

Comparative Analysis of Pharmacokinetic Properties of the FDA-Approved Ovarian, Fallopian Tube, and Primary Peritoneal Cancer Drugs

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Abstract: *Introduction:* Ovarian, Fallopian tube, and peritoneal cancers are cancers that are commonly observed in post-menopausal women. In the general description, "ovarian cancer" is the term used in describing these cancers. Ovarian cancer is the 5th leading cause of cancer deaths in women with a 5-year survival rate. Ovarian cancer is commonly diagnosed in women aged 65 years or older. Early detection and appropriate treatment options can help in steadily decreasing the death rates. *Materials and methods:* The detailed study is performed by using online bioinformatics web tools such as NCI to retrieve the list of query drugs, PubChem to obtain the canonical smiles of the drugs, and Swiss ADME to compute the Absorption, Distribution, Metabolism, and Excretion properties of each drug candidate. *Result:* The study succeeded in identifying the best drug candidates among the list of FDA-approved (Food and Drug Administration) drugs in the treatment of ovarian, fallopian tube, and peritoneal cancers by analyzing various pharmacokinetic properties.

Keywords: Ovarian Cancer, NCI, PubChem, Swiss ADME

1. Introduction

Cancer is a chronic disease and is the second leading cause of death worldwide. Though the mortality rates have been shown to decrease with various strategies developed to treat and diagnose cancer, the percentage of success is quite low in the case of some cancers. Among all the cancers, Ovarian, fallopian tube, and peritoneal cancers, in particular, are diseases commonly occurring in postmenopausal women. [1] It is estimated that about 90% of ovarian cancers originate from the epithelium and since fallopian tube and peritoneal cancers share similar histology, spread pattern as that of epithelial ovarian cancer, they are grouped under ovarian cancer or described as pelvic serous carcinomas. However, studies are underway in identifying if these cancers can be considered as separate entities or not. [2] [3] [4] According to the GLOBOCAN 2020 statistics, the incidence of ovarian cancer among the 9.2 million new cases was 3.4% and mortality rates were 4.7% of 4.4 million deaths reported in the case of female-specific cancers. [5]

Ovarian cancers are considered malignant tumors as they are usually detected at advanced stages and have a poor prognosis. [6] The main risk factors for ovarian cancers include age, reproductive factors, obesity, endometriosis, family history, etc. Studies have reported that 5-10% of ovarian cancers have a strong genetic background. [2] The germline mutations in *BRCA1* and *BRCA2* genes are commonly reported in breast and ovarian cancers. The lifetime risk of ovarian cancers ranges between 20% for germline mutations in the *BRCA2* gene and >50% for *BRCA1* mutations. Mutations in *PALB2*, *RAD51C*, *RAD51D*, *CHEK2*, *MRE11*, etc have also been reported in familial ovarian cancer patients. [7]

It is noted that the high mortality rates in the case of ovarian, fallopian, and peritoneal cancers are often due to the presence of nonspecific symptoms and not merely due to the lack of screening tests. The notable signs and symptoms include menstrual problems, frequent urination, abdominal

pain, presence of pelvic mass upon pelvic examinations, etc. [8]

Bilateral risk reduction salpingo-oophorectomy (RRSO) has been shown to reduce the risk of ovarian cancer, peritoneal, and fallopian tube cancer in women with a mutation in *BRCA1* and *BRCA2* genes after undergoing (RRSO). It is highly recommended for women aged 35-40 years carrying a mutation in the *BRCA1* gene and who do not wish to have children in the future and women aged 40-45 years in case of *BRCA2* carriers. The age difference is due to the early development of ovarian cancer in the case of mutated *BRCA1* carriers. It is important to undergo regular surveillance as the risk of developing peritoneal cancer is about 1-4% after RRSO treatment as the RRSO treatment retains the onset of peritoneal cancers. [9] Other treatment options available include the use of PARP inhibitors, platinum-based chemotherapy which has shown to be highly promising, and effective in reducing the chances of cancer recurrence rates and leads to improved prognosis. [10]

Despite the new medical advancements in treating ovarian cancers, cancer recurrence is reported within 2-3 years after successful surgery or platinum-based chemotherapies. Therefore, new strategies are being developed to specifically detect circulating tumor cells that majorly contribute to cancer treatment resistance and are considered to be highly promising candidates. [11] The study aims to evaluate the pharmacokinetic properties and predict the ADME parameters of the FDA approved drugs in treating ovarian, fallopian, and peritoneal cancers and identify the best drug candidate.

2. Materials and Methods

Data Retrieval

The list of query drugs approved by the FDA was obtained from the NIH- National Cancer Institute website. The National Cancer Institute abbreviated as NCI is a part of NIH (National Health Organization) and a principal agency

conducting cancer research and training with a strong motive to help people lead a longer and healthier lifestyle. The website provides a complete list of FDA-approved drugs for various cancers and conditions related to cancer. A total of 13 drugs were retrieved which includes:

Alkeran (Melphalan), Carboplatin, Cisplatin, Cyclophosphamide, Doxorubicin Hydrochloride, Doxorubicin Hydrochloride Liposome, Gemcitabine Hydrochloride, Hycamtin (Topotecan Hydrochloride), Lynparza (Olaparib), Melphalan, Niraparib Tosylate Monohydrate, Paclitaxel, Rubraca (Rucaparib Camsylate), and Tepadina (Thiotepa).

Evaluation of the pharmacokinetic and ADME properties

The ADME properties of each query drug were analyzed using the SWISS ADME web tool. The canonical smiles of each query drug were taken from PubChem (<https://pubchem.ncbi.nlm.nih.gov/>) which is a public repository web page containing free and accessible information of chemical substances and pasted into SWISS ADME (<http://www.swissadme.ch/>) to compute ADME (absorption, distribution, metabolism, excretion) parameters, various pharmacokinetic properties and drug likeness of each target molecule. The physiological properties taken into account are:



- 1) **Molecular weight (MW):** defined as the sum of atomic masses of atoms constituting the molecule. Molecular weight is used as a parameter in creating a wide range of new microstructures with specific transport properties.
- 2) **Water Solubility (ESOL):** Water solubility is an important parameter in determining the bioavailability of the drug. A drug is considered to have high solubility in the pH range of 1-7.5. A positive value indicates high solubility and a negative value corresponds to low solubility.
- 3) **No. of Hydrogen bond acceptor and donor:** An H-bond is formed when an H-atom attached to an electronegative atom combines with another electronegative atom. Hydrogen bonds play a critical role in determining the ligand-binding sites and are an important parameter to be taken into consideration while designing a drug.
- 4) **No. of Rotatable bonds:** The number of rotatable bonds is an important parameter that helps in determining the bioavailability of the drug. The higher the rotatable bond, the greater is the bioavailability.
- 5) **No. of aromatic heavy atoms:** Aromatic compounds particularly aromatic rings are widely employed for developing various drugs. Drugs candidates are considered to be desirable if they have less than 3 aromatic rings.
- 6) **LogP (iLogP):** The value of log P value is to determine the permeability of drugs in the target tissues and helps in choosing the proper delivery system of drugs to the target sites. It's a component of the Lipinski rule of 5

and measures lipophilicity. A negative LogP indicates increase affinity towards the aqueous phase, a positive value indicates high lipophilicity, and a LogP value of 0 corresponds to partition between the aqueous and lipid phase.

- 7) **Lipinski:** Lipinski rule devised by Lipinski and his co-workers helps in accessing the success rate of the drugs obeying 2 or more of the 5 rules of Lipinski.
 1. Molecular weight less than 500 Da.
 2. Less than 10 H-bond acceptors.
 3. Less than 5 H-bond acceptors.
 4. LogP value not exceeding 5.
- 8) **Lipophilicity (XLOGP3):** Lipophilicity refers to the ability of the drug to cross the lipid cell membrane and reach the target site to exhibit its action. Higher the lipophilicity, the higher the absorption of the drug.
- 9) **Leadlikeness:** The property of Leadlikeness helps in optimizing the drug candidates to be delivered. The drugs are modified sometimes to increase their potency by adding extra functional groups and following the rule of 3
 1. MW less than or equal to 300 Da.
 2. clogP less than or equal to 3.
 3. H-bond acceptor and donor less than or equal to 3.
- 10) **Synthetic accessibility:** This is a measure of the degree of difficulty level to synthesize a chemical molecule. A score of 1 indicates that a drug can be easily synthesized and a score of 10 refers to a drug that's difficult to synthesize.
- 11) **GI absorption:** The absorption of drugs is mainly through passive diffusion. The small intestine in the GI tract is where most of the drugs are absorbed. A perfect combination and balance of hydrophilicity and lipophilicity are preferred for maximum drug bioavailability. The 3 main factors that affect the permeability of the drug are lipophilicity, the molecular size of the drug, and the polarity of the drug.
- 12) **Blood-brain barrier permeant:** Indicates the ability of the drug to pass through the blood-brain barrier, a selectively semi-permeable membrane denying access to solutes from entering the ECF of CNS. Only small molecules weighing less than 400 Da crosses BBB. Most drugs cross BBB by transmembrane diffusion mechanism.

3. Results

The data obtained are plotted into a bar graph for comparison analysis.

-  Drug with highest value
-  Drug with lowest value

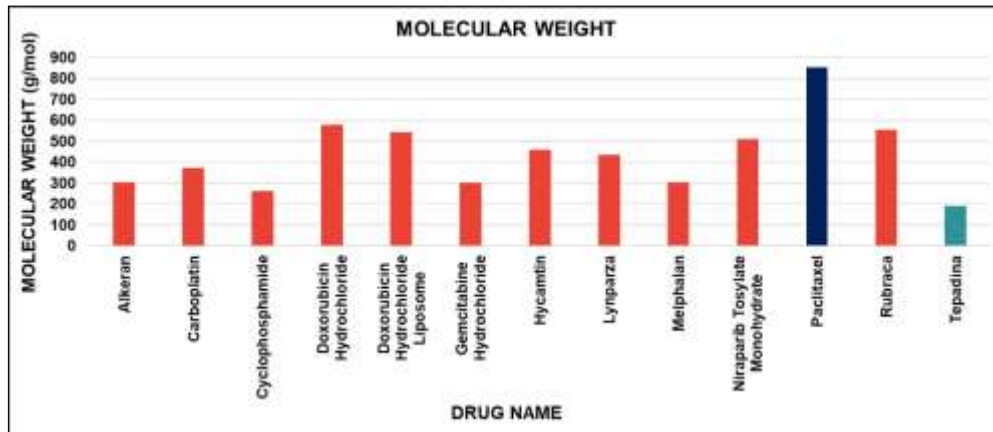


Figure 1: Bar graph showing the comparison of Molecular weight of query drugs.

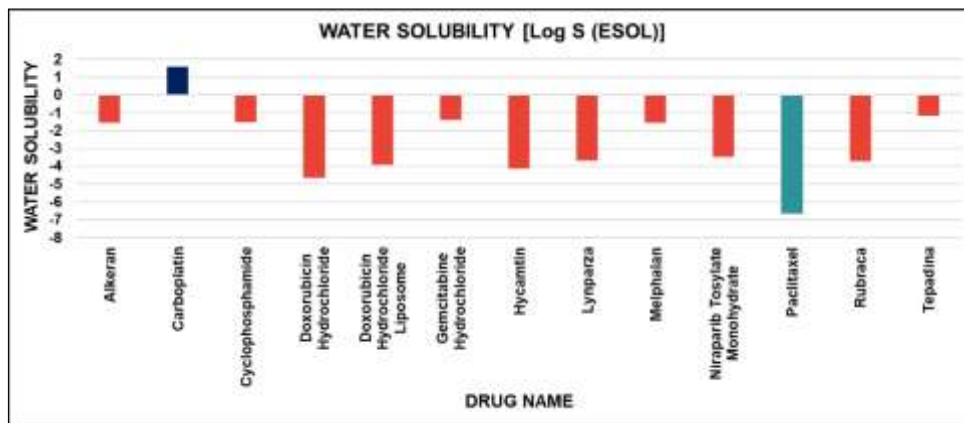


Figure 2: Bar graph showing the comparison of Water Solubility of query drugs.

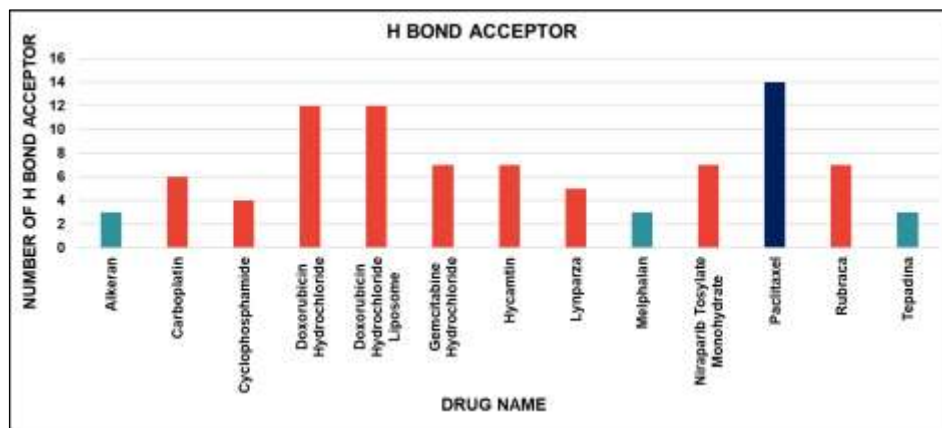


Figure 3: Bar graph showing the comparison of H-bond Acceptor of query drugs.

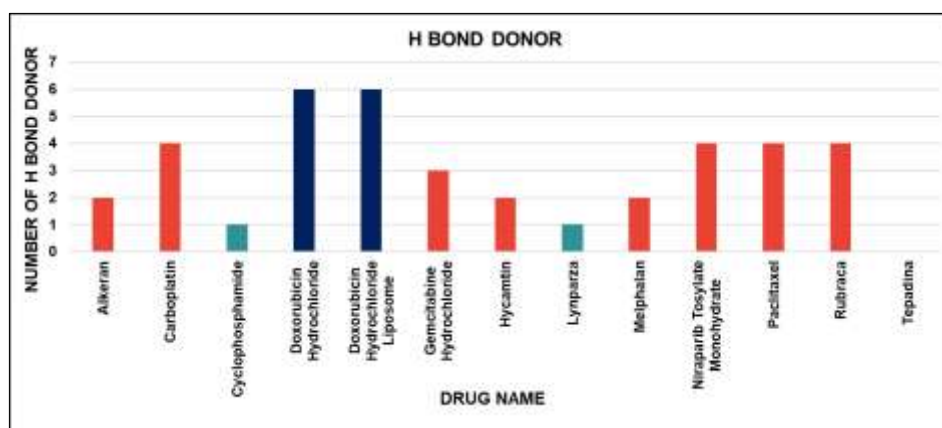


Figure 4: Bar graph showing the comparison of H-bond Donor of query drugs.

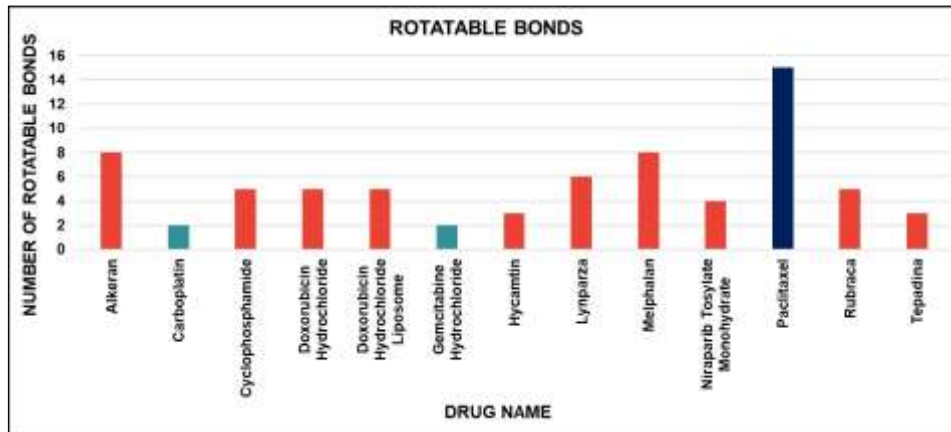


Figure 5: Bar graph showing the comparison of Rotatable Bonds of query drugs.

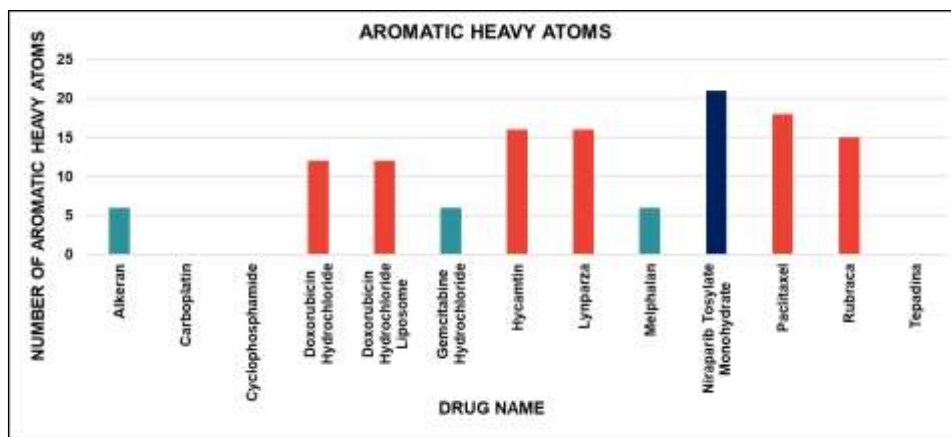


Figure 6: Bar graph showing the comparison of Aromatic Bonds of query drugs.

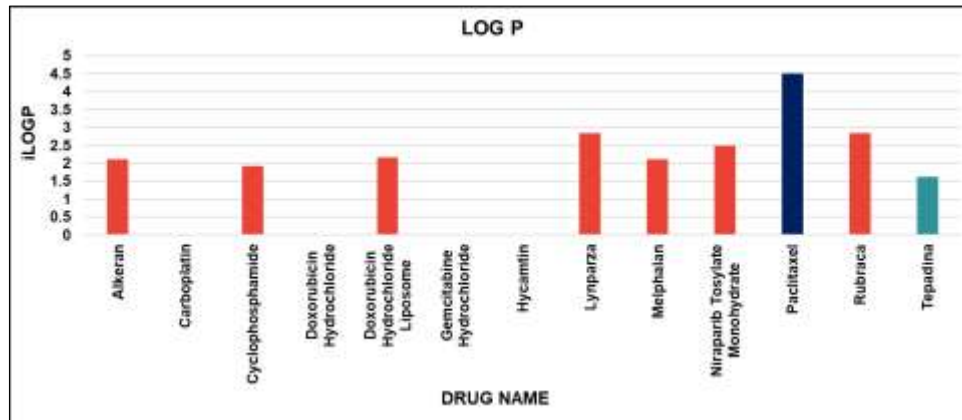


Figure 7: Bar graph showing the comparison of Log P of query drugs.

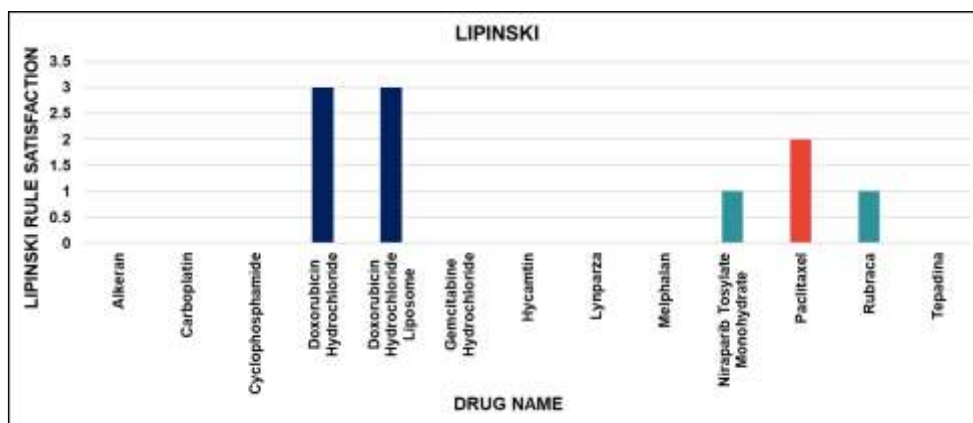


Figure 8: Bar graph showing the comparison of Lipinski of query drugs.

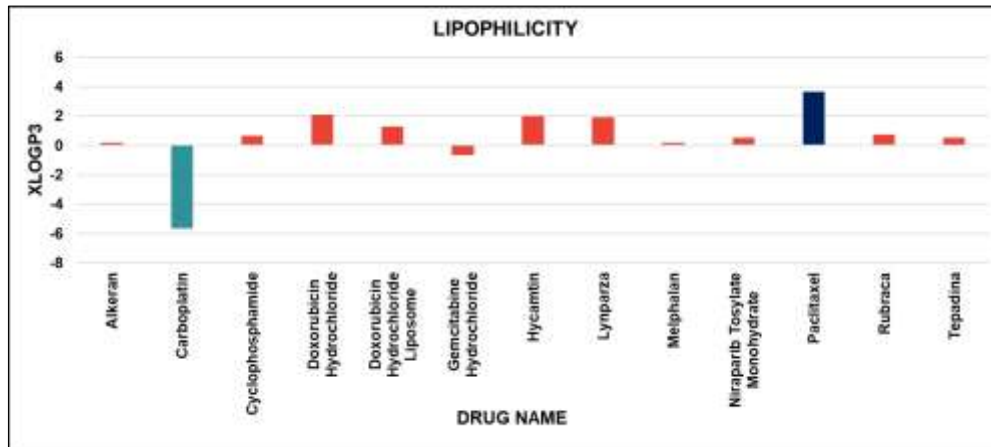


Figure 9: Bar graph showing the comparison of Lipophilicity of query drugs.

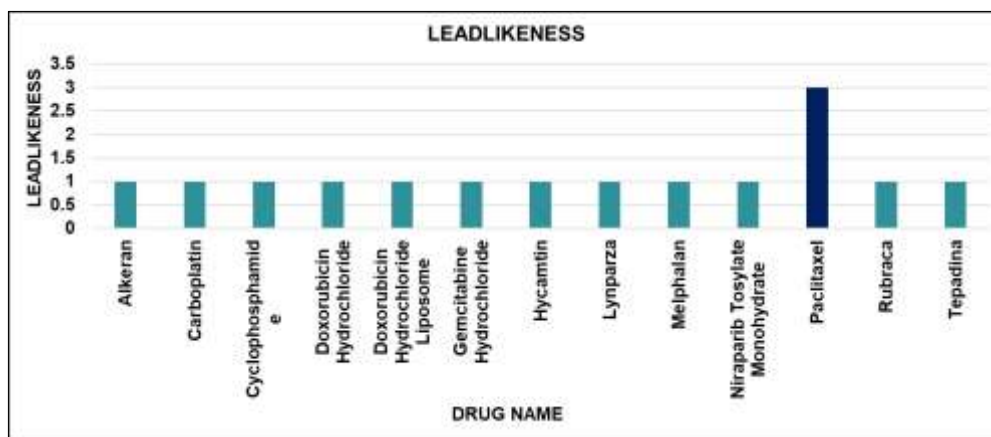


Figure 10: Bar graph showing the comparison of Leadlikeness of query drugs.

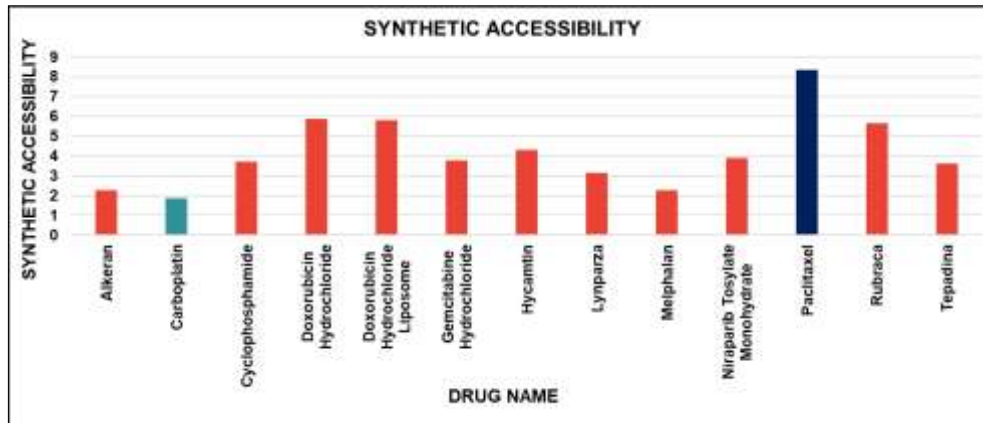


Figure 11: Bar graph showing the comparison of Synthetic Accessibility of query drugs

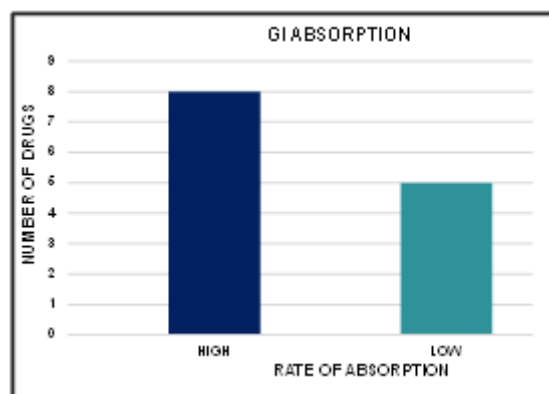


Figure 12: Bar graph showing the rate of GI absorption of the drugs.

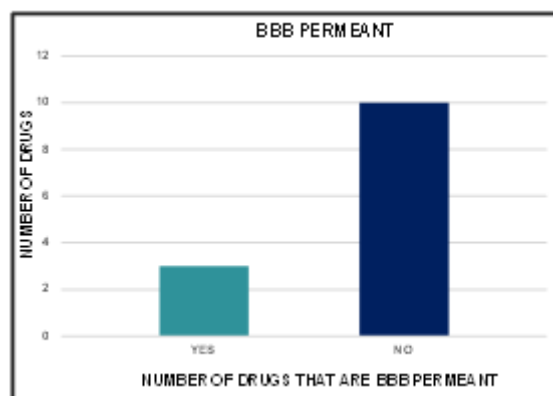


Figure 13: Bar graph showing the number of drugs that are BBB Permeant.

4. Discussion

The Absorption, Distribution, Metabolism, and Excretion properties of each of the drugs were retrieved using SWISS ADME software. The data was tabulated and graphically represented for the comparison analysis. *Figure 1* represents the comparison of the molecular weight of the 13 drugs. Among the 13 drugs, Paclitaxel had the highest molecular weight of 853.91 g/mol, Tepadina had the lowest molecular weight of 189.22 g/mol, and the average molecular weight of all the drugs was 435.97 g/mol. *Figure 2* represents the comparison of the water solubility of the 13 drugs. Among the 13 drugs, Carboplatin had the highest water solubility with a positive ESOL value of 1.55, Paclitaxel had the lowest water solubility with a negative ESOL value of -6.66, and the average water solubility of all the drugs were -2.75. *Figure 3* represents a comparison of H-bond acceptors of the 13 drugs. Among the 13 drugs, Paclitaxel had the highest H-bond acceptor value of 14, Alkeran, Tepadina, and Melphalan had the lowest H-bond acceptor value of 3, and the average H-bond acceptor of all the drugs was 6.92. *Figure 4* represents a comparison of H-bond donors of the 13 drugs. Among the 13 drugs, Doxorubicin Hydrochloride and Doxorubicin Hydrochloride Liposome had the highest H-bond donor value of 6, Cyclophosphamide and Lynparza had the lowest H-bond donor values of 1, and the average H-bond donor value of all the drugs were 3. *Figure 5* represents the comparison of the number of rotatable bonds of the 13 drugs. Among the 13 drugs, Paclitaxel had the highest number of rotatable bonds of 15, Carboplatin and Gemcitabine Hydrochloride had the lowest rotatable bonds of 2, and the average number of rotatable bonds of all the drugs was 5.46. *Figure 6* represents the comparison of the number of aromatic heavy atoms of the 13 drugs. Among the 13 drugs, Niraparib Tosylate Monohydrate had the highest number of aromatic heavy atoms of 21, Alkeran, Melphalan, and Gemcitabine Hydrochloride had the lowest number of aromatic heavy atoms of 6, and the average number of aromatic heavy atoms of all the drugs was 9.84. *Figure 7* represents the comparison of Log *P* values of the 13 drugs. Among the 13 drugs, Paclitaxel had the highest Log *P* value of 4.51, Tepadina had the lowest Log *P* value of 1.62, and the average Log *P* value of all the drugs was 1.73. *Figure 8* represents the comparison of Lipinski of the 13 drugs. Among the 13 drugs, Doxorubicin Hydrochloride and Doxorubicin Hydrochloride Liposome had satisfied 3 Lipinski rules, Paclitaxel had satisfied 2 Lipinski rules, Niraparib Tosylate Monohydrate, and Rubraca had satisfied

1 Lipinski rule and all the other drugs did not satisfy any of the Lipinski rules. *Figure 9* represents the comparison of lipophilicity of the 13 drugs. Among the 13 drugs, Paclitaxel had the highest Lipophilicity value of 3.66, Carboplatin had the lowest Lipophilicity value of -5.65 and the average lipophilicity value of all the drugs was 0.57. *Figure 10* represents the comparison of Leadlikeness of the 13 drugs. Among the 13 drugs, Paclitaxel had the highest Leadlikeness value of 3, and all other drugs had the lowest lead likeness value of 1, the average lead likeness value of all the drugs was 1.15. *Figure 11* represents a comparison of the synthetic accessibility of 13 drugs. Among the 13 drugs, Paclitaxel had the highest synthetic accessibility value of 8.34, Carboplatin had the lowest synthetic accessibility value of 1.87 and the average synthetic accessibility value of all the drugs was 4.19. *Figure 12* represents the rate of GI absorption of the 13 drugs. Among the 13 drugs, 8 drugs are said to have high GI Absorption and 5 drugs are said to have low GI Absorption. *Figure 13* represents the number of drugs that are BBB Permeant. Among the 13 drugs, 3 drugs are said to be BBB Permeant and 10 drugs are not BBB Permeant.

5. Conclusion

Ovarian, fallopian tube, and primary peritoneal cancers arise from the same type of tissue lining the ovaries, fallopian tube, and peritoneum, hence have similar treatment methods. Some of the common risk factors of these cancers include inherited gene mutations, endometriosis, obesity, and postmenopausal hormone therapy and the standard treating methods are surgery, targeted therapy, and chemotherapy.

The main aim of our study is to analyze and predict the Absorption, Distribution, Metabolism, and Excretion properties of all the FDA-approved drugs and identify the most effective drug for the treatment of ovarian, fallopian tube, and primary peritoneal cancer.

By analyzing the ADME properties and graphical representations of the thirteen drugs i.e. Alkeran, Carboplatin, Cisplatin, Cyclophosphamide, Doxorubicin Hydrochloride, Doxorubicin Hydrochloride Liposome, Gemcitabine Hydrochloride, Hycamtin, Lynparza, Melphalan, Niraparib Tosylate Monohydrate, Paclitaxel, Rubraca, and Tepadina, we were able to predict that Paclitaxel, Doxorubicin Hydrochloride, and Doxorubicin Hydrochloride Liposome are the most effective drugs and

they satisfy the majority of the ADME properties when compared to the other drugs.

6. Abbreviations

BBB – Blood Brain Barrier, GI- Gastrointestinal, CNS- Central nervous system, ECS- Extracellular Fluid.

7. Competing interests

We declare that we have no competing interests.

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