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In silico assessment of cannabinoids and related compounds as multi-target modulators of IL-2, TNF-α, HSP70/HSP90, EGF signaling, and MMP-2/MMP-9 in ovarian cancer

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Abstract

Ovarian cancer is one of the most lethal gynecological diseases and remains a formidable challenge because of its high mortality and intrinsic resistance to conventional treatment approaches. Recent advances in molecular biology and drug discovery have identified several proteins, such as interleukin-2 (IL-2), tumor necrosis factor-alpha (TNF-α), heat shock proteins (HSPs), epidermal growth factor (EGF), and matrix metalloproteinases (MMPs), as potential therapeutic targets. Tetrahydrocannabinol (THC), cannabinol, elasterol, and 2-methylenecholestan-3-ol are among the substances that have shown promise in modulating these targets. This study aims to evaluate, *in silico*, the potential of 2-methylenecholestan-3-ol, elastrol, THC, and cannabinol to modulate IL-2, TNF-α, HSPs, EGF signaling, and MMPs in ovarian cancer. Bioinformatics databases were used to identify potential therapeutic agents for ovarian cancer. Molecular docking, protein–ligand complex analysis, SwissADME, admetSAR, and toxicity prediction were performed as key components of the workflow. Overall, the *in silico* analyses suggest that these compounds may interact with key proteins implicated in ovarian cancer progression. Particularly, elasterol and 2-methylenecholestan-3-ol showed good therapeutic properties against OC targeting HSP70 and HSP90, whereas THC and cannabinol show adequate interactions with MMPs and TNF-α. These findings suggest potential therapeutic relevance, opening up a promising avenue for improving ovarian cancer treatment.

Keywords: Ovarian cancer; Phytocompounds; HSP-70; MMPs; Molecular docking; admetSAR

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1. Introduction

Ovarian cancer is one of the most lethal gynecological malignancies and is characterized by uncontrolled cellular proliferation. Early-stage disease is difficult to detect because symptoms are often mild or nonspecific. Ovarian cancer is influenced by multiple

factors, such as hormonal factors, genetic changes,[1] older age (particularly >60), obesity, family history, inherited gene mutations (e.g., *BRCA1*/*BRCA2*) or Lynch syndrome,[2] and endometriosis.[3] Risk also increases with age. In 2018, there were approximately 22,240 new cases of ovarian cancer and 14,070 deaths in the United States.[4] In the United Kingdom (2017–2019), on average each year, more than half of new cases occurred in females aged 75 years and older; age-specific incidence rates increase steadily from ages of 10–14 years and rise more sharply from around ages of 40–44 years, with the highest rates observed in the 75–79 years of age group.[5]

Most of the patients have no symptoms in the early stages; however, in the later stages, symptoms may include abdominal swelling, abdominal or lower abdominal pain, early satiety (feeling full after consuming a small amount of food), tiredness, leg swelling, back pain, shortness of breath, abnormal vaginal bleeding, irregular menstrual periods, and weight gain or loss.[6] Treatment options include surgery (removal of the reproductive organs and other involved tissues, commonly performed via laparotomy),[7] chemotherapy (drugs used before or after surgery to kill cancer cells), targeted therapy (drugs used to identify and attack cancer cells and inhibit their growth and division), hormone therapy (drugs used to block or slow hormone-driven disease),[8] and radiation therapy (high-energy X-rays used to damage cancer cells and inhibit their growth).[9]

Gynecologic cancers in reproductive-age women raise important fertility-preservation considerations. Endometrial cancer is often detected earlier due to irregular uterine bleeding than ovarian cancer, which may present with mild clinical manifestations. Obesity, polycystic ovarian syndrome, thyroid dysfunction, and inherited disorders are risk factors for these conditions and may reduce fertility. Young women with gynecologic cancer may require fertility preservation, and oocyte vitrification is a commonly used approach to preserve reproductive potential before treatment. Furthermore, women with thyroid dysfunction, which is common in infertility pathways, may require tailored therapy to maximize reproductive and oncological outcomes.[10] Once pregnancy is established, early use of non-invasive prenatal testing and monitoring of neonatal outcomes may be considered, particularly in infants born from frozen embryos. These procedures, combined with long-term follow-up, may help protect maternal and offspring health.

At present, available treatments are not sufficient for all patients with ovarian cancer. Computational techniques have increasingly been used to support the identification of plant-derived therapeutic compounds for the treatment of ovarian cancer.[11] Integrated *in silico* personalized medicine approach for ovarian cancer, leveraging genomic and proteomic data to identify actionable therapeutic targets and improve clinical outcomes.[12] Furthermore, this study aims to investigate novel ligands through molecular docking analysis to compare their therapeutic potential against ovarian cancer. Carboplatin is the United States Food and Drug Administration (FDA)-approved treatment for ovarian cancer, but its efficacy is often limited by drug resistance. The selected phytocompounds (2-methylenecholestan-3-ol, elasterol, tetrahydrocannabinol [THC], cannabinol, 1-*n*-hexadecylindan, 4,6-dimethoxy-*o*-toluate, nabilone, 1-ethyl-3-propyladamantane, squalene, cannabidiol [CBD], cannabigerolate [CBGA], 4,2-cresotic acid, tetrahydrocannabivarin [THCV]) showed predicted binding affinity against the targeted proteins tumor necrosis factor-alpha (TNF-α), interleukin-2 (IL-2), heat shock protein (HSP)70, HSP90, epidermal growth factor (EGF), matrix metalloproteinase (MMP)-9, and MMP-2, suggesting potential relevance for ovarian cancer. While challenges remain, ongoing technological and research advancements hold promise for enhancing outcomes and quality of health for women affected by ovarian cancer in the future.

2. Materials and methods

An *in silico* approach was used to predict plant-derived cannabinoids against ovarian cancer with associated targets. Relevant proteins and cannabis structures were retrieved from databases, followed by molecular docking to determine the binding affinity and complex stability. Drug-likeness, ADMET, and toxicity profiles were predicted computationally to find prospective lead compounds.

2.1. Data sources and compound selection

The screened compounds—2-methylenecholestan-3-ol, elasterol, THC, cannabinol, 1-*n*-hexadecylindan, 4,6-dimethoxy-*o*-toluate, nabilone, 1-ethyl-3-propyladamantane, squalene, CBD, CBGA, cannabigerolic acid, 4,2-cresotic acid, and THCV—were retrieved from PubChem (https://pubchem.ncbi.nlm.nih.gov). Carboplatin (Paraplatin), an FDA-approved drug used in ovarian cancer treatment, was included as a reference compound for comparison and validation. Receptor structures were downloaded from the RCSB Protein Data Bank (PDB; www.pdb.org/pdb) in PDB format. The target proteins and PDB IDs were TNF-α (1EXT), IL-2 (1M47), HSP-70 (3ATU), HSP-90 (3HYZ), EGF (3NJP), MMP-9 (5TH6), and MMP-2 (8H78).

2.2. Protein preparation

The downloaded protein structures were prepared using Discovery Studio Visualizer (https://discover.3ds.com/discovery-studio-visualizer-downloded) by removing

undesired molecules from the receptor structures. Hydrogen atoms were added, and the prepared receptors were saved in PDB format for subsequent analyses.

2.3. Ligand preparation

Ligand structures obtained from the PubChem were downloaded in Standard Data Format format.[13] Ligands were imported into PyRx (https://pyrx.sourceforge.io/),[14] and the Open Babel function in PyRx was used to convert ligand files to PDB format. Ligands were then prepared for docking and converted to PDBQT format within PyRx after energy minimization.

2.4. Molecular docking

Molecular docking was performed using PyRx (AutoDock Vina) to evaluate protein–ligand interactions between the selected ligands and the target proteins (TNFR1, IL-2, HSP70, HSP90, EGFR/EGF complex, MMP-9, and MMP-2). Each receptor was uploaded and prepared individually in PyRx and converted to a macromolecule. Ligands were uploaded one by one, energy-minimized, and converted to PDBQT format.

Gard boxes were defined for docking using the following box dimensions: TNF-α (X = 107.23, Y = 97.43, Z = 86.91), IL-2 (X = 46.51, Y = 54.17, Z = 54.07), HSP-70 (X = 73.20, Y = 76.15, Z = 71.68), HSP-90 (X = 72.18, Y = 75.95, Z = 103.01), EGF (X = 160.25, Y = 154.39, Z = 112.45), MMP-9 (X = 114.40, Y = 84.68, Z = 112.60), and MMP-2 (X = 94.73, Y = 68.84, Z = 73.43). Docking runs were executed in PyRx, and docking scores were recorded for downstream comparison.

2.5. Protein–ligand interaction analysis

Docked complexes were analyzed using Discovery Studio Visualizer to evaluate 2D interaction profiles and key interaction features, including hydrogen bonding and hydrophobic interactions, as well as the residues involved in ligand binding.

2.6. Drug-likeness and toxicity prediction

Drug-likeness properties were assessed using SwissADME (www.swissadme.ch/index.php).[15] Canonical SMILES strings were obtained from PubChem and submitted to the SwissADME, and compounds were evaluated for compliance with Lipinski's rule of five.

Toxicity prediction was performed using ProTox-III (https://tox.charite.de/protox3/). Canonical SMILES strings retrieved from PubChem were submitted to ProTox-III to predict immunogenicity, mutagenicity, cytotoxicity, carcinogenicity, hepatotoxicity, AMES toxicity, and oral toxicity.[16]

3. Results

Molecular docking is widely used in drug discovery to estimate protein–ligand binding poses and docking scores. Table 1 summarizes docking scores for the screened ligands against the selected targets. In ovarian cancer, several key proteins, including TNF-α, IL-2, HSP-70, HSP-90, EGF, MMP-2, and MMP-9, have been implicated in processes such as inflammation, tumor growth, metastasis, and chemotherapy resistance. In this study, docking analysis was performed to evaluate the binding of screened ligands against these targets. Overall, 13 ligands exhibited favorable docking scores (more negative values), indicating predicted stable interactions with the selected proteins. Several ligands also showed more favorable docking scores than carboplatin in this docking analysis. Such outcomes suggest that the screened ligands may not only inhibit multiple pathways involved in ovarian cancer progression but also provide a therapeutic advantage over conventional therapy. By targeting proteins associated with immune modulation, heat shock response, growth signaling, and extracellular matrix degradation, these ligands could act as multi-target inhibitors, potentially reducing tumor growth, metastasis, and drug resistance.

The docking scores (kcal/mol) indicate the predicted binding of the tested compounds to the target proteins. For TNF-α, the ligands showed affinities of −7.3, −7, −7, and −7.8, while for IL-2, the values were −6.8, −6.4, −6.5, and −6.7. In the case of HSP-70, the affinities were −7.6, −7.1, −7.5, and −7.3, and for HSP-90, they ranged from −8.2 to −8.0. EGF showed values of −8, −8.6, −7.8, and −8. MMP-9 had −8, −8.3, −8.1, and −8.2, and MMP-2 ranged from −8.7 to −7.9. In comparison, the standard drug carboplatin showed lower binding affinities (−5.7, −5.5, −5.4, and −5.3), indicating that the tested ligands bind more strongly to these targets. Among the 13 compounds analyzed, four ligands per target were selected for further study based on their high binding affinity, as summarized in Table 2.

The results indicate that following amino acid residues are involved in the predicted interactions of the selected ligands with the target proteins: TNF-α (PHE:115, HIS:105), IL-2 (PHE:42, TYR: 45, LYS:97, ALA:50, CYS:58, PRO:65, ALA:73), HSP-70 (LYS:257, VAL:260, ARG:261, TYR:41, ALA:70, VAL:369, THR:226), HSP-90 (ARG:182, LEU:56, GYB:55, HIS:77, GLU:75, TRP:162, PHE:138, VAL:150, TYR:139, LYS:185, ASN:106), EGF (CRY:287, VAL:312, ARG:310, CYS:287, ALA:286, TYR:292, TYR:602, PRO:602, CYS:612, TRL:614), MMP-9 (TYR:50, ARG:51, PHE:181, PHE:192, ILE:198, PHE425, PHE:396), and MMP-2 (HIS:85, TYR:74, HIS:125, HIS:121, HIS:131, ALA84, VAL118, LEU:83, TYR:143, ALA:84). Overall, MMP-2 emerged as the most promising ovarian cancer

Table 1. Docking analysis of receptor proteins with selected ligands

Docking analysis		Ligand name						
S. No.	Protein (PDB ID)	2-methylenecholestan-3-ol	Elasterol	Tetrahydrocannabinol	Cannabinol	1-*n*-hexadecylindan	4,6-dimethoxy-*o*-toluate	Nabilone
1	TNF-α (1EXT)	−7.3	−7	−6.8	−7	−4.5	−6.7	−6.5
2	IL-2 (1M47)	−6.8	−6.4	−5.9	−6.5	−4.4	−6.2	−6.3
3	HSP70 (3ATU)	−7.6	−7	−7.1	−7	−4.4	−7.5	−7.3
4	HSP90 (3HYZ)	−8.2	−7.9	−7.1	−8.2	−6.7	−7.6	−8.1
5	EGF (3NJP)	−8	−8.6	−7.3	−7.5	−4.8	−7.8	−7.4
6	MMP-9 (5TH6)	−8	−8.3	−8	−8.1	−5.7	−6.8	−7.3
7	MMP-2 (8H78)	−8.7	−7.7	−7.7	−7.6	−4.7	−7.8	−7.7
8	FDA-approved drug: Carboplatin 10339178 (brand names: Paraplatin)	–	–	–	–	–	–	−4.6
Docking analysis		**Ligand name**						
S. No.	**Protein (PDB ID)**	**1-ethyl-3-propyladamantane**	**Squalene**	**Cannabidiol**	**Cannabigerolate**	**4,2-cresotic acid**	**Tetrahydrocannabivarin**	
1	TNF-α (1EXT)	−5.5	−4.6	−5.8	−6.6	−5	−7.8	
2	IL-2 (1M47)	−6.1	−6.3	−6.4	−6	−5	−6.7	
3	HSP70 (3ATU)	−6.1	−6.5	−6.1	−6.1	−5.3	−6.8	
4	HSP90 (3HYZ)	−7.1	−6.3	−6.9	−7.3	−6.4	−8	
5	EGF (3NJP)	−6	−4.8	−6.6	−6.9	−5.3	−8	
6	MMP-9 (5TH6)	−6.3	−6.6	−7.2	−7	−6.1	−8.2	
7	MMP-2 (8H78)	−6.5	−7.1	−8.4	−7.6	−6.3	−7.9	
8	FDA-approved drug: Carboplatin 10339178 (brand names: Paraplatin)	−4.8	−4.8	−5.5	−5.3	−5.7	−5.4	

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Table 2. Molecular docking and complex analysis results for selected ligands

S. No.	Protein	Ligands	Binding affinity (kcal/mol)	Interaction type	Category	Active amino acid residues
1	TNF-α	2-methylenecholestan-3-ol	−7.3	Hydrophobic	Pi-sigma	PHE: 115
		Elasterol	−7	Hydrophobic	Van dar Waals	PHE: 115
		Cannabinol	−7	Hydrophobic	Pi–pi stacked, Pi–alkyl, pi–pi t-shaped	PHE: 115, HIS: 105
		Tetrahydrocannabivarin	−8	Hydrophobic	Alkyl	VAL: 95
2	IL-2	2-methylenecholestan-3-ol	−6.8	Hydrophobic	Pi–alkyl	PHE: 42, TYR: 45
		Elasterol	−6.4	Hydrophobic	Alkyl	LYS: 97, ALA: 50, CYS: 58
		Cannabinol	−6.5	Hydrophobic	Pi–alkyl	PRO: 65
		Tetrahydrocannabivarin	−6.7	Hydrophobic	Pi–alkyl	ALA: 73
3	HSP70	2-methylenecholestan-3-ol	−7.6	Hydrophobic	Alkyl	LYS: 257, VAL: 260, ARG: 261
		Tetrahydrocannabinol	−7.1	Hydrophobic	Pi–alkyl	ALA: 70, TYR: 41
		4,6-dimethoxy-*o*-toluate	−7.5	Hydrophobic	Alkyl	VAL: 369
		Nabilone	−7.3	Hydrogen	Carbon hydrogen bond	THR: 226
4	HSP90	2-methylenecholestan-3-ol	−8.2	Hydrogen	Conventional hydrogen bond, covalent bond, unfavorable acceptor–acceptor interaction	HIS: 77, ARG: 182, GLU: 75, LEU: 56
		Cannabinol	−8.2	Hydrophobic	Pi–pi stacked, pi–alkyl	TRP: 162, TYR: 139, PHE: 138, VAL: 150
		Nabilone	−8.1	Hydrogen	Conventional hydrogen bond	LYS: 185
		Tetrahydrocannabivarin	−8	Hydrophobic	Pi–alkyl	TYR: 139, PHE: 138, TRP: 162, ASN: 106, VAL: 150
5	EGF	2-methylenecholestan-3-ol	−8	Hydrophobic	Alkyl	VAL: 312, ARG: 310, CYS: 287
		Elasterol	−8.6	Hydrophobic	Alkyl	CYS: 287, VAL: 312
		4,6-dimethoxy-*o*-toluate	−7.8	Hydrogen	Carbon hydrogen bond, alkyl	ALA: 286, CYS: 287, ARG: 310, GLU: 293
		Tetrahydrocannabivarin	−8	Hydrogen	Pi–sigma, pi–alkyl, pi–donor hydrogen bond	THR: 614, TYR: 602, PRO: 613, CYS: 612
6	MMP-9	2-methylenecholestan-3-ol	−8	Hydrophobic	Alkyl, pi–alkyl	TYR: 50, ARG: 51
		Elasterol	−8.3	Hydrophobic	Pi–alkyl	PHE: 181, ILE: 198, PHE: 192
		Cannabinol	−8.1	Hydrophobic	Pi–alkyl	PHE: 425
		Tetrahydrocannabivarin	−8.2	Hydrophobic	Pi–alkyl	PHE: 396
7	MMP-2	2-methylenecholestan-3-ol	−8.7	Hydrophobic	Pi–alkyl	HIS: 85, TYR: 74, HIS: 125, HIS: 121
		4,6-dimethoxy-*o*-toluate	−7.8	Hydrophobic	Pi–pi t-shaped, pi–alkyl, pi–pi stacked	HIS: 131, HIS: 125
		Cannabidiol	−8.4	Hydrophobic	Pi–alkyl, alkyl	HIS: 131, ALA: 84, VAL: 181, HIS: 121, LEU: 83, HIS: 125
		Tetrahydrocannabivarin	−7.9	Hydrophobic	Pi–pi t-shaped, pi–alkyl, alkyl	HIS: 121, TYR: 143, LEU: 83, ALA: 84, VAL: 118

target, with the screened compounds showing high binding affinity and the most favorable docking scores. Figures 1-4 show the 2D and 3D interaction maps for the selected ligands docked to MMP-2. Additional interaction maps for other protein–ligand complexes are provided in Figures S1-S24.

3.1. Probable drug-like compounds

The drug-likeness of the selected compounds was evaluated using the SwissADME bioinformatic tool, which predicts ADME properties (absorption, distribution, metabolism, and excretion). Canonical SMILES for each compound were obtained from PubChem and analyzed in

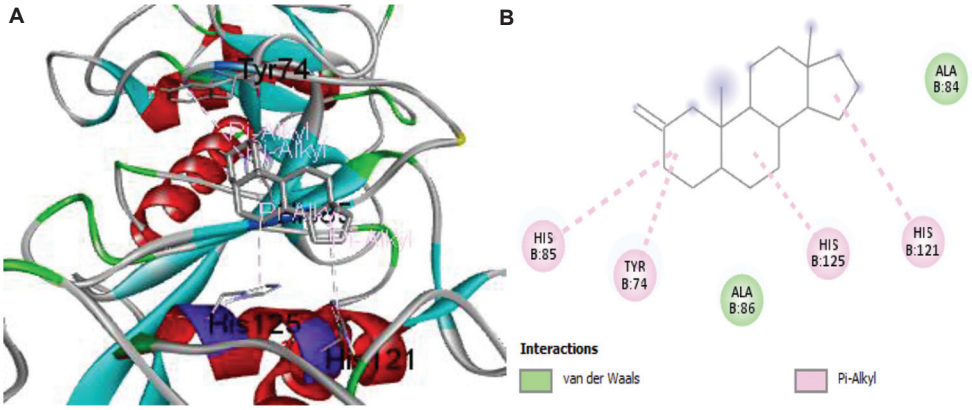

Figure 1. Binding interaction of 2-methylenecholestan-3-ol with MMP-2. (A) 3D binding pose highlighting key interacting residues; (B) corresponding 2D interaction map.

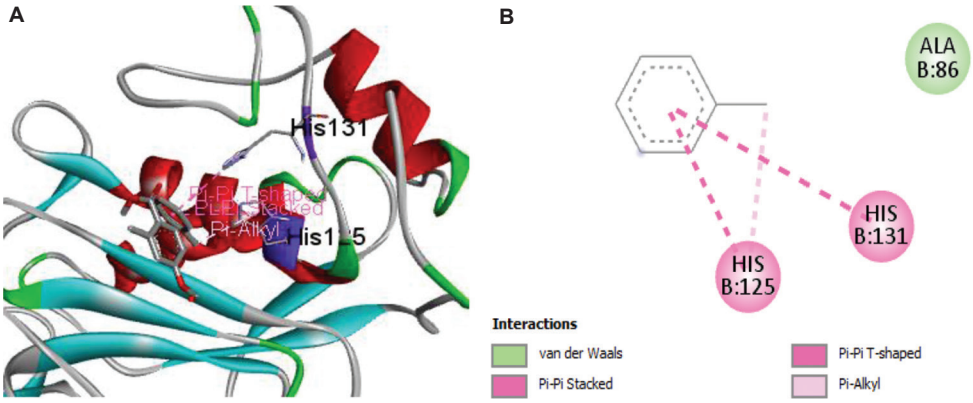

Figure 2. Binding interaction of 4,6-dimethoxy-*o*-toluate with MMP-2. (A) 3D binding pose highlighting key interacting residues; (B) corresponding 2D interaction map.

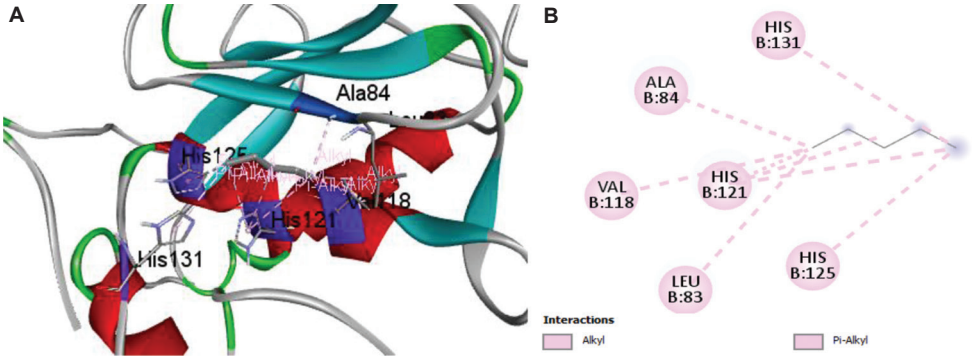

Figure 3. Binding interaction of cannabidiol with MMP-2. (A) 3D binding pose highlighting key interacting residues; (B) corresponding 2D interaction map.

SwissADME. Compounds were assessed against Lipinski's rule of five (molecular weight ≤500, H-bond acceptors ≤10, H-bond donors ≤5, molar refractivity 40–140, and logP ≤5). Most compounds, including several cannabinoids (THC, CBD, CBN, CBGA, and THCV), showed predicted high gastrointestinal absorption and met most criteria, with one or more predicted violations commonly related to high lipophilicity (logP). The standard drug, carboplatin, complied with Lipinski's criteria and showed predicted high gastrointestinal absorption. Larger, more hydrophobic molecules such as elasterol and squalene exceeded limits for logP or size, making them less favorable as drug candidates, whereas smaller molecules such as 4,2-cresotic acid showed no Lipinski violations and favorable drug-like properties. Overall, Table 3 summarizes the ADME and drug-likeness predictions for the selected ligands.

Table 3. ADME analysis and drug-likeness properties of ligands

Molecule	Molecular weight	H-bond acceptors (*n*)	H-bond donors (*n*)	Molecular refractivity	Silicos-IT LogP	Gastrointestinal absorption	Lipinski violations (*n*)	Lead-likeness violations (*n*)	Aromatic heavy atoms (*n*)	Topological polar surface area	Silicos-IT LogSw
Carboplatin (Paraplatin)	144.1	4	2	32.13	0.15	High	0	1	0	74.6	0.3
2-methylenecholestan-3-ol	400.7	1	1	128.42	6.8	Low	1	2	0	20.23	−6.17
Elasterol	410.7	1	1	132.28	7.04	Low	1	2	0	20.23	−6.18
Tetrahydrocannabinol	314.5	2	1	97.91	5.41	High	1	1	6	29.46	−5.93
Cannabinol	310.4	2	1	97.1	6.15	High	1	1	12	29.46	−7.49
1-*n*-hexadecylindan	342.6	0	0	115.98	8.92	Low	1	2	6	0	−9.42
4,6-dimethoxy-*o*-toluate	538.5	10	0	141.39	5.92	High	1	3	18	115.8	−8.34
Nabilone	372.5	3	1	112.89	6.28	High	1	2	6	46.53	−6.87
1-ethyl-3-propyladamantane	206.4	0	0	67.36	4.59	Low	1	2	0	0	−4.16
Squalene	410.7	0	0	143.48	10.41	Low	1	3	0	0	−7.48
Cannabidiol	314.5	2	2	99.85	5.42	High	1	1	6	40.46	−5.41
Cannabigerolate, cannabigerolic9	360.5	4	3	108.92	5.75	High	1	3	6	77.76	−5.14
4,2-cresotic acid	152.2	3	2	40.39	1.19	High	0	1	6	57.53	−1.57
Tetrahydrocannabivarin	286.4	2	1	88.3	4.62	High	0	1	6	29.46	−5.13

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3.2. Toxicity prediction

The selected compounds were further evaluated for predicted toxicity using ProTox-III. Canonical SMILES were obtained from PubChem and submitted to ProTox-III to predict hepatotoxicity, carcinogenicity, mutagenicity, cytotoxicity, and immunogenicity (Table 4). Toxicity prediction is a crucial stage in drug design to identify potential adverse effects to help prioritize compounds for experimental testing. Compared with traditional animal-based toxicity testing, computational approaches can provide faster and lower-cost preliminary screening. Table 4 shows that the shortlisted compounds, including carboplatin/paraplatin (standard drug), 2-methylenecholestan-3-ol, elasterol, tetrahydrocannabinol, cannabinol, 1-n-hexadecylindan, 4,6-dimethoxy-o-toluate, nabilone, 1-ethyl-3-propyladamantane, squalene, cannabidiol, CBGA, cannabigerolic acid, 4,2-cresotic acid, and THCV, were identified as therapeutic compounds with a promising toxicity profile. The compounds demonstrated non-carcinogenic, non-mutagenic, cytotoxic, and non-hepatotoxic effects on the human body, as well as the capability to activate the human immune response against OC.

4. Discussion

In reproductive-aged women, endometrial cancer treatment is becoming more interdisciplinary and technology-driven. Artificial intelligence may improve diagnosis, treatment response assessment, and fertility preservation, especially for infertile women who may require assisted reproduction. Thyroid dysfunction is relevant to both carcinogenesis and infertility and should be appropriately assessed.[10] Oocyte vitrification before

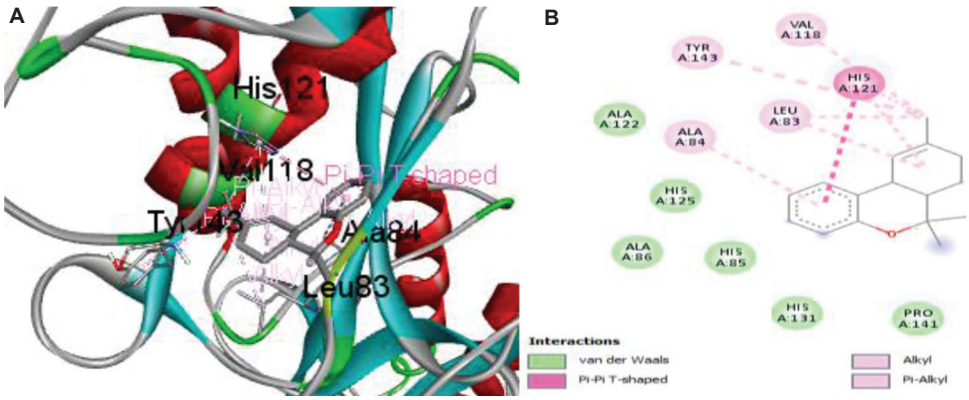

Figure 4. Binding interaction of tetrahydrocannabivarin with MMP-2. (A) 3D binding pose highlighting key interacting residues; (B) corresponding 2D interaction map.

Table 4. Toxicity prediction of standard and ligand compounds

Compound	Hepatotoxicity	Carcinogenicity	Immunotoxicity	Mutagenicity	Cytotoxicity
Carboplatin (Paraplatin) (standard)	Inactive	Inactive	Inactive	Inactive	Inactive
2-methylenecholestan-3-ol	Inactive	Inactive	Active	Inactive	Inactive
Elasterol	Inactive	inactive	Active	Inactive	Inactive
Tetrahydrocannabinol	Inactive	Inactive	Active	Inactive	Inactive
Cannabinol	Inactive	Inactive	Active	Inactive	Inactive
1-*n*-hexadecylindan	Inactive	Inactive	Inactive	Inactive	Inactive
4,6-dimethoxy-*o*-toluate	Inactive	Inactive	Inactive	Inactive	Inactive
Nabilone	Inactive	Inactive	Active	Inactive	Inactive
1-ethyl-3-propyladamantane	Inactive	Inactive	Inactive	Inactive	Inactive
Squalene	Inactive	Inactive	Inactive	Inactive	Inactive
Cannabidiol	Inactive	Inactive	Active	Inactive	Inactive
Cannabigerolate, cannabigerolic acid	Inactive	Inactive	Active	Inactive	Inactive
4,2-cresotic acid	Active	Inactive	Inactive	Inactive	Inactive
Tetrahydrocannabivarin	Inactive	Inactive	Active	inactive	Inactive

treatment remains a cornerstone of fertility preservation; however, early non-invasive prenatal testing, long-term monitoring of children conceived through frozen embryo transfer, and awareness of obstetric risks (e.g., postpartum hemorrhage) are also crucial. These advances, combined with molecular classification and evidence-based therapies, may provide these patients with a more tailored, safe, and successful fertility-sparing approach.

The treatment for ovarian cancer remains particularly difficult because of high mortality and frequent late-stage detection, highlighting the necessity for improved therapeutic strategies. Recent research suggests that specific proteins[17] and pathways implicated in cancer progression may be therapeutically targeted. Targets commonly discussed in this context include TNF-α, HSP70, HSP90, MMP-2, MMP-9, IL-2, and EGF.[18] *In silico* screening of ligands such as elasterol, 2-methylenecholestan-3-ol, cannabinol, and THC represents one approach to explore interactions with these targets. THC has been reported to induce apoptosis in some cancer models and to modulate immune responses.[19] It has also been reported to influence IL-2 signaling to boost immunity against tumors and TNF-α to reduce inflammation, which promotes tumor growth.[20]

In this study, receptor structures (TNF-α, IL-2, HSP-70, HSP-90, EGF, MMP-9, and MMP-2) were screened against multiple ligands (2-methylenecholestan-3-ol, elasterol, THC, cannabinol, 1-*n*-hexadecylindan, 4,6-dimethoxy-*o*-toluate, nabilone, 1-ethyl-3-propyladamantane, squalene, CBD, CBGA, cannabigerolic acid, 4,2-cresotic acid, and THCV) to evaluate predicted binding in molecular docking analyses.[21,22] Similar *in silico* approaches have been reported using phytocompounds in ovarian cancer research. For instance, curcumin has been shown to induce apoptosis in ovarian cancer cells by modulating reactive oxygen species generation and reprogramming the tumor microenvironment, while quercetin has been reported to enhance the efficacy of paclitaxel and to inhibit MMP-1, thereby reducing metastasis and chemoresistance.[23] Resveratrol and its analog oxyresveratrol have been reported to exhibit anti-angiogenic and pro-apoptotic effects, particularly when combined with cisplatin, and berberine has been demonstrated to synergize with poly(ADP-ribose) polymerase inhibition to suppress proliferation and metastasis in resistant ovarian cancer models. Likewise, epigallocatechin gallate from green tea has been reported to overcome cisplatin resistance through nuclear factor kappa B (NF-κB)/p53 signaling,[24] and ginsenosides (e.g., Rg3) have been shown to modulate hypoxia-inducible factor 1-alpha/squalene epoxidase and NF-κB pathways to suppress ovarian tumor progression.

Based on the docking results, elasterol showed favorable predicted binding to HSP90, which may be relevant to pathways associated with treatment response. Cannabinoids also showed favorable predicted binding to growth factor-related signaling targets, and ligands such as 2-methylenecholestan-3-ol showed favorable predicted binding to MMPs, which may be relevant to invasion-associated processes. These findings were based on *in silico* prediction and do not validate inhibition, synergy, or clinical effectiveness, which are influenced by pharmacokinetics and pharmacodynamics in a real biological system. Comprehensive *in vitro* and *in vivo* validation, followed by clinical research, is necessary to show therapeutic relevance.

5. Conclusion

In this study, selected phytocompound-based ligands demonstrated favorable docking scores and predicted protein–ligand interactions against ovarian cancer-related targets such as TNF-α, IL-2, HSP-70, HSP-90, EGF, MMP-9, and MMP-2. These results suggest that natural compounds, including cannabinoids and other bioactive phytochemicals, hold strong therapeutic potential as multi-target inhibitors, which aligns with growing evidence on agents such as curcumin, quercetin, resveratrol, berberine, and epigallocatechin gallate, that regulate oncogenic pathways, enhance chemotherapy efficacy, and overcome drug resistance in ovarian cancer. Together, the integration of computational docking with the therapeutic promise of phytocompounds provides a valuable roadmap for developing safer, more effective ovarian cancer treatments; however, further *in vitro*, *in vivo*, and clinical validation remains essential to translate these natural compounds into viable therapies capable of improving survival and quality of life for affected patients.

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Conflict of interest

The authors declare that they have no competing interests.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

All data from the study are presented in the article.

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