

How to Cite:

Choudhary, S., Lal, A., Gokul, N. L., & Raj, S. (2023). Molecular dynamics study of marine-derived compounds as potential inhibitors for endometrial cancer. *International Journal of Health Sciences*, 7(S1), 2610–2629. <https://doi.org/10.53730/ijhs.v7nS1.14552>

Molecular dynamics study of marine-derived compounds as potential inhibitors for endometrial cancer

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Abstract---Among women, endometrial carcinoma is by far the most common form of gynecological cancer. The molecular processes underlying the development and progression of endometrial cancer are not well understood, despite substantial breakthroughs in detection and therapy. This research paper aims to explore the role of Integrin beta-3 (ITGB3) and HOX genes in endometrial cancer, shedding light on their potential as biomarkers and therapeutic targets. Among the many biological activities that integrin beta-3 (ITGB3) contributes to include cell proliferation, migration, and angiogenesis, to name a few. Numerous studies have implicated ITGB3 in tumor development and metastasis. There is evidence that ITGB3 has a role in the development and prognosis of endometrial cancer due to its altered expression and dysregulation. The homeobox gene (HOX) family encodes transcription factors necessary for proper cell differentiation and development at all stages of embryonic life. Endometrial cancer is only one of several types of cancer linked to HOX gene dysregulation. The study provides an overview of the specific HOX genes involved in endometrial cancer and their functional significance in disease progression. It also discusses the potential utility of HOX genes as diagnostic markers and therapeutic targets in endometrial cancer management. To unravel the intricate interplay between ITGB3, HOX

genes, and endometrial cancer, various experimental and clinical studies have been conducted. The findings from these investigations have contributed to a better understanding of the molecular mechanisms underlying endometrial cancer pathogenesis. This research paper highlights the significant roles of Integrin beta-3 (ITGB3) and HOX genes in endometrial cancer. The elucidation of their molecular functions and dysregulation in the context of endometrial cancer provides valuable insights into the disease's etiology and progression. Moreover, the identification of ITGB3 and HOX genes as potential biomarkers and therapeutic targets opens new avenues for precision medicine in endometrial cancer treatment.

Keywords---Integrin beta-3, HOX genes, endometrial, treatment, cancer, women.

Introduction

Cancer may form in the endometrium, which is the uterine lining. It's caused by a proliferation of rogue cells that may infiltrate and spread to other organs. Vaginal bleeding that is not connected with a menstrual cycle is generally the first symptom. In addition, you may have discomfort while urinating, during having sexual relations, or in your pelvis. Endometrial cancer is more common in women after menopause. Obesity is linked to around 40% of occurrences. Endometrial cancer has been related to High levels of estrogen, hypertension and diabetes. Combinations of estrogen and progestogen lessen the risk of endometrial cancer, as is the case with the vast majority of oral contraceptives. It is estimated that heredity contributes to just 2%-5% of all occurrences. The term "uterine cancer" is sometimes used interchangeably with "endometrial cancer," despite the fact that these two diseases are quite different. More than 80% of instances of endometrial cancer are caused by endometrioid carcinoma. Endometrial biopsies and sample collection during dilatation and curettage are frequently used diagnostic tools for endometrial cancer. In most cases, a pap smear will not detect endometrial cancer. People who are not at a high risk should not get routine screenings.

Surgical removal of the uterus (abdominal hysterectomy) and both Fallopian tubes and ovaries (bilateral salpingo-oophorectomy) are the most frequent therapies for endometrial cancer. In extreme cases, hormone therapy, chemotherapy, and radiation therapy may be used. The prognosis is good if caught early, and the five-year survival rate in the United States is over 80% if caught early. In 2012, there were 3,20,00 new cases of endometrial cancer, which resulted in 76,000 fatalities. Breast cancer is the third most common cancer among women, behind ovarian and cervical cancer. This is the most common kind of cancer in women, and it is more common in the industrialized world. Between the years 1980 and 2010, endometrial cancer rates increased in a lot of nations. The rising prevalence of overweight and elderly populations is suspected to be to blame. Cancer of the endometrium is a kind of uterine cancer. The uterus, a pear-shaped pelvic organ with a hollow interior, is responsible for fetal development. The uterine lining (endometrium) is the site of origin for endometrial

cancer. Uterine cancer is another name for endometrial cancer. Uterine sarcoma is another kind of cancer that may develop in the uterus, albeit it is considerably less prevalent than endometrial cancer. One of the most noticeable signs of endometrial cancer is abnormal vaginal bleeding. When caught early, endometrial cancer is frequently curable by surgically removing the uterus.

Symptoms

Vaginal bleeding or spotting occurs in 90% of women with endometrial cancer after menopause. Two-thirds of adenocarcinoma patients will have bleeding at some point during treatment. Endometrial cancer may also manifest in premenopausal women with abnormal menstrual cycles or abnormally lengthy, heavy, or frequent bouts of bleeding. Bleeding is the only frequent symptom; other symptoms are rare. Postmenopausal women may also have a clear or white vaginal discharge. When an illness has progressed, it manifests itself in ways that are easy to see by looking at the patient. Lower abdomen discomfort or pelvic cramps might be caused by an enlarged uterus or the body's malignancy spreading to other organs. Less frequent symptoms of endometrial cancer include discomfort during sexual activity or difficulty urinating. Pyometrea is the accumulation of pus in the uterus. Between 10 and 15 percent of women who have these unusual symptoms (vulvar discharge, pelvic discomfort, and pus) really have cancer. Possible symptoms of endometrial cancer:

- Bleeding between periods
- Pelvic pain
- Vaginal bleeding after menopause(Clinic, n.d.)

Malignant (cancer) cells develop in the endometrial tissues, making up the illness known as endometrial cancer. Endometrial cancer risk may be raised in those who are overweight or who suffer from metabolic syndrome. Endometrial cancer risk is increased when estrogen is used without progesterone or when tamoxifen is used to treat breast cancer. Unusual vaginal bleeding or pelvic discomfort are two signs that may indicate endometrial cancer. Endometrial cancer is diagnosed with the use of tests that look at the uterine lining. The prognosis (the likelihood of recovery) and available treatments are influenced by a number of variables.(National Cancer Institute, n.d.)

Types of endometrial cancer

Endometrial cancer, often called uterine lining cancer or endometrial carcinoma, is cancer that starts in the uterine lining. This kind of uterine cancer accounts for the vast majority of cases. Cellular characteristics allow for classification of endometrial carcinomas into subtypes. (These are referred to as histologic subtypes.) Some of them are:

- Small cell carcinoma
- Transitional carcinoma
- Adenocarcinoma (most endometrial cancers are a type of adenocarcinoma called endometrioid cancer)
- Uterine carcinosarcoma or CS (covered below in the grading section)
- Squamous cell carcinoma

- Serous carcinoma

Clear-cell carcinoma, mucinous adenocarcinoma, undifferentiated carcinoma, dedifferentiated carcinoma, and serous adenocarcinoma are all less common types of endometrial cancer. In comparison to other forms of endometrial cancer, they progress and spread more rapidly. By the time they are identified, they have typically spread outside the uterus.(American cancer society, n.d.)

Cancers of the uterine lining are classified into four broad types:

- POLE mutation
- Copy number high
- p53 mutation
- Copy number low

Treatments for malignancies in each of these categories are being evaluated in clinical trials. This includes experimental immunotherapy studies.(Johns hopkins, n.d.)

Risk Factors for Endometrial Cancer

Women beyond menopause are disproportionately affected by endometrial cancer. Nearly all occurrences of endometrial cancer occur in women over the age of 40. After menopause, women are at an increased risk for developing endometrial cancer if they match the following criteria:

- Have diabetes or high blood pressure
- Have few or no children
- Have a history of infertility, irregular periods, or abnormal cells in the endometrium (called endometrial hyperplasia)
- Got their first period early
- Went through menopause late
- Are obese
- Have a family history of endometrial, colorectal, or breast cancer

The chance of developing endometrial cancer is marginally increased for women who use tamoxifen for the treatment or prevention of breast cancer. Using birth control decreases a woman's chance of acquiring endometrial cancer by 50% after menopause. All-estrogen hormone replacement therapy increases a woman's risk of developing endometrial cancer. Therefore, estrogen-only hormone replacement treatment is not recommended for women who have not had a hysterectomy. Even though endometrial cancer is uncommon, it is more likely in women who have ovarian tumors that produce estrogen. Endometrial and colon cancers are among those that may be exacerbated by a diet high in fat, particularly one that includes red meat.(Pathak, 2022)

Prevention of endometrial cancer

It is currently not possible to avoid endometrial cancer. However, there are measures that females may do to reduce their vulnerability. The risk can be reduced by using birth control, but you should discuss the advantages and risks with your doctor beforehand. You may help reduce your risk by being healthy

overall, eating well, and maintaining a healthy weight. Endometrial cancer's precise origin remains a mystery. However, medical professionals agree that avoiding recognized risk factors wherever feasible, taking oral contraceptives or other hormonal birth control, and managing weight and blood sugar levels are the most effective approaches to reduce the chance of getting endometrial cancer.(Pathak, 2022)

Connection between HOX gene and Endometrial Cancer

The HOX gene family regulates cell differentiation and plays a critical role in embryonic development. They are responsible for providing instructions for the proper formation of body structures and organs. Multiple cancers, including endometrial cancer, have been linked to changes in the expression or activity of HOX genes.

Endometrial carcinoma is the most common kind of gynecological cancer in developed countries. It develops from the endometrium, the uterine lining. Multiple studies have linked HOX genes to the initiation and spread of endometrial cancer. Here are a few key findings:

Overexpression of HOXA genes: Several studies have shown the upregulation of HOXA genes, particularly HOXA9, HOXA10, and HOXA11, in endometrial cancer. The increased expression of these genes has been linked to a worse prognosis, a more aggressive tumor, and a more advanced stage of illness.(Taylor, Igarashi, Olive, & Arici, 1999)

Loss of HOXA genes: However, other research has shown that endometrial cancer is associated with a decline in expression of several HOXA genes. The downregulation of HOXA genes, such as HOXA5 and HOXA9, has been correlated with tumor progression, metastasis, and reduced patient survival.(Du & Taylor, 2016)

HOXB genes and cell adhesion: HOXB genes have also been implicated in endometrial cancer through their involvement in cell adhesion processes. The dysregulation of HOXB genes, specifically HOXB2 and HOXB13, has been associated with disrupted cell adhesion, increased invasiveness, and metastasis in endometrial cancer.(Shah et al., 2013)

HOXC genes and hormone signaling: HOXC genes have been linked to endometrial cancer through their interaction with hormone signaling pathways. HOXC6 and HOXC8 have been found to modulate estrogen receptor signaling and promote endometrial cancer cell proliferation.(Liu et al., 2018)

Various studies highlight the complex involvement of HOX genes in endometrial cancer, with different genes exhibiting both upregulation and downregulation in various stages and subtypes of the disease. When HOX genes are misregulated, it may cause cancer cells to proliferate uncontrollably, invade nearby tissues, and metastasize.

The homeobox (HOX) genes regulate embryonic development and tissue patterning and are a highly conserved collection of genes. Endometrial cancer is only one kind of cancer that has been linked to alterations in HOX gene expression.

Endometrial carcinoma is the most common kind of gynecological cancer in developed countries. It originates in the uterine lining, or endometrium. Multiple studies have linked HOX genes to endometrial cancer, both in its early stages and as it develops.(Ashary, Laheri, & Modi, 2020)

Connection between Integrin beta-3 and HOX genes

Integrin beta-3 (ITGB3) belongs to the integrin family of cell adhesion molecules, which plays a crucial role in cell-cell and cell-matrix interactions. Tissues as diverse as skin, skeletal muscle, and the heart all express integrin beta-3. It has been related to many disorders, including cancer and arthritis, and plays a role in cell migration and cell signaling.(Zhang et al., 2019) HOX genes, which operate as transcription factors to control the expression of other genes, have also been connected to integrin beta-3. The HOX genes are involved in the production of many different tissues and organs during embryonic development. Both ITGB3 and HOX genes play critical roles in controlling cell migration and differentiation. There are several examples of interactions between ITGB3 and HOX genes. It has been discovered, for instance, that ITGB3 has a role in the control of HOX gene expression. Additional evidence suggests that the two genes work together to govern cell destiny by controlling the expression of other genes. It has also been discovered that ITGB3 has a role in controlling the expression of the HOX genes in cancer cells. This provides more evidence that ITGB3 may have a role in carcinogenesis, tumor growth, and metastasis. Overall, Integrin beta-3 and HOX genes are known to interact and influence each other's expression. Further research is needed to understand the exact roles that these two genes play in disease and development.(Zhao, Wu, Ma, Liu, & Yue, 2016)

Similar to HOX genes, integrin beta-3 (ITGB3) is essential for development, differentiation, and tissue homeostasis. While they have distinct functions, there are certain connections between Integrin beta-3 and HOX genes that have been studied.

1. Regulation of HOX Genes by Integrin Signaling: The expression of homeobox genes (HOX) has been demonstrated to be regulated by integrin beta-3 through integrin signaling pathways. Integrin engagement with the extracellular matrix (ECM) activates signaling cascades that can influence gene expression. One study demonstrated that Integrin beta-3 activation led to the upregulation of HOXB7 gene expression in prostate cancer cells. This suggests that Integrin beta-3 signaling can directly impact the expression of HOX genes, potentially affecting cellular processes such as cell migration, invasion, and metastasis.(Huang & Rofstad, 2018)
2. Interaction between HOX Proteins and Integrin Beta-3: HOX proteins can physically interact with Integrin beta-3, forming protein complexes that modulate cell adhesion and migration. For example, in endothelial cells, the HOXB7 protein was found to directly bind to Integrin beta-3, leading to increased cell adhesion and angiogenesis. This interaction suggests a functional connection between specific HOX proteins and Integrin beta-3 in the context of cell adhesion and angiogenic processes.(Topczewska et al., 2006)

Role of Integrin beta-3 (ITGB3) and HOX genes in endometrial cancer

Endometrial cancer has been linked to the integrin beta-3 (ITGB3) and homeobox (HOX) genes. Let's discuss their roles individually:

Integrin beta-3 (ITGB3): The integrins facilitate adhesion and communication between cells and are a class of cell surface receptors. ITGB3 is a specific integrin beta subunit that forms heterodimeric complexes with different alpha subunits, resulting in diverse integrin receptors. It is well established that ITGB3 is involved in tumor angiogenesis, invasion, and metastasis. (Xiong, Klausen, Cheng, Zhu, & Leung, 2015)

In endometrial cancer, ITGB3 has been associated with several aspects of tumor progression. Research suggests that ITGB3 overexpression in endometrial cancer cells promotes tumor angiogenesis by enhancing endothelial cell migration and tube formation. The modulation of epithelial-mesenchymal transition (EMT) processes by upregulated ITGB3 has also been associated to increased tumor cell invasion and metastasis. (Li et al., 2014)

HOX genes: The homeobox (HOX) genes are essential for normal embryonic development and tissue patterning. These genes are involved in regulating cell proliferation, differentiation, and organ morphogenesis. Endometrial cancer is only one of several cancers in which HOX gene dysregulation has been identified. In endometrial cancer, specific HOX genes have been found to be aberrantly expressed. Alterations in the expression patterns of HOX genes can disrupt normal cellular processes and contribute to tumor initiation and progression. For example, endometrial hyperplasia and early-stage endometrial cancer have both been associated with overexpression of HOXA10. Downregulation of HOXA9 and HOXD10 has also been linked to increased cell proliferation and impaired apoptosis in endometrial cancer cells. (Zanatta et al., 2010)

The lining of the uterus (the endometrium) is a typical target for the disease known as endometrial carcinoma. Because of both hereditary and environmental causes, it is the most frequent form of gynecological cancer in females. Endometrial cancer is mostly caused by the aberrant expression of genes like integrin beta-3 (ITGB3) and homeobox (HOX) genes. Cell adhesion and migration are regulated by integrin beta-3, a receptor protein found on cell surfaces. An important contributor to the development of endometrial cancer. In endometrial cancer, ITGB3 is overexpressed, which leads to increased cell motility and invasion, resulting in tumor metastasis. Angiogenesis and inflammation, both of which contribute significantly to the development of endometrial cancer, have also been associated to ITGB3. (Germeyer, Savaris, Jauckus, & Lessey, 2014) In embryonic development, organogenesis, and tissue patterning, HOX genes function as transcription factors. Endometrial cancer has been linked to the aberrant expression of HOX genes. For example, overexpression of the HOXA5 gene has been associated with increased cell proliferation and invasiveness in endometrial cancer. Increased risk of metastasis in endometrial cancer is similarly associated with overexpression of HOXA11. In conclusion, HOX genes and integrin beta-3 are involved in both the onset and development of endometrial cancer. Overexpression of both of these genes is linked to enhanced cell

proliferation, migration, and metastasis in endometrial cancer.(Kong, Zhu, Li, Xue, & Chen, 2021).

Compound (s)	Species	Origin	Pathways inhibited	Reference
Ellagic acid	P. boryana	brown alga	Several different kinds of fruit and plants contain the polyphenol ellagic acid (EA). Antitumor effects of EA have been shown in a variety of malignancies, including endometrial cancer. Using a collection of bioinformatics tools including DrugBank, STRING, WebGestalt, and cBioPortal, we were able to determine that PIK3CA and PIK3R1 are important targets of EA. EA greatly inhibited cell invasion and migration, as shown by Transwell tests. The proliferation and survival of endometrial cancer cells were both decreased by EA, as measured by CCK8 assays and flow cytometry. The expression of PIK3CA and PIK3R was inhibited by EA, as shown by real-time polymerase chain reaction. In addition, western blotting research showed that EA suppressed MMP9 expression through inhibiting PI3K phosphorylation.	(Hassan et al., 2021)
Resveratrol	Alternaria sp. R6	mangrove endophytic fungus	Treatment of experimental endometriosis with resveratrol is effective because it reduces oxidative stress and lipid peroxidation. However, it also demonstrates anti-inflammatory efficacy by reducing endometriosis-related NF-κB, TNF-, and inflammatory cytokine production. Resveratrol's significant antioxidative characteristics may explain why it proved effective in treating endometriotic implants in a rat endometriosis model.	(Torno, Staats, De Pascual-Teresa, Rimbach, & Schulz, 2017)
	Rainbow Trout (Oncorhynchus mykiss)	Fish		
Apigenin	Acanthopora spicifera	Marine Red Alga	Apigenin inhibited Ishikawa cell growth. To a degree unrelated to public relations. Since progesterone inhibits endometrial cancer development, we examined whether or not apigenin and progesterone might slow the growth of Ishikawa PR-B cells. Cancer of the human uterus Apigenin was shown to induce apoptosis and decrease migration in Ishikawa cells	(El Shoubaky, Abdel-Daim, Mansour, & Salem, 2016)

			through the PI3K-AKT-GSK-3 pathway and endoplasmic reticulum stress.	
Quercetin	Streptomyces fradiae PE7	actinobacterium	The development and spread of various malignancies, particularly breast and endometrial cancers, may be considerably slowed by quercetin. Quercetin's ability to inhibit the c-Jun N-terminal kinase (JNK) signaling pathway has been linked to a decrease in androgen receptor (AR) expression and activity, which in turn may lessen the aggressiveness of prostate cancer. Quercetin inhibits tumor development by blocking the Wnt signaling pathway, which it uses to down-regulate genes involved in the cell cycle and up-regulate anti-cancer genes like p27. Tumor angiogenesis is another process quercetin may stop. Quercetin treatment in tumor-bearing mice has been linked to decreased neo-vessel density and VEGF expression.	(Gopikrishnan, Radhakrishnan, Shanmugasundaram, Pazhanimurugan, & Balagurunathan, 2016)
Luteolin	Zostera	seagrasses	Anti-inflammatory and cancer-preventing properties of luteolin have been shown. Endometriosis is a painful disorder defined by the ectopic development of endometrial tissue and pelvic inflammation, although the impact of luteolin on endometriosis is yet unknown. Luteolin inhibited the growth of 12Z human endometriotic cells and triggered apoptosis by activating caspase-3, -8, and -9. Luteolin significantly reduced the synthesis of C-C motif chemokine ligand 2 (CCL2) and C-C motif chemokine ligand 5 (CCL5), two crucial chemokines for monocyte/macrophage influx at endometriotic sites. Luteolin inhibited the intracellular expression of M2 markers and endometriosis-promoting factors in macrophages activated by endometriotic cells in one experiment.	(Kozlovskaya et al., 2022)
Beta caryophyllene	Ascotricha sp. ZJ-M-5	Fungus	SphK1 expression is significantly upregulated in tumor tissues and cultured tumor cells from a variety of malignancies, including breast cancer, gastric cancer, endometrial cancer, and others.	(Styshova, Popov, Artyukov, & Klimovich, 2017)

			Treatment with -caryophyllene for NSCLC led to elevated levels of miR-659-3p, apoptotic factors (cleaved caspase-3 and BAX), antioxidant factors (SOD, CAT, and GPx), and lowered levels of oxidative stress (ROS and NO) and SphK1. Proliferation, apoptosis, and biochemical indicators of NSCLC were all affected by the miR-659-3p mimic and siRNA.	
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Material and Methods

1. Protein preparation

The 3D structures of protein were derived from the PDBe-KB. Simultaneously the hetero atoms were removed from the retrieved PDB file in order to prepare the proteins for docking and the structures of each of these proteins have been visualized in the Pymol visualization studio to obtain a better understanding of our blind docking studies

2. Ligand preparation

The ligand used for targeting specific protein have been screened through an extensive literature review. Accessing the PubChem database (library (<https://pubchem.ncbi.nlm.nih.gov>) and seeing the ligand's 3D structure in Pymol (<https://pymol.org/software>)). The Simplified Molecular-Input Line-Entry System (SMILES) is a line notation that may be used to express the connectivity and chirality of a molecule. We used the online SMILES Translator (<https://cactus.nci.nih.gov/translate/>) to transform the compound's canonical SMILES from PubChem into the PDB format. In order to carry out docking with the corresponding protein, the SDF format files were converted to PDB format. The selected phytochemicals include – Apigenin (Compound CID: 5280443), Beta caryophyllene (Compound CID: 20831623), Ellagic acid (CID: 5281855), Luteolin, Quercetin and Resveratrol (Compound CID: 445154) respectively.

Apigenin (Compound CID: 5280443):

- Marine source: While apigenin is predominantly found in various plants such as chamomile, parsley, and celery, there is no specific marine source identified for this compound.
- Chemical property: Apigenin is a flavonoid, characterized by its yellow color and a phenolic structure. It is soluble in hot water, ethanol, and ethyl acetate.
- Pathway inhibition related to Endometrial Cancer: Apigenin has been studied for its putative inhibitory effects on the PI3K/AKT/mTOR pathway, which is critical for the proliferation and survival of endometrial cancer cells.

Beta-caryophyllene (Compound CID: 20831623):

- Marine source: Beta-caryophyllene is a sesquiterpene found in various plants, including some marine sources like marine algae.
- Chemical property: Beta-caryophyllene is a bicyclic sesquiterpene hydrocarbon. It is insoluble in water but soluble in organic solvents like ethanol.

- Pathway inhibition related to Endometrial Cancer: Research on beta-caryophyllene's specific pathway inhibition related to endometrial cancer is limited. However, it has been studied for its potential anti-inflammatory and anticancer effects through interactions with various molecular targets, including cannabinoid receptors.

Ellagic acid (CID: 5281855):

- Marine source: Ellagic acid is primarily found in various fruits like strawberries, raspberries, and pomegranates. There is no specific marine source identified for this compound.
- Chemical property: Ellagic acid is a polyphenol, consisting of a fused four-ring structure. It is sparingly soluble in water but soluble in organic solvents like ethanol.
- Pathway inhibition related to Endometrial Cancer: Endometrial cancer is associated with the Wnt/-catenin signaling pathway, both in its development and its progression, hence ellagic acid has been studied for its ability to suppress this pathway.

Luteolin (Compound CID: 5280445):

- Marine source: The flavonoid luteolin has been detected in sea algae and may be present in a broad range of plant diets.
- Chemical property: Luteolin is a yellow crystalline compound with a flavone structure. It is sparingly soluble in water but soluble in organic solvents like ethanol.
- Pathway inhibition related to Endometrial Cancer: Luteolin has been demonstrated to have potential inhibitory effects on the PI3K/AKT/mTOR pathway, which has been studied due to its significance in endometrial cancer cell proliferation, survival, and metastasis.

Quercetin (Compound CID: 5280343):

- Marine source: There is no known oceanic source for quercetin, a flavonoid present in many fruits, vegetables, and plants.
- Chemical property: Quercetin is a yellow crystalline compound with a flavonol structure. It is sparingly soluble in water but soluble in organic solvents like ethanol.
- Pathway inhibition related to Endometrial Cancer: Quercetin has been studied for its potential inhibitory effects on various pathways involved in endometrial cancer, including the NF-kappa B pathway, PI3K/AKT/mTOR pathway and Wnt/ β -catenin pathway.

Resveratrol (Compound CID: 445154):

- Marine source: The polyphenol resveratrol may be found in a wide range of plant materials, including some marine ones like seaweed.
- Chemical property: Resveratrol is a stilbenoid compound. It is sparingly soluble in water but soluble in organic solvents like ethanol.
- Pathway inhibition related to Endometrial Cancer: Resveratrol has been studied for its potential inhibitory effects on various pathways associated with endometrial cancer, including the Wnt/ β -catenin pathway, PI3K/AKT/mTOR pathway and NF-kappa B pathway. Its anti-inflammatory and antioxidant qualities have also been studied for their possible role in its anticancer benefits.

3. Pharmacological properties of the compounds

In order to execute an initial screening, SWISS ADME an online web-based server was utilized to assess the pharmacological fidelity of the phytochemicals as drug candidates (Vikas et al 2022). Several descriptors were taken into consideration such as ADME parameters, pharmacokinetic parameters, drug-like behavior, and the medicinal friendliness of each of the considered molecules to support the therapeutic process (Vikas et al 2022).

The drug-like and non-drug-like characteristics of a molecule may be distinguished using Lipinski's rule of 5. Based on the Lipinski golden triangle rule such as the no of acceptor hydrogen atoms (no more than 5) and donors (no more than 10), octanol-water coefficient (log P not more than 5), molecular mass less than 500Da molecular refractivity index between 40 and 130. Hence the ability of these compounds being used as drug molecules were determined (Benet, et al., 2015).

Lipinski Rule of Five

Drug-like substances can be separated from those that aren't using the Lipinski rule of 5. For molecules meeting 2 or more of the following criteria, it provides a strong indication of whether or not they will be successful as drugs.

- Less than 5 hydrogen bond donors
- Molecular mass less than 500 Dalton
- High lipophilicity (expressed as Log P less than 5)
- Less than 10 hydrogen bond acceptors
- Molar refractivity should be between 40-130

4. Molecular docking

Autodock-4.2 was used for molecular docking analyses to look at how the six drugs interacted with the protein Integrin beta-3. The ligand was able to choose its preferred binding sites through blind docking. Gasteiger-Marsili and Kollman charges were used to determine the protein and ligand partial charges, respectively. The grid box covered the whole protein since blind docking was employed. The ligand-bound protein conformers were generated by a Lamarckian evolutionary strategy. We used the default settings for everything else and set the

number of docking runs to 10. The results of Autodock-4.2 were analyzed using Discovery Studio Visualizer v20.1.0.19295 by Dassault Systems Bio through corp.

Lipinski Rule of Five Results –

Apigenin

Mass: 270.000000
Hydrogen bond donor: 3
Hydrogen bond acceptors: 5
LOGP: 2.419599
Molar Refractivity: 70.813881

Luteolin

Mass: 286.000000
Hydrogen bond donor: 4
Hydrogen bond acceptors: 6
LOGP: 2.125200
Molar Refractivity: 72.478676

Ellagic-acid

Mass: 302.000000
Hydrogen bond donor: 4
Hydrogen bond acceptors: 8
LOGP: 1.241200
Molar Refractivity: 68.454185

Beta-caryophyllene

Mass: 204.000000
Hydrogen bond donor: 0
Hydrogen bond acceptors: 0
LOGP: 4.725199
Molar Refractivity: 66.742981

Quercetin

Mass: 302.000000
Hydrogen bond donor: 5
Hydrogen bond acceptors: 7
LOGP: 2.010900
Molar Refractivity: 74.050476

Resveratrol

Mass: 228.000000
Hydrogen bond donor: 3
Hydrogen bond acceptors: 3
LOGP: 2.973799
Molar Refractivity: 66.806381

Docking results

Table 1: The table below depicts the binding energy of with different ligands

S. No	Ligand	"Binding energy (Kcal/mole)"
1	Apigenin	-7.4
2	Beta caryophyllene	-6.4
3	Ellagic acid	-7.3
4	Luteolin	-7.3
5	Quercetin	-7.5*
6	Resveratrol	-6.6

Table 2: The table below depicts the bioavailability and proof that it follows all the 5 Lipinski rules

Marine bioactive compounds	Lipinski's Rule	Bioavailability	Hydrogen bond donar	Hydrogen bond acceptors	LOGP	Molar Refractivity
Apigenin	Accepted	0.55	3	5	2.419599	70.813881
Beta caryophyllene	Accepted	0.55	0	0	4.725199	66.742981
Ellagic acid	Accepted	0.55	4	8	1.241200	68.454185
Luteolin	Accepted	0.55	4	6	2.125200	72.478676
Quercetin	Accepted	0.55	5	7	2.010900	74.050476
Resveratrol	Accepted	0.55	3	3	2.973799	66.806381

Results and Discussion

1. Molecular docking of the compounds

Six chemicals were docked into the active site of Endometrial cancer target (Integrin beta-3 or CD61 or ITGB3) from a variety of marine sources (Apigenin, Beta caryophyllene, Ellagic acid, Luteolin, Quercetin, Resveratrol). Binding energy estimates (in kcal/mol) were calculated by taking the minimum from a set of 10 conformations for each docked complex and are shown in Table 1. Among all the targets for endometrial cancer, quercetin was determined to have the lowest binding energy. As a result, we focused our attention and research on quercetin as the most effective inhibitor against endometrial cancer targets. Several features of endometrial cancer are inhibited by quercetin treatment. These include signal transduction, cancer cell death, tumor development, invasion, and metastasis.

2. Drug likeness and ADME properties prediction

SwissADME (<http://www.swiss-ame.ch/>) was used to assess the pharmacokinetic features of quercetin compounds. Quercetin has been proved to have drug-like characteristics based on Lipinski's rule. The compounds contain between five and ten hydrogen bond donors (HBD), a molecular weight of less than 500 kDa, and a predicted octanol/water partition coefficient (LogP) of less than 5. However, the Veber rule shows that the molecule has fewer than 10 rotatable bonds and a smaller than 140 Å² polar surface area. According to Lipinski and Veber, all of these expected features are suitable for druglike compounds.

- We also used the web-based prediction program admetSAR (<http://lmmd.ecust.edu.cn/admetSar2>) to examine the quercetin

compounds' absorption, distribution, metabolism, and excretion (ADME) features. Quercetin was well absorbed, with an absorption level of less than one. A solubility in water of less than -2.999 implies low solubility. Properties with a BBB rating of '0' are very vulnerable to BBB attacks, as opposed to those with a BBB rating of '1'. Quercetin had a PPB of 1.164, indicating that it was poorly bound and could thus easily cross cell membranes or disperse. In terms of pharmacokinetics, all values were within safe limits for human consumption.

3. Amino acid interaction analysis

Two-dimensional plots show how amino acids interact with the ligand component in the binding pocket (Figures 1–6). Apigenin has been revealed to include one h-bond as well as the polar residue THN588 (figure1). Four hydrogen bonds can be seen in the Quercetin molecule (Figure 5), and the polar residues are the amino acids MET413, ARG662, LEU600, and SER411. It was shown that the ligand, ellagic acid, interacted with residues SER577, ASP578, and ARG430. Resveratrol's THR590 also occupied a binge pocket, but its h-bond distance was just 2.33 angstroms. Beta-caryophyllene had no h-bond whereas Luteolin showed two h-bonds, THR588 and GLY408. The quercetin complex enhanced stability by docking onto the cage's polar, non-polar, and negatively charged residues.

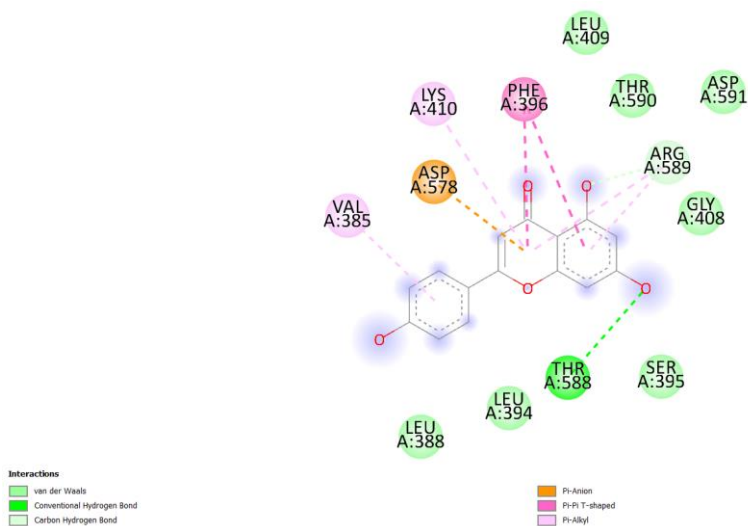


Figure 1: 2D structure of Apigenin

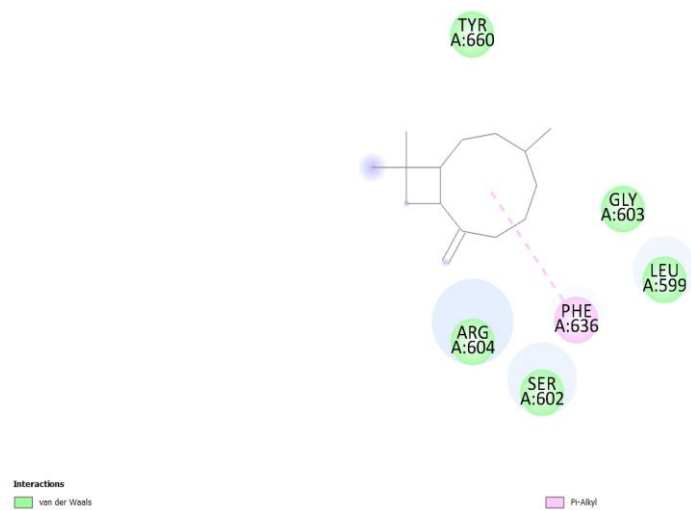


Figure 2: 2D structure of Beta-caryophyllene

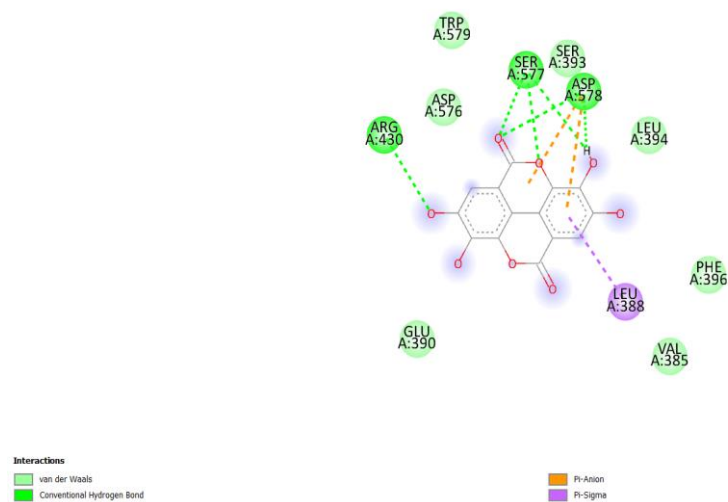


Figure 3: 2D structure of Ellagic Acid

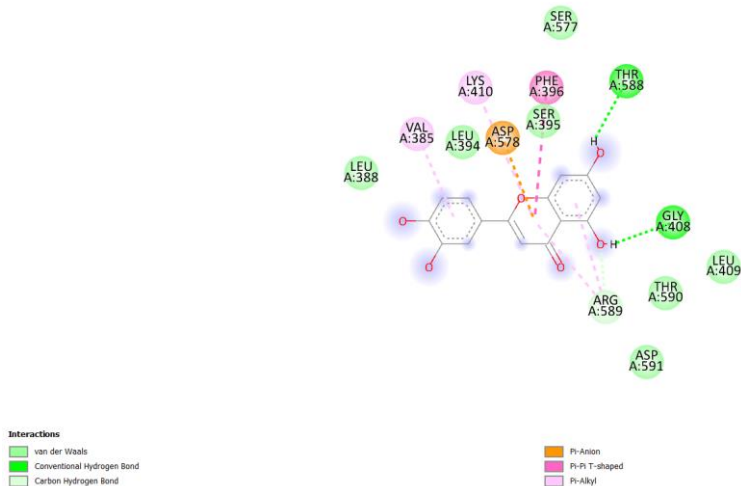


Figure 4: 2D structure of Luteolin

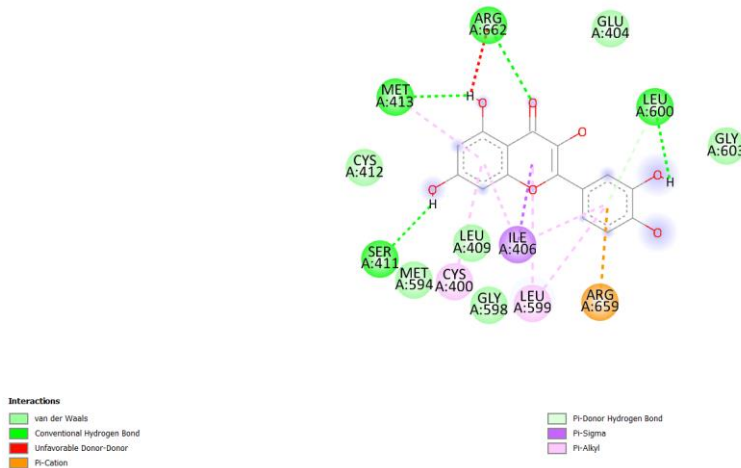


Figure 5: 2D structure of Quercetin

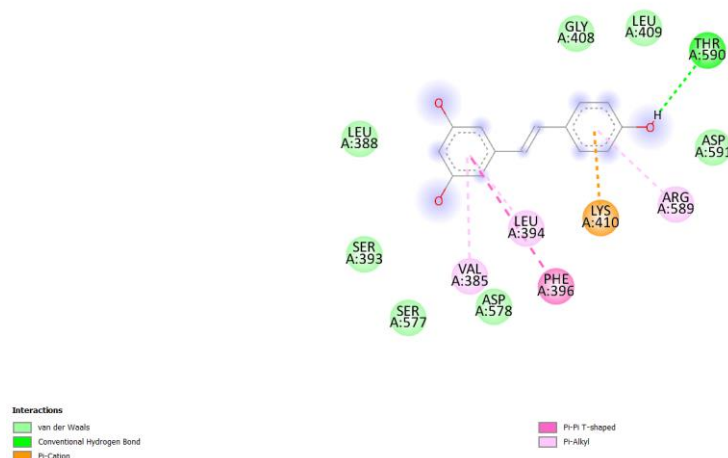


Figure 6: 2D structure of Resveratrol

Conclusion

Overexpression of protein targets is one possible explanation for the recent substantial increase in the worldwide death rate attributable to endometrial cancer. Candidates like ITGB3 are the primary points of emphasis. Drugs are required. Therefore, molecules derived from natural sources are necessary for developing more effective, selective, and safe inhibitors for the aforementioned targets. This in-silico research provides new information on how to block the endometrial cancer target using natural chemicals. Here, we show that molecular docking and ADMET investigations may be used to virtually screen these drugs with the protein target and identify a potent inhibitor. Compounds found in the ocean were able to bind to ITGB3's specific binding pocket. We discovered that of all the targets for endometrial cancer, quercetin had the lowest binding energy. Inhibiting tumor development by causing cell cycle arrest and boosting apoptotic cell death, quercetin showed promise as a cancer chemo preventive drug in toxicity tests. Further hydrogen bond formation in the simulated compound suggests that quercetin may be an efficient inhibitor. Quantitative computational approaches now available support quercetin's role as a potent inhibitor.

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