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In-silico Study of Oyster Mushroom (Pleurotus Ostreatus) Targeting PARP Protein (4UND)

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ABSTRACT

Oyster mushroom (Pleurotus ostreatus) is belong to the group of healthy foods, as they contain high levels of proteins, vitamins and different classes of compounds, it is discovered that oyster mushrooms could play a key role in maintaining good health. Oyster mushroom (Pleurotus sp.) Class Basidiomycetes and Family Agaricaceae are widely known as 'dhingri' in India. Pleurotus Ostreatus have several medicinal properties including;, antitumor, immune modulatory, anti-inflammatory, anticancer, antigenotoxic, anti-arthritic, hypo-cholesterolaemic, antihyperglycaemic, antioxidant, antihypertensive, antiplatelet aggregating, antiviral and antimicrobial activities.. In this paper studied that effects of chemical constituents of oyster mushroom (Pleurotus sp.) on DNA damaging protein which analyzed its activity of PARP inhibiting or vice – versa.

For this analysis we choose the molecular docking technique to check the effects of different chemical constituents of oyster mushroom (Pleurotus sp.) on DNA damaging protein and compare their results to PARP inhibitory drugs which taken as standard. We perform the molecular docking in between chemical constituents of oyster mushroom (Pleurotus sp.) and 4UND protein compare to performance of molecular docking in between standard PARP inhibitory drugs and 4UND protein with the help of PyRx and BIOVIA Discovery studio software.

The analysis of molecular docking shows that some chemical constituents of oyster mushroom (Pleurotus sp.) having more binding affinity than standard PARP inhibitory drugs. The Rutin shows better binding affinity than PARP inhibitory drugs on the same protein.

KEY WORDS: *Oyster mushroom (Pleurotus sp.), PARP Protein, 4UND Protein, Molecular Docking, PyRx, BIOVIA Drug Discovery*

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INTRODUCTION

Oyster mushroom (Pleurotus sp.) Class Basidiomycetes and Family Agaricaceae are widely known as 'dhingri' in India and grow naturally in low-lying and tropical forests in dead and decaying woody trees or sometimes in dead wood or frozen wood logs (1). Oyster mushrooms, scientifically called Pleurotus sp. are saprophytic organisms that receive nutrients by combining inanimate organisms (2). Oyster mushrooms thrive in the western part of Kenya and are also easily grown artificially. They belong to the class Basidiomycetes, the family Polyporaceae and the genus Pleurotus (3). Pleurotus ostreatus, A less common name is Pleurotus ostreatus (Jacq.ex.fr) P.kumm. The genus Pleurotus has about 40 species and is often called the "oyster mushroom", growing in tropical and subtropical climates (4).

Oyster mushrooms are also known to be a rich source of various classes of compounds including; flavonoids, triterpenoids, Polysaccharides, lentinan, lovastatin, Xanthones, pleuran, steroids, glycopeptides, saponins, alkaloids, ß-glucan, Coumarin, proteoglucan, lectin, purin, fenil, fatty acids and propanoid (5).

Whereas scientific classification of P. ostreatus mushrooms were belongs to,

Taxonomic Description:

Family	Pleurotaceae
Class	Agaricomycetes
Species	P.ostreatus
Genus	Pleurotus

The oyster mushrooms have three fantastic components - a fleshy shell or spatula shaped cap (pileus), a brief or lengthy lateral or important stalk called stipe and prolonged ridges and furrows under the pileus called gills or lamellae. The mycelium of Pleurotus is natural white in color (1).

Active Constituents :

A large number of reports on P. ostreatus chemicals have been published. Ostreatus and related species. In many studies, the nutritional value of mushrooms has been given as dried fruit bodies. While, the fungal cellular wall is rich in starchy polysaccharides, of which β-glucan are the maximum interesting materials and phenolic compounds such as gallic acid, homogentisic acid, protocatechuic acid, rutin, naringin, myrictin, chrysin tocopherol such as α-tocopherol and γ- tocopherol, ascorbic acid and β-carotene each have its own therapeutic effects. In addition, it is a healthy, protein-rich diet, carbohydrates, vitamins lipids and minerals but low in calories and content. (Table 1).

Table 1: Macronutrients of P. ostreatus

Nutrients	Content (g/100g dried mushroom)
Protein	17-42
Moisture	85-87%
Minerals	4-10
Fibers	24-31
Lipids	0.5-5
Carbohydrates	37-48

Table 2: Amino acids composition of P. ostreatus

Amino Acids	Content (g/100g dried mushroom)
Aspartic acid	31.4
Thronine	17.1
Serine	18.1
Glutamic Acid	53.3
Glycine	17.1
Alanine	28.6
Valine	21.0*
Crysteine	3.8
Methionine	3.8
Isoleucine	16.2
Leucine	25.7
Tyrosine	13.3
Phenylalanine	15.2
Lysine	22.9
Histadine	12.4
Arginine	27.6
Tryptophan	4.8
Proline	15.2
Total essential Amino acids	126.7
Total amino acids	347.5

Mushrooms fruit bodies are rich in vitamins, mainly vitamin-B1, vitamin- B2, vitamin-C and vitamin-D2. (4) Ergocalciferol contains mg/100g dried mushroom is 0.3 and mg/100g fresh mushroom is 0.02 (6).

Table 3: Vitamins content of P. ostreatus

Vitamins	Contents (mg/100g dried mushroom)
Thiamin	1.9-2.0
Riboflavin	1.8-5.1
Niacin	30-65
Folate	0.3-0.7
Ascorbic Acid	28-35
Ergocalciferol	0.3

Table 4: Minerals content of P. ostreatus mushroom

Minerals	Contents (mg/100 g dried mushrooms)
Potassium	1400
Calcium	2-36
Sodium	3
Magnesium	9-17
Zinc	3-27
Iron	55-65
Manganese	0.5-3
Copper	0.65
Selenium	0.011

Fig. No. 1- Oyster Mushroom (Pleurotus Ostreatus)

Chemical Components :

The past examination was done to decide the conceivable compound segments from P. ostreatus by GC-MS Technique. This examination uncovered that the unpredictable non-polar mixtures for P. ostreatus extricate with the most elevated standardized sums were 1, 3-dimethylbenzene (32.803%) and phenyl ethyl liquor (21.557%). Different mixtures like 1-octen-3-ol (0.864%), 1,2-Benzenedicarboxylic corrosive (0.783%), n-undecane (0.127%), cedrol (0.106%) and heptadecane (0.146%) were additionally gotten as minor segments from the P. ostreatus unrefined concentrate of hexane (3). Protocatechuic corrosive, Gallic corrosive, Homogentisic corrosive, Rutin, Myricetin, Naringin (7). Flavone (chrysin) and flavonol (rutin) constituents of the mushroom remove were identified by a HPLC technique (8), and furthermore contains alpha tocopherol, beta tocopherol, gamma tocopherol, delta tocopherol (9).

P. ostreatus, prompted its articulated possibilities, for example, of being antidiabetic, antibacterial, anticholestrolic, antiarthritic, cancer prevention agent, anticancer, and its high healthy benefits; P. ostreatus can offer huge help to human against ailing health and diseases (4).

PARP :

Poly (ADP-ribose) polymerase (PARP) is an own group of proteins worried in various cell measures along with DNA fix, genomic steadiness, and customized cell passing (10). Poly (ADP-ribose) polymerase catalyzes the covalent connection of ADP-ribose contraptions from NAD+ to itself and to a bound wide assortment of other DNA restricting proteins, which diminishes their proclivity for DNA. Poly (ADP-ribose) polymerase is an administrative segment achieved through DNA harm (11).Some of cell substrates for PARP were depicted, and a larger part of these proteins are atomic proteins that are stressed in nucleic corrosive digestion, balance of chromatin shape, DNA union and DNA fix (12). Albeit a couple isoforms along with PARP1 and PARP2 are first – rate for their association in DNA fix procedures, its miles now certain that those and distinctive PARPs play an imperative part in a few cell strategies which incorporates cell multiplication and cell demise (13).PARP1 recognizes and ties to sites of single strand DNA harm through the DNA-restricting space. It then, at that point incorporates poly (ADP) ribose (PAR) and moves it to acceptor proteins. Standard volunteers other fix proteins to the wrecked DNA site. Inside the instance of exorbitant of unreasonable DNA harm, likewise with ischemia, PARP1 hyper activation prompts exhaustion of NAD+ and ATP, bringing about cell death via rot or apoptosis. Standard is engaged with twofold strand breaks (DSBs) fix as nicely (14). Standard enlisted people MRE11, and topoisomerase 1, which can be stressed in DSBs repair (14,15).

Research Gap :

Pleorotus ostreatus is notable as anticancer specialist that hinders angiogenesis. Molecular docking was performed to perceive the connection among lovastatin and MMP-2 and MMP-9. Lovastatin had higher liking to bond with either MMP-2 or MMP-9 than local ligand. Generally, EEP could be created as anticancer specialist which was focused on MMP-2 and MMP-9 (16). Beforehand insilico study was performed on Oyster mushroom (P, species) from that lovastatin is taken for that check the anticancer movement of lovastatin on MMP-2 or MMP-9. While doing this research we have identified the research gap that no one else has used 4UND protein before for molecular docking of chemical constituents of Oyster Mushroom (P. species) on PARP inhibitor activity so we have used 4UND protein.

Hypothesis :

Based on above information, we have carried out insilico study of chemical constituents of oyster mushroom (P. ostreatus) with 4UND DNA damaging protein. So we are going to this study in that we check binding affinity of chemical constituents of oyster mushroom and compare with its binding affinity of present PARP inhibitor drugs, if the result acquired are good then we can create a new drug which can show better PARP inhibitor activity than present drugs which are available (.Olaparib, Rucaparib, Niraparib, Talazoparib).

The purpose of this study was to know about the docking affinity of the chemical constituents of oyster mushroom and PARP inhibitors Drugs which are Olaparib, Rucaparib, Niraparib, Talazoparib. The molecular docking was done by using the PyRx software and BIOVIA Drug Discovery. The necessary proteins and ligands were downloaded from protein bank and Pubchem respectively.

Toxicity Of Oyster Mushroom :

Ostreolysin (Oly), an acidic, 15 kDa protein from the palatable shellfish mushroom (Pleurotus ostreatus), is a poisonous, pore-framing cytolysin (17).

Materials and Methods :

Materials :

PyRx is a software written in Python language (18), PyRx is a virtual screening programme that is free and open source. It's a mash-up of various programmes. AutoDock 4.2, AutoDock Vina, Open Babel, Mayavi and others are examples. PyRx is

based on Vina and AutoDock 4.2.software for docking. Along with BIOVIA Drug Discovery (19) Software for molecular Docking.

Ligands and Proteins were used for molecular docking from Pubchem (20) in SDF format, the downloaded ligands were 1, 3-dimethylbenzene 1,2-Benzenedicarboxylic acid, cedrol, Rutin, Gallic acid, Homogentisic acid, Rutin, Myricetin, Protocatechuic acid Naringin, Flavone (chrysin) and flavonol (rutin), alpha tocopherol, beta tocopherol, gamma tocopherol, delta tocopherol, Arachiodonic acid and Linoleic acid and the downloaded Proteins were downloaded from Protein Data Bank (21) in pdt format as same as standard PARP inhibitor drugs.

Molecular Docking :

Molecular docking is a computational strategy used to foresee the cooperation of two particles producing a limiting model. In many medication disclosure applications, docking is done between a little particle and a macromolecule for instance, protein-ligand docking (22). In this paper, compare their binding affinity by molecular docking is done in between the protein (4UND) and ligand (chemical constituents and vitamins contain oyster mushroom) and docking in between standard PARP inhibitor drugs (olaparib, rucaparib, niraparib, tolazaparib) and protein (4UND) by using PyRx (Autodock) software.

Methods :

PyRx is a virtual screening programme that is free and open source. It's a mash-up of various programmes. AutoDock 4.2, AutoDock Vina, Open Babel, Mayavi, and others are examples. PyRx is based on Vina and AutoDock 4.2.software for docking.

1. Download the free version of PyRx (18).
2. Use upper left button which is for load the molecules of proteins and ligands into PyRx workspace.
3. When loading of molecules are successfully done into PyRx workspace then after convert them into Autodock input files (pdqt files) as :
   Right click on ligand (s) > AutoDock > Make ligand
   Right click on protein > AutoDock > Make Macromolecule
4. You will see them under Autodock tab there are coverting pdb files into Autodock input files or pdqt files. (if you don't see any files, right click and refresh under AutoDock tab)
   - Now the protein and ligand (s) files are ready for docking.
   - Click on Start Here button under Vina Wizard.
   - Select Local button under Vina executioin Mode
   - Click start button
5. Select protein and ligand (s) by simply clicking on them. If you selecting for multiple ligands and proteins then press the ctrl tab continue and then select. You will see the selected ligands and macromolecules.
6. Click forward to Run Vina.
7. When you Run Vina then you will see the white gridbox with round handles in the 3D scene. This framework box permits you to choose search space (Part of the protein, where we will perform mooring, normally the limiting site) in the protein.
8. Make sure you select the lattice box size adequately large to permit the ligand to move unreservedly in the hunt space.
9. Use the hunt space (Vina search space) values close the ones mentioned, to get better results.
10. Once the calculations are done, results will be populated as seen in the table with the Binding Affinity (kcal/mol) values. More negative the binding affinity better the orientation of the ligand in the binding site.

Result :

4UND PARP Protein :

Table No. 1 A) Chemical Constituents Of Oyster Mushroom (P. Ostreatus)

Complex (Protein + Ligand)	Molecules	Binding Affinity (kcal/mol)
4und_ (1) _A_5280805_uff_E=751.59	Rutin	-12.4
4und_ (1) _A_442428_uff_E=615.92	Naringin	-11.3

Table No. 2 B) Standard Drugs (PARP Inhibitors)

Complex (Protein + Ligand)	Molecules	Binding Affinity (kcal/mol)
4und_ (1) _A_135565082_uff_E=560.92	Talazoparib	-10.4
4und_ (1) _A_24958200_uff_E=461.77	Niraparib	-9.8
4und_ (1) _A_9931954_uff_E=653.31	Rucaparib	-9.4
4und_ (1) _A_23725625_uff_E=1707.13	Olaparib	-10.9

Table No. 1 shows binding affinity of chemical constituents of oyster mushroom (P. ostreatus) and Table No. 2 shows binding affinity of standard PARP inhibitor drugs with 4UND PARP protein. From both tables it shows that binding affinity of chemical constituents of oyster mushroom shows more as compared to standard PARP inhibitor drugs.

The remaining images and some chemical constituents with their binding affinity of Oyster mushroom (Pleurotus ostreatus) with 4UND protein are added in the Appendix section. (Table No. 3)

Images Of Binding Ligands to Protein (4UND) :

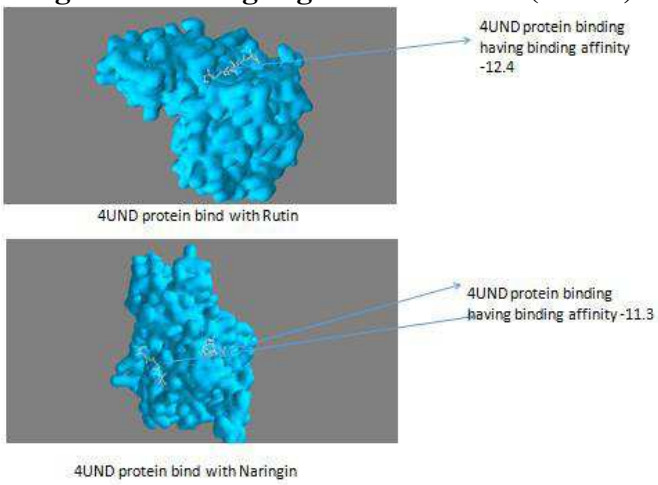

Fig. No. 2 – In above figure, Molecular interaction of 4UND protein with Rutin and Naringin, Having better binding affinity as compared to standard PARP inhibitor drugs. Rutin having binding affinity -12.4 kcal/mol and Naringin having binding affinity -11.3 kcal/mol. The figure shows the protein and the ligand marked by blue arrows. The figure shows that molecular interaction of Rutin, Naringin which are chemical constituents of oyster mushroom as ligand with 4UND protein, in that ball and stick model represent particular ligand and remaining portion is 4UND protein.

Discussion :

By the result of molecular docking of all chemical constituents and PARP inhibitors drugs with the 4UND protein. It is observed that Rutin is found in Oyster mushroom (Pleurotus sp.) and it has better binding affinity among all constituents of (P.species) and also better than standard PARP inhibitors drugs (olaparib rucaparib, niraparib, tolazaparib). Flavonoids have been found to have anti-cancer properties through anti-proliferation, pro-apoptosis, and anti-inflammatory pathways (23,24,25).

Citrus fruits, buckwheat, and onions all contain rutin (rhamno-glycosyl form) (26,27,28).

Rutin is the glycoside of quercetin, a flavonol, and rutinose, a diasaccharide (29).

Rutin in one of the bioactive compunds which might be found in significant quantity in plants (30). Rutin, also called as rutoside and vitamin P (31). Rutin's bioactivity experiment revealed 24 distinct off-targets implicated in several physiological processes linked to radiation response manifestations such as inflammation, DNA repair, cellular development, differentiation, and neural function (32).

Naringenin, discovered in selection of Citrus fruit contains a bitter flavanone called limonene, which is found in both fruits and herbs. The naringeinin-7-O-glycoside is naringin (33). Naringin is a flavanone glycoside formed by combining the flavanone naringenin with the disaccharide neohesperidose (34). In addition, Naringin has a strong binding affinity with all of the elements of the oyster mushroom (P.species). Naringin has antioxidant, anti-inflammatory, and anti-apoptotic properties anti-ulcer, anti-osteoporotic and anti-carcinogenic properties (35).

Previous research found that naringenin inhibited cellular proliferation and migration in B16F10 and SK-MEL-28 cells in a dose-dependent manner. Previous research also found that naringenin killed tumour cells by inducing apoptosis, and that naringenin treatment significantly upregulated the expression of activated cas3 and PARP at 400 M. (36).

These flavonoids have a variety of biological activities, along with anti – inflammatory, anti-oxidant, unfastened radical scavenging, boom apoptosis rate, lipid peroxidation inhibition effect and cell proliferation inhibition (37).One of these activities is the inhibition of poly (ADP-ribose) polymerase (PARP), which leads to synthetic lethality for BRCA2-poor cells (38,39).

Olaparib (LynparzaTM) is a poly (ADP-ribose) polymerase inhibitor being studied for the treatment of solid tumours, especially BRCA mutation positive ovarian cancer (40). Rucaparib is a novel drug approved by the US Food and Drug Administration in 2016 for the treatment of patients with advanced ovarian cancer who have a BRCA mutation that causes the cancer to spread (41). Niraparib (ZejulaTM) is an orally administered small molecule inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes such PARP-1 and PARP-2 (42). Tesaro Inc. is developing the medication for use in the treatment of various solid tumours (43). Talazoparib (TALZENNATM), an oral PARP inhibitor, was developed by Pfzer (44). Talazoparib is also being explored as a neoadjuvant therapy for early triple negative breast cancer and metastatic castration-resistant prostate cancer (CRPC) (45). Are the main

PARP inhibitors drugs which shows anticancer activity. Many studies have demonstrated several pharmacological properties of rutin,in that it also have anticancer activity (46). Therefore, it would be beneficial to take the Oyster mushroom (Pleurotus sp.) in order to against DNA damaging.

From above analysis we can see that binding affinity of Rutin which is found to be -12.4 kcal/mol and Naringin which was also found to be -11.3 kcal/mol which is the best amongst all chemical constituents of Oyster mushroom (P. Species) (Table No. 1).From this we can see that binding affinity of Rutin and Naringin was found to be better than binding affinity of Olaparib and Talazoparib, which are PARP inhibitor drugs (Table No. 2).

And also we studied that binding affinity of Chrysin -9.5 kcal/mol, Myreicetin -9 kcal/mol and Alpha tocopherol -9.2 kcal/mol (Table No. 3 in appendix section) which are better than Olaparib and Talazoparib. Chrysin having binding affinity was found to be -9.5 kcal/mol which is better than Rucaparib, and Niraparib also.

Binding affinity of Alpha tocopherol is -9.2 kcal/mol, Gamma tocopherol is -8.1 kcal/mol and Beta tocopherol is -8.2 kcal/mol (Table No. 3 in appendix section) which are better than Rucaparib.

Conclusion :

Binding affinity of Chemical Constituents of Oyster Mushroom (P. species) (from Table No. 1) was found by molecular docking analysis in that some constituents shows better binding affinity as compared to PARP inhibitors drugs (from Table No.2). Others are mention in appendix section (Table No.3).

1. Rutin : -12.4 kcal/mol
2. Naringin :-11.3 kcal/mol
3. Chrysin : -9.5 kcal/mol
4. Alpha tocopherol : -9.2 kcal/mol
5. Myricetin : -9 kcal/mol

From above molecular docking analysis it is concluded that protien binding affinity of Rutin which is chemical constituents of Oyster mushroom (Pleurotus sp.) is more as compared to binding affinity of PARP inhibitors, and also naringin have good biding affinity than PARP inhibitor drugs. From above analysis Rutin having binding affinity -12.4 kcal/mol and Naringin having binding affinity -11.3 kcal/mol which are better as compared to olaparib and talazoparib PARP inhibitors. From all progressive data it is concluded that the aim of this project is match with the expected result and Oyster mushroom (Pleurotus sp.) is used for DNA repairing activity or PARP inhibitor activity.

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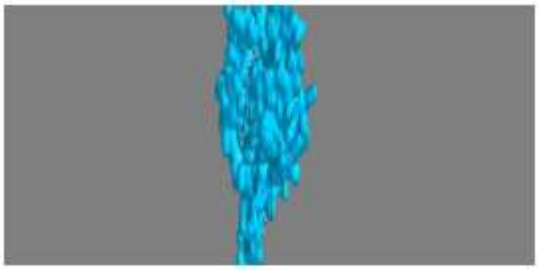
Appendix:

Table No. 3 Chemical Constituents Of Oyster Mushroom (P.Ostreatus)

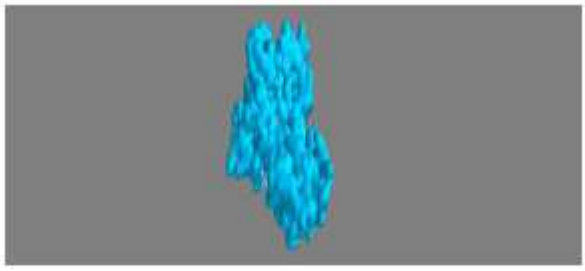
Complex (Protein + Ligands)	Molecules	Binding Affinity (kcal/mol)
4und_ (1) _A_6054_uff_E=95.74	Phenyl ethyl alcohol	-5.8
4und_ (1) _A_18827_uff_E=41.81	1- Octen -3-ol	-5.1
4und_ (1) _A_14257_uff_E=30.71	n-undecan	-5.1
4und_ (1) _A_12398_uff_E=50.10	Heptadecane	-5.4
4und_ (1) _A_445639_uff_E=80.35	Oleic acid	-5.6
4und_ (1) _A_72_uff_E=70.72	Protocatechuic acid	-6.5
4und_ (1) _A_370_uff_E=77.82	Gallic acid	-6.5

4und_ (1) _A_780_uff_E=96.73	Homogentisic acid	-6.4
4und_ (1) _A_5281607_uff_E=229.60	Chrycin	-9.5
4und_ (1) _A_5281672_uff_E=388.01	Myricetin	-9
4und_ (1) _A_5280489_uff_E=674.37	Beta carotein	-7.8
4und_ (1) _A_5280450_uff_E=147.99	Lenoleic acid	-6.7
4und_ (1) _A_444899_uff_E=143.35	Arachiodonic acid	-6
4und_ (1) _A_1742129_uff_E=298.64	Alpha tocopherol	-9.2
4und_ (1) _A_6857447_uff_E=255.66	Beta tocopherol	-8.2
4und_ (1) _A_92729_uff_E=258.14	Gamma tocopherol	-8.1
4und_ (1) _A_92094_uff_E=239.38	Delta tocopherol	-7.7
4und_ (1) _A_7929_uff_E=102.73	1, 3-dimethylbenzene	-6.1
4und_ (1) _A_1017_uff_E=151.39	1,2- Benzenedicarboxylic acid	-6
4und_ (1) _A_65575_uff_E=580.54	Cedrol	-7.2

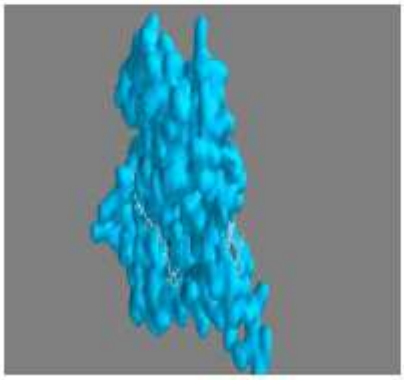
Images of binding of ligand's to protein:



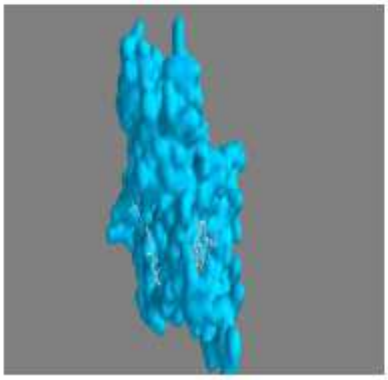
4und with Protocatechuic acid



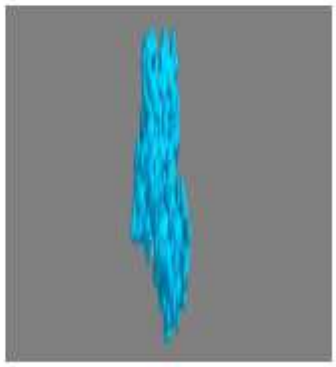
4und with Gallic acid



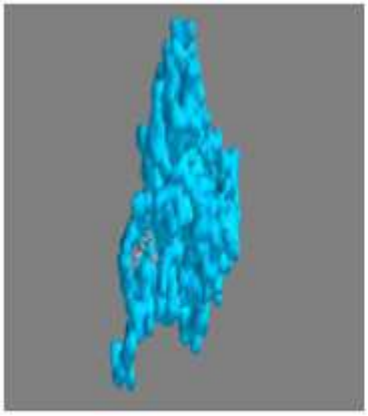
4und with Chrycin



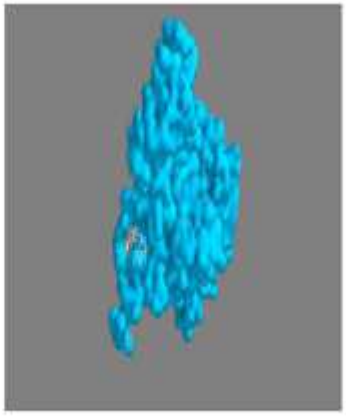
4und with Myricetin



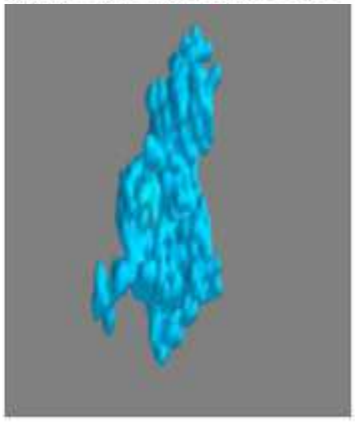
4und with Homogenitisic



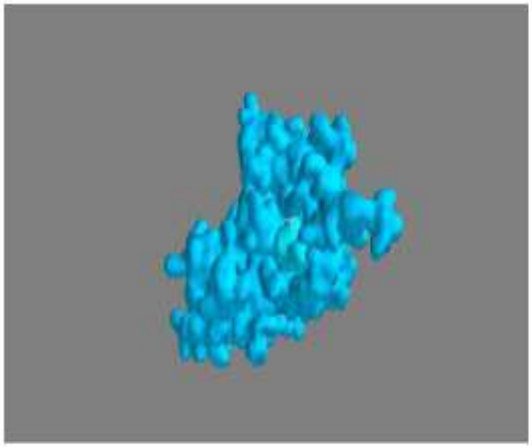
4und with Beta carotein



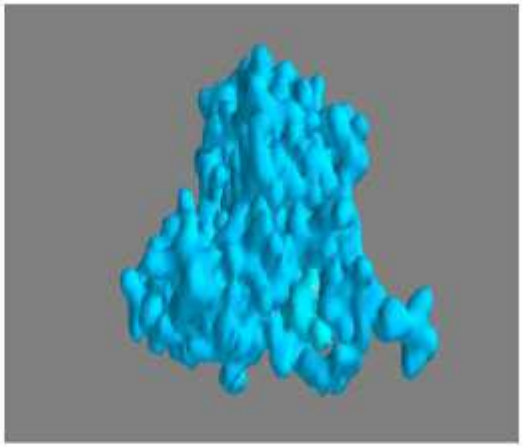
4und with Lenoleic acid



4und with Arachiodonic acid



4und with Alpha tocopherol



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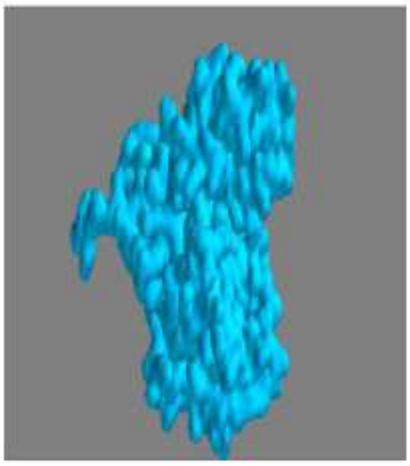
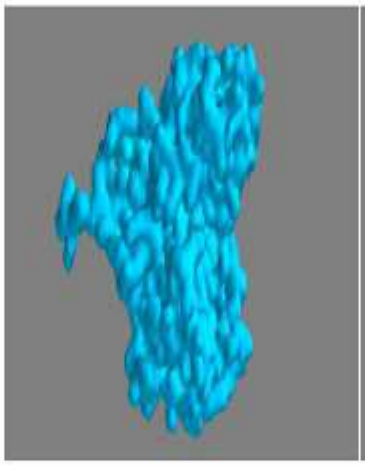
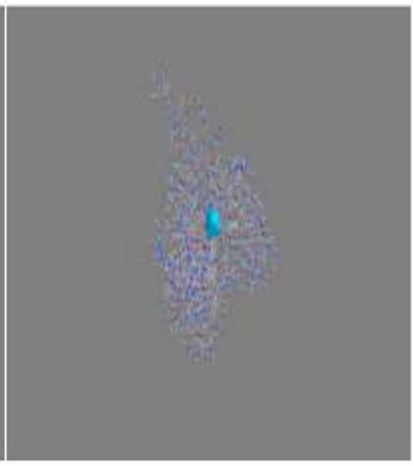


4undwithGammatocopherol



4undwithDeltatocopherol



4undwith1,2Benzenedicarboxylic acid