TARGETTING PARP1 INHIBITION IN TRIPLE NEGATIVE BREAST CANCER (TNBC): INSIGHTS FROM DRUG REPURPOSING & COMPUTATIONAL ANALYSIS

A Dissertation

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by:

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CANDIDATE'S DECLARATION

I Aayush Ratna Bajpai, hereby indorse that the project work is being presented as the Major Project in the thesis entitled "Targetting PARP1 Inhibition In Triple Negative Breast Cancer (TNBC): Insights From Drug Repurposing & Computational Analysis" in fractional accomplishment of the obligation for the award of the Degree of Master of Science in Biotechnology and submitted to the Department of Biotechnology, Delhi Technological University, Delhi, is a reliable and authentic record of my work, carried out during the period from January 2025 to June 2025 under the supervision of Prof. Yasha Hasija.

I have not submitted the insides presented in the report for the award of any other degree of this or any other institute/University.

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It is certified that **Aayush Ratna Bajpai (23/MSCBIO/71)** has performed their research work presented in this thesis entitled **"Targetting PARP1 Inhibition in Triple Negative Breast Cancer (TNBC): Insights from Drug Repurposing & Computational Analysis**" for the granting of a Master of Science degree in Biotechnology, and submitted to the Department of Biotechnology at Delhi Technological University, Delhi, under my supervision. This thesis represents the findings of novel research conducted by the student himself, and the insides of the thesis do not constitute the foundation for the granting of any other degree to the candidate or anyone else from this or any other University/Institution.

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TARGETTING PARP1 INHIBITION IN TRIPLE NEGATIVE BREAST CANCER (TNBC): INSIGHTS FROM DRUG REPURPOSING & COMPUTATIONAL ANALYSIS

Aayush Ratna Bajpai

ABSTRACT

Aim : The resolution of this study is to inspect the possibility of targeting PARP1 {Poly (ADP-ribose) Polymerase 1}, a polymerase enzyme linked to repairing alteration in the DNA molecule, by working through the mechanism of Base excision repair. In Triple Negative Breast Cancer (TNBC), PARP1 works to repair DNA damage under the influence of nonattendance of the Estrogen receptors, Progesterone receptors and HER2 (Human epidermal growth factor 2). This investigation mainly focuses on assessing small molecule modulators that can interact with PARP1, given the pressing need for disease-modifying treatments in TNBC. The binding interactions of Niraparib, a known FDA-approved drug, and thirteen other compounds)investigated through ZINC database and filtered through ADME profiling) were evaluated using molecular docking techniques. To find important residues inside PARP1 functional area, active site prediction was carried out using the Biodiscovery Studio. To determine drug-likeness profiles, pharmacokinetic characteristics, and binding affinity, docking simulations were utilized alongside with ADME studies.

Keywords – Triple Negative Breast Cancer, Estrogen receptors, Progesterone receptors, Human epidermal growth factor 2, PARP1 {Poly (ADP-ribose) Polymerase 1}, Niraparib, Molecular Docking

Result : According to the docking studies, Niraparib has a binding affinity of -9.5 kcal/mol for the predicted PARP1 active site, whereas the novel molecule, 4-[4-(4-Hydroxybenzoyl)piperidine-1-carbonyl]-2-phenylphthalazin-1-one (Pubchem ID : 24615465) has a higher binding affinity of -11.8 kcal/mol. Both substances showed higher binding affinity towards the PARP1 functional domain. According to the ADME profiling, the new molecule has better pharmacokinetic characteristics, such as full compliance to Lipinski's Rule of Five and strong lipophilicity. In comparison to Niraparib, the compound was found to have a lower solubility, but with the help of further research, as explained further in this thesis, the solubility can be enhanced, and consequently, the compound will mark itself as good anticancer drug.

Conclusion : Consequently, the discovery of this novel molecule as a more powerful binder with advantageous drug-like characteristics raises the possibility that it could be used as a substitute lead molecule to target PARP1 in TNBC. Methods used in this investigation included ADME analysis validation and molecular docking. Thus, suggesting to a successful method for finding new therapeutic agents for TNBC and offering a positive roadmap for upcoming drug development and experimental validation attempts.

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LIST OF ABBREVIATIONS

TNBC	Triple Negative Breast Cancer
ER	Estrogen Receptor
PR	Progesterone Receptor
HER2	Human Epidermal Growth Factor 2
FDA	Food and Drug Administration
BRCA1	Breast Cancer 1
BRCA2	Breast Cancer 2
HRR	Homologous Recombination Repair
HRD	Homologous Recombination Deficit
SSBs	Single Strand Breaks
PARP1	Poly {(ADP ribose) polymerase 1}
DSB	Double Strand breaks
BL1	Basal Like 1
BL2	Basal Like 2
IM	Immunomodulatory
M	Mesenchymal
MSL	Mesenchymal stem-like
LAR	Luminal androgen receptor
TIL	Tumour infiltrating lymphocytes
DBD	DNA binding domain
LBD	Ligand Binding Domain
ERE	Estrogen response elements
SERM	Selective estrogen receptor modulators
SERD	Selective estrogen receptor degraders
ERBB2	Erb-B2 receptor tyrosine kinase 2
PARPi	Poly {(ADP ribose) polymerase 1} inhibitor
BER	Base excision repair

INTRODUCTION

Cancer is the second largest reason, which leads a human to the ultimate end of life, globally. Overall, the prevalence of cancer around the humankind has increased; in the United States alone, roughly 1,665,540 people were diagnosed with cancer, with 585,720 dying as a consequence of the illness in 2014 [1].

This is an tremendously stern condition that has been disturbing humans in huge statistics for a lengthy period of time.

Men are supplementarily probable to progress cancer in their prostate, lung, colon, and bladder. Women are more likely to advance it in the breast, lung and bronchus, colon and rectum, uterine corpus, and thyroid [2].

Prostate and breast cancer are the most widespread in men and women, respectively [3].

Breast cancer is the most recurrent form of tumour among women worldwide, which accounts for, approximately 1.4 million new cases in an individual year [4].

The current cataloguing of breast cancer includes triple-negative breast cancer (TNBC), which is ER (oestrogen) negative, PR (progesterone) negative, and lacks overexpression of HER2 (Human epidermal growth factor receptor) [5]. This cancer form is denoted as the 'Triple Negative' because it lacks expression of all three variables.

With the nonattendance or lack of expression of Estrogen receptors, Progesterone receptors, and the HER2 factor, treatments or therapeutic procedures linked with targeting these three subjects are out of question.

Triple negative breast cancer accounts for coarsely 10-20% of all aggressive breast cancers.

Based on gene expression patterns, TNBC was characterized as a basal-like BC subtype [6]. Linked to other breast cancer subtypes, TNBC commonly arises in young females and is connected with higher aggressiveness and demise [7, 8].

The FDA (Food and Drug Administration) has permitted anti-metabolites, paclitaxel, and anthracyclines for adjuvant and neoadjuvant chemotherapy regimens in TNBC patients [9, 10]. Traditional chemotherapy has demonstrated some usefulness in TNBC patients. However, chemotherapy is risky to patients, and some people continue to experience no medical advantage. As a result, recognizing effective targets for accurate TNBC healing is a grim and critical therapeutic problem to overcome.

According to epidemiological research, approximately 10-40% of TNBC patients harboured breast cancer vulnerability gene variations (BRCA1 and BRCA2) [11]. These genes are associated with homologous recombination repair (HRR), a highly error-free process that involves several stages. When HRR-associated genes are defective or altered, it causes homologous recombination deficit (HRD). This gives an advantage to the single strand breaks (SSBs) repair process [12].

BRCA1 and BRCA2 proteins preserve genomic integrity by repairing DNA accurately through homologous recombination [13, 14]. Harm of BRCA abilities causes genomic uncertainty,

which leads to oncogenic transformation of non-tumorigenic cells into tumor originating cells, or cancer stem cells (CSCs), and subsequent tumour evolution.

PARPs, or Poly ADP-ribose polymerases, are a category of DNA damage repair enzyme that trails the single strand break (SSB) repair method, binding chains of ADP-ribose subunits to themselves or other proteins with negatively charged PAR moieties.

Among the several PARP forms, PARP1 is the most prominent polymerase that detects DNA damage and is necessary for efficient single-strand break repair. When DNA is broken, PARP1 attributes to the damaged region, triggers, and associates DNA damage repair proteins via self-modified PAR chains, prompting multiple downstream DNA repair progressions. In addition to PARP-dominated SSB repair, homologous recombination repair (HRR)-dominated DNA double-strand breaks (DSB) repair is crucial for genomic integrity [15]. However, the HRR-dominated repair is unable to occur due to transformations in the BRCA1 and 2 genes.

Obstructing PARP1 genes harvests an increase in single and double-stranded DNA disruptions. Tumour cells that lack the BRCA1 and BRCA2 genes are exclusively responsive to PARP1 inhibition [16]. These inhibitors target the PARP1 proteins, producing DNA damage that is not restored, growing cellular death.

Upregulation of PARP1 in BRCA (Breast Cancer genes) mutations is also a principal cause of chemotherapy confrontation in cancer cells [17].

As a result, constraining PARP1 becomes important again to avert chemotherapy resistance.

CHAPTER 2

REVIEW OF LITERATURE

2.1 Triple Negative Breast Cancer (TNBC)

TNBC is a very hostile subtype of breast malignance that does not exhibit estrogen receptors (ER), progesterone receptors (PR), or human epidermal growth factor receptor 2 (HER2) expression [18]. It holds for approximately 10-15% of all breast cancers and is supplementarily frequent in fresher women, African American women, and those with BRCA1 mutations [19]. TNBC is impervious to hormonal or HER2-targeted healing because it shows inattendance of these receptors, making the treatment additionally difficult.

Clinically, TNBC is distinguished, or uniquely identified by its fast advancement, superior rates of metastasis (especially to the lungs and brain), and amplified risk of reappearance during the first three years after treatment [20]. Unlike hormone receptor-positive breast tumors, TNBC has limited treatment choices, with chemotherapy being the existing standard.

TNBC tumors stereotypically invasive ductal carcinoma, which is superior in nature with heightened mitotic action and a high propagation index. These tumors recurrently represents core necrosis and lymphocytic infiltrates, demonstrating an immunogenic microenvironment [21]. Morphologically, TNBC thoroughly resembles the basal-like subtype of breast cancer, however not all TNBCs are basal-like, and not all basal-like tumors are triple-negative.

The diversity of TNBC is one of the most difficult aspects of grasping it. Lehmann et al. (2011) used gene expression patterns to categorize TNBC into six different subtypes: basal-like 1 (BL1), basal-like 2 (BL2), immunomodulatory (IM), mesenchymal (M), mesenchymal stem-like (MSL), and luminal androgen receptor (LAR) [22]. This cataloguing has since driven efforts to acclimatize future treatment practices, although medical translation is still restricted.

A substantial proportion of TNBC cases, predominantly in younger womankind, are linked to BRCA1 gene abnormalities. As Robson et al. (2017) reported, BRCA1-deficient cancers generally show basal-like features and genomic instability, resulting in hostile behaviour and primary onset [23]. These genetic predispositions highlight the obligation for genetic screening in high-risk groups.

TNBC's immunogenicity has also been emphasized in studies. Tumour-infiltrating lymphocytes (TILs) are more regularly seen in TNBC than in other kinds of breast cancer, signifying that immune surveillance plays an important role in disease expansion [21]. This characteristic leads to the amplified interest in immunological profiling of TNBC, even beyond direct therapeutic uses.

The following therapies may be a route through the TNBC invasion:

Chemotherapy remains the chief first-line treatment. Anthracyclines (e.g., doxorubicin) and taxanes (e.g., paclitaxel) are habitually used in regimens, either alone or together [24].

However, the aggressive nature of TNBC frequently leads to treatment confrontation, imposing the development of new methods.

Immunotherapy has showed promising results in recent years. The FDA has authorized atezolizumab (an anti-PD-L1 antibody) in combination with nab-paclitaxel for PD-L1-positive metastatic TNBC [25]. Immunotherapeutic treatment procedures are projected to improve the patient's immune system's ability to recognize and terminate cancer cells, which is an especially tempting option given the high mutational burden of TNBC tumors [26].

PARP inhibitors, such as olaparib and talazoparib, have been sanctioned for patients with germline BRCA-mutated TNBC and will continue to be conversed in this work. These medicines target DNA repair pathways, taking lead of the faulty homologous recombination repair lane found in BRCA-mutant cells [27]. The principle of synthetic lethality underpins this method, which has opened up new possibilities towards targeted cancer therapy.

Targeted therapy for various molecular characteristics of TNBC are being examined. In therapeutic studies, inhibitors of androgen receptors, PI3K/AKT/mTOR pathways, and EGFR have had varying degrees of effectiveness [28].

TNBC is a difficult subtype of breast cancer due to its destructive nature and the scarceness of targeted therapy. However, innovations in immunotherapy, targeted treatment, and precision medicine are progressively improving the prognosis for people with TNBC.

Table 1: summarizes the key molecular pathways disrupted in Triple Negative Breast Cancer and highlights major proteins and genes implicated.

Pathway	Key Proteins Involved	Normal Role	Effect in TNBC	References
DNA Damage Repair (HRR)	BRCA1, BRCA2, RAD51	Homologous recombination repair (HRR) of double-stranded DNA breaks	Frequently mutated or epigenetically silenced, resulting in impaired HRR and genomic instability.	[29]
PARP Pathway	PARP1, PARP2	Repairs single-strand DNA breaks via base excision repair	PARP inhibitors can target upregulated genes that compensate for HRR deficiencies.	[30]
PI3K/AKT/mTOR	PIK3CA, AKT1, mTOR	Stimulates cell growth,	Frequently mutated (e.g., PIK3CA) or	[31]

		multiplication, and survival.	hyperactive, resulting in uncontrolled growth and survival.	
TP53 (Tumor Suppressor)	TP53	Regulates cell cycle arrest, DNA repair, and apoptosis in response to stress.	Mutations occur in around 80% of TNBC patients, resulting in loss of genomic surveillance.	[32]
EGFR Signalling	EGFR, MAPK, ERK	Regulates cell proliferation and differentiation.	Overexpressed in many TNBC cancers, leading to the aggressive character.	[33]
Androgen Receptor (AR)	AR	Regulates gene expression in hormone-responsive tissues.	Expressed in some TNBC subtypes ("LAR" subtype); possible therapeutic target.	[34]
Wnt/β-catenin	β-catenin, Wnt ligands, GSK-3β	Expressed in some TNBC subtypes ("LAR"), a possible therapeutic target	Aberrant activation promotes stemness and tumor development in TNBC.	[35]
Notch signalling	Notch1, Notch3, DLL4, Jagged	Regulates stem cell maintenance and differentiation.	Overactivity in TNBC is related with tumor starting cells and a poor prognosis.	[36]
Immune regulation	PD-L1, CTLA-4	Prevents autoimmunity and controls T-cell activation.	PD-L1 is often expressed in TNBC, showing immune evasion fostered and targetable with	[37]

			checkpoint inhibitors.	
Apoptosis Regulation	BCL-2, BAX, Caspases	Regulates programmed cell death.	BCL-2 is often downregulated; faulty apoptosis leads to treatment resistance.	[38]

2.2 Estrogen and Progesterone Receptors

ESTROGEN RECEPTORS :

There are two main types of estrogen receptors:

- **ERα (Estrogen Receptor Alpha)** – encoded by the *ESR1* gene
- **ERβ (Estrogen Receptor Beta)** – encoded by the *ESR2* gene

Both belong to the **nuclear receptor superfamily**. Each has:

- **DNA-binding domain (DBD)**
- **Ligand-binding domain (LBD)**
- **Transactivation domains (AF-1 and AF-2)**

These receptors are mostly present in the nucleus, but they also find themselves in the cytoplasm and connected with the cell membrane of the cells, where they participate in non-genomic signalling.

Upon binding to estrogen, ERs undergo a conformational shift that leads them down to dimerize. These dimers afterward go to the nucleus and get attached to particular DNA sequences known as Estrogen Response Elements (EREs) found in the promoter regions of target genes [39]. This interaction allows for the recruitment or stimulation of the coactivator or corepressor proteins, which regulates transcriptional action. Through this genomic network, ERs control a vast array of genes which take part in cell cycle regulation, apoptosis suppression, and tissue remodelling [40].

In addition to this basic genomic method, ERs have non-genomic effectiveness via activating numerous kinase cascades, including the MAPK/ERK and PI3K/AKT pathways. These membrane-initiated signalling events do not walk down the lane of directly affecting gene expression, but instead form the basis of fast cellular responses such as calcium influx, cytoskeletal remodelling, and kinase activation. These fast effects play primary or principal roles in procedures such as vascular tone control, insulin sensitivity, and immunological modulation [41].

Estrogen receptors are vital in many physiological processes. In the reproductive system, ERs tend to control the menstrual cycle, endometrial thickness, and ovulation. They also reassure the growth of mammary glands, particularly the ductal system, throughout puberty and pregnancy. In the skeletal system, ERs are known to put a limit on bone resorption and promote

bone growth, lowering the risk of osteoporosis. In the cardiovascular system, ERs help in endothelial function, lipid control, and vasodilation. Furthermore, ERs in the central nervous system stimulate cognitive performance, mood modulation, and neuroprotection, which tones down the risk of age-related neurodegenerative disorders [42].

The scientific importance of estrogen receptors is especially evident in breast cancer. Approximately 70% of breast cancers are ER-positive, which tends to explain that they are dependent on estrogen signalling for progression and survival. These malignancies frequently have better prognoses and are susceptible, in an increased manner to endocrine therapy including selective estrogen receptor modulators (SERMs, such as tamoxifen), aromatase inhibitors, and selective estrogen receptor degraders (SERDs) [43]. ER expression thus provides an important indication for breast cancer diagnosis, prognosis, and therapy planning.

PROGESTERONE RECEPTORS :

Progesterone receptors (PRs) are the nuclear hormone receptors that perform the function to control the actions of the steroid hormone, 'progesterone'. They play significant roles in reproductive physiology, immunological regulation, and cancer formation. PRs are characterized into two isoforms, PR-A and PR-B, which have unique but somewhat overlapping functionalities in several organs. PRs have critical roles in the female reproductive system, which tends to support ovulation, implantation, and pregnancy maintenance. They influence gene expression in endometrial cells, which encourages differentiation and prepares the uterus for embryo implantation [44]. During pregnancy, PR signalling activity aids to build ducts and alveoli in the mammary glands [45]. PRs also control hypothalamic-pituitary signalling and behavioural response [46]. Beyond reproductive functions, PRs have immunomodulatory properties, such as reducing inflammatory responses during pregnancy to increase fetal tolerance [47]. Moreover, abnormal PR signalling is connected to hormone-driven malignancies, notably breast and endometrial cancers, where PRs shed light on tumor proliferation and differentiation [48]. Understanding, those, many roles of progesterone receptors is significant for treatment methods directing reproductive diseases and hormone-related cancers.

2.3 Human epidermal growth factor receptor 2 (HER2)

HER2 (also called as ERBB2) is a receptor tyrosine kinase in the ErbB family that controls cell proliferation, differentiation, and survival. HER2, contrasting other ErbB receptors, has a documented ligand but serves as a preferred dimerization partner for other family members such as EGFR (ERBB1), HER3 (ERBB3), and HER4 (ERBB4), which subsequently boosts downstream signalling cascades [49]. When HER2 dimerizes, it promotes a number of critical signalling procedures, including the PI3K/AKT and MAPK/ERK pathways, which control cellular proliferation, metabolism, and apoptosis [50]. Overexpression or gene amplification of HER2 is seen in 15-20% of breast tumors and is linked to aggressive tumor behaviour and deprived clinical outcomes [51].

In addition to breast cancer, HER2 dysregulation has been reported in gastric, ovarian, and lung malignancies, and is recurrently associated with a poor prognosis [52]. HER2's oncogenic

functionality has made it an important therapeutic mark; the introduction of anti-HER2 treatments such as trastuzumab and pertuzumab has intensely improved survival in HER2-positive tumors. Furthermore, HER2 signalling can modify the tumor microenvironment by leading down the lane to increase the angiogenesis and regulating immune cell infiltration, which hence, contributes to tumor growth [53].

2.4 Poly {(ADP ribose) polymerase 1} (PARP1)

PARP1 (poly(ADP-ribose) polymerase 1) is a nuclear enzyme that functions to detect and repair DNA damage. It is essential, and follows through the mechanism of the base excision repair (BER) pathway, identifying DNA single-strand breaks and promoting or stimulating repair by recruiting other repair proteins [54]. When PARP1 perceives DNA damage, it catalyzes the attachment of ADP-ribose polymers (PARylation) to itself and other nuclear proteins, fluctuating chromatin structure and dropping access to repair machinery [55].

Beyond DNA repair, PARP1 even affects transcription and chromatin remodelling by working out its interaction with transcription factors and histones, hence, consequently altering gene expression, specifically in response to stress signals [56]. PARP1 is also caught up in programmed cell death; with severe DNA damage, heightened PARP1 activation causes NAD+ and ATP depletion, resulting in parthanatos [57]. PARP1 is however, commonly or frequently overexpressed in cancer and hence backs tumor survival, particularly in those cells which represent homologous recombination repair imperfections (e.g., BRCA1/2 mutations). This has resulted in the construction of PARP inhibitors (PARPi), which use artificial lethality to function selectively and apply it to terminate cancer cells [58].

PARP1 also regulates inflammatory and immunological responses by bringing essential emendations to cytokine production and NF-κB signalling pathways [59]. Thus, PARP1 is known as a multifunctional protein that works to maintain genomic integrity, regulate cell destiny, and serve as a therapeutic treatment target in relevance to cancer and inflammation.

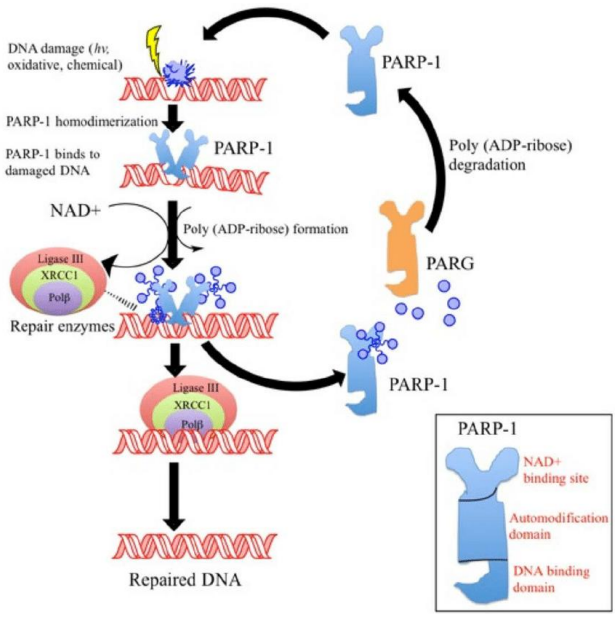


Figure 1 : Mechanism of action of PARP1 in repairing the DNA damage

2.5 Impact of Triple negative breast cancer on the aforementioned receptors and the onset of PARP1 enzyme

1) Estrogen Receptors (ERs) are normally the main way cells control gene use in response to estrogen. They also help cells in the breast grow and change. But in TNBC cells do not have ER so are not able to use hormone drugs like tamoxifen or aromatase inhibitors that go after this way. Cells are also not under hormone control and this is part of the reason these cells grow quickly and are more likely to spread [60].

2) Progesteron Receptors (PRs) are changed by estrogen. They are usually a sign that the ER pathway is working. But in TNBC cells do not have ER and PR so they do not have any of the ER or PR transcription parts, and this is why they are not likely to be help with hormone drugs. PR is also a sign that these cells are more like stem cells and can change to other types of cells, which makes it easier for them to spread [61].

3) HER2 (Human Epidermal Growth Factor Receptor 2) is a receptor tyrosine kinase that promotes cell growth and survival via the PI3K/AKT and MAPK pathways. In TNBC, HER2 is not overexpressed or amplified, which excludes the use of anti-HER2 targeted therapies (e.g., trastuzumab). The absence of HER2 is partly why TNBC has limited targeted treatment options and a poorer prognosis compared to HER2-positive subtypes [62]

4) PARP1 (Poly ADP-Ribose Polymerase 1) is a nuclear enzyme crucial for repairing single-strand DNA breaks (SSBs) through the base excision repair (BER) pathway. When SSBs occur, PARP1 detects the damage, binds to DNA, and catalyzes the addition of poly-ADP-ribose (PAR) chains, thereby recruiting other DNA repair proteins to the site of damage [63]

In cells that can do HR well, if you stop PARP1 and SSBs stay in DNA when it is being copied, the DSB that are made can be fixed by HRR well. But, when you take away PARP1 in TNBC cells that can't do HR, the DSB are not fixed well because of HRD that was caused by changes in BRCA1/2. The DSB that are made cause big problems in cell make up, need more copying, and lead to cell death. This happens a lot when you treat these cells with PARP1 [64].

This plan for treatment uses the idea of synthetically slaying, where the mix of PARP1 and HRD kills cells, but if you only have one of those it wouldn't kill cells [65]

2.6 Niraparib as a potential PARP1 inhibitor

Niraparib is a strong and focused pill that blocks the action of poly(ADP-ribose) polymerase (PARP1), the enzymes that help to fix single-strand DNA breaks. They do this though the base excision repair (BER) pathway. Its main hope as a drug is based on the idea of synthetic lethality, where stopping PARP1 in cancer cells with bad homologous recombination repair (HRR) such those with BRCA1/2 mutations causes the build-up of DNA damage that isn't fixed. This finally kills those cells. Niraparib has shown great power in HR-deficient cancers, including triple-negative breast cancer (TNBC). These cancers often have BRCA1 loss or HRD. Other trials, like the PRIMA trial, have shown that niraparib can greatly lengthen the time people with platinum-sensitive ovarian cancer go without their cancer getting worse. This was especially true for people with HRD-positive tumors [66].

Additionally, Niraparib, when combined with the immune checkpoint inhibitor pembrolizumab, yielded clinical benefit even in patients without BRCA mutations, highlighting its potential in broader TNBC subgroups [67]

Although these encouraging results, Niraparib suffers some limitations in relation to its pharmacokinetic profile. The compound shows binding energy which is lower, and thus it can change the interaction between the Niraparib and the PARP1 enzyme. With a lower released binding energy, the rate of reaction is changed and a weaker bond forms. This makes the therapeutic treatment quite weak. The lipophilicity of Niraparib is also low, which makes it hard for it to get into the cell, through the phospholipid bilayer, making it hard to deliver the drug. These limitations here, hence, lay the foundation stone for the need to find or make other compounds which have better pharmacokinetic properties, while still keeping the good properties of Niraparib.

2.7 Virtual screening and molecular docking in drug discovery

Traditional ways to find new drugs are slow, costly, and often fail. But, new ways that use computers, called molecular docking and virtual screening, have become very important parts of making drugs today [68]. Virtual screening is a way to look at many thousands of chemicals fast. It helps find the ones that might stick to a certain biological target. These fast computer checks make it quicker and easier to find possible drug compounds, and it cuts down on the many lab tests that would be needed [69].

Both, the approach based on ligand and the structure-based virtual screening approach, are often used, the latter predicts favourable binding interactions on the basis of analysis of target protein's three-dimensional structure. Molecular docking is a significant and important tool for structure-based virtual screening. Its goal is to assess the complex's binding affinity and predict the preferred orientation of a small molecule when attached to a protein target [70]. Algorithms predicated on docking insert the ligand within the target protein's active site and evaluate binding modes by using scoring techniques that consider features such as hydrogen bonding, hydrophobic interactions, electrostatic complementarity, and steric fit [71]. The determination of the specific binding pocket or active site on the target protein is critical to the accuracy of docking investigations. Active site prediction systems, such as Biodiscovery Studio were developed to assist researchers in identifying potential ligand-binding sites based on structural features &pocket shape [72]

These strategies work by placing the docking on places that matter in the body. This way virtual screening will work better and be more dependable. Today, docking and virtual screening are much better and used a lot because the algorithms are more complex, and we have more power to do the work. Many drugs that might work have been found or made with these methods. Therefore, these methods are very important in the first part of making drug. [73].Structure based virtual screening of key targets like PARP1 can be very good in finding new small drugs that can stop the enzyme. This will kill the cancer cells. Predicting where to find the drug, docking of the drug with the target, and testing how the drug will act in the body work as a team to give good options for tests that follow.

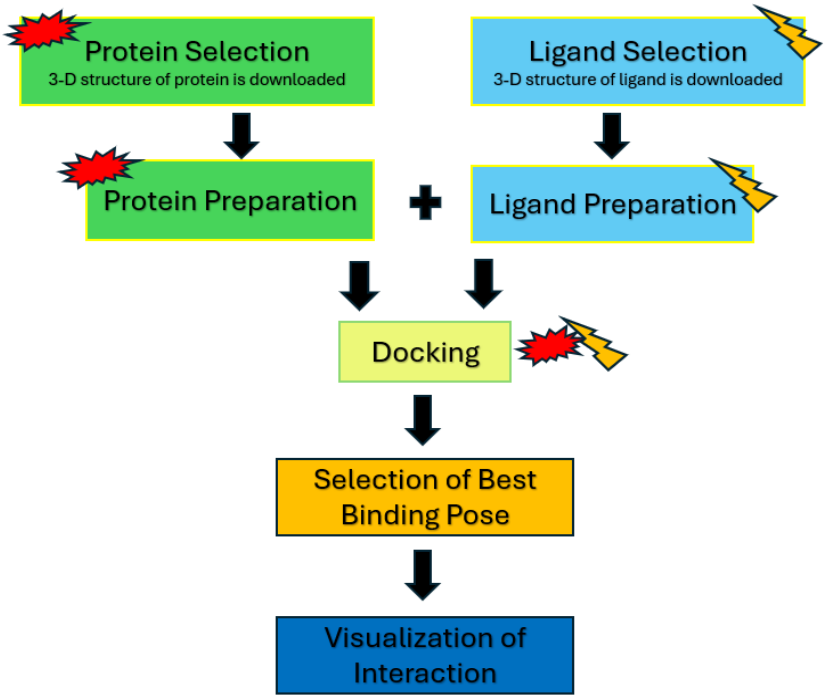


Figure 2 : Flowchart showing Overall steps involving molecular docking

2.8 Application of zinc database in drug discovery

Access to large and diverse chemical libraries is typically required for the synthesis of novel bioactive molecules. The ZINC database ("ZINC Is Not Commercial") is a popular tool for virtual screening in drug development programs [74]. It provides a free, carefully curated range of commercially available chemicals designed specifically for use in silico screening. ZINC includes millions of chemicals in ready-to-dock 3D formats, allowing researchers to rapidly screen biological targets utilizing structure-based virtual screening. Each molecule is tailored for docking by ensuring correct protonation states, tautomers, and 3- Dimensional conformations during physiological conditions [75]. The database is an effective tool for lead finding and optimization, since it is regularly updated to reflect the availability of compounds from various producers. ZINC's extensive filtration capabilities are one of its central advantages. Researchers can customize compound subsets based on molecular weight,Lipophilicity (LogP), the number of rotatable bonds, and sticking to drug-likeness guidelines such as Lipinski's Rule of Five [76] were used to help find compounds with good pharmacokinetic properties before docking. Virtual screening of compounds based on their shape with ZINC compounds had aided in the finding of molecules or compounds that had a high affinity while binding with PARP1. Researchers can identify compounds from the ZINC database for further biological testing by using a combination of molecular docking, ADME/Tox profiling, and active site prediction methods. In this way, they will be able to find small compounds that bind better to PARP1.The current work used a computer based plan to look through the ZINC database. Computer studies of how molecules sit on each other and studies of how drugs work in the body found a new chemical called 4-[4-(4-Hydroxybenzoyl)piperidine-1-carbonyl]-2-phenylphthalazin-1-one. It had better scores when

sitting on a molecule and better quality for use as a drug than the first chemical, Niraparib. Using the ZINC database shows how tools that use computers can speed up how we find new drugs in early stages and add to the number of possible molecules for hard to treat targets like PARP1.

2.9 ADME profiling during drug development

Earlier examination and inspection of candidate molecules' pharmacokinetic characteristics, abbreviated ADME (Absorption, Distribution, Metabolism, and Excretion), lays down the foundation of modern drug development [77].

A molecule's ability to pass through the biological membranes (lipid membranes) and reach the systemic blood circulation following oral ingestion is administered by its absorption profile. Molecular weight, hydrogen bonding ability, lipophilicity (LogP), and the polar surface area, all have an effect on gastrointestinal absorption and bioavailability [78]. Metabolism influences the chemical stability and susceptibility, that a molecule exhibits towards biotransformation, by hepatic enzymes such as cytochrome P450 isoforms. Unfavourable metabolic profiles may cause rapid clearance, establishment of toxic metabolites, or drug-drug interactions [79].

Excretion functions towards medication clearance from the body and determine toxicity profiles and dose regimens, typically via the renal or biliary systems. SwissADME and other in silico ADME prediction methods are in modern world, becoming critical in early-stage drug development. SwissADME through its comprehensive working model, provides a rapid and comprehensive assessment of bioavailability scores, drug-likeness using Lipinski's Rule of Five, and pharmacokinetic features [80].

Using such platforms, researchers may hence choose the compounds, which can be novel and having favourable ADME profiles prior to the validation based on experiments, boosting the efficiency and success rate of drug discovery inventiveness. In the current work, candidate molecules from the ZINC subset were filtered by SwissADME to find compounds with the ideal physicochemical attributes favourable to drug development. The parameters studied were molecular weights between 250 and 500 Da, LogP values within the ranges which are acceptable, minimum hydrogen bond donors and acceptors, and adherence to the Lipinski's criterion.

This technique assured that the chosen compounds, including the new chemical discovered, had not only a high binding affinity for bonding with the PARP1 protein, but also favourable pharmacokinetic properties suited for possible therapeutic practice in Triple Negative Breast Cancer.

CHAPTER 2

METHODOLOGY

3.1 Selection of protein parp1 & ligand molecules

Information, that which target protein and reference molecule, one is going to work on, is obtained by reviewing the literature. Initially, the literature was collected with the help of some comprehensive webservers like PubMed (https://pubmed.ncbi.nlm.nih.gov/) & Google Scholar (https://scholar.google.com/). The DNA repairing polymerase enzyme PARP1, was selected as the therapeutic target based on its central role in undoing the damage done to the DNA in cancerous cells. Swisssimilarity search (http://www.swisssimilarity.ch/) is used to collect all the compounds that are similar to Niraparib from the ZINC database (https://zinc.docking.org/), specifically from the ZINC drug like subset. The ZINC database is mainly used for virtual screening. The database produced a list of 400 compounds, which were further filtered using parameters such as medicine bioavailability and the Lipinski rule of five. After applying the filter, we got 13 molecules. These compounds have substantial structural similarities with Niraparib.

3.2 Retrieval of target protein and ligand

The three-dimensional crystal structure of human PARP1 was obtained from the Protein Data Bank in .pdb format. The structure was hence visualized and checked for its completeness with the BIOVIA Discovery Studio Visualizer. The 3D structures of the ligands were acquired from PubChem in the SDF format. (https://pubchem.ncbi.nlm.nih.gov/).

3.3 Protein & ligand preparations

Protein is prepared using BIOVIA Discovery Studio , which removes water, heteroatoms and adds Kollman charges. Only hydrogen atoms are then added to the polar. The .pdbqt format is used to store the protein structure. All ligand molecules in .sdf format were converted into.pdb format using Open Babel in order to perform docking within PyRx. Open Babel in PyRx adds polar hydrogen, computes gasteiger charges, combines non-polar hydrogen and minimizes all. The receptor and ligand grid map has been created with the following dimensions, x = 25; y = 25; z = 25)and the center :(x = -32.60; y = 21.38; z = 1.8)

3.4 Active site prediction:

Identifying the active site of a protein is critical for understanding molecular interactions since it plays an important role in the protein's activity. Accurate prediction of these binding sites facilitates more efficient drug creation by directing the selection of prospective ligands that can interact with the protein's active site. There are numerous computational methodologies and tools available for predicting these binding locations.

The BIOVIA Discovery Studio was used to determine the likely active site residues of the PARP1 protein. The PDB structure was uploaded, and the highest-ranked binding pocket based on ligandability score was chosen for molecular docking. Predicted residues were identified and compared to ligand binding residues after docking to validate particular interactions.

3.5 Molecular docking

A computer method called molecular docking estimates how effectively ligands will bind to receptor proteins. The services of AutoDock Vina embedded with the PyRx virtual screen tool were used to perform molecular docking. PyRx integrates with open-source software like AutoDock and AutoDock Vina to perform molecular docking, predicting how well small molecules might bind to a target protein. It's designed to help identify potential drug candidates by screening libraries of molecules against target proteins. It has many advantages, for eg. being open source, supporting multiple platforms etc.

Docking simulations have been run using the tool, and the progress is monitored. PyRx provides tools to analyze the docking scores, which indicates the binding affinity of the ligands to the protein. Docking scores were analysed and the best molecules with the highest binding affinity were determined.

3.6 Protein-ligand interactions analysis

After the docking process was completed, all of the target-ligand interaction structures were captured in the out. pdbqt file and converted to PDB format. To evaluate every encounter, BIOVIA Discovery Studio (version v25.1.0.24284) was utilized.

3.7 Pharmacokinetic and toxicity prediction (ADME/pkCSM)

SwissADME (http://www.swissadme.ch/), an open-access online software, was used for analyzing pharmacokinetic properties of compounds. ADME analysis is used for each of the 13 drug compounds that were selected from 400 drug candidate. The main criteria used in the evaluation was water solubility, lipophilicity, high GI absorption, violations of Lipinski's Rule, and bioavailability.

Toxicity profiling was conducted using pkCSM, focussing on hepatotoxicity, carcinogenicity, and LD_{50} class prediction to assess safety and tolerability.

Table 2: List of common tools used in Virtual Screening and Molecular Docking in Drug Discovery

Category	Tools/Database	Function	Link
Compound Libraries	ZINC	Database of purchasable compounds for virtual screening	https://zinc.docking.org
	DrugBank	Drug information & repurposing database	https://go.drugbank .com
	PubChem	Public database of chemical molecules	https://pubchem.ncbi .nlm.nih.gov
Ligand Preparation	Open Babel	Format conversion and molecule optimization	https://openbabel.org
Protein Preparation	Pymol	Visualization and ligand manipulation	https://pymol.org
	AutoDock4	Flexible docking of ligands into target proteins	https://autodock.scripps.edu/download-autodock4/
Active site prediction	Ft server	Predicts active/binding sites on proteins	https://ftsite.bu.edu/cite
	PrankWeb	Predicts active/binding sites on proteins	https://prankweb.cz
Molecular Docking	AutoDock	Flexible docking of ligands into target proteins	https://autodock.scripps.edu/download-autodock4/
	AutoDock Vina	Docking of ligands into target proteins	https://vina.scripps.edu/downloads/
Visualization & analysis	Discovery Studio visualizer	Ligand-protein interaction visualization	https://discover.3ds.com/discovery-studio-visualizer-download
	Chimera	Protein/ligand complex rendering and RMSD	https://www.cgl.ucsf .edu/chimera
Pharmacokinetics & Toxicology Prediction	SwissADME	Predicts drug-likeness, GI absorption, BBB, etc.	http://www.swissadme .ch
	pkCSM	In silico toxicity profiling	http://biosig.unimelb .edu.au/pkcsm
	Pro Tox	Predicts ADME/Tox using graph-based signatures	https://tox.charite.de/protox3/

CHAPTER – 4

RESULT

4.1 Molecular docking result

The molecular docking analysis revealed notable variation in binding affinities among the 13 screened compounds when docked against the PARP1 protein. Niraparib, the reference compound, showed a binding energy of -9.5 kcal/mol.

Upon comparison, several structurally similar compounds demonstrated stronger predicted affinities, with binding energies reaching as high as -11.8 kcal/mol. The lower side depicted a release of 9.8 kcal/mol, upon bonding. This range of -9.8 to -11.8 was represented by the top 3 compounds out of the 13 compounds which were filtered on the basis of pharmacokinetic profiling. Such differences developed in docking scores suggest enhanced ligand–receptor interactions for selected candidates over the reference drug.

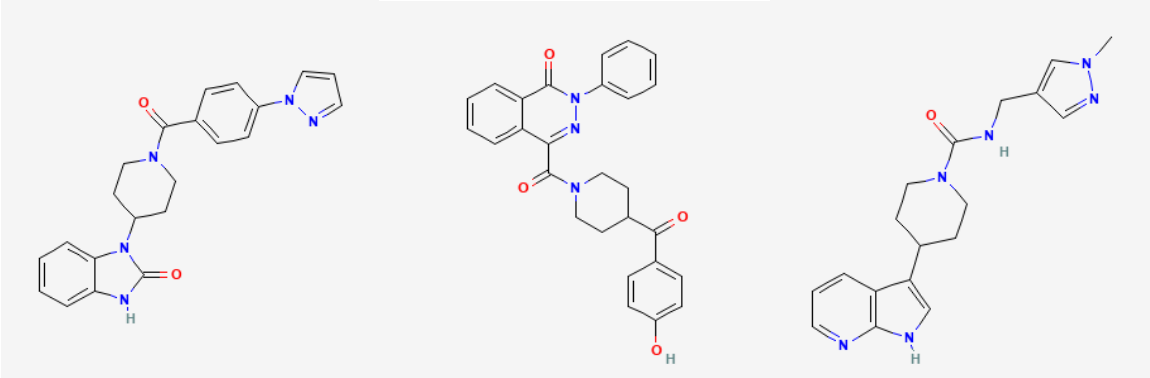
The compounds screened were structural analogs of Niraparib selected based on their drug-likeness and potential to target PARP1. All ligands were docked into the top-ranked active site pocket identified through Biodiscovery Studio, ensuring biological relevance of the docking site.

The docking results, summarized in Table X, present each ligand's PubChem ID, chemical formula, and its corresponding released binding energy. Notably, several candidate molecules exhibited binding energies more favourable than Niraparib, suggesting enhanced interaction with the PARP1 binding pocket. The ZINC-screened compounds ID 24615465, ID 16378513 and ID 132358455 exhibited binding energies of -11.8 kcal/mol, -10.7 kcal/mol and -9.8 kcal/mol respectively, indicating stronger thermodynamic stability within the PARP1 active site. These findings offer a strong basis for subsequent analysis of pharmacokinetic properties, toxicity, and molecular interaction profiles to identify promising therapeutic leads.

The compound, with Pubchem ID 24615465, exhibited maximum release of binding energy when it docked over the PARP1 enzyme. This consequently tells that the mentioned molecule reacts significantly better in comparison to the reference molecule Niraparib. The mentioned compound not only represents a better binding affinity, but also a higher lipophilicity, which increases its chances to enter the intracellular matrix via the phospholipid bilayer. The compound also does not violate the Lipinski's rule of five. However, the solubility of this compounds is less, as compared to Niraparib, which can make it quite difficult to enter the category of a good drug. But, with the help of further research, the solubility of this compound can be improved. With the addition of polar groups (eg. hydroxyl groups), shortening or removal of non polar groups or transforming the compound into a salt (by interaction with acidic or basic groups upon the compound), and many other methods can be opted to enhance the solubility of the compound. If we also take into account, the enhancement of the solubility, 4-[4-(4-Hydroxybenzoyl)piperidine-1-carbonyl]-2-phenylphthalazin-1-one, can be a far better drug, to act as an anticancer agent.

Table 3: Top three compounds along with pub chem IDs, binding energy, interacting residues (amino acid) and other possible interactions. (N=number of hydrogen bonds)

Compound Name	Pub Chem ID	Chemical formula	Binding energy
3-[1-(4-pyrazol-1-ylbenzoyl)piperidin-4-yl]-1H-benzimidazol-2-one	16378513	C22H21N5O2	-10.7 Kcal/mol
4-[4-(4-Hydroxybenzoyl)piperidine-1-carbonyl]-2-phenylphthalazin-1-one	24615465	C27H23N3O4	-11.8 Kcal/mol
N-[(1-methylpyrazol-4-yl)methyl]-4-(1H-pyrrolo[2,3-b]pyridin-3-yl)piperidine-1-carboxamide	132358455	C18H22N6O	-9.8 Kcal/mol



16378153 24615465 132358455

Figure 3 : Structures of the top three compounds along with pub chem IDs, which represented binding energies, higher than NIRAPARIB (reference molecule)

Table 4: Representation of the top 3 compounds with Binding energies along with their interacting residues

PubChem ID of compound	Binding energy in Kcal/mol	Interacting Residues
16378513	-10.7	TYR907, HIS 862 SER864, LEU769, ARG878, ASP766, ALA880
24615465	-11.8	ASP766, ASN868, ASP770, TYR907, TYR896
132358455	-9.8	ALA762, TYR889, GLN759, GLU763, LYS903, ALA898, TYR 896, SER904, TYR907, HIS862, GLY863

4.1.1 Ranked Compounds Based on Binding Affinity

Out of a total of 13 compounds docked against the PARP1 protein, the top three molecules exhibiting the most favourable binding affinities were shortlisted based on their docking scores. The three compounds are depicted in the aforementioned tabulation. Out of these compounds, the one representing PubChem Id 24615465, is selected for further analysis due to its significantly higher binding energy, as compared to the reference drug, Niraparib (PubChem Id: 24958200), which recorded a binding energy of -11.5 kcal/mol.

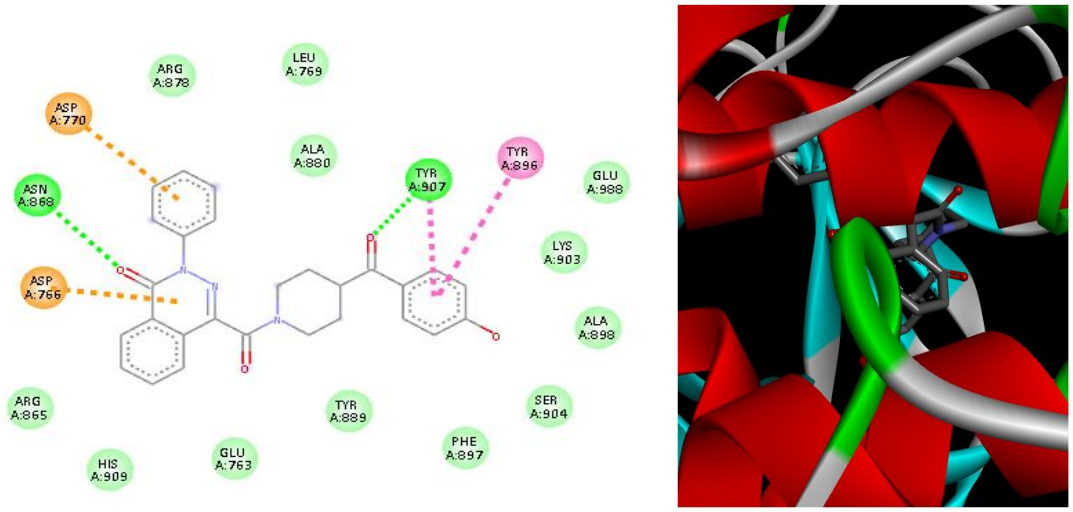


Figure 4 : Interaction of 4-[4-(4-Hydroxybenzoyl)piperidine-1-carbonyl]-2 phenylphthalazin-1-one (24615465) with PARP1 protein

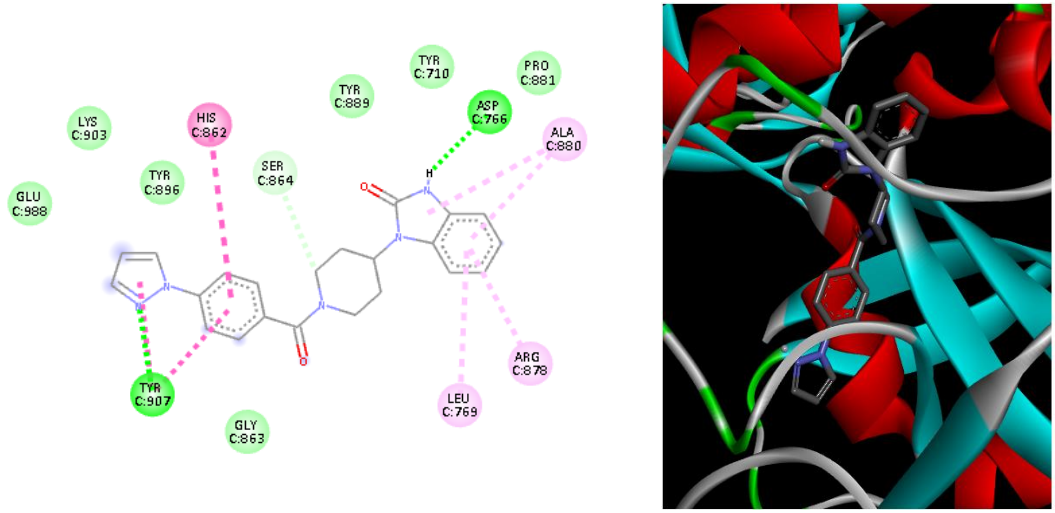


Figure 5 : Interaction of 3-[1-(4-pyrazol-1-ylbenzoyl)piperidin-4-yl]-1H-benzimidazol-2-one (16378513) with PARP1 target protein

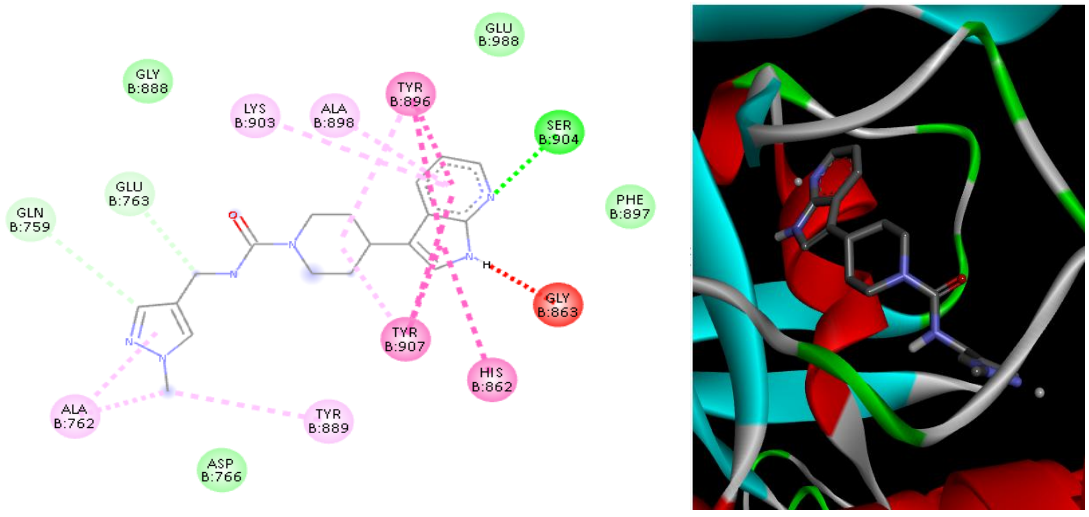


Figure 6 : Interaction of N-[(1-methylpyrazol-4-yl)methyl]-4-(1H-pyrrolo[2,3-b]pyridin-3-yl)piperidine-1-carboxamide (132358455) with PARP1 target protein

4.2 ADME prediction results

The pharmacokinetic profiles of both the reference compound (Niraparib) and the novel compound (Pubchem ID : 24615465) which shows highest negative binding energy were evaluated using the SwissADME web server. Parameters assessed included Lipinski's Rule of Five compliance, gastrointestinal (GI) absorption, bioavailability score, lipophilicity and other key physicochemical properties relevant to drug-likeness.

4.2.1 Lipinski's Rule of Five:

Both compounds complied with Lipinski's criteria, indicating good oral bioavailability potential. No violations were observed for molecular weight, LogP, hydrogen bond donors, or hydrogen bond acceptors in either molecule.

4.2.2 Lipophilicity

The novel compound, showed an improved lipophilicity, as compared to the reference Niraparib. This means that the novel drug can be introduced into the intracellular matrix more easily in comparison to, Niraparib.

4.2.3 Bioavailability Score:

A moderate bioavailability score of 0.55 was demonstrated by both drugs, indicating the possibility of systemic exposure with the right formulation techniques.

4.2.4 Other Properties:

The solubility of the compound is somewhat lesser, as compared to the Niraparib, but with the aid of further research, and enhancing the solubility of the novel compound, with several methods, the novel compound can be a fantastic anticancer drug

4.2.5 Interpretation:

Overall, the compound outperformed Niraparib in terms of pharmacokinetic properties, especially when it came to lipophilicity. Its suitability as an anticancer drug that targets the PARP1 enzyme to prevent DNA repair in cancerous cells is improved by these characteristics.

Table 5: Represent the ADME analysis using SwissADME

Property	Niraparib (Ref. Drug)	PUBCHEM ID 24615465
Lipinski's Rule of five	0	0
GI absorption	High	High
Lipophilicity	Low	High
Bioavailability score	0.55	0.55
Drug-likeness	Good	Good
Water solubility	Moderate	Low

CONCLUSION & DISCUSSION

Triple-negative breast cancer (TNBC) continues to pose significant clinical challenges due to its aggressive behaviour, limited treatment options, and poor prognosis. Unlike other breast cancer subtypes, TNBC lacks the key therapeutic targets—ER, PR, and HER2—that guide hormonal or targeted therapies.

Its aggressive nature, high recurrence rates, and limited treatment options underscore the urgent need for precision medicine approaches. While chemotherapy remains the current standard of care, advances in genomics have begun to reveal exploitable vulnerabilities, such as DNA repair deficiencies and immune evasion mechanism.

These insights are not only expanding our therapeutic arsenal—with agents like PARP inhibitors and immune checkpoint blockers, but also transforming our understanding of TNBC as a dynamic and adaptable cancer subtype

The thesis work mentions the use of a scheme to find new analogs of Niraparib that we could use in the real world, and that could be both safer and have different, but not worse, effects. From SwissSimilarity, we looked through a library of 400 drug-like (or similar) compounds, then filtered on their drug-like and pharmacokinetic effects to meet the rules of SwissADME

This high-throughput screen whittled the list down to just 13 compounds on the list based on Lipinski's Rule of five rule, high safe use (GIA) and the right set of solubility rules. The abstract filters made sure that only drugs that had a good chance of being used as oral drugs and that looked like they might work as a drug were considered for the next round of research.

The next step used AutoDock Vina in the PyRx box to do the work of binding the best drugs onto the shape of the 3D form of human PARP1. The goal was to see how well each of the candidate drugs fit in the Sandwich Binding Site. As a group, five of the drugs that were looked at (PubChem IDs: 16378513, 24615465 and 132358455) fit in the site better than Niraparib did, hence representing higher binding affinities (from -9.6 Kcal/mol to -11.8 Kcal/mol)

The molecules had stepped on to key bodies that hold the PARP1 back. We saw by the use of visuals that the drugs cased the molecules very deep in the PARP1 site leading to good bonds with other molecules like hydrogen, π–π and things that stick to each other. We used pkCSM and SwissADME to look at how these drugs could act in an animal's body. These compounds could do a lot of good things in work and body. Only one drug (Pubchem ID 24615465) showed the best affinity of all three. It made the strongest bonds (-11.8 kcal/mol), and could go through a body with a quick tour around the blood train.

Our results show how in silico models can be very useful for early drug research. These models let us test many new drugs fast and at low cost. We can do this before performing the more costly tests in lab and in animals. The good points of our work must be taken with caution. First, the estimates of count of bonds and ADMET points are only guesses. They need to be checked in the lab. Second, we did not look at what side effects can happen when new drugs work with the body. Third, though we looked at many similar drugs, there could be other drugs like these. Finally, things like how flexible the compound or cell is and how they work freely in the body are not taken into account.

As we look ahead, it is necessary to do real lab tests on the best compounds so that we can see how they stop PARP1 from working, if they go into the cell, and if they are safe. We should then use animal models to test how they can change behaviour, get into the body, and if there are any side effects. Also, using machine learning, there are QSAR models we could use in the future to predict how active they might be over more compounds.

In the end, this work points to find good Niraparib-like compounds that might work better by binding to PARP1, and be easier on the body. Compound (Pubchem ID 24615465) is strong candidate to move ahead as a new anticancer agent. This work gives a start for more lab work and shows how using computers for drug work can lead to a safer and better work on mental health drugs.

REFERENCES

[1] Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin. 2013 Jan;63(1):11-30. doi: 10.3322/caac.21166. Epub 2013 Jan 17. PMID: 23335087.

[2] Seyed Hossein Hassanpour, Mohammadamin Dehghani, Review of cancer from perspective of molecular, Journal of Cancer Research and Practice, Volume 4, Issue 4, 2017, Pages 127-129, ISSN 2311-3006, link for date of issue : https://doi.org/10.1016/j.jcrpr.2017.07.001. (https://www.sciencedirect.com/science/article/pii/S2311300617300125)

[3] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016 Jan-Feb;66(1):7-30. doi: 10.3322/caac.21332. Epub 2016 Jan 7. PMID: 26742998.

[4] Boyle, Peter, and Bernard Levin. World cancer report 2008.

[5] P. Boyle, Triple-negative breast cancer: epidemiological considerations and recommendations, Annals of Oncology, Volume 23, Supplement 6, 2012, Pages vi7-vi12, ISSN 0923-7534,https://doi.org/10.1093/annonc/mds187. (https://www.sciencedirect.com/science/article/pii/S09 23753419376355)

[6] Perou CM, Sørlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, Pollack JR, Ross DT, Johnsen H, Akslen LA, Fluge O, Pergamenschikov A, Williams C, Zhu SX, Lønning PE, Børresen-Dale AL, Brown PO, Botstein D. Molecular portraits of human breast tumours. Nature. 2000 Aug 17;406(6797):747-52. doi: 10.1038/35021093. PMID: 10963602.

[7] Morris GJ, Naidu S, Topham AK, Guiles F, Xu Y, McCue P, Schwartz GF, Park PK, Rosenberg AL, Brill K, Mitchell EP. Differences in breast carcinoma characteristics in newly diagnosed African-American and Caucasian patients: a single-institution compilation compared with the National Cancer Institute's Surveillance, Epidemiology, and End Results database. Cancer. 2007 Aug 15;110(4):876-84. doi: 10.1002/cncr.22836. PMID: 17620276.

[8] Dent R, Trudeau M, Pritchard KI, Hanna WM, Kahn HK, Sawka CA, Lickley LA, Rawlinson E, Sun P, Narod SA. Triple-negative breast cancer: clinical features and patterns of recurrence. Clin Cancer Res. 2007 Aug 1;13(15 Pt 1):4429-34. doi: 10.1158/1078-0432.CCR-06-3045. PMID: 17671126.

[9] author = {Peter Schmid and Sylvia Adams and Hope S. Rugo and Andreas Schneeweiss and Carlos H. Barrios and Hiroji Iwata and Véronique Diéras and Roberto Hegg and Seock-Ah Im and Gail Shaw Wright and Volkmar Henschel and Luciana Molinero and Stephen Y. Chui and Roel Funke and Amreen Husain and Eric P. Winer and Sherene Loi and Leisha A. Emens }, title = {Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer}, journal = {New England Journal of Medicine}, volume = {379}, number = {22}, pages = {2108-2121}, year = {2018}, doi = {10.1056/NEJMoa1809615},

[10] Duffy MJ, McGowan PM, Crown J. Targeted therapy for triple-negative breast cancer: where are we? Int J Cancer. 2012 Dec 1;131(11):2471-7. doi: 10.1002/ijc.27632. Epub 2012 Jun 7. PMID: 22581656.

[11] Chopra N, Tovey H, Pearson A, Cutts R, Toms C, Proszek P, Hubank M, Dowsett M, Dodson A, Daley F, Kriplani D, Gevensleben H, Davies HR, Degasperi A, Roylance R, Chan S, Tutt A, Skene A, Evans A, Bliss JM, Nik-Zainal S, Turner NC. Homologous recombination

DNA repair deficiency and PARP inhibition activity in primary triple negative breast cancer. Nat Commun. 2020 May 29;11(1):2662. doi: 10.1038/s41467-020-16142-7. PMID: 32471999; PMCID: PMC7260192.

[12] King MC, Marks JH, Mandell JB; New York Breast Cancer Study Group. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. Science. 2003 Oct 24;302(5645):643-6. doi: 10.1126/science.1088759. PMID: 14576434.

[13] Lord CJ, Ashworth A. The DNA damage response and cancer therapy. Nature. 2012 Jan 18;481(7381):287-94. doi: 10.1038/nature10760. PMID: 22258607.

[14] Jiang Q, Greenberg RA. Deciphering the BRCA1 Tumor Suppressor Network. J Biol Chem. 2015 Jul 17;290(29):17724-17732. doi: 10.1074/jbc.R115.667931. Epub 2015 Jun 5. PMID: 26048987; PMCID: PMC4505021.

[15] Gong R, Ma Z, He L, Jiang S, Cao D, Cheng Y. Identification and evaluation of a novel PARP1 inhibitor for the treatment of triple-negative breast cancer. Chem Biol Interact. 2023 Sep 1;382:110567. doi: 10.1016/j.cbi.2023.110567. Epub 2023 Jun 2. PMID: 37271214.

[16] author = {Shamim, Md. and Ali, Md. Sumon and Hossain, Md. Arju and Hossain, Md. Alfaz and Kavey, Md. Reduanul Haque and Hoque, Md. Mobinul and Rahman, Md Ataur and Harrath, Abdel Halim and Rahman, Md Habibur}, title = {Discovery of novel PARP1 inhibitors through computational drug design approaches}, year = {2025}, issue_date = {Jun 2025}, publisher = {Elsevier Science Publishers B. V.},

[17] Sundararajan P, Dharmaraj Rajaselvi D, Vivekananthan S, Priya Ramasamy S. In-silico method for elucidation of prodigiosin as PARP-1 inhibitor a prime target of Triple-negative breast cancer. Bioorg Chem. 2023 Sep;138:106618. doi: 10.1016/j.bioorg.2023.106618. Epub 2023 May 19. PMID: 37244231.

[18] Bianchini G, Balko JM, Mayer IA, Sanders ME, Gianni L. Triple-negative breast cancer: challenges and opportunities of a heterogeneous disease. Nat Rev Clin Oncol. 2016 Nov;13(11):674-690. doi: 10.1038/nrclinonc.2016.66. Epub 2016 May 17. PMID: 27184417; PMCID: PMC5461122.

[19] Foulkes WD, Smith IE, Reis-Filho JS. Triple-negative breast cancer. N Engl J Med. 2010 Nov 11;363(20):1938-48. doi: 10.1056/NEJMra1001389. PMID: 21067385.

[20] Dent R, Trudeau M, Pritchard KI, Hanna WM, Kahn HK, Sawka CA, Lickley LA, Rawlinson E, Sun P, Narod SA. Triple-negative breast cancer: clinical features and patterns of recurrence. Clin Cancer Res. 2007 Aug 1;13(15 Pt 1):4429-34. doi: 10.1158/1078-0432.CCR-06-3045. PMID: 17671126.

[21] Bianchini G, Balko JM, Mayer IA, Sanders ME, Gianni L. Triple-negative breast cancer: challenges and opportunities of a heterogeneous disease. Nat Rev Clin Oncol. 2016 Nov;13(11):674-690. doi: 10.1038/nrclinonc.2016.66. Epub 2016 May 17. PMID: 27184417; PMCID: PMC5461122.

[22] Lehmann BD, Bauer JA, Chen X, Sanders ME, Chakravarthy AB, Shyr Y, Pietenpol JA. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. J Clin Invest. 2011 Jul;121(7):2750-67. doi: 10.1172/JCI45014. PMID: 21633166; PMCID: PMC3127435.

[23] Robson M, Im SA, Senkus E, Xu B, Domchek SM, Masuda N, Delaloge S, Li W, Tung N, Armstrong A, Wu W, Goessl C, Runswick S, Conte P. Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. N Engl J Med. 2017 Aug 10;377(6):523-533. doi: 10.1056/NEJMoa1706450. Epub 2017 Jun 4. Erratum in: N Engl J Med. 2017 Oct 26;377(17):1700. doi: 10.1056/NEJMx170012. PMID: 28578601.

[24] Liedtke C, Mazouni C, Hess KR, André F, Tordai A, Mejia JA, Symmans WF, Gonzalez-Angulo AM, Hennessy B, Green M, Cristofanilli M, Hortobagyi GN, Pusztai L. Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. J Clin Oncol. 2008 Mar 10;26(8):1275-81. doi: 10.1200/JCO.2007.14.4147. Epub 2008 Feb 4. PMID: 18250347.

[25] Schmid P, Adams S, Rugo HS, Schneeweiss A, Barrios CH, Iwata H, Diéras V, Hegg R, Im SA, Shaw Wright G, Henschel V, Molinero L, Chui SY, Funke R, Husain A, Winer EP, Loi S, Emens LA; IMpassion130 Trial Investigators. Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. N Engl J Med. 2018 Nov 29;379(22):2108-2121. doi: 10.1056/NEJMoa1809615. Epub 2018 Oct 20. PMID: 30345906.

[26] Emens LA, Cruz C, Eder JP, Braiteh F, Chung C, Tolaney SM, Kuter I, Nanda R, Cassier PA, Delord JP, Gordon MS, ElGabry E, Chang CW, Sarkar I, Grossman W, O'Hear C, Fassò M, Molinero L, Schmid P. Long-term Clinical Outcomes and Biomarker Analyses of Atezolizumab Therapy for Patients With Metastatic Triple-Negative Breast Cancer: A Phase 1 Study. JAMA Oncol. 2019 Jan 1;5(1):74-82. doi: 10.1001/jamaoncol.2018.4224. PMID: 30242306; PMCID: PMC6439773.

[27] Robson M, Im SA, Senkus E, Xu B, Domchek SM, Masuda N, Delaloge S, Li W, Tung N, Armstrong A, Wu W, Goessl C, Runswick S, Conte P. Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. N Engl J Med. 2017 Aug 10;377(6):523-533. doi: 10.1056/NEJMoa1706450. Epub 2017 Jun 4. Erratum in: N Engl J Med. 2017 Oct 26;377(17):1700. doi: 10.1056/NEJMx170012. PMID: 28578601.

[28] Lehmann BD, Bauer JA, Chen X, Sanders ME, Chakravarthy AB, Shyr Y, Pietenpol JA. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. J Clin Invest. 2011 Jul;121(7):2750-67. doi: 10.1172/JCI45014. PMID: 21633166; PMCID: PMC3127435.

[29] Prakash R, Zhang Y, Feng W, Jasin M. Homologous recombination and human health: the roles of BRCA1, BRCA2, and associated proteins. Cold Spring Harb Perspect Biol. 2015 Apr 1;7(4):a016600. doi: 10.1101/cshperspect.a016600. PMID: 25833843; PMCID: PMC4382744.

[30] del Rivero J, Kohn EC. PARP Inhibitors: The Cornerstone of DNA Repair-Targeted Therapies. Oncology (Williston Park). 2017 Apr 15;31(4):265-73. PMID: 28412778.

[31] Glaviano A, Foo ASC, Lam HY, Yap KCH, Jacot W, Jones RH, Eng H, Nair MG, Makvandi P, Geoerger B, Kulke MH, Baird RD, Prabhu JS, Carbone D, Pecoraro C, Teh DBL, Sethi G, Cavalieri V, Lin KH, Javidi-Sharifi NR, Toska E, Davids MS, Brown JR, Diana P, Stebbing J, Fruman DA, Kumar AP. PI3K/AKT/mTOR signaling transduction pathway and targeted therapies in cancer. Mol Cancer. 2023 Aug 18;22(1):138. doi: 10.1186/s12943-023-01827-6. PMID: 37596643; PMCID: PMC10436543.

[32] Hernández Borrero LJ, El-Deiry WS. Tumor suppressor p53: Biology, signaling pathways, and therapeutic targeting. Biochim Biophys Acta Rev Cancer. 2021 Aug;1876(1):188556. doi: 10.1016/j.bbcan.2021.188556. Epub 2021 Apr 29. PMID: 33932560; PMCID: PMC8730328.

[33] Masuda H, Zhang D, Bartholomeusz C, Doihara H, Hortobagyi GN, Ueno NT. Role of epidermal growth factor receptor in breast cancer. Breast Cancer Res Treat. 2012 Nov;136(2):331-45. doi: 10.1007/s10549-012-2289-9. Epub 2012 Oct 17. PMID: 23073759; PMCID: PMC3832208.

[34] Rampurwala M, Wisinski KB, O'Regan R. Role of the androgen receptor in triple-negative breast cancer. Clin Adv Hematol Oncol. 2016 Mar;14(3):186-93. PMID: 27058032; PMCID: PMC5221599.

[35] Song P, Gao Z, Bao Y, Chen L, Huang Y, Liu Y, Dong Q, Wei X. Wnt/β-catenin signaling pathway in carcinogenesis and cancer therapy. J Hematol Oncol. 2024 Jun 18;17(1):46. doi: 10.1186/s13045-024-01563-4. PMID: 38886806; PMCID: PMC11184729.

[36] Giuli MV, Giuliani E, Screpanti I, Bellavia D, Checquolo S. Notch Signaling Activation as a Hallmark for Triple-Negative Breast Cancer Subtype. J Oncol. 2019 Jul 11;2019:8707053. doi: 10.1155/2019/8707053. PMID: 31379945; PMCID: PMC6657611.

[37] Zhang H, Dai Z, Wu W, Wang Z, Zhang N, Zhang L, Zeng WJ, Liu Z, Cheng Q. Regulatory mechanisms of immune checkpoints PD-L1 and CTLA-4 in cancer. J Exp Clin Cancer Res. 2021 Jun 4;40(1):184. doi: 10.1186/s13046-021-01987-7. PMID: 34088360; PMCID: PMC8178863.

[38] Qian S, Wei Z, Yang W, Huang J, Yang Y, Wang J. The role of BCL-2 family proteins in regulating apoptosis and cancer therapy. Front Oncol. 2022 Oct 12;12:985363. doi: 10.3389/fonc.2022.985363. PMID: 36313628; PMCID: PMC9597512.

[39] Fuentes N, Silveyra P. Estrogen receptor signaling mechanisms. Adv Protein Chem Struct Biol. 2019;116:135-170. doi: 10.1016/bs.apcsb.2019.01.001. Epub 2019 Feb 4. PMID: 31036290; PMCID: PMC6533072.

[40] Katzenellenbogen BS, Sun J, Harrington WR, Kraichely DM, Ganessunker D, Katzenellenbogen JA. Structure-function relationships in estrogen receptors and the characterization of novel selective estrogen receptor modulators with unique pharmacological profiles. Ann N Y Acad Sci. 2001 Dec;949:6-15. doi: 10.1111/j.1749-6632.2001.tb03998.x. PMID: 11795381.

[41] Dama A, Baggio C, Boscaro C, Albiero M, Cignarella A. Estrogen Receptor Functions and Pathways at the Vascular Immune Interface. Int J Mol Sci. 2021 Apr 20;22(8):4254. doi: 10.3390/ijms22084254. PMID: 33923905; PMCID: PMC8073008.

[42] Fuentes N, Silveyra P. Estrogen receptor signaling mechanisms. Adv Protein Chem Struct Biol. 2019;116:135-170. doi: 10.1016/bs.apcsb.2019.01.001. Epub 2019 Feb 4. PMID: 31036290; PMCID: PMC6533072.

[43] Miziak P, Baran M, Błaszczak E, Przybyszewska-Podstawka A, Kałafut J, Smok-Kalwat J, Dmoszyńska-Graniczka M, Kiełbus M, Stepulak A. Estrogen Receptor Signaling in Breast Cancer. Cancers (Basel). 2023 Sep 23;15(19):4689. doi: 10.3390/cancers15194689. PMID: 37835383; PMCID: PMC10572081.

[44] Graham JD, Clarke CL. Physiological action of progesterone in target tissues. Endocr Rev. 1997 Aug;18(4):502-19. doi: 10.1210/edrv.18.4.0308. PMID: 9267762.

[45] Conneely OM, Mulac-Jericevic B, DeMayo F, Lydon JP, O'Malley BW. Reproductive functions of progesterone receptors. Recent Prog Horm Res. 2002;57:339-55. doi: 10.1210/rp.57.1.339. PMID: 12017551.

[46] Levine JE, Chappell PE, Schneider JS, Sleiter NC, Szabo M. Progesterone receptors as neuroendocrine integrators. Front Neuroendocrinol. 2001 Apr;22(2):69-106. doi: 10.1006/frne.2001.0210. PMID: 11259133.

[47] Arck PC, Hecher K. Fetomaternal immune cross-talk and its consequences for maternal and offspring's health. Nat Med. 2013 May;19(5):548-56. doi: 10.1038/nm.3160. Epub 2013 May 7. PMID: 23652115.

[48] Hagan CR, Lange CA. (2018). Molecular mechanisms of progesterone receptor action in hormone-responsive cancers. PMID: 29241596, DOI: 10.1016/j.mce.2017.12.009

[49] Yarden Y, Sliwkowski MX. Untangling the ErbB signalling network. Nat Rev Mol Cell Biol. 2001 Feb;2(2):127-37. doi: 10.1038/35052073. PMID: 11252954.

[50] Moasser MM. The oncogene HER2: its signaling and transforming functions and its role in human cancer pathogenesis. Oncogene. 2007 Oct 4;26(45):6469-87. doi: 10.1038/sj.onc.1210477. Epub 2007 Apr 30. PMID: 17471238; PMCID: PMC3021475.

[51] Waks AG, Winer EP. Breast Cancer Treatment: A Review. JAMA. 2019 Jan 22;321(3):288-300. doi: 10.1001/jama.2018.19323. PMID: 30667505.

[52] Gravalos C, Jimeno A. HER2 in gastric cancer: a new prognostic factor and a novel therapeutic target. Ann Oncol. 2008 Sep;19(9):1523-9. doi: 10.1093/annonc/mdn169. Epub 2008 Apr 25. PMID: 18441328.

[53] Gonzalez H, Hagerling C, Werb Z. Roles of the immune system in cancer: from tumor initiation to metastatic progression. Genes Dev. 2018 Oct 1;32(19-20):1267-1284. doi: 10.1101/gad.314617.118. PMID: 30275043; PMCID: PMC6169832.

[54] Schreiber V, et al. (2006). Poly(ADP-ribose): novel functions for an old molecule. PMID: 15189136, DOI: 10.1016/j.tibs.2004.05.004

[55] D'Amours D, Desnoyers S, D'Silva I, Poirier GG. Poly(ADP-ribosyl)ation reactions in the regulation of nuclear functions. Biochem J. 1999 Sep 1;342 (Pt 2)(Pt 2):249-68. PMID: 10455009; PMCID: PMC1220459.

[56] Gibson BA, et al. (2010). Chromatin structure and the regulation of transcription by PARP1. PMID: 20504360, DOI: 10.1016/j.cell.2010.05.034

[57] David KK, Andrabi SA, Dawson TM, Dawson VL. Parthanatos, a messenger of death. Front Biosci (Landmark Ed). 2009 Jan 1;14(3):1116-28. doi: 10.2741/3297. PMID: 19273119; PMCID: PMC4450718.

[58] Lord CJ, Ashworth A. PARP inhibitors: Synthetic lethality in the clinic. Science. 2017 Mar 17;355(6330):1152-1158. doi: 10.1126/science.aam7344. Epub 2017 Mar 16. PMID: 28302823; PMCID: PMC6175050.

[59] D'Amours D, Desnoyers S, D'Silva I, Poirier GG. Poly(ADP-ribosyl)ation reactions in the regulation of nuclear functions. Biochem J. 1999 Sep 1;342 (Pt 2)(Pt 2):249-68. PMID: 10455009; PMCID: PMC1220459.

[60] Lehmann BD, Bauer JA, Chen X, Sanders ME, Chakravarthy AB, Shyr Y, Pietenpol JA. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. J Clin Invest. 2011 Jul;121(7):2750-67. doi: 10.1172/JCI45014. PMID: 21633166; PMCID: PMC3127435.

[61] Horwitz KB, Sartorius CA. 90 YEARS OF PROGESTERONE: Progesterone and progesterone receptors in breast cancer: past, present, future. J Mol Endocrinol. 2020 Jul;65(1):T49-T63. doi: 10.1530/JME-20-0104. PMID: 32485679; PMCID: PMC8525510.

[62] Dent R, Trudeau M, Pritchard KI, Hanna WM, Kahn HK, Sawka CA, Lickley LA, Rawlinson E, Sun P, Narod SA. Triple-negative breast cancer: clinical features and patterns of recurrence. Clin Cancer Res. 2007 Aug 1;13(15 Pt 1):4429-34. doi: 10.1158/1078-0432.CCR-06-3045. PMID: 17671126.

[63] Farmer H, McCabe N, Lord CJ, Tutt AN, Johnson DA, Richardson TB, Santarosa M, Dillon KJ, Hickson I, Knights C, Martin NM, Jackson SP, Smith GC, Ashworth A. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature. 2005 Apr 14;434(7035):917-21. doi: 10.1038/nature03445. PMID: 15829967.

[64] Fong PC, Boss DS, Yap TA, Tutt A, Wu P, Mergui-Roelvink M, Mortimer P, Swaisland H, Lau A, O'Connor MJ, Ashworth A, Carmichael J, Kaye SB, Schellens JH, de Bono JS. Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. N Engl J Med. 2009 Jul 9;361(2):123-34. doi: 10.1056/NEJMoa0900212. Epub 2009 Jun 24. PMID: 19553641.

[65] Christopher J. Lord, Alan Ashworth, PARP inhibitors: Synthetic lethality in the clinic.*Science*355,1152-1158(2017).DOI:10.1126/science.aam7344

[66] González-Martín A, Pothuri B, Vergote I, DePont Christensen R, Graybill W, Mirza MR, McCormick C, Lorusso D, Hoskins P, Freyer G, Baumann K, Jardon K, Redondo A, Moore RG, Vulsteke C, O'Cearbhaill RE, Lund B, Backes F, Barretina-Ginesta P, Haggerty AF, Rubio-Pérez MJ, Shahin MS, Mangili G, Bradley WH, Bruchim I, Sun K, Malinowska IA, Li Y, Gupta D, Monk BJ; PRIMA/ENGOT-OV26/GOG-3012 Investigators. Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N Engl J Med. 2019 Dec 19;381(25):2391-2402. doi: 10.1056/NEJMoa1910962. Epub 2019 Sep 28. PMID: 31562799.

[67] Li DG, Mostaghimi A. Restrictive FDA Requirements and the Development of Generic Topical Medications-Reply. JAMA Dermatol. 2019 Apr 1;155(4):503-504. doi: 10.1001/jamadermatol.2018.4990. PMID: 30810704.

[68] Veber, D. F., Johnson, S. R., Cheng, H. Y., Smith, B. R., Ward, K. W., & Kopple, K. D. (2002). Molecular properties that influence the oral bioavailability of drug candidates. *Journal of Medicinal Chemistry, 45*(12), 2615–2623. https://doi.org/10.1021/jm020017n

[69] Egan, W. J., Merz, K. M., & Baldwin, J. J. (2000). Prediction of drug absorption using multivariate statistics. *Journal of Medicinal Chemistry, 43*(21), 3867–3877. https://doi.org/10.1021/jm000292e

[70] Muegge, I. (2003). Selection criteria for drug-like compounds. *Medicinal Research Reviews, 23*(3), 302–321. https://doi.org/10.1002/med.10041

[71] Oprea, T. I., & Gottfries, J. (2001). Chemography: The art of navigating in chemical space. *Journal of Combinatorial Chemistry, 3*(2), 157–166. https://doi.org/10.1021/cc000038b

[72] Daina, A., Michielin, O., & Zoete, V. (2019). SwissTargetPrediction: Updated data and new features for efficient prediction of protein targets of small molecules. *Nucleic Acids Research, 47*(W1), W357–W364. https://doi.org/10.1093/nar/gkz382

[73] Gfeller, D., Grosdidier, A., Wirth, M., Daina, A., Michielin, O., & Zoete, V. (2014). SwissTargetPrediction: A web server for target prediction of bioactive small molecules. *Nucleic Acids Research, 42*(W1), W32–W38. https://doi.org/10.1093/nar/gku293

[74] Kuhn, M., Letunic, I., Jensen, L. J., & Bork, P. (2016). The SIDER database of drugs and side effects. *Nucleic Acids Research, 44*(D1), D1075–D1079. https://doi.org/10.1093/nar/gkv1075

[75] Cheng, F., Li, W., Zhou, Y., Shen, J., Wu, Z., Liu, G., Lee, P. W., & Tang, Y. (2012). admetSAR: A comprehensive source and free tool for assessment of chemical ADMET properties. *Journal of Chemical Information and Modeling, 52*(11), 3099–3105. https://doi.org/10.1021/ci300367a

[76] Pires, D. E., Blundell, T. L., & Ascher, D. B. (2015). pkCSM: Predicting small-molecule pharmacokinetic and toxicity properties using graph-based signatures. *Journal of Medicinal Chemistry, 58*(9), 4066–4072. https://doi.org/10.1021/acs.jmedchem.5b00104

[77] Sterling, T., & Irwin, J. J. (2015). ZINC 15–ligand discovery for everyone. *Journal of Chemical Information and Modeling, 55*(11), 2324–2337. https://doi.org/10.1021/acs.jcim.5b00559

[78] Wang, Y., Bryant, S. H., Cheng, T., Wang, J., Gindulyte, A., Shoemaker, B. A., & Bolton, E. E. (2017). PubChem BioAssay: 2017 update. *Nucleic Acids Research, 45*(D1), D955–D963. https://doi.org/10.1093/nar/gkw1118

[79] Bento, A. P., Gaulton, A., Hersey, A., Bellis, L. J., Chambers, J., Davies, M., Krüger, F. A., Light, Y., Mak, L., McGlinchey, S., Nowotka, M., Papadatos, G., Santos, R., & Overington, J. P. (2014). The ChEMBL bioactivity database: An update. *Nucleic Acids Research, 42*(D1), D1083–D1090. https://doi.org/10.1093/nar/gkt1031

[80] Wang, Y., Xiao, J., Suzek, T. O., Zhang, J., Wang, J., Zhou, Z., Han, L., Karapetyan, K., Dracheva, S., Shoemaker, B. A., Bolton, E., Gindulyte, A., Bryant, S. H. (2012). PubChem's BioAssay database. *Nucleic Acids Research, 40*(D1), D400–D412. https://doi.org/10.1093/nar/gkr1132

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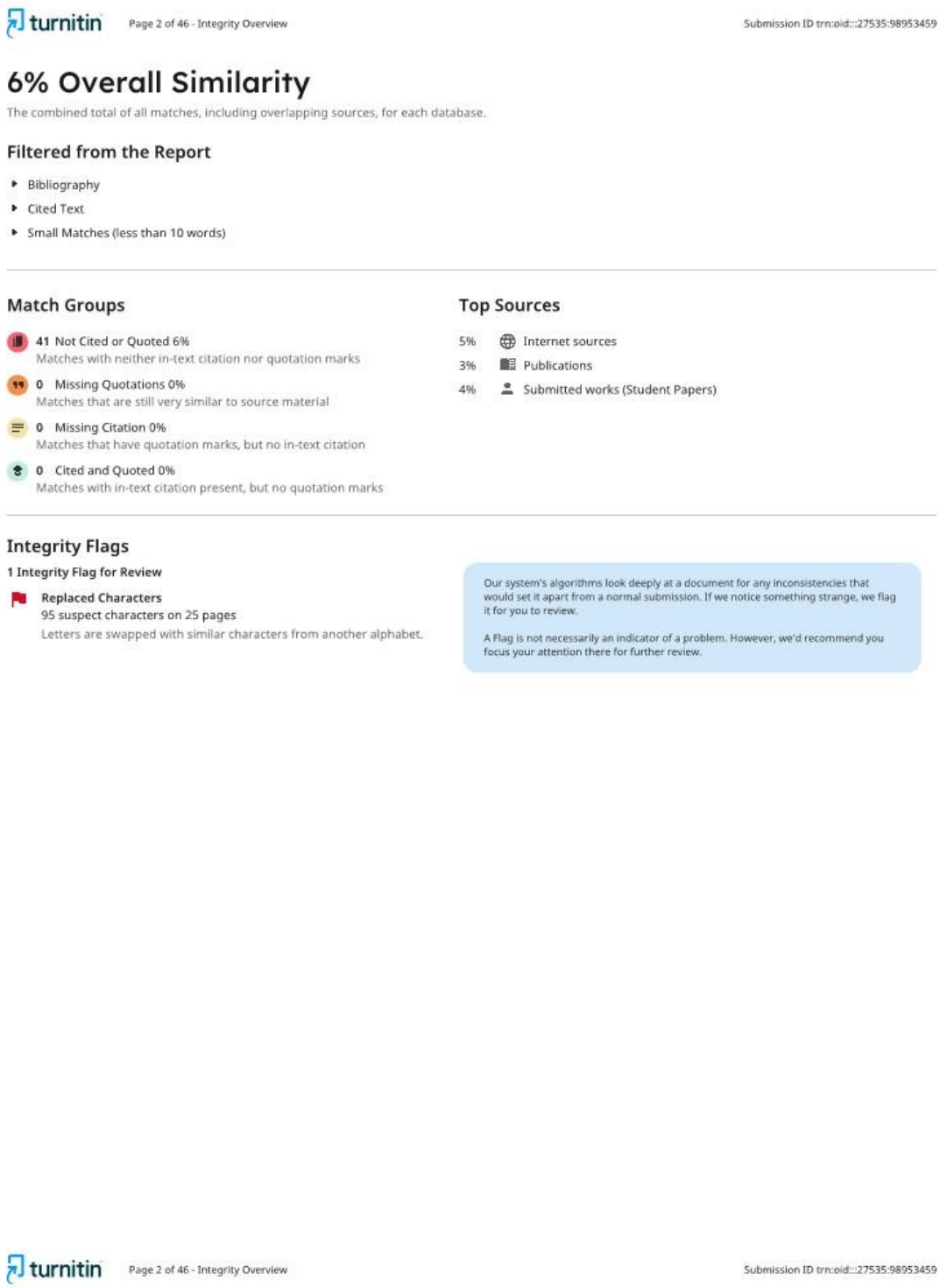

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