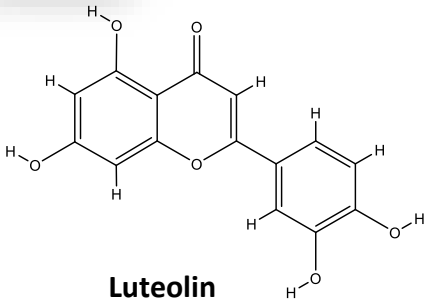
H14

CDK-6 interactions with Luteolin

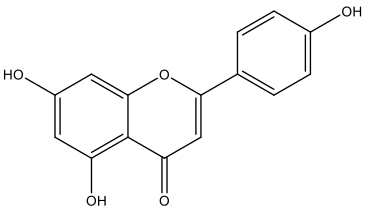




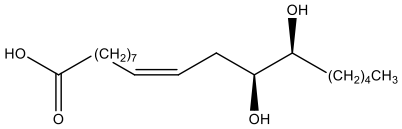
RESULTS AND DISCUSSION



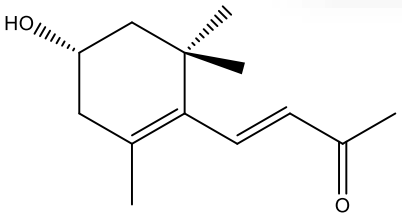
Luteolin



Hirsutinolide structure 15

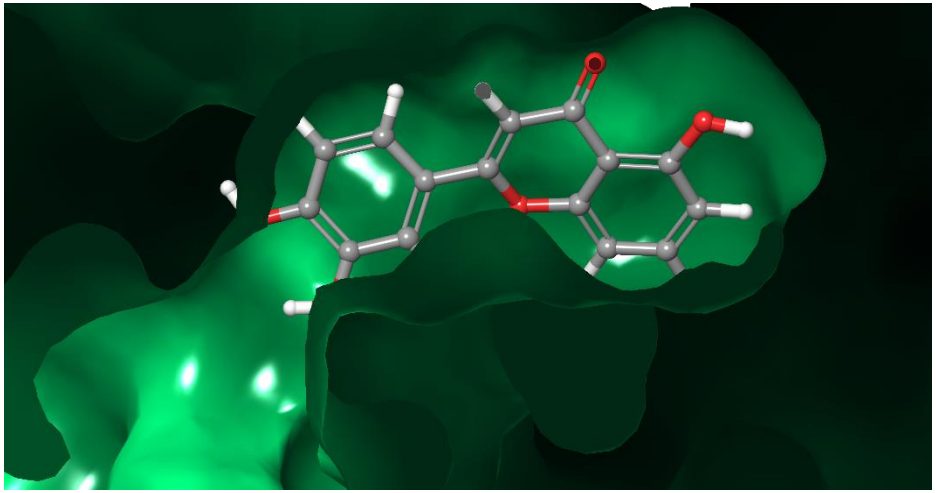


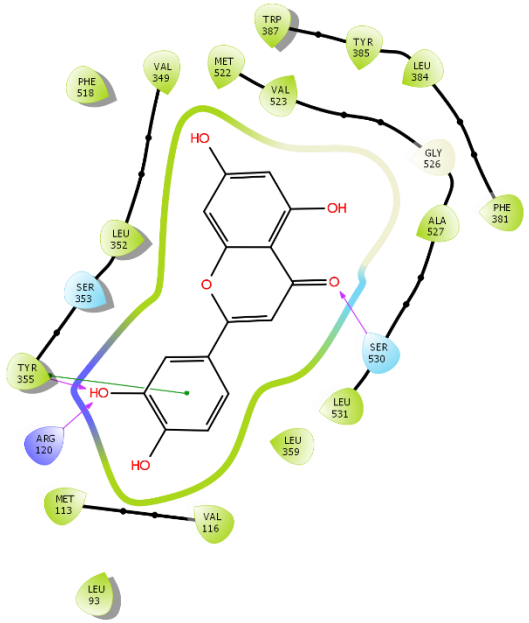
Hirsutinolide structure 16



H14

COX-2 interactions with Luteolin





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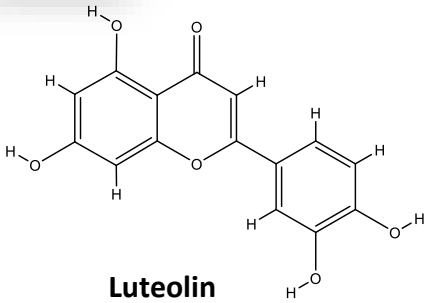
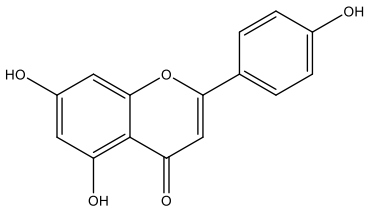
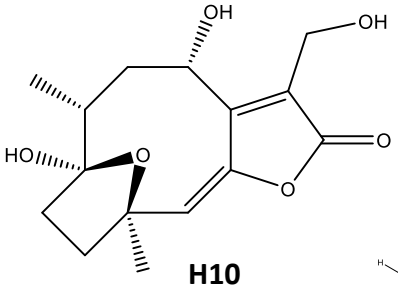


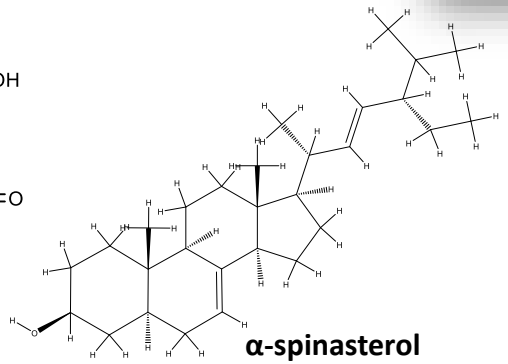
Luteolin



Hirsutinolide structure 15

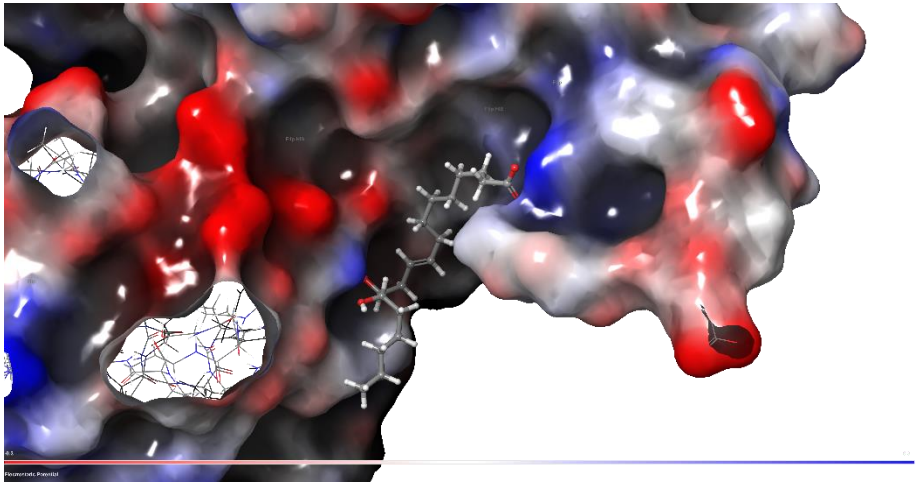


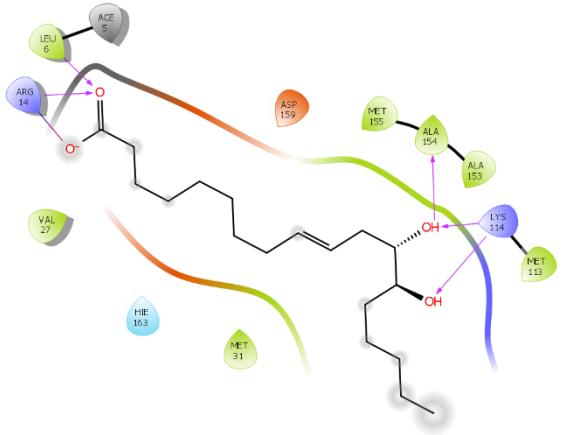
H10



α-spinasterol

Cyclin D interactions with Hirsutinolide structures 16





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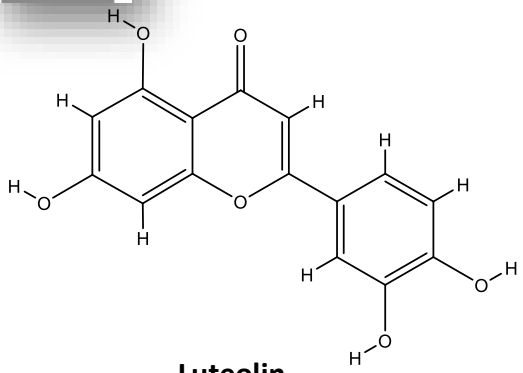
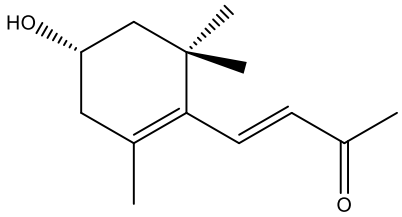
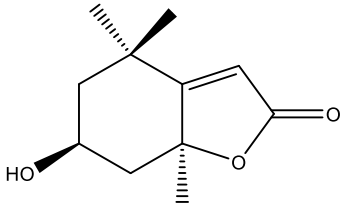


Luteolin

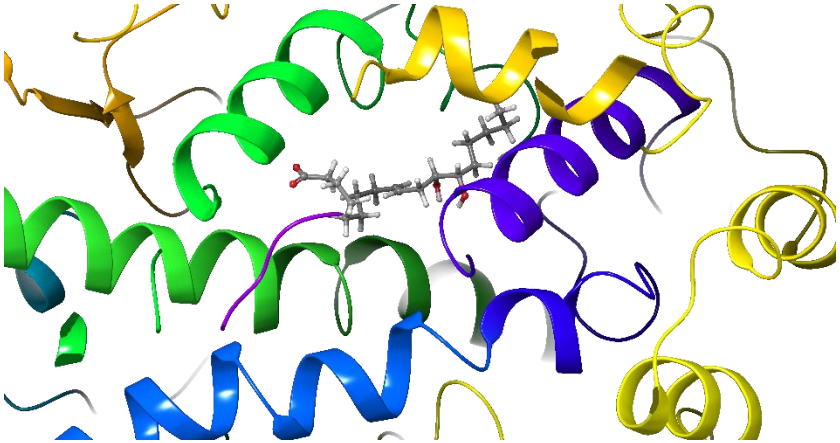


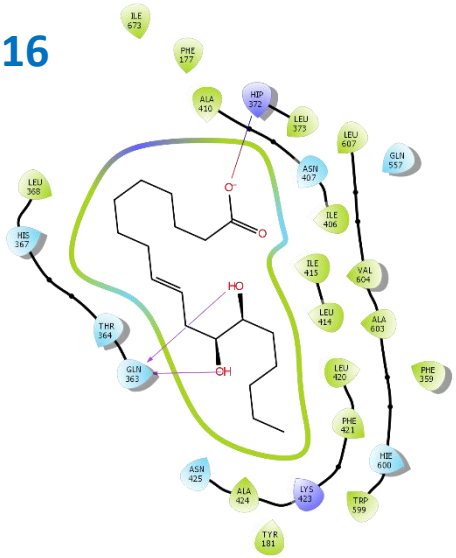
H14



H13

5 LOX interactions with Hirsutinolide structures 16





CONCLUSION

- Luteolin
- Hirsutinolide structure 15
- H10
- H14
- Hirsutinolide structure 16
- 8-(4-hydroxytigloyloxy)hirsutinolide

Non-selective Inhibitors

Selective Inhibitors

- ✓ Vernolide B
- ✓ α-spinasterol
- ✓ Stigmasterol
- ✓ β-Sitosterol

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