www.revistageintec.net
ISSN: 2237-0722
revista GEINTEC Gestão, Inovação e Tecnologias

In-silico Screening of Synthetic Inhibitors for Human Poly (Adp-ribose) Polymerase 2 Enzyme Using Patch Dock Software for Ovarian Cancer Therapy

V.S. Swathi Raj[1]; Dr.M. Monisha[2*]; Dr. Gokul Paramasivam[3]

[1]Research Scholar, Department of Biomedical Engineering, Saveetha School of Engineering, SIMATS, Saveetha University, Chennai, Tamil Nadu, India.

[1]vsswathiraj2017@gmail.com

[2*]Project Guide, Department of Biomedical Engineering, SIMATS, Saveetha University, Chennai, Tamil Nadu, India.

[2*]monisham.sse@saveetha.com

[3]Project Co-Guide, Department of Biomedical Engineering, Saveetha School of Engineering, SIMATS, Saveetha University, Chennai, Tamil Nadu, India.

[3]gokulp.sse@saveetha.com

Abstract

Aim: *This research deals with the identification of drug synthetic inhibitors docked with PARP enzyme by In silico screening using patch Dock for targeted ovarian cancer.*

Materials and methods: *The sample size (N= 51) preparation is of two-dimensional structures for 50 synthetic compounds and a reference compound (Rucaparib) that were retrieved and collected from the NCBI-PubChem compound database. The ligand molecule was prepared using the LigPrep wizard of the Schrödinger suite. Patch Dock software was used to conduct a molecular docking study of PARP with plant-derived compounds. This program uses an algorithm to generate output complexes based on biomolecule shape complementarity. The best poses were analyzed for non-covalent interaction using PLIP and discovery studio visualizer.* ***Results:*** *Molecular docking analysis revealed (Lyngabyabelline, Sansalvamide, Dolastatin, Beta-carotene, Butulinic) from Plant derived could bind PARP protein with higher affinity, ability to competitively inhibit PARP as a stable drug candidate in comparison with Rucaparib and also show similar residue interaction patterns when compared with other PARP inhibitors that would report an affirmative prognostic factor.* ***Conclusion:*** *The identified inhibitor complexes from plant derived synthetic molecules are expected to bind with PARP protein with better efficiency in comparison with Rucaparib, hence they can be further considered for in vivo and in vitro analysis.*

Key-words: PARP (Poly (ADP)-ribose Polymerase), Reference Compound, Molecular Docking, Shape Complementarity, Synthetic Medicament, Novel Drug Inhibitor, Computational Biology.

1. Introduction

The study investigates the role of small molecule inhibitors of poly (ADP-ribose) polymerase (PARP) enzyme in cancer using sources derived from plant synthetic molecules. A method of cancer treatment that uses drugs to recognize and attack cancer cells. The PARP enzyme participates in a variety of cell processes, including DNA repairs, certain anticancer medications and radiation for cancer that can cause damage to the DNA molecule inhibitors (Staples and Goodm 2013) of PARP enzyme in cancer using sources derived from plant synthetic molecules. Studies suggest that PARP is over-expressed in tumor cells, hence small molecule inhibitors are identified as being involved in targeted ovarian cancer. Such therapies target the inner workings of the cancer cells, that makes them separate from healthy cells. Each type of targeted therapy performs differently, but all of them alter the way cancer cells expand, split, repair or incorporate itself (Oche and Olaposi 2018). The importance of this study is to establish safe and efficient drugs for treating cancer and eventually cure them. The major application is to find inhibitors with higher affinity that are in use and focus on the current and future use of targeted therapy in Epithelial ovarian cancer (Bazzaro 2018).

Based on the literature survey, "PARP inhibitors in ovarian cancer" (Staples and Goodm 2013) is stated one among the best reviews over the information related to PARP enzyme. We searched for most cited articles in Google Scholar and science direct database and ended up with 302 articles published in this area. The medicines known as inhibitors of PARP (poly(ADP)-ribose polymerase) are Olaparib, Veliparib, Rucaparib, 3-aminobenzamide and Niaparib (Staples and Goodm 2013). These medications make it impossible for tumor cells with an abnormal BRCA gene to repair damaged DNA, which is also responsible for the death of the cells, by blocking the PARP pathway. Studies state the development process in finding the drug inhibition molecules docked with PARP as a protein enzyme for ovarian cancer in the past 10 years. (Gien and Mackay 2010). As compared to the complete simulated screened compounds with preferable affinity, the overall energy of Rucaparib inhibitor interacting with the PARP is higher that states to be the best study among the available literature.

Previously our team has a rich experience in working on various research projects across multiple disciplines (Sathish and Karthick 2020; Varghese, Ramesh, and Veeraiyan 2019; S.R. Samuel, Acharya, and Rao 2020; Venu, Raju, and Subramani 2019; M. S. Samuel et al. 2019; Venu, Subramani, and Raju 2019; Mehta et al. 2019; Sharma et al. 2019; Malli Sureshbabu et al. 2019; Krishnaswamy et al. 2020; Muthukrishnan et al. 2020; Gheena and Ezhilarasan 2019; Vignesh et al.

2019; Ke et al. 2019; Vijayakumar Jain et al. 2019; Jose, Ajitha, and Subbaiyan 2020). Now the growing trend in this area motivated us to pursue this project.

The lacunae in the existing research is the lack of effective inhibitor molecules for PARP in treatment of targeted ovarian cancer. The study was intended to check if inhibitors derived from plant synthetic could inhibit PARP enzyme than other prevailing drugs in the market. The primary function of PARP (found in the nucleus of the cell) is to recognize and activate an instant cellular reaction by communicating the enzymatic mechanism involved in the repair of the SSB to metabolic. It also plays a significant part in inhibition caused by cleavage (Gien and Mackay 2010). The authors of this study have experience in the computational biology field which allowed us to efficiently carry out our research, based on the detection of small molecular inhibitors of different anticancer medicines for targeted ovarian cancer therapy as stable drugs. The aim states by identifying a synthetic inhibitor molecule for Human poly (ADP-ribose) polymerase 2 inhibitor enzymes using patch dock. The study aims at identifying small molecule inhibitors derived from plants against PARP in treatment of ovarian cancer.

2. Materials and Methods

The research work was done by online softwares (PLIP, Discovery studio Visualizer, PyMol, Patch dock) that resulted in identification of stable drug compounds and internet based work was provided by Saveetha School of Engineering. The power calculation was done using pretest power g of 80% (Jung et al. 2018). Ethical approval is not applicable as no human samples were considered for analysis. Two groups were considered for this research work i.e synthetic compounds and a reference compound. By retrieving the list of 50 plants derived synthetic compounds that act as inhibitors agents for anti cancer therapy. These compounds were listed out and were carried out in Patch dock software that was extracted as an individual ligand compound in PDB format along with the results by finding their higher binding affinity in (Table 1). So, N=51 samples were considered for identifying an stable drug inhibitor.

Table 1 - List of Retrieved Hit Compounds: Lyngbyabellin, Sansalvamide, Dolastatin, Beta-Carotene & Butulinic which has shown Higher Affinities when compared with the Reference Compound (Rucaparib) of -178.88 kcal/mol in given table below. Among these 5 hit Compounds Beta Carotene shows the Highest ACE of -323.06 kcal/mol

Compound Name	Score (kcal/mol)	Area	ACE
Lyngbyabellin B	6350	686.60	-253.88
Sansalvamide	4716	621.30	-314.48
Dolastatin	7360	1003.90	-320.77
Beta carotene	7536	933.40	-323.06
Butulinic	5354	687.80	-289.50

The two-dimensional structure of 50 synthetic compounds derived from plant sources considering them as a drug inhibitor were retrieved and collected for molecular docking and analysis using PyMol software. Considering 50 synthetic compounds as Group 1.

The two-dimensional structure of a reference compound (Rucaparib) is derived as a PARP drug inhibitor that was retrieved and collected for molecular docking and analysis using PyMol software. Considered the derived reference compound as Group 2.

The interaction between amino acids residues of PARP and ligand was evaluated using the testing setup of Discovery Studio Visualizer. Binding affinity with association of the active site residue in PARP protein are the best confirmatory conditions for ligand. The optimal locations for the use of Discovery Studio Visualizer 2.5 and PLIP (Salentin et al. 2017) were analyzed in non-covalent interactions. PyMOL is a molecular and renderer capable. Protein-Ligand Interaction Profiler (PLIP) is the following testing procedure that is used to retrieve the ACE measurements of drug complex inhibitors that is fully automated detection and visualization of relevant noncovalent protein-ligand contacts in 3D structures.(Annunziata and Zorn 2016). PLIP a new web service for complete identification and analysis of associated non-covalent protein–linking contacts in 3D structures. (Oche and Olaposi 2018; Morales et al. 2014).

3. Results

In Table 1, it is observed that five hit compounds (lyngbyabellin, sansalvamide, dolastatin, Beta-Carotene & Butulinic) were retrieved from 50 Synthetic molecules based on its atomic contact energy that describes the affinity complex of the drug inhibitor which is considered for further analysis and are called the novel drug inhibitors for this research. These five-hits lyngbyabellin, sansalvamide, dolastatin, Beta-Carotene & Butulinic which showed higher affinities when compared with the reference compound (Rucaparib) of -178.88 kcal/mol. Among these 5 hit compounds, Beta carotene shows the highest ACE of -323.06 kcal/mol. Atomic contact energy is high for the above-listed compound, and it is further suitable for finding drug inhibitors for targeted therapies. These novel classes of anti-cancer medicines to be used as single agents or in combination with radiation and chemotherapy.

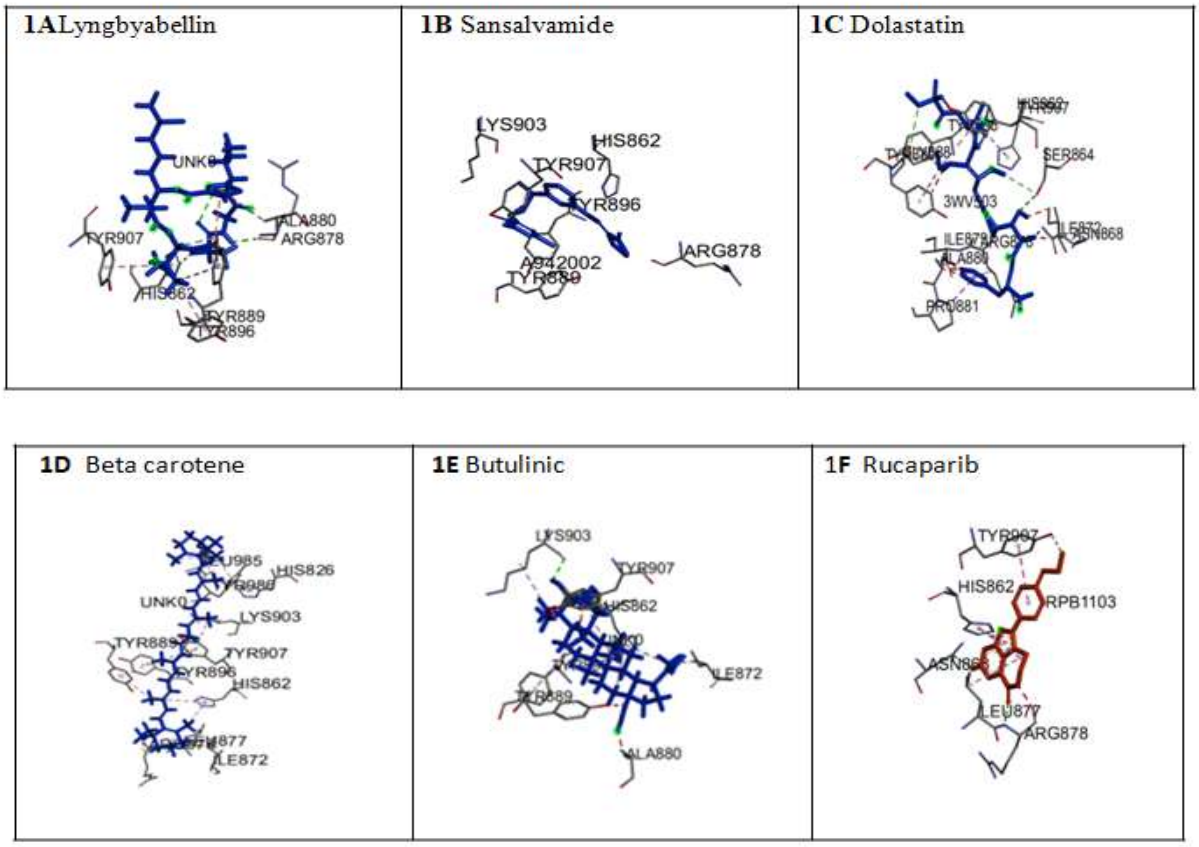
In Figure 1, results in Interaction analysis of PARP with plant derived compounds using discovery studio visualizer. Interaction of PARP with 1A.lyngbyabellin, 1B.sansalvamide, 1C.dolastatin, 1D. Beta-Carotene & 1E. Butulinic. The structure of inhibitors and amino acids residues of PARP are represented in blue and black sticks respectively. Interaction of PARP with 1**F.**

Rucaparib in red and black sticks. Table 1(a) shows the binding affinity of the reference compound (Rucaparib) of -178.88 kcal/mol.

Table 1(a) - The Binding Affinity of the Reference Compound (Rucaparib) of -178.88 kcal/mol is Given in table Below

Reference Compound Name	Score (kcal/mol)	Area	ACE
Rucaparib	4466	519.70	-178.88

Fig. 1 - Interaction Analysis of PARP with Plant Derived Compounds Using Discovery Studio Visualizer. Interaction of PARP with 1A. Lyngbyabellin, 1B. Sansalvamide, 1C. Dolastatin, 1D. Beta-Carotene & 1E. Butulinic. The structure of inhibitors and amino acids residues of PARP are represented in blue and black sticks respectively. Interaction of PARP with 1**F.** Rucaparib in red and black sticks. Atomic contact energy is high for the above listed hit compounds and it is further suitable for finding drug inhibitors for targeted therapies



From Table 2 & Fig. 2, results in Interaction of Lynbyabelin with HIS862, TYR896, TYR907, TYR889, ARG878, ALA880 as active binding residues with cartoon, ligand residue and Surface representation that showed highest in TYR889 with a bond length of 3.72 pm that bonds with hydrophobic interaction and with higher Atomic contact energy of -253.88 kcal/mol.

Fig. 2 - Interaction analysis of PARP with plant derived using Discovery studio visualizer. Interaction of PARP with Lyngbyabellin with (a) cartoon (b) ligand residue and (c) Surface. The structure of inhibitors and amino acid residues of PARP are represented in Orange and pink sticks, respectively with higher Atomic contact energy of -253.88 kcal/mol.

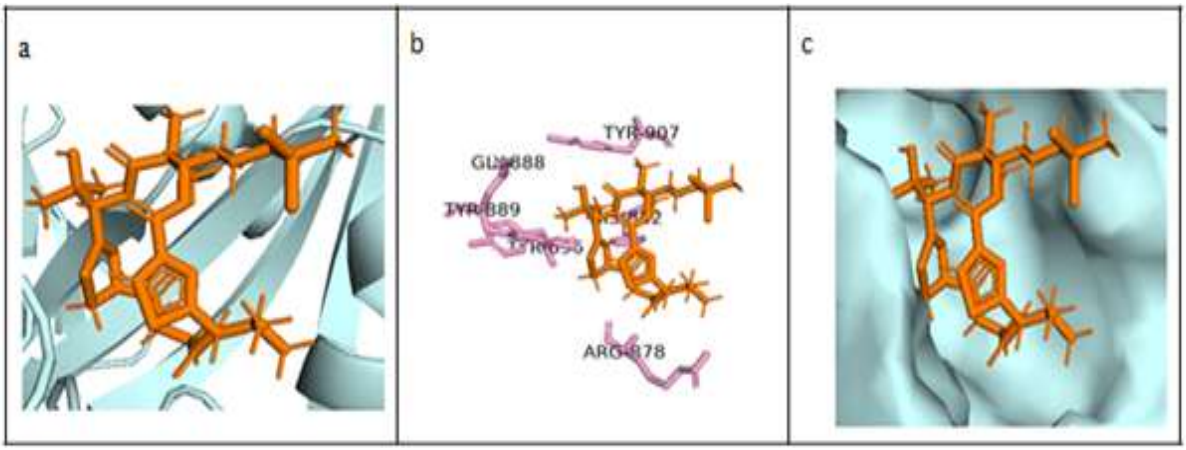


Table 2 - Interaction of Lynbyabelin with HIS862, TYR896, TYR907, TYR889, ARG878, ALA880 as active binding residues that showed highest in TYR889 with a bond length of 3.72 pm that bonds with hydrophobic interaction

Index	Residue	AA	Bond length	Nature of interaction
1	889A	TYR	3.72	Hydrophobic
2	896A	TYR	3.03	Hydrophobic
3	907A	TYR	3.54	Hydrophobic
4	864A	SER	3.57	Hydrophobic
5	878A	ARG	2.53	Hydrogen
6	878A	ARG	2.47	Hydrogen
7	889A	TYR	3.09	Hydrogen

From Table 3 & Fig. 3, results in Interaction of Sansalvamide with LYS903, HIS862, TYR907, TYR896, ARG878, TYR889 as active binding residues with cartoon, ligand residue and Surface representation that showed highest in GLU988 with a bond length of 4.13pm that bonds with Hydrogen interaction and with higher atomic contact energy of -314.48 kcal/mol.

Fig. 3 - Interaction analysis of PARP with plant derived using Discovery studio visualizer. Interaction of PARP with Sansalvamide with (a) cartoon (b) ligand residue and (c) Surface. The structure of inhibitors and amino acid residues of PARP are represented in Orange and pink sticks, respectively with higher atomic contact energy of -314.48 kcal/mol.

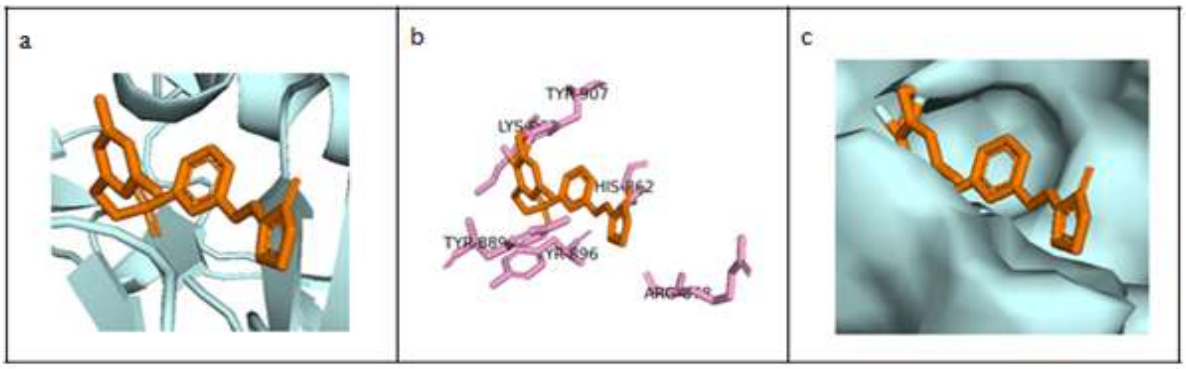


Table 3 - Interaction of Sansalvamide with LYS903, HIS862, TYR907, TYR896, ARG878, TYR889 as active binding residues that showed highest in GLU988 with a bond length of 4.13pm that bonds with Hydrogen interaction.

Index	Residue	AA	Bond length	Nature Of interaction
1	889A	TYR	3.80	Hydrophobic
2	907A	TYR	3.41	Hydrophobic
3	864A	SER	3.63	Hydrophobic
4	878A	ARG	2.75	Hydrogen
5	897A	PHE	3.43	Hydrogen
6	988A	GLU	4.13	Hydrogen

From Table 4 & Fig. 4, results in Interaction of Dolastatin with SER864, PRO881, ILE879, ILE872, ASN868, TYR907, TYR896, TYR907, TYR889, HIS862, ARD878 as active binding residues with cartoon, ligand residue and Surface representation that showed highest in LYS903 with a bond length of 3.97pm that bonds with hydrophobic interaction and with higher atomic contact energy of -320.77 kcal/mol.

Fig. 4 - Interaction analysis of PARP with plant derived using Discovery studio visualizer. Interaction of PARP with Dolastatin with (a) cartoon (b) ligand residue and (c) Surface. The structure of inhibitors and amino acid residues of PARP are represented in Orange and pink sticks, respectively with higher Atomic contact energy of -320.77 kcal/mol

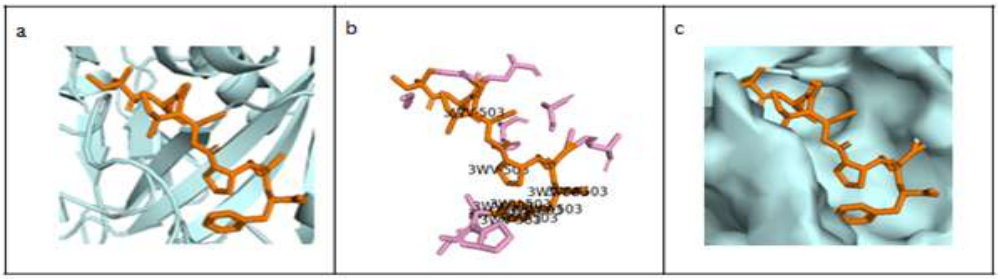


Table 4 - Interaction of Dolastatin with SER864, PRO881, ILE879, ILE872, ASN868, TYR907, TYR896, TYR907, TYR889, HIS862, ARD878 as active binding residues that showed highest in LYS903 with a bond length of 3.97pm that bonds with hydrophobic interaction

Index	Residue	AA	Bond length	Nature of interaction
1	872A	ILE	2.28	Hydrophobic
2	877A	LEU	3.58	Hydrophobic
3	878A	ARG	3.42	Hydrophobic
4	880A	ALA	2.86	Hydrophobic
5	889A	TYR	2.26	Hydrophobic
6	896A	TYR	3.90	Hydrophobic
7	903A	LYS	3.97	Hydrophobic
8	907A	TYR	3.80	Hydrophobic
9	907A	TYR	1.23	Hydrophobic
10	907A	TYR	2.97	Hydrophobic
11	864A	SER	2.08	Hydrogen
12	868A	ASN	3.58	Hydrogen
13	907A	TYR	2.02	Hydrogen

From Table 5 & Fig. 5, results in Interaction of Beta carotene with TYR907, TYR896, HIS862, ILE872, LYS903, TYR986, LEU985, HIS826, ARG878 as active binding residues with cartoon, ligand residue and Surface representation that show highest in ARG878 with a bond length of 3.97 pm that bonds with hydrophobic interaction and with higher atomic contact energy of -323.06 kcal/mol.

Fig. 5 - Interaction analysis of PARP with plant derived using Discovery studio visualizer. Interaction of PARP with Beta carotene with (a) cartoon (b) ligand residue and (c) Surface. The structure of inhibitors and amino acid residues of PARP are represented in Orange and pink sticks, respectively with higher Atomic contact energy of -323.06 kcal/mol.

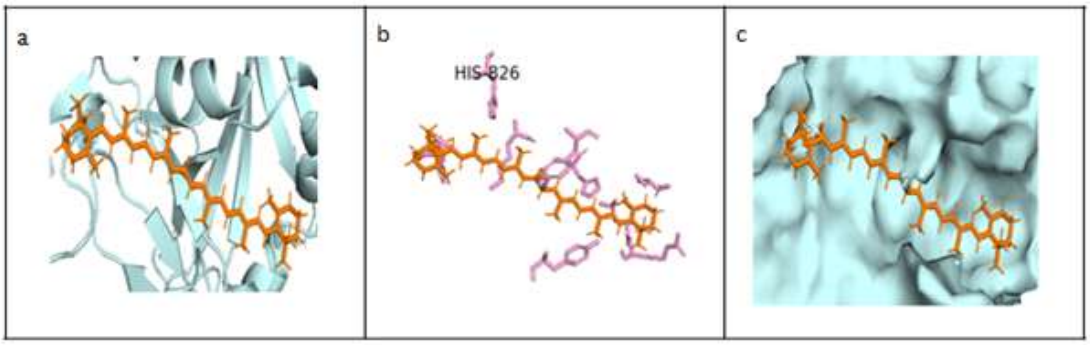


Table 5 - Interaction of Beta carotene with TYR907, TYR896, HIS862, ILE872, LYS903, TYR986, LEU985, HIS826, ARG878 as active binding residues that show highest in ARG878 with a bond length of 3.97 pm that bonds with hydrophobic interaction

Index	Residue	AA	Bond length	Nature of interaction
1	825A	THR	3.50	Hydrophobic
2	872A	ILE	3.04	Hydrophobic
3	872A	ILE	3.26	Hydrophobic
4	877A	LEU	3.19	Hydrophobic
5	878A	ARG	3.97	Hydrophobic
6	896A	TYR	3.53	Hydrophobic
7	903A	LYS	3.54	Hydrophobic
8	903A	LYS	3.81	Hydrophobic
9	907A	TYR	3.84	Hydrophobic
10	907A	TYR	1.53	Hydrophobic
11	907A	TYR	1.82	Hydrophobic
12	985A	LEU	1.20	Hydrophobic
13	985A	LEU	0.81	Hydrophobic
14	985A	LEU	1.81	Hydrophobic
15	985A	LEU	0.76	Hydrophobic
16	986A	TYR	3.74	Hydrophobic
17	986A	TYR	3.87	Hydrophobic

From Table 6 & Fig. 6, results in Interaction of Butulinic with LYS903, TYR907, ILE872, ALA880, TYR889, HIS862, TYR896 as active binding residues with cartoon, ligand residue and Surface representation that show highest in TRY907 with a bond length of 3.58 pm that bonds with hydrophobic interaction and with higher atomic contact energy of -289.50 kcal/mol.

Fig. 6 - Interaction analysis of PARP with plant derived using Discovery studio visualizer. Interaction of PARP with Butulinic with (a) cartoon (b) ligand residue and (c) Surface. The structure of inhibitors and amino acid residues of PARP are represented in Orange and pink sticks, respectively with higher Atomic contact energy of -289.50 kcal/mol.

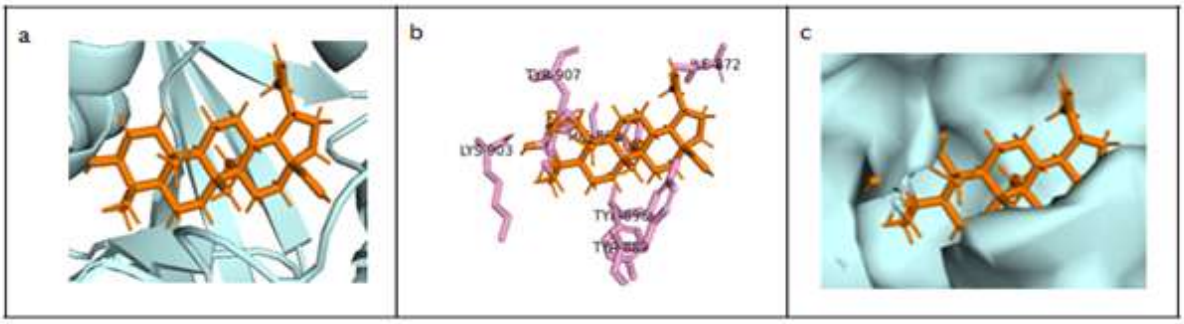


Table 6 - Interaction of Butulinic with LYS903, TYR907, ILE872, ALA880, TYR889, HIS862, TYR896 as active binding residues that show highest in TRY907 with a bond length of 3.58 pm that bonds with hydrophobic interaction.

Index	Residue	AA	Bond length	Nature of interaction
1	862A	HIS	1.58	Hydrophobic
2	872A	ILE	3.06	Hydrophobic
3	889A	TYR	2.56	Hydrophobic
4	896A	TYR	2.56	Hydrophobic
5	907A	TYR	1.13	Hydrophobic
6	907A	TYR	3.58	Hydrophobic
7	907A	TYR	2.23	Hydrophobic
8	907A	TYR	1.82	Hydrophobic
9	880A	ALA	2.17	Hydrogen
10	889A	TYR	3.49	Hydrogen
11	903A	LYS	2.41	Hydrogen

4. Discussion

The research was developed to identify the optimal lead and drug compounds with stronger affinity to PARP with a ligand- protein complex inhibitory results. The PARP enzyme was docked to 50 synthesis molecules. (Badria 2017). Among them, 5 synthesis compounds (lyngabyabellin, salvanide, dolastatin, beta-carotene, and butulinic) that bind to Have high affinity between the 50 complex molecules. Results show that 5 hits are the safety drug candidates that were selected for further analysis. Since in water they have a good degree of solubility and a good level of adsorption

(Hashemzadeh and Raissi 2021). Despite their other possible toxicities, the remaining 45 molecules have the possibility of fibers in the drug production.

As PARP protein was docked with 50 plant derived synthetic compounds using Patch Dock software. Prevailing studies have reported Rucaparib as a potential PARP inhibitor in ovarian tumor cells (Skalniak et al. 2017). Interestingly, our docking results revealed that lyngbyabellin, sansalvamide, dolastatin, Beta-Carotene & Butulinic compounds from plants that demonstrated higher binding affinity in comparison with Rucaparib (Strosznajder 2016). It was found that Rucaparib binds with PARP with the binding affinity of -178.kcal/mol, whereas the anticancer inhibitor, namely lyngbyabellin, sansalvamide, dolastatin, Beta-Carotene & Butulinic, binds with a higher affinity of -253.88, -314.48, -320.77, -323.06 and -289.50 Kcal/mol, respectively. (Shen and Zhao 2018).

Similar findings state that PARP and its inhibitors exhibit improved efficacy and solubility with small molecules when compared to other protein enzymes (Lord and Ashworth 2008). Opposite findings results that iniparib is not an actual polymerase inhibitor (PARP) of ADP-ribose, so the clinical outcome should not be extrapolated in development of any cancer drugs therapies (Mateo et al. 2013). Prior to the initiation of clinical studies or clinical trials of iniparib, the mechanism of activation of this agent was not sufficiency elucidated when compared to PARP enzyme. So. PARP was taken and docked with synthetic compounds.

Our institution is passionate about high quality evidence based research and has excelled in various fields ((Vijayashree Priyadharsini 2019; Ezhilarasan, Apoorva, and Ashok Vardhan 2019; Ramesh et al. 2018; Mathew et al. 2020; Sridharan et al. 2019; Pc, Marimuthu, and Devadoss 2018; Ramadurai et al. 2019). We hope this study adds to this rich legacy.

The limitations state that the above listed top complexes will have to undergo clinical trials to determine its efficiency towards PARP enzyme for the treatment of targeted ovarian cancer (Salentin et al. 2017; Kumar et al. 2021). Since *in-silico* screening is the initial step considered for finding the drug inhibitor in the research. (Nussbaum 2014; Strosznajder 2016). This lengthy pipeline of development has to cope with increased costs and other limitations such as lack of validity for existing animal models, insufficient awareness of underlying disease mechanisms, heterogeneity of patients, lack of targets and biomarkers, a high rate of failing clinical trials and regulatory difficulties. (Forum on Neuroscience and Nervous System Disorders, Board on Health Sciences Policy, and Institute of Medicine 2013). The future study is to consider these compounds lyngbyabellin, sansalvamide, dolastatin, Beta-Carotene, and Butulinic that can yield to model and produce better anticancer drugs after consideration for in-vivo and in-vitro analysis.

5. Conclusion

The Novel small molecule inhibitors are derived from plant synthetic compounds using *in-silico* analysis. Among the five hit compounds, the beta-carotene is having the highest atomic contact energy which is suitable to treat targeted ovarian cancers.

Declarations

Conflict of Interests

No conflict of interest in this manuscript.

Authors Contributions

Author VSSR was involved in data collection, data analysis and manuscript writing. Author MM was involved in Conceptualization. Author GP was involved in data validation and critical review of the manuscript.

Acknowledgements

The authors would like to express their gratitude towards Saveetha School of engineering, Saveetha Institute of Medical and Technical Sciences (Formerly known as Saveetha University) for providing the necessary infrastructure to carry out this work successfully.

Funding

We thank the following organization for providing financial support that enabled us to complete the study.

1. Kaa Shiv infotech, Chennai, India.
2. Saveetha university
3. Saveetha Institute of Medical and Technical Sciences
4. Saveetha School of engineering

References

Annunziata, Christina, and Kristin Zorn. 2016. *Inhibiting PARP as a Strategic Target in Cancer*. Frontiers Media SA.

Badria, Farid A. 2017. *Natural Products and Cancer Drug Discovery*. BoD – Books on Demand.

Bazzaro, Martina. 2018. "Abstract A41: Ovarian Cancer as an Infectious Disease. Targeting of Mitochondrial Activity to Prevent and Treat Recurrent Ovarian Cancer." *Metabolic Changes in Ovarian Cancer*. https://doi.org/10.1158/1557-3265.ovca17-a41.

Ezhilarasan, Devaraj, Velluru S. Apoorva, and Nandhigam Ashok Vardhan. 2019. "Syzygium Cumini Extract Induced Reactive Oxygen Species-Mediated Apoptosis in Human Oral Squamous Carcinoma Cells." *Journal of Oral Pathology & Medicine: Official Publication of the International Association of Oral Pathologists and the American Academy of Oral Pathology 48*(2): 115–21.

Forum on Neuroscience and Nervous System Disorders, Board on Health Sciences Policy, and Institute of Medicine. 2013. *Improving and Accelerating Therapeutic Development for Nervous System Disorders: Workshop Summary*. Washington (DC): National Academies Press (US).

Gheena, S., and D. Ezhilarasan. 2019. "Syringic Acid Triggers Reactive Oxygen Species-Mediated Cytotoxicity in HepG2 Cells." *Human & Experimental Toxicology* 38(6): 694–702.

Gien, Lilian T., and Helen J. Mackay. 2010. "The Emerging Role of PARP Inhibitors in the Treatment of Epithelial Ovarian Cancer." *Journal of Oncology* 2010: 151750.

Hashemzadeh, Hassan, and Heidar Raissi. 2021. "Design of New Drug Delivery Platform Based on Surface Functionalization of Black Phosphorus Nanosheet with a Smart Polymer for Enhancing the Efficiency of Doxorubicin in the Treatment of Cancer." *Journal of Biomedical Materials Research. Part A*, April. https://doi.org/10.1002/jbm.a.37183.

Jose, Jerry, Ajitha, and Haripriya Subbaiyan. 2020. "Different Treatment Modalities Followed by Dental Practitioners for Ellis Class 2 Fracture – A Questionnaire-Based Survey." *The Open Dentistry Journal* 14(1): 59–65.

Jung, Inkyung, Hee Jung Ko, Sun Young Rha, and Chung Mo Nam. 2018. "Reconsideration of Sample Size and Power Calculation for Overall Survival in Cancer Clinical Trials." *Contemporary Clinical Trials Communications*. https://doi.org/10.1016/j.conctc.2018.09.007.

Ke, Yang, Mohammed Saleh Al Aboody, Wael Alturaiki, Suliman A. Alsagaby, Faiz Abdulaziz Alfaiz, Vishnu Priya Veeraraghavan, and Suresh Mickymaray. 2019. "Photosynthesized Gold Nanoparticles from Catharanthus Roseus Induces Caspase-Mediated Apoptosis in Cervical Cancer Cells (HeLa)." *Artificial Cells, Nanomedicine, and Biotechnology* 47(1): 1938–46.

Krishnaswamy, Haribabu, Sivaprakash Muthukrishnan, Sathish Thanikodi, Godwin Arockiaraj Antony, and Vijayan Venkatraman. 2020. "Investigation of Air Conditioning Temperature Variation by Modifying the Structure of Passenger Car Using Computational Fluid Dynamics." *Thermal Science* 24 (1 Part B): 495–98.

Kumar, Saraswathisreeram Pranush, Deeki Doma Sherpa, Amit Kumar Sahu, Tarang Jadav, Rakesh Kumar Tekade, and Pinaki Sengupta. 2021. "Innovation in Bioanalytical Strategies and Drug-Drug Interaction Study Approaches in Drug Discovery." *Bioanalysis*, https://doi.org/10.4155/bio-2021-0001.

Lord, Christopher J., and Alan Ashworth. 2008. "Targeted Therapy for Cancer Using PARP Inhibitors." *Current Opinion in Pharmacology*. https://doi.org/10.1016/j.coph.2008.06.016.

Malli Sureshbabu, Nivedhitha, Kathiravan Selvarasu, Jayanth Kumar V, Mahalakshmi Nandakumar, and Deepak Selvam. 2019. "Concentrated Growth Factors as an Ingenious Biomaterial in Regeneration of Bony Defects after Periapical Surgery: A Report of Two Cases." *Case Reports in Dentistry* 2019 (January): 7046203.

Mateo, Joaquin, Michael Ong, David S. P. Tan, Michael A. Gonzalez, and Johann S. de Bono. 2013. "Appraising Iniparib, the PARP Inhibitor That Never Was—what Must We Learn?" *Nature Reviews Clinical Oncology*. https://doi.org/10.1038/nrclinonc.2013.177.

Mathew, M. G., S. R. Samuel, A. J. Soni, and K. B. Roopa. 2020. "Evaluation of Adhesion of Streptococcus Mutans, Plaque Accumulation on Zirconia and Stainless Steel Crowns, and Surrounding Gingival Inflammation in Primary …." *Clinical Oral Investigations*. https://link.springer.com/article/10.1007/s00784-020-03204-9.

Mehta, Meenu, Deeksha, Devesh Tewari, Gaurav Gupta, Rajendra Awasthi, Harjeet Singh, Parijat Pandey, et al. 2019. "Oligonucleotide Therapy: An Emerging Focus Area for Drug Delivery in Chronic Inflammatory Respiratory Diseases." *Chemico-Biological Interactions* 308 (August): 206–15.

Morales, Julio, Longshan Li, Farjana J. Fattah, Ying Dong, Erik A. Bey, Malina Patel, Jinming Gao, and David A. Boothman. 2014. "Review of Poly (ADP-Ribose) Polymerase (PARP) Mechanisms of Action and Rationale for Targeting in Cancer and Other Diseases." *Critical Reviews in Eukaryotic Gene Expression*. https://doi.org/10.1615/critreveukaryotgeneexpr.2013006875.

Muthukrishnan, Sivaprakash, Haribabu Krishnaswamy, Sathish Thanikodi, Dinesh Sundaresan, and Vijayan Venkatraman. 2020. "Support Vector Machine for Modelling and Simulation of Heat Exchangers." *Thermal Science* 24 (1 Part B): 499–503.

Nussbaum, Robert L. 2014. "Functional Analysis of Variants of Unknown Significance in BRCA1 and BRCA2 Using Complementation of a Synthetic Lethal Interaction with PARP Inhibition." https://doi.org/10.21236/ada619698.

Oche, George, and Omotuyi Olaposi. 2018. "Lupeol from Lycopersicon Esculentum as a Potential Antagonist of the Poly(ADP-Ribose) Polymerase-1 (PARP-1) for Cancer Chemotherapy: An in Silico Study." Unpublished. https://doi.org/10.13140/RG.2.2.32562.86725.

Pc, J., T. Marimuthu, and P. Devadoss. 2018. "Prevalence and Measurement of Anterior Loop of the Mandibular Canal Using CBCT: A Cross Sectional Study." *Clinical Implant Dentistry and Related Research*. https://europepmc.org/article/med/29624863.

Ramadurai, Neeraja, Deepa Gurunathan, A. Victor Samuel, Emg Subramanian, and Steven J. L. Rodrigues. 2019. "Effectiveness of 2% Articaine as an Anesthetic Agent in Children: Randomized Controlled Trial." *Clinical Oral Investigations 23*(9): 3543–50.

Ramesh, Asha, Sheeja Varghese, Nadathur D. Jayakumar, and Sankari Malaiappan. 2018. "Comparative Estimation of Sulfiredoxin Levels between Chronic Periodontitis and Healthy Patients - A Case-Control Study." *Journal of Periodontology* 89 (10): 1241–48.

Salentin, Sebastian, Melissa F. Adasme, Jörg C. Heinrich, V. Joachim Haupt, Simone Daminelli, Yixin Zhang, and Michael Schroeder. 2017. "From Malaria to Cancer: Computational Drug Repositioning of Amodiaquine Using PLIP Interaction Patterns." *Scientific Reports* 7 (1): 11401.

Samuel, Melvin S., Jayanta Bhattacharya, Sankalp Raj, Needhidasan Santhanam, Hemant Singh, and N. D. Pradeep Singh. 2019. "Efficient Removal of Chromium (VI) from Aqueous Solution Using Chitosan Grafted Graphene Oxide (CS-GO) Nanocomposite." *International Journal of Biological Macromolecules* 121 (January): 285–92.

Samuel, Srinivasan Raj, Shashidhar Acharya, and Jeevika Chandrasekar Rao. 2020. "School Interventions-Based Prevention of Early-Childhood Caries among 3-5-Year-Old Children from Very Low Socioeconomic Status: Two-Year Randomized Trial." *Journal of Public Health Dentistry* 80 (1): 51–60.

Sathish, T., and S. Karthick. 2020. "Wear Behaviour Analysis on Aluminium Alloy 7050 with Reinforced SiC through Taguchi Approach." *Journal of Japan Research Institute for Advanced Copper-Base Materials and Technologies* 9 (3): 3481–87.

Sharma, Parvarish, Meenu Mehta, Daljeet Singh Dhanjal, Simran Kaur, Gaurav Gupta, Harjeet Singh, Lakshmi Thangavelu, et al. 2019. "Emerging Trends in the Novel Drug Delivery Approaches for the Treatment of Lung Cancer." *Chemico-Biological Interactions* 309 (August): 108720.

Shen, Xian, and Bin Zhao. 2018. "Efficacy of PD-1 or PD-L1 Inhibitors and PD-L1 Expression Status in Cancer: Meta-Analysis." *BMJ*. https://doi.org/10.1136/bmj.k3529.

Skalniak, Lukasz, Krzysztof M. Zak, Katarzyna Guzik, Katarzyna Magiera, Bogdan Musielak, Magdalena Pachota, Bozena Szelazek, et al. 2017. "Small-Molecule Inhibitors of PD-1/PD-L1 Immune Checkpoint Alleviate the PD-L1-Induced Exhaustion of T-Cells." *Oncotarget* 8 (42): 72167–81.

Sridharan, Gokul, Pratibha Ramani, Sangeeta Patankar, and Rajagopalan Vijayaraghavan. 2019. "Evaluation of Salivary Metabolomics in Oral Leukoplakia and Oral Squamous Cell Carcinoma." *Journal of Oral Pathology & Medicine: Official Publication of the International Association of Oral Pathologists and the American Academy of Oral Pathology* 48 (4): 299–306.

Staples, Jeanine, and Annekathryn Goodm. 2013. "PARP Inhibitors in Ovarian Cancer." In *Ovarian Cancer - A Clinical and Translational Update*. InTech.

Strosznajder, J. B. 2016. "PARP-1 Inhibition Modulates Gene Expression of Mitochondria Sirtuins and APP Secretases: The Role of PARP and Sirts Interaction in Amyloid Beta Toxicity." *Journal of Neurology & Neurophysiology*. https://doi.org/10.4172/2155-9562.c1.039.

Varghese, Sheeja Saji, Asha Ramesh, and Deepak Nallaswamy Veeraiyan. 2019. "Blended Module-Based Teaching in Biostatistics and Research Methodology: A Retrospective Study with Postgraduate Dental Students." *Journal of Dental Education* 83 (4): 445–50.

Venu, Harish, V. Dhana Raju, and Lingesan Subramani. 2019. "Combined Effect of Influence of Nano Additives, Combustion Chamber Geometry and Injection Timing in a DI Diesel Engine Fuelled with Ternary (diesel-Biodiesel-Ethanol) Blends." *Energy* 174 (May): 386–406.

Venu, Harish, Lingesan Subramani, and V. Dhana Raju. 2019. "Emission Reduction in a DI Diesel Engine Using Exhaust Gas Recirculation (EGR) of Palm Biodiesel Blended with TiO2 Nano Additives." *Renewable Energy* 140 (September): 245–63.

Vignesh, R., Ditto Sharmin, C. Vishnu Rekha, Sankar Annamalai, and Parisa Norouzi Baghkomeh. 2019. "Management of Complicated Crown-Root Fracture by Extra-Oral Fragment Reattachment and Intentional Reimplantation with 2 Years Review." *Contemporary Clinical Dentistry* 10 (2): 397–401.

Vijayakumar Jain, S., M. R. Muthusekhar, M. F. Baig, P. Senthilnathan, S. Loganathan, P. U. Abdul Wahab, M. Madhulakshmi, and Yogaen Vohra. 2019. "Evaluation of Three-Dimensional Changes in Pharyngeal Airway Following Isolated Lefort One Osteotomy for the Correction of Vertical Maxillary Excess: A Prospective Study." *Journal of Maxillofacial and Oral Surgery* 18 (1): 139–46.

Vijayashree Priyadharsini, Jayaseelan. 2019. "In Silico Validation of the Non-Antibiotic Drugs Acetaminophen and Ibuprofen as Antibacterial Agents against Red Complex Pathogens." *Journal of Periodontology* 90 (12): 1441–48.