International Journal of Natural Medicine and Health Sciences
ISSN (Online):2790-2471 ISSN (Print): 2790-2463
Volume 3 (4) September; 2024
Journal homepage: https://journals.iub.edu.pk/index.php/ijnms

Original Research

Unlocking the therapeutic power of ayurvedic plants with advanced computational techniques for ovarian cancer treatment targeting FK506-binding protein

Saba Bilal[a], Aamir Rasool[a*], Gohar Shah[a], Asadullah[b], Maqbool Ahmed[c], Kaleem Ullah[d], Robina Manzor[e]

[a] Institute of Biochemistry, University of Balochistan, Quetta 87300, Pakistan
[b] Department of Urology, Sandeman Provisional Hospital, Quetta 87300, Pakistan
[c] Bolan University of Medical and Health Sciences (BUMHS), Quetta 87300, Pakistan
[d] Department of Microbiology, University of Balochistan, Quetta 87300, Pakistan
[e] Department of Biotechnology and Bioinformatics, LUAWMS, Uthal 90150, Pakistan

Correspondence:
rasool.amir@gmail.com

Keywords: Ayurvedic Plants, Computational Techniques, Ovarian Cancer, FK506-Binding Protein

Abstract

The objectives of current study were to investigate FK506-binding protein (FKBP) can be used as a treatment target for ovarian cancer. In this project, we aim to use the medicinal potential of Ayurvedic botanical to develop new medicines for ovarian cancer that target fkbp. The methodology combines a variety of computational methods and molecular modeling techniques to make it easier to identify and analyze bioactive molecules that are highly specific to Fkbp. The molecular operating environment was used to view and enhance the structure of Fkbp (ID: 7BPZ), which was downloaded from pdb for docking Purposes. The structure was cleared of all water molecules and excess ligands. Protonation was used using default parameters to fill up the blank gaps. The present investigation effectively investigated the molecular interaction Potential of specific bioactive compounds derived from South African Ayurvedic plants, against FKBP protein that target ovarian cancer.

Citation: Saba Bilal, Aamir Rasool, Gohar Shah, Asadullah, Maqbool Ahmed, Kaleem Ullah, Robina Manzor. Unlocking the therapeutic power of ayurvedic plants with advanced computational techniques for ovarian cancer treatment targeting FK506-binding protein. IJNMS. 2024 3(4): 21-28.

Introduction: Ovarian cancer (OVC) arises from the rapid growth and division of one of the ovary's three primary cell types: germ cells, stromal cells, or epithelial cells. The ovaries, two almond-shaped glands, produce eggs and the hormones estrogen and progesterone. OVC often lacks early symptoms, is typically diagnosed at an advanced stage, and has poor survival rates. Despite representing only about 4% of all female cancers, it ranks fourth in cancer-related deaths among women, making it the deadliest gynecologic cancer, according to the National Cancer Institute[12]. Bioinformatics has revolutionized ovarian cancer research by enabling rapid data analysis, precise drug targeting, and personalized treatment strategies. Advancements in computing power and data processing have facilitated the development of targeted therapies, such as PARP inhibitors, and have enhanced our understanding of the disease at a molecular level [2].

Genomic Profiling: Projects like The Cancer Genome Atlas (TCGA) have provided comprehensive genomic data, revealing mutations in genes such as TP53, BRCA1, and BRCA2 in high-grade serous ovarian cancer. This information is crucial for identifying potential drug targets and understanding tumor behavior. Targeted Therapy Development: Bioinformatics tools have facilitated the development of PARP inhibitors, which are particularly effective in tumors with BRCA mutations. These inhibitors exploit the DNA repair weaknesses in cancer cells, leading to their death while sparing normal cells. Resistance Mechanism Analysis: Studies utilizing bioinformatics have identified mechanisms of resistance to therapies like PARP inhibitors. For instance, the combination of PARP inhibitors with other agents, such as methyl stat, has been shown to overcome resistance by impairing DNA repair pathways in cancer cells [10].

Several factors independently and significantly influence the prognosis of ovarian cancer, including the tumor stage, patient age, overall health, and the amount of residual tumor remaining after surgery. Among the different histological types, mucinous tumors are associated with a notably poorer prognosis compared to serous papillary and endometrioid cancers, and they tend to respond less effectively to standard platinum-based combination chemotherapy [3]. *Centella asiatica* (commonly known as Gotu Kola) is widely used in traditional Indian medicine to enhance memory and treat skin conditions and nervous system disorders. Its medicinal properties have also been long recognized in regions such as Java and Indonesia. In China, where it is also known as Gotu Kola, the plant was documented over 2,000 years ago as one of the "miracle elixirs of life".

Herbal medicines like *C. asiatica* can function as adaptogens natural substances that help the body resist stress by modulating stress responses, particularly during the alarm phase, and offering some protection against prolonged stress exposure. Belonging to the Umbelliferae family (syn. *Hydrocotyle asiatica*), *C. asiatica* is traditionally used throughout India to treat a wide range of ailments, including body aches, headaches, mental disorders, asthma, leprosy, ulcers, eczema, and for promoting wound healing [8].

Medicinal plants are widely used to treat various infectious diseases in humans. In this study, *Solanum nigrum* was evaluated for its antibacterial activity against pathogens isolated from sputum samples of patients with respiratory tract infections. The aim was to screen and characterize bacterial isolates and assess the efficacy of different *Solanum nigrum* extracts aqueous, ethanol, and diethyl ether against these pathogens. Each extract was tested at four different concentrations. Among the extracts, the ethanolic extract exhibited the highest antibacterial activity. Phytochemical analysis revealed the presence of alkaloids, terpenoids, flavonoids, saponins, steroids, and phenols, all of which are known for their antimicrobial properties. These findings suggest that *Solanum nigrum* possesses significant antimicrobial activity and holds potential for the development of novel antibacterial agents for the treatment of respiratory tract infections [2].

Research Methodology: In this project, we aim to use the medicinal potential of Ayurvedic botanicals to develop new medicines for ovarian cancer that target FKBP. The methodology combines a variety of computational methods and molecular modeling techniques to make it easier to identify and analyze bioactive molecules that are highly specific to FKBP. Our method begins with the selection of three Ayurvedic plants that have historically been utilized in ovarian cancer treatment or that contain bioactive compounds with anticancer characteristics. The technique then entails gathering data on bioactive compounds and using computer-aided drug design (CADD) to virtually test these compounds for FKBP binding affinity.

What is Molecular Modeling?

Molecular modeling includes all theoretical and computational methods used to simulate molecular behavior. It's widely applied in: Computational chemistry, Drug design, Computational biology, Materials science. It covers systems from small molecules to large biological complexes and materials, and is essential for understanding their structure, properties, and dynamics [5].

1. Molecular Modeling:

Molecular modeling refers to the collection of theoretical approaches and computational methods used to simulate or predict the behavior of molecules. These techniques are widely applied in areas such as computational chemistry, drug development, computational biology, and materials science, and are used to study systems ranging from small molecules to complex biological macromolecules and material structures. While simple models can be worked out manually, molecular modeling of any substantial

system requires the use of computers. A defining feature of molecular modeling is the atomistic representation of molecular systems. Typically, a molecular modeling study involves three main stages:
Stage 1: Model Selection: A suitable model is chosen to describe both intra- and intermolecular interactions. The two primary modeling approaches are quantum mechanics and molecular mechanics. These frameworks allow researchers to calculate the energy of molecular arrangements and to examine how energy changes with atomic or molecular movements.
Stage 2: Computational Execution: This phase involves performing calculations such as energy minimization, molecular dynamics simulations, Monte Carlo simulations, or conformational searches.
Stage 3: Analysis: After computation, results are analyzed to derive properties and ensure that the simulation or calculation was carried out correctly [5].
Natural chemical compounds have been extensively studied for their ability to induce programmed necrosis. A traditional approach to screening such compounds involves the use of concentrated plant extracts without isolating specific active constituents, aiming to assess their pharmacological effects. Over the past two decades, modern drug development has primarily focused on the isolation and purification of one or two complex, often isomeric, active compounds. However, the concept of multi-target drugs has evolved significantly—from a novel idea introduced in the early 2000s to a prominent strategy in drug discovery by 2021. In parallel, fragment-based drug discovery has emerged as a promising method for identifying potent natural anticancer agents. Unlike traditional approaches that utilize complex natural mixtures, this method focuses on defined molecular fragments for target-specific drug development. This review highlights recent advancements in natural anticancer compounds, emphasizing computer-assisted and fragment-based structural elucidation techniques, as well as multi-target strategies for drug exploration [4].

Protein FKBP 506: (fkbp51): Findings for prostate cancer aligned with those reported by Periyasamy et al, showing that totally prostate tumor trials exhibited extreme FKBP51 immunize activity, which remained exclusively tumor-specific. Similarly, ovary cancer samples also demonstrated strong FKBP51 staining. Notably, FKBP51 immunize activity in lung cancer samples was localized to the nucleus. Among the 12 tumor samples with low or no FKBP51 immunore activity were all breast tumor examples and pancreatic cancers. Captivatingly, these two pancreatic cancers gone to the fine distinguished history type (G1). Real-time PCR analysis of FKBP51 mRNA planes in deparaffinized materials corroborated the immunohistochemistry results [11].

Roles of FKBP51 and FKBP52 in Steroid Hormone Receptor Localization: In the absence of ligand binding, steroid hormone receptors (SHRs) can predominantly localize either in the cytoplasm or the nucleus. However, regardless of their main location, SHRs are not restricted to a single cellular compartment and continuously shuttle between the cytoplasm and nucleus. Traditionally, this movement was believed to occur via passive diffusion. However, studies have shown that components of the dynein dynactin motor complex co-immuno precipitate with the HSP90–FKBP52 complex, as well as with glucocorticoid receptors (GR) and mineralocorticoid receptors (MR), suggesting that active transport mechanisms powered by motor proteins may be responsible for retrograde receptor trafficking.
Research investigating FKBP52's role in both receptor maturation/hormone binding and receptor subcellular localization has traditionally been approached as separate lines of inquiry. This review brings both perspectives together. Evidence indicates that FKBP52 plays a dual role regulating both hormone binding and receptor localization [11].
Furthermore, FKBP52 enhances receptor hormone binding affinity, suggesting that it associates with the receptor–chaperone complex prior to hormone binding and potentially primes the receptor for ligand engagement. FKBP52-containing complexes are indeed observed even in the absence of hormone. The FK1 domain of FKBP52 appears crucial for this regulatory role, possibly interacting directly with the receptor's ligand-binding domain (LBD) to facilitate hormone binding, as suggested Figure 2 [11].

Sampling:
The sampling process involved selecting a diversity of plants with diverse bioactive compounds to ensure broad representation of the Ayurvedic medicinal flora. The plant compounds were sampled not only established on their verified use in cancer treatment, but also on their chemical diversity, pharmacological potential, and structural compatibility with FKBP. This systematic approach objective to explore new therapeutic applicants and combine traditional knowledge with modern computational technologies to obtain further effective herbal therapeutics for ovarian cancer.

2.4. Drug development and cancer vaccines

2.4.1. Small molecule inhibitors: Currently, virtual screening stands as the primary computational method for identifying these drug targets, offering a cost-effective approach. This technique has aided in the discovery of potential targets within kinase families, such as CAMK4 [13] and MARK4 [14]. In the context of ovarian cancer, an orally active novel small molecule— a gp130 inhibitor—has been identified for therapeutic use. Additionally, several active small molecule compounds have been found to inhibit ovarian cancer cell proliferation, invasion, and tumor angiogenesis. More recently, in silico screening has led to the discovery of a novel small molecule inhibitor capable of overcoming PARP inhibitor resistance in ovarian cancer. Studies have

also shown that the small molecule inhibitor TL4 effectively suppresses ovarian cancer cell proliferation proliferation [13].

Research Analysis Tools:

Docking Validation: To confirm that the docking protocol delivers consistent and precise docking scores, we employed a well-established validation procedure, following the guidelines typically accepted in computational screening workflows. This molecule docked complex was then superimposed to the original PDB complex (PDB ID: 7B9Z) to get the RMSD (root mean square deviation) value. The RMSD is acceptable, less than 2Å and superimposition of the complex established the docking protocol as the both complexes superimpose on each other at same binding site.

Drug likeness Analysis: Drug likeness analysis refers to the procedure to predict the potential of a compound (or its metabolite) to act as a drug. For predictions on drug likeness of our compounds, we used the Lipinski rule, Ghose rule, Veber rule, EGAN rule, MUEGGE rule, and bioavailability score. Compounds with docking score better than standard imatinib were selected for drug likeness prediction through Swiss ADME server (http:///www.swissadme.ch/).

Pharmacokinetic Analysis: We applied ADMET Lab 3.0 (https://admetlab3.scbdd.com/) to pharmacokinetic datasets of lead compounds compliant with Lipinski's rule. This cloud-based platform systematically profiles ADMET parameters. ADMET denotes how candidate molecules behave in vivo, focusing on human intestinal absorption, volume of distribution at steady state (VDss), permeability versus the blood-brain barrier (BBB), transport across the Caco-2 monolayer, inhibition of key cytochrome P450 isoforms, predictive clearance, AMES mutagenicity, carcinogenic risk, and additional toxicokinetic metrics.

Generating Essential Pharmacophore: To investigate the molecular interactions of the most active ligands at the FKBP receptor's active site, a comprehensive pharmacophore model was constructed using the Pharmacophore Query Editor, a component of the MOE software package. This improved model identified a number of important pharmacophoric factors required for binding, including as hydrophobic atoms, aromatic and Pi ring centers, hydrogen bond donors and acceptors, and charged anionic and cationic atoms. All pharmacophoric properties were carefully calibrated to a radius of 1.0 Å, with a tolerance of 1.2 and a minimum inclusion threshold of 50%, in order to ensure accuracy.

3. Results: The structure of FKBP (ID: 7BPZ) was downloaded from PDB and was viewed and was refined using Molecular Operating Environment for docking purposes. All the water molecule and extra ligands was eradicated from structure. The empty spaces were filled by protonation with default parameters.

3.1 Physical and Chemical Properties: ProtParam is a tool provided by ExPASy (Expert Protein Analysis System) that analyzes the phyciochemical properties of a protein sequence. You input either the FASTA format or the raw amino acids sequence, and it calculates various important parameters that helps in protein characterization. We used ExPASy PortParam to predicted the Physical and chemical properties of FKBP.

3.2 Active Site prediction: Molecular Operating Environment was used to predict Active site of the FKBP where our desire molecular will attach and inhibit cell to cell communication. The green labeled compound shown is in active site.

3.3 Ligand Preparation: Through a thorough review of the literature, we looked into the three South African ayurvedic plants that are known to have anti-ovarian cancer properties. Centella asiatica, Drimia robusta, and Solanum nigrum were used to create an internal collection of secondary metabolites. For our investigation, we used the Imatinib (Tyrosine Kinase Inhibitor) as a standard. Using the PubCHEM database, the structures of all ligands and the standard were created in ChemDraw and stored in mdl mol format. Every structure in MOE was transformed into an MDB database for the docking procedure, which was followed by energy minimization.

4. Discussion and Future Aspects: The current study used an in-silico technique to find putative natural inhibitors of FKBP, a protein associated with tumor growth, specifically in ovarian cancer. Our study used pharmacokinetic analysis, pharmacophore modeling, and molecular docking to screen phytochemicals from traditional South African Ayurvedic plants for drug-likeness and binding affinity. Low S-scores and RMSD values in the docking data showed that a number of chemicals derived from plants had substantial interactions with the FKBP active site. Strong binding affinities and stable interactions at the active site were demonstrated by compounds including medioresinol, cadayenol, patuletin, rosmarinic acid, and isochlorogenic acid. These compounds were on par with or better than the common medication imatinib. These results imply that FKBP can be efficiently inhibited by natural phytoconstituents, which may interfere with the proliferation and signaling of cancer cells [14].

Crucially, the pharmacokinetic analysis confirmed that many of the lead compounds were drug-like. The majority of the nominated compounds were able to obtain effective systemic exposure with low toxicity, according to parameters including human intestinal absorption, volume of distribution, CaCo2 permeability, and clearance. Because of their good ADMET profiles and lack of CYP450 enzyme inhibition or projected carcinogenicity,

Neochlorogenic Acid, Cryptochlorogenic Acid, and Caffeoylquinic Acid stood out as viable options with little chance of drug-drug interactions [5].

By identifying recurring molecular characteristics essential for receptor-ligand interaction, the pharmacophore modeling significantly increased the validity of these results. These included hydrophobic areas, aromatic ring contacts, and hydrogen bond acceptors and donors—all of which are known to be crucial for maintaining ligand binding within the FKBP active site. Accurate binding predictions and structural similarity among active drugs are indicated by the low RMSD values derived from pharmacophore alignment.

Our findings are consistent with earlier research describing the anticancer properties of substances like apigenin, quercetin, and kaempferol, which are known to have antiproliferative effects via a variety of molecular mechanisms, such as oxidative stress regulation and tyrosine kinase inhibition. Our study adds to the mounting evidence that plant-based secondary metabolites can be useful sources for the development of anticancer drugs by discovering several candidates with positive pharmacodynamics and compliance with medicinal chemistry criteria [6].

Nevertheless, it is important to recognize some limitations in spite of the promising in silico results. Although very useful, computational predictions are unable to adequately represent the intricacy of biological systems. To verify the biological activity, bioavailability, and safety characteristics of the chosen drugs, in vitro tests, animal models, and ultimately clinical studies are necessary. In-depth research is also required to examine possible off-target effects and interactions with other signaling pathways [13].

Conclusions: The present investigation effectively investigated the molecular interaction potential of specific bioactive compounds derived from South African Ayurvedic plants, including Drimia robusta, Solanum nigrum, and Centella asiatica, against the FKBP protein receptor (PDB ID: 7BPZ), a target linked to ovarian cancer. We screened for potent natural inhibitors that might block FKBP-mediated oncogenic signaling using an integrated molecular docking, pharmacokinetic profiling, and pharmacophore modeling strategy using Molecular Operating Environment (MOE) software. S-scores and RMSD values were used to assess the binding affinities of phytochemicals and the standard drug imatinib after they were docked. The potential of several compounds as lead compounds was highlighted by their binding affinities, which were either comparable to or better than those of the conventional medication. These compounds included Cadiyenol, Rosmarinic Acid, Patuletin, Isochlorogenic Acid, and Medioresinol. Future work should include in-vitro and in-vivo validation to confirm binding affinity and biological efficacy. The drug-likeness of the chosen phytochemicals was further confirmed by pharmacokinetic study using the ADMET and SwissADME platforms. Numerous compounds satisfied the standards established by Pfizer, GSK, Lipinski's Rule of Five, and other filters related to medicinal chemistry. Notably, substances like caffeineylquinic acid, neochlorogenic acid, and cryptochlorogenic acid showed good toxicity, absorption, and distribution profiles in addition to low CYP450 enzyme inhibition, which is essential for preventing drug-drug interactions

Acknowledgment: I wish to sincerely thank honorable supervisor of mine who has guided me through my research with wisdom and his constant good advice. I would like to thank my co -supervisor very much who has such bright ideas and motivates me. Special word of gratitude to my friend Hira Bs (Biochemistry), on his wonderful support and motivating and encouraging comradeship.

References:

1. Beg A, Parveen R. Review of bioinformatics tools and techniques to accelerate ovarian Cancer research. Int J Bioinf Intell Comput. 2022;1(1):01-10.
2. Basha SJ, Mallapu K. A review on Solanum nigrum. Published January 2017. 2018.
3. Burges A, Schmalfeldt B. Ovarialkarzinom: Dagnostik und therapie. Dtsch Arztebl. 2011;108(38):635–641.
4. Chavda VP, Ertas YN, Walhekar V, et al. Advanced computational methodologies used in the discovery of new natural anticancer compounds. Front Pharmacol. 2021;12(August):115.
5. Eweas AF, Maghrabi IA, Namarneh AI. Advances in molecular modeling and docking as a tool for modern drug discovery. Der Pharma Chemica. 2014;6(6):211–228.
6. Iwaloye O, Ottu PO, Olawale F, et al. Computer-aided drug design in anti-cancer drug discovery: What have we learnt and what is the way forward? Informatics Med Unlocked. 2023;41(June):101332.
7. Palanisamy CP, Cui B, Zhang H, et al. Anti-ovarian cancer potential of phytocompound and extract from South African medicinal plants and their role in the development of chemotherapeutic agents. Am J Cancer Res. 2021;11(5):1828–1844.
8. Prakash V, Jaiswal N, Srivastava M. A review on medicinal properties of Centella asiatica. Asian J Pharm Clin Res. 2017;10(10):69–74.
9. Saraswathi J, Venkatesh K, Baburao N, Hilal MH, Rani AR. Phytopharmacological importance of Pelargonium species. Published July 2011.
10. Sharma A, Gupta S, Sarethy I, Gabrani R. AMR. Published March 2011.
11. Storer CL, Dickey CA, Galigniana MD, Rein T, Cox MB. FKBP51 and FKBP52 in signaling and disease. Trends Endocrinol Metab. 2011;22(12):481–490.
12. Williams TI, Toups KL, Saggese DA, et al. Epithelial ovarian cancer: Disease etiology, treatment, detection, and investigational gene, metabolite, and protein biomarkers. J Proteome Res. 2007;6(8):2936–2962.
13. Article R. Review of bioinformatics tools and techniques to accelerate ovarian cancer research. 2022;1(1):1–10. [Note: This appears to be a duplicate/misformatted entry of reference 1].
14. Kolos JM, Voll AM, Bauder M, Hausch F. FKBP ligands—Where we are and where to go? Front Pharmacol. 2018;9(December).10.

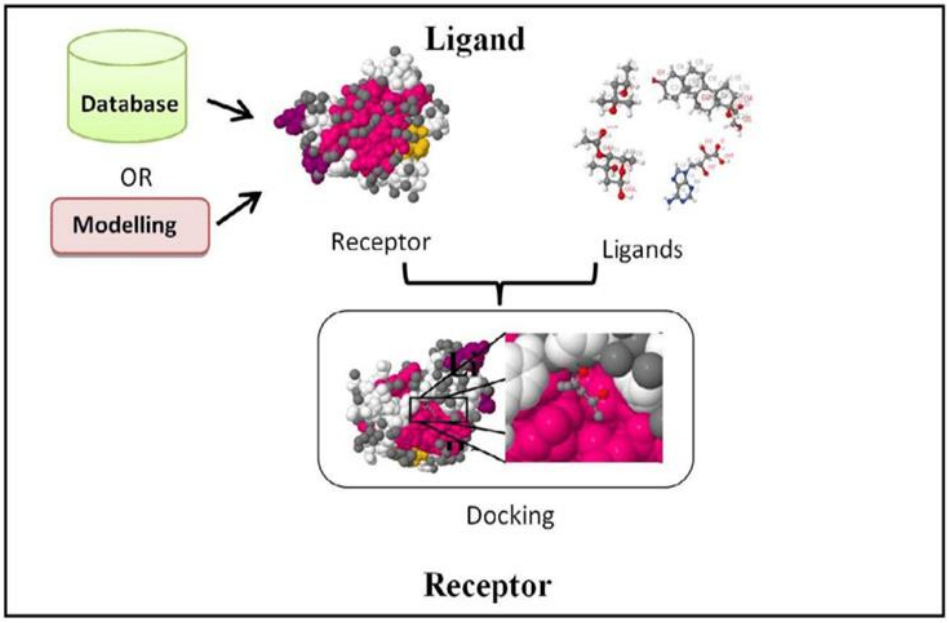


Fig I. Molecular docking flow chart1

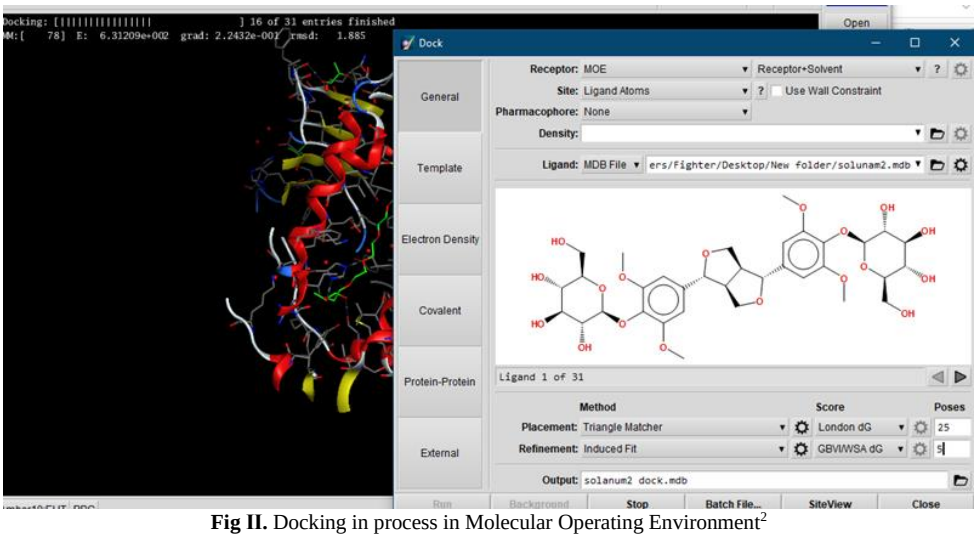


Fig II. Docking in process in Molecular Operating Environment[2]

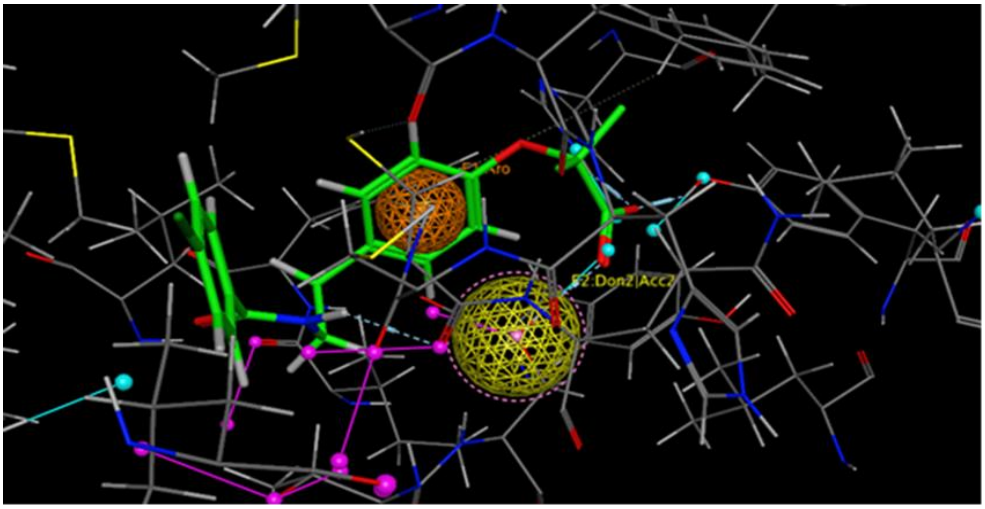
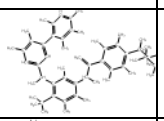
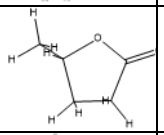
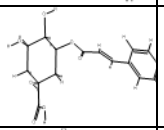
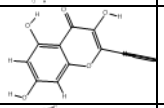
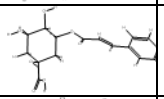
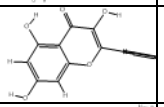
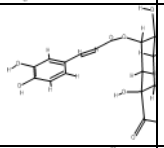
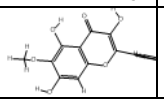


Fig III. Shows the pharmacophore Query in Molecular Operating Environment[3]

Table 1. Shows the RMSD of every Docking done[1]

rmsd_refine	E_conf	E_place	E_score1	E_refine	E_score2
1.3972	18.2994	-62.7454	-9.2625	-20.9668	-6.1388
2.2392	6.8738	-53.5971	-8.4859	-28.8499	-5.9892
1.8080	8.2445	-50.6678	-8.7523	-29.9490	-5.9866
0.6555	9.5675	-51.1591	-8.2127	-28.3799	-5.9024
1.5895	8.1626	-65.4711	-8.9826	-27.8239	-5.8701
0.9910	-15.9656	-39.7242	-5.8124	-18.2938	-4.7994
1.2709	-16.4329	-32.2714	-5.8216	-16.6260	-4.6924
0.7642	-16.5044	-32.9364	-5.7301	-17.7255	-4.4286
1.0740	-16.2619	-37.9138	-6.5146	-17.1755	-4.4205
1.5960	-16.4501	-42.2995	-6.0300	-16.3215	-4.4121
1.0959	-10.7667	-71.9551	-12.0305	-29.4373	-6.3044
1.6200	-2.7420	-72.9807	-11.0911	-28.8322	-6.0201
1.3955	-12.4021	-68.3137	-10.9468	-28.2469	-5.9996

Table 2. Shows the drug likeness analysis of Compounds[2]

Sno	Compound Name	Structure	Compound family	Pubchem ID	Plant name	S-Score	RMSD
1	Imatinib		Tyrosine Kinase Inhibitor	5291	Standard	-9.7472	1.7013
2	8 lactones (4-pentanolide		lactones	7921	Aspathalus linearis	-4.7994	0.9910
3	Caffeoylquinic Acid		Quinic Acid family (phenolic acids)	1794427	Centella Asiatica	-7.1575	1.0289
4	Kaempferol		flavonols	5280863	Centella Asiatica	-6.5284	1.1299
5	Chlorogenic Acid		polyphenol family	1794427	Centella Asiatica	-7.1575	1.0289
6	Myricetin		flavonoids	5281672	Centella Asiatica	-6.4199	1.6216
7	Neochlorogenic Acid		quinic acids and derivatives	5280633	Centella Asiatica	-6.9482	1.2231
8	Patuletin		flavonoid or phenolic compound	5281678	Centella Asiatica	-7.2781	1.2781

9	Epicatechin		catechins,	72276	Centella Asiatica	-6.5342	1.7669
10	Eugenol Acetate		phenol esters	7136	Centella Asiatica	-6.1388	1.3972