In Silico Interaction Studies of Salacinol with Inhibitors of IAP Proteins

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Abstract

Salacia reticulata is an important medicinal plant, that is widely distributed in some parts of the sub-continent of India. Salacinol, a biologically active component found in the plant, has been shown through numerous pharmaceutical studies to have anticancer potential. Apoptosis exerts a significant influence on the regulation of cellular processes. A crucial phenomenon in biological systems is the induction of apoptosis by endogenous and exogenous stimuli like UV rays, oxidative stress, and genotoxic chemicals. DNA damage regulates other proteins that activate intrinsic and extrinsic apoptotic pathways, stabilizes p53 in the nucleus and cytoplasm Apoptotic pathway dysfunction may result in conditions like autoimmune disorders, neurodegenerative disorders, and cancer. Recently, powerful apoptosis-inducing substances connected to human health were discovered to inhibit the promotion, growth, and occurrence of tumors as well as cellular inflammatory reactions. Apoptosis-inducing medications are used in therapy to treat both cancerous and non-cancerous cells. A group of structurally and functionally related proteins known as the Inhibitors of Apoptosis (IAP) act as endogenous inhibitors of programmed cell death. In this current study, salacinol was analyzed and subjected to pharmacokinetics screening. An attempt was made to study the interaction between three IAP proteins (BIRC5-3UIH, 3UII, 3UIK) with salacinol using Auto dock software. Salacinol was found to have the best interaction with the IAP target protein.

Keywords: Salacia Reticulata, Salacinol, Inhibitors of Apoptosis (IAP) Proteins, Medicinal Plants, Computational Approach, Molecular Docking.

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INTRODUCTION

For the entirety of their existence, humans require plants. Herbal medicine has a long history that dates back to the dawn of human civilization. The herb salacia is indigenous to Sri Lanka and India. Medicine is made from the stem and root. The enormous natural flora that has been given to Indians is where the country's wealth is kept. The significance of medicinal and aromatic plants has occasionally been emphasized due to their greater safety and lower risk of side effects. [1-3]

Salaretin and mangiferin, which are found in Salacia reticulata, lower blood glucose levels and shield the body from any diabetes-related secondary side effects. Its primary application in conventional Ayurvedic medicine to treat diabetes is almost legendary. Salacia reticulate's mangiferin prevents the production of LDL, maintaining the blood lipid profiles. Salacia reticulate also has a neuroprotective effect, according to Indian research. It is therefore also utilized as a liver tonic. When it comes to menstrual irregularities, skin conditions, rheumatism, spermatorrhoea, and inflammations, salacia reticulata is very effective. [4-6]

The main bioactive components of this plant are known to be salacinol such as Kotalonal, D-arabinofranosyl, sulfate anion, Kolanol, Salaprinol, and Sulfoxide groups. Salacinol compounds have been reported to possess inhibits apoptosis activity against cancer cells. [7- 10]

From the Literature Survey, it was revealed that the Salacia reticulata possess various pharmacological properties like Antibiotics, Ant diabetic agents, Anti-inflammatory agents, Antilipemic agents, Antimalarial agents, Antineoplastic agents, Antiobesity agents, Antiparasitic agents, Cardiovascular agents, Antibacterials, Anti-inflammatory herbs, Antilipemics, Antimalarial herbs and supplements, Antineoplastics, Antiobesity herbs and supplements, Antioxidants, Antiparasitics.[11-14]

Apoptosis (Cell Death) functions in the survival of maintaining the homeostasis in higher organisms and mange several Genetic Diseases because dysfunction of the

apoptosis pathway causes several disorders leading to uncontrolled growth of cells, neurological disorders, and autoimmune disorders.[15] Current research proved synthetic and natural compounds regulate the defective gene responsible for the apoptosis pathway.[16,17] At present, Although the fundamentals of apoptosis have been established, its implications for therapeutic uses remain to be determined.[18-25]

However, there are numerous studies on salacinol against different diseases at the same time there is no study that has conducted salacinol compound against IAP protein. Moreover, In silico approaches have determined appropriate therapeutic drugs in the drug development process. [26, 27, 28, 29] molecular docking process becomes deft to the development of novel drug management.

This study used molecular docking to assess the salacinol compound as the best anticancer against IAP protein and revealed some pharma-activities by using computer approach. [30, 31]

Methods and Materials

Selecting and Making Protein Targets

The Inhibitors of Apoptosis (3UIH, 3UII, and 3UIK) 3D structure was fetched from the PDB at (www.pdb.org/pdb) (Protein Data Bank). The protein data bank has nucleic acid and proteins experimental structures. [32] Protein preparation for docking was carried out through water molecule removal on Pymol software. [33]

Prediction of Active Sites

Computed Atlas of Surface Topography of Proteins (CASTP) is used to determine a target protein's Binding Pocket (active site) (http://sts.bioe.uic.edu/castp/calculation.html).[34]

Ligand Selection and Preparation

The natural biochemical compound Salacinol from the plant (*Salacia reticulata*) was obtained from the Public repository (available at https://www.ncbi.nlm.nih.gov/compound). (PubChem)[35]

Ligands Drug-likeness

To identify Ligand drug-likeness screened by Lipinski rule. (molecular weight 500 or less, AlogP might be less than 5, hydrogen bond acceptors ought not to be more than 10, and under 5 hydrogen bond donors).[36] prediction of drug-likeness done by ADMETSar server. [37-38]

ADMET Identification of Ligand

The proposed drug risk assessment is to be determined by adsorption, distribution, metabolism, excretion, and toxicity (ADMET). Toxicology was determined using the OSIRIS Property Explorer and A server called ADMETSar is used to forecast a compound's ADMET properties. [39-40]

Visualization and Validation

The relationship between the ligand and the target protein (salacinol) is visualized by using pymol software, Ligplot+ [41], and Protein-Ligand Interaction Profiler. [42]

Molecular Docking

Through Autodock tools 1.5.6, molecular docking is carried out. In the actual process of determining x-ray structure, it can be a useful tool. AutoDock can assist in limiting the conformational options and assisting in the identification of a suitable structure given the electron density for a ligand. Researchers can use the Auto dock as a computational tool to identify biomolecular complexes. [43]

Results and Discussion

ADME and Toxicity

The drug-likeness of ligand (salacinol) parameters was in the range of the Lipinski rule. Finally, the ligand shows the best acceptable value. Table: 1 describes the ligand drug-likeness property.

Table 1: Lipinski Parameters of the Ligand

S. No	Lipinski Parameters	Range
1	Hydrogen bond donors	5
2	hydrogen bond acceptors	9
3	molecular weight	334.0
4	Violation	0
5	Logp	-5.30

In addition to that toxicity and physicochemical property were done by OSIRIS property explorer. The compound shows good solubility (0.41), TPSA, drug score, and drug likeness and there is no mutagenicity, tumorigenicity, reproductive effect, and irritation. The properties score is shown in table: 2.

Table 2. Toxicity Risks and Physicochemical Properties

S. No	Properties	Score
1	solubility	0.41
2	Topological surface area (TPSA)	175.9
3	Drug-likeness	-5.16
4	Drug score	0.47
5	Tumorigenicity	1.0
6	Reproductive effect	1.0
7	Mutagenicity	1.0
8	Irritation	1.0

Molecular Docking Analysis

Before the analysis, the docking protocol was followed as mentioned in the materials and method part. These important points were done to retrieve accurate binding

energy. The biochemical compound Salacinol from the plant (*Salacia reticulata)* was retrieved from the Drug bank and interaction studies were performed using the IAP targets. Depicts that the protein targets (3UIH, 3UII, 3UIK) were docked with a small molecule using Auto Dock. The following results were obtained.

The grid formation Exercise was adjusted to the success and accuracy of molecular docking. The present work was done for all three target proteins. The Grid Parameters are provided (Table: 3)

Table 3. Grid Formations of Target Proteins

1	Grid pts per map	Dimension			Spacing	Center Grid Box					
		X	Y	Z		Center			offset		
						X	Y	Z	X	Y	Z
3UII	7370009	90	90	88	0.542	20.354	9.492	21.846	2.8006	0.2782	4.4722
3UIK	19516069	126	126	120	0.375	21.115	11.24	22.338	3.5556	2.2782	4.7222
3UIH	20483833	126	126	126	0.393	-14.947	10.829	-17.163	2.7222	2.0833	0.1944

Molecular Interaction Analysis

In the current study, salacinol was docked with Target Proteins (BIRC5-, 3UII, 3UIK, 3UIH). After finishing the molecular docking least binding energy is considered the best docking. Protein 3UII (human crystal structure Survivin in complex with the peptide H3 (1-10)), 3UIK (Human Survivin mutant K62Y/H80W in combination with H3 (1-10) peptide), crystal structure), 3UIH (Human Survivin mutant K62Y/H80W in combination with H3 (1-10) peptide, crystal structure) was used for the Investigation. Figures 1, 2, and 3 illustrate the interaction between target proteins and the salacinol component of pymol.

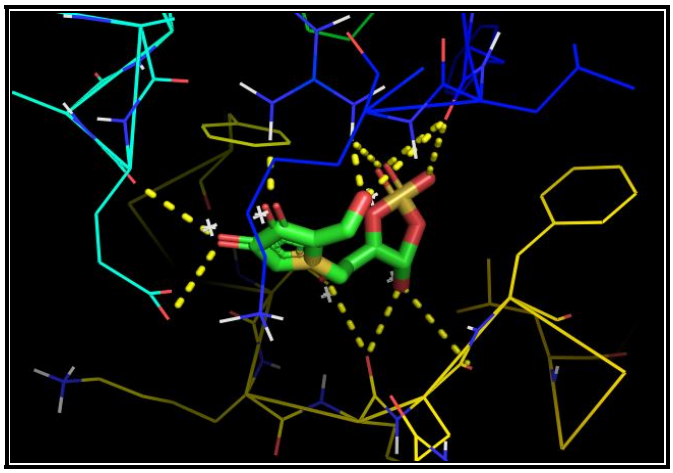

Figure 1: Salacinol Interaction with BIRC5 (3UII)

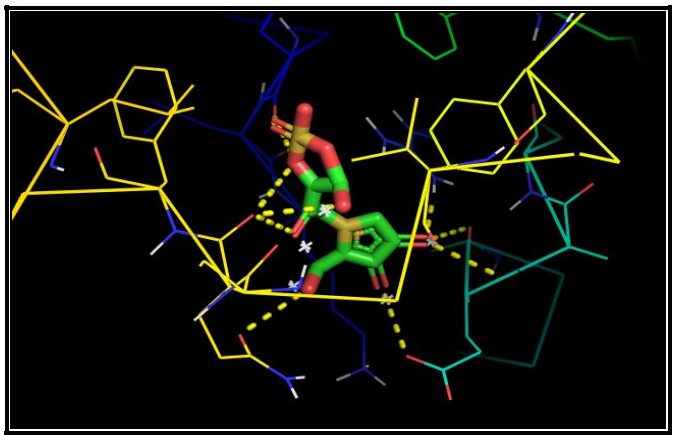

Figure 2: Interaction of Salacinol with BIRC5 (3UIK)

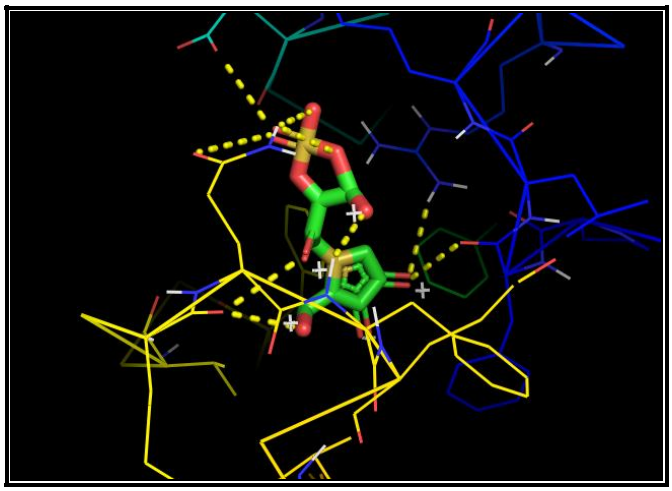

Figure 3: Interaction of Salacinol with BIRC5 (3UIH)

(Table: 4, Table: 5, Table: 6) showing No of Receptor, Amino acid type, Distance between acceptor and hydrogen atoms (A-H), Distance in between acceptor and donor atoms (A-D), donor atom, and acceptor atom. Thus this study showing ligand (salacinol) interacted with target proteins in a good manner.

Table 4: Protein-Ligand Interactions (3UII-salacinol)

S.NO	Residue	AA	Range A-H	Range A-D	Angle	Atom Donor	Atom Acceptor
1	13B	PHE	3.12	3.46	118.98	2710 [O3]	1431 [O2]
2	15B	LYS	2.96	3.64	124.70	1448 [Nam]	2710 [O3]
3	18B	ARG	1.83	2.84	167.58	1494 [Ng+]	2712 [O2]
4	18B	ARG	1.67	2.66	162.81	1497 [Ng+]	2710 [O3]
5	40B	GLU	3.42	3.99	155.42	2712 [O2]	1707 [O2]
6	40B	GLU	2.36	2.82	132.64	2714 [O2]	1703 [O2]
7	91B	LYS	2.23	2.78	149.35	2717 [O3]	2184 [O2]

Table 5: Protein-Ligand Interactions (3UIK-salacinol Interaction)

S.NO	Residue	AA	Range H-A	Range D-A	Angle	Atom Donor	Atom Acceptor
1	15A	LYS	3.16	3.81	122.92	106 [N3+]	2732 [O2]
2	18A	ARG	2.02	2.97	153.12	143 [Ng+]	2734 [O2]
3	18A	ARG	3.35	3.98	122.13	146 [Ng+]	2734 [O2]
4	39A	ALA	2.36	2.95	159.53	2734 [O2]	346 [O2]
5	40A	GLU	2.11	2.70	157.70	2732 [O2]	356 [O2]
6	92A	GLN	3.12	3.51	103.69	854 [Nam]	2730 [O3]
7	92A	GLN	2.34	2.72	121.68	2730 [O3]	857 [O2]
8	92A	GLN	3.72	3.88	100.72	2718 [O3]	857 [O2]
9	92A	GLN	2.08	2.65	155.37	2727 [O3]	850 [O2]

Table 6: Protein-Ligand Interactions (3UIK-salacinol Interaction)

S.No	Residue	AA	Range H-A	Range D-A	Angle	Atom Donor	Atom Acceptor
1	13B	PHE	2.15	2.40	106.85	2717 [O2]	1428 [O2]
2	18B	ARG	2.61	3.49	143.36	1491 [Ng+]	2717 [O2]
3	40B	GLU	2.82	3.76	163.59	2725 [O3]	1704 [O3]
4	91B	LYS	2.14	2.70	150.80	2713 [O3]	2181 [O2]
5	92B	GLN	3.70	3.96	109.95	2720 [O3]	2194 [O2]
6	92B	GLN	2.52	3.19	122.55	2198 [Nam]	2727 [O3]
7	93B	PHE	2.27	3.08	135.55	2202	2729 [O3]

In this current study were docked salacinol with IAP protein. Binding energy, Ligand Efficiency, Inhibit Constant, Electrostatic energy, Torsional energy, Internal energy, and binding Distance are tabulated in Below Table: 7.

Table 7: Docking Results of BIRC5 (3UII, 3UIK, 3UIH)

Protein	Docking Score	Ligand capability	inhibition constant (u/M)	Electrostatic Energy	Desolv Energy	Torsional Energy	Internal Energy	Binding Distance (A)
3UII	-8.27 **kcal/mol**	-0.41	861.02	-0.07	-11.19	2.98	-11.26	2.42-2.84
3UIK	-8.8 **kcal/mol**	-0.44	351.9	0.01	-11.8	2.98	-11.79	2.72-2.95
3UIH	-9.06 **kcal/mol**	-0.45	228.09	0.05	-12.1	2.98	-12.04	2.04-3.08

The interaction of 3UII salacinol compound established a hydrogen bond with 7amino acid residues such as Lys15, Arg18, Val87, Phe13, Gln92, Phe86, Leu 96, Phe 93 and salt bridges with two amino acids such as Arg18 (sulfate), GlU40 (sulfonium) ligand group. (Figure: 4).

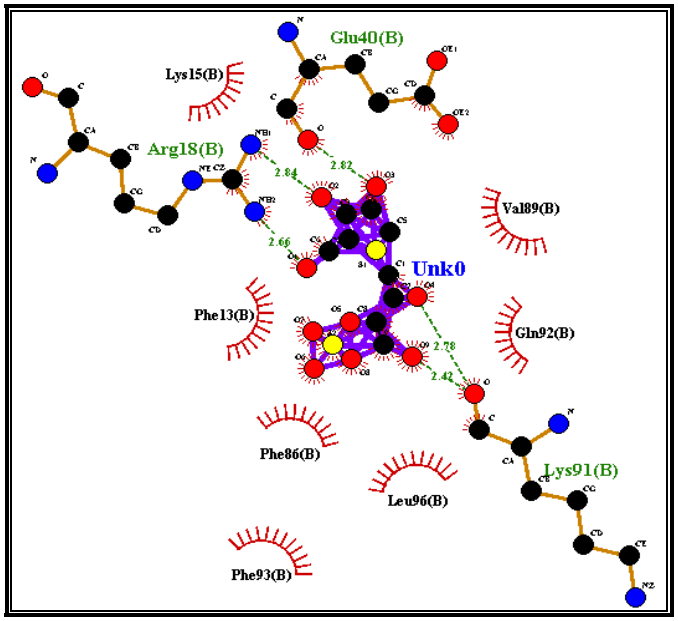

Figure 4: Binding Mode and Molecular Interaction between 3UII and Salacinol

The interaction of 3UIK salacinol compound established five residues of amino acid with Hydrogen bond , namely Lys15, Arg18, Ala39, Glu40, Gln92 and non covalent molecular interaction with Arg18(aromatic)ligand group (Figure: 5)

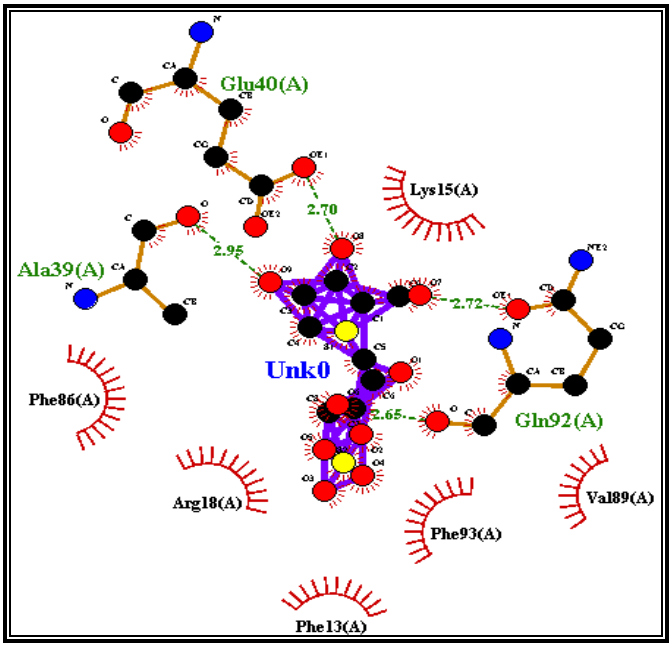

Figure 5: Binding Mode and Molecular Interaction between 3UIK and Salacinol

The interaction of 3UIH salacinol compound established five residues of amino acid with Hydrogen bond , specifically Phe13, Arg18, Glu40, Lys91, Gln92, Phe93, non-covalent molecular interaction with Arg18, Phe86(aromatic)ligand group, and salt bridge with Lys15(sulfate) ligand group. (Figure: 6).

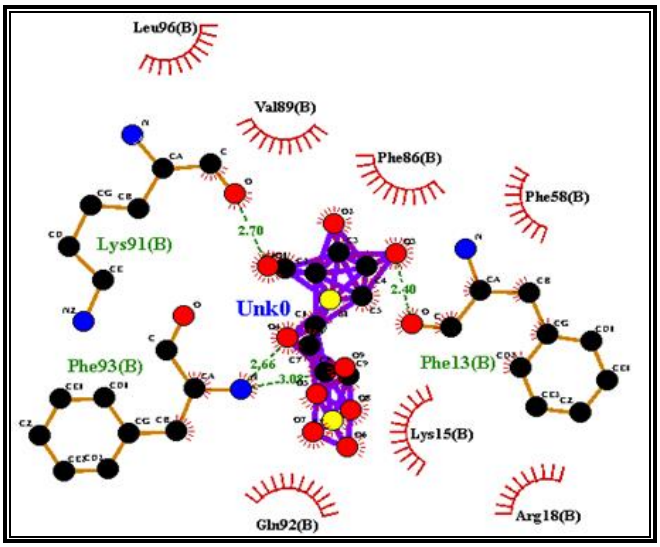

Figure 6: Binding Mode and Molecular Interaction between 3UIH and Salacinol

The results obtained reveal that 3UII docking score is -8.27 kilocalorie per mole (Fig: 1), 3UIK has a docking score is 8.8 kilocalorie per mole (Fig: 2), 3UIH docking score is –9.06 kilocalorie per mole (Fig: 3), The BIRC5 (3UIH) with binding energy -9.06 kcal/mol is the best docking result.

Conclusion

Thus the current study indicates that ADMET results of the drug (salacinol) might be safe and at low toxicity level. Salacinol compound is a potent anti-tumor agent and may have a leading role in the ongoing struggle against cancer treatment. Salacinol with the BIRC5 (3UIH) had significant binding efficiency and hence the small molecule may be considered to be used in therapeutic treatments that inhibit apoptosis activity. Thus Salacinol are suggested to be used clinically as anti-tumor agents. *In silico* studies reduce the time and cost of the drug discovery process. However future studies are needed for authenticating this drug recognition. Molecular dynamic study and in-vitro studies would provide good insights with the above molecule.

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