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COMPUTATIONAL ANALYSIS OF TRANSCRIPTION FACTORS AS CANCER DRUG TARGETS WITH POTENTIAL INHIBITORS FROM THE NPACT DATABASE

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ABSTRACT

Transcription factors have proven to be promising targets for the treatment of cancer. Transcription factors are involved in the production of oxygen. External cervical events are initiated by receptors, such as cytotoxic exposures or cytokine receptors that trigger signalling cascades that activate transcription factors. Transcriptional factors are known to be highly active in most human cancer cells, making them suitable for the study and development of anticancer therapies. Three transcription factors were investigated as potential targets in this study. Analysis of string interactions reveals their interaction network. DNA-TF binding was followed by docking with 96 natural compounds to the DNA binding pocket of the transcription factor. Using post-docking processing, compounds were ranked according to their binding energy, hydrogen bond number, and dissociation constant; Withanolide D targeted more than one transcription factor. Therefore, the compound is suitable for in vitro testing using different cancer cell lines.

Keywords: *In silico* analysis, Transcription Factors, Natural compounds, Molecular docking

ABBREVIATION:

TF: Transcription Factors
DNA: Deoxyribonucleic Acid
YASARA: Yet Another Scientific Artificial Reality Application
PDB: Protein Databank
NPACT: Naturally Occurring Plant-based Anti-cancer Compound-Activity-Target database.
ATF4: Activating transcription factor 4
CBFB: Core-binding factor subunit beta gene
BRCA1: Breast Cancer gene 1
RUNX1: Runt-related transcription factor 1

INTRODUCTION:

The uncontrolled multiplication of abnormal cells in any body part is called cancer. Currently, there are over 200 different types of cancer (Hanahan and Weinberg). Original/normal tissue from which the aberrant cells originate is used to identify many tumours and abnormal cells (for example, breast cancer, lung cancer, and colorectal cancer) (Soltanian and Matin). TMEs can provide various conditions to make cancer cells respond (Hayward et al.). Among the most dangerous cancers, lung cancer has a high mortality rate and incidence rate. Lung cancer treatment has changed radically due to molecular targeted therapy and immunotherapy (Liu et al.).

A cancerous growth is called a carcinoma. The process begins in the epithelium of the skin or in tissues that line internal organs, such as the liver or kidneys. A carcinoma may spread to other body regions or remain localized within the primary site. Sarcomas are an extra scarcef cancer. Sarcomas are distinguished from the more common carcinomas because they are found in another type of tissue. These cancers develop in connective tissues, which are cells that support other tissues within the body (Al-Benna et al.). Organs that have been infiltrated by cancer cells may also exhibit symptoms of leukemia. The presence of cancer in the central nervous system may result in headaches, nausea, vomiting, disorientation, loss of muscle control, and seizures (Armstrong and Gilbert). A solid tumour is known as a blastoma. This type of tumor occurs when cells fail to mature properly before birth or during childhood. Consequently, the tissue is still in its embryonic state. This syndrome is frequently observed at birth in an infant suffering from a blastoma (Aubry and Chateil).

According to the area of the body affected, there are different signs and symptoms of cancer. The following are some generic indicators and symptoms associated with cancer but may not be specific to it: fatigue; the patient may sometimes feel a lump under the skin. Several factors can contribute to the aging process, including erratic body weight, yellowing, darkening, or redness of skin redness et al.). Transcription factors are proteins that bind to DNA to regulate the transcription of eukaryotic genes. Specifically, these factors bind to sequences in the promoter regions of the genes they regulate. The DNA-binding domain is used to transcription factors into familiesDidiasova et al.). In humans, transcription factors are a significant class of cancer cell dependencies that are usually altered due to tumour pathophysiology. Transcription factors, therefore, constitute promising targets for cancer therapies (Yan & Higgins). Transcription factors regulate gene expression by interacting with transcription corepressor/enhancer complexes and the downstream signal transduction (Hosoya et al.). Invertebrates have a variety of transcription factors (TFs) that bind to gene regulatory elements (promoters, enhancers, and silencers) to influence the expression of genes (Levine). To activate and regulate the transcription machinery (cis-elements), DNA-binding transcription factors (also known as trans-factors) occupy specific DNA sequences at control sites. Human malignancies typically include the activation/mutation of myc as a major oncogenic event; however, these transcription factors are difficult to stop pharmacologically. Thus, myc-dependent downstream effectors may be more tractable therapeutic targets (Pimentel et al., 2009).

ATF4 is an activating transcription factor of the ATF/CREB family that has been demonstrated to be enhanced by a range of microenvironmental stress signals. Mutations in the ATF4 gene are associated with several human malignancies, including colorectal cancer (Wang et al.). Hereditary mutations in the BRCA1 gene (HGSC) have been linked to developing high-grade serous ovarian cancer (Cancer and Atlas). BRCA1 plays a vital role in response to DNA damage and transcription control (Huen et al.). Two highly conserved domains are found in BRCA1: a RING domain located at the N-terminus that interacts with BRCA1-associated RING domain 1 (BARD1) to form an E3 ubiquitin ligase; and a RING domain located at the C-terminus that acts as an E3 ubiquitin ligase (BARD1) (Roy et al, 2009). An essential part of molecular modeling is integrating computer-based methods and methods for examining and predicting the structures and reactions of molecules, as well as the properties dependent on the structures (Pagadala et al.). Through molecular docking, the behavior of tiny molecules at the binding site of a target protein is evaluated. Molecular docking is becoming more popular with the discovery of newer protein structures utilizing X-ray crystallography or nuclear magnetic resonance (NMR) spectroscopy (Chaudhary and Mishra). A primary goal of this molecular docking is to perform a computer simulation of the molecular identification process to achieve an optimized conformation that minimizes the free energy of the overall system (Agarwal and Mehrotra).

Several computational techniques have been developed in the past three decades to design drugs, which have yielded promising outcomes in identifying drugs (Keute et al.). In molecular docking, small molecules or ligands are sorted according to their optimal orientation on the target. The approach is able to predict different binding modes of ligands in the groove of a target molecule (Rosales-Hernandez et al.). Two of these computational approaches are quantum mechanics (ab initio and density functional theories) and molecular mechanics (docking, molecular dynamics, and protein folding). For identifying cancer targets, docking, and molecular dynamics are the most common computational approaches (Massarotti et al). Molecular docking is a technique for analyzing the molecular behavior of target proteins when they bind. It is a widely used tool in the development of pharmaceuticals. Regarding software, the top five companies are Yasara, AutoDock, Vina, MOE-Dock, FLexX, and GOLD, while AutoDock, Vina, MOE-Dock, FLexX, and GOLD are the most popular (Gschwend et al.).

MATERIALS AND METHODS:

Tools and database used:

Numerous databases were used for protein selection and molecular docking. More than three transcription factors involved in the cancer process were discovered after reading and examining various publications. Ninety-six natural chemicals were chosen based on the review and literature for using the PubChem database. Hex tool was used for protein-DNA docking investigation. These protein structures were retrieved from the PDB database, cleaned up, and added water using the Discovery studio visualizer, followed by Molecular Docking using YASARA Software.

Protein preparation:

The three-dimensional protein structures were obtained from PDB. Identifying the specific transcription factors was the first step in protein preparation. Following this step, the target protein was cleaned, and energy was minimized. The DNA sequence for the protein-DNA docking was prepared using the Hex database. The Discovery Studio visualizer discovered the active site, and the Simulation cell was designed using the binding pocket in the active site.

Ligand Preparation:

They identified specific natural compounds used in cancer treatment and retrieved their structure from the National Cancer Institute's NPACT database. Drawing, editing, and cleaning ligand structures using BIOVIA discovery studio visualizer. Then, the structure is converted into 2D and 3D formats and checked for errors. Moreover, it also included creating a single .sdf file for all ligands in the Marvin sketch to facilitate docking. (Table 1) shows a list of the selected natural compounds from the NPACT database.

(Table 1: Natural compound list)

Allicin	Allyl isothiocyanate	AndrographaloidD	apigenin
Apiole	AntineoplastoneA10	Capsaicin	Catechin
Chlorogenic Acid	Coumarin	Coumestrol	curcumin
Cyanidin	Diallyl sulphide	Ellagic Acid	Epigallocatechin gallate(EGCG)
Gallic Acid	Genistein	Gingerol	Gossypol
Hesperidin	Indole-3-carbinol	Kaempferol	Methyl allyl trisulfide
Piperine	Quercetin	Resveratrol	Silymarin
Theaflavin	Zeaxanthin	Naringenin	Bergenin
Embelin	Nitidine choride	Protopine	Psoralen
Aloe-emodin	Thymoquinone	Cicutoxin	Epipodophyllotoxin
Elliptinium	Ursolic acid	Quassin	PinocembrinTetrandrine
Neohesperidin	Ginsenosides C-K	10-Gingerols	Rubiadin
flavonol 3-O-glycoside	Damnacanthol	Mallato phenone (1)	Podophyllotoxin bromide
Diterpenes(aconitine)	Lupeol	Withaferin A	Spartine

Homoharringtonine	Cardiac glucosides (Ouabain)	Bruceantin	WithanolideD
Oridonin	Fangchinoline	Dehydrocostuslactone	Xanthone
Combretastatins	(E)-γ-bisabolene	Emodin tetraacetate	Cynaropicrin
Dithymoquinone	Psorospermin	Berberine	Chelidonine
Ginkgetin	Galangin	Hyperoside	Rhamnetin
Psoralidin	Curcumol	Germacranolide	LicoagrochalconeA
Mangiferin	Quercetin-3-gluconide	Costunolide	Quassinoid
Ginkgolides B	RubescensineJ	Germacrone	Podophyllotoxin
Spirosolane	Bavachinin	Curdione	Daidzein
Andrographolide	Trichothecenes	Ginkgolides A	Ponicidine

Molecular Docking:
In virtual screening, molecular docking is an important stage used to identify potential hits based on the interaction between the receptor and the ligand. Structure-based drug development is dependent upon molecular docking. Docking results for the listed compounds with the corresponding target proteins were obtained using YASARA. In this study, the energy-minimized compounds were imported, the docking conformations were conducted twice using an evolutionary genetic procedure, and the docked structures' fitness was assessed. The YASARA software calculated hydrogen bonds, residues, dissociation constants, and binding energies. The YASARA structure is used in protein binding pockets and ligand docking as a starting point. The best binding ligand was identified using its binding energy and a protein-ligand interaction study for multiple receptor proteins with the highest binding energy. Furthermore, the protein-ligand interaction of the best-bound ligand is compared to that of its inbound ligand. Molecular docking analysis was conducted using YASARA. An Amber force field was used to perform molecular docking research, including water removal, chain selection, and energy minimization factors. We analyzed dock poses, docking energies, and interacting amino acid residues for predicting binding affinity using the following equation:

$\Delta G = \Delta GvdW + \Delta GHbond + \Delta Gelec + \Delta Gtor + \Delta Gdesolv$

Where,

ΔGvdW = Docking energy is referred to as van der Waals energy.
ΔGHbond = for docking energy, the H bonding term is used.
ΔGelec = Docking energy is referred to as electrostatic energy.
ΔGtor = When a ligand transitions from an unbound to a bound state, it has a torsional free energy term.
ΔGdesolv = docking energy desolvation phrase (Schleinkofer et al.).

Transcription factors List:
(Table 2) It shows the transcription factors list and a protein Id along with its chain and resolution. This information is helpful for the selection of proteins. There arethree3 transcription factors and three protein IDs, and their information has been made available in this table. Using the String network, these three transcription Factors show their interaction and connection between them.

(**Table 2: Transcription Factors list**)

Sr. no	Transcription Factors	Protein Id	Chain	Resolution
1	ATF4	1CI6	A, B	2.6Å
2	CBFB	1H9D	A, B, C, D	2.6Å
3	BRCA1	2BKF	A	1.56Å

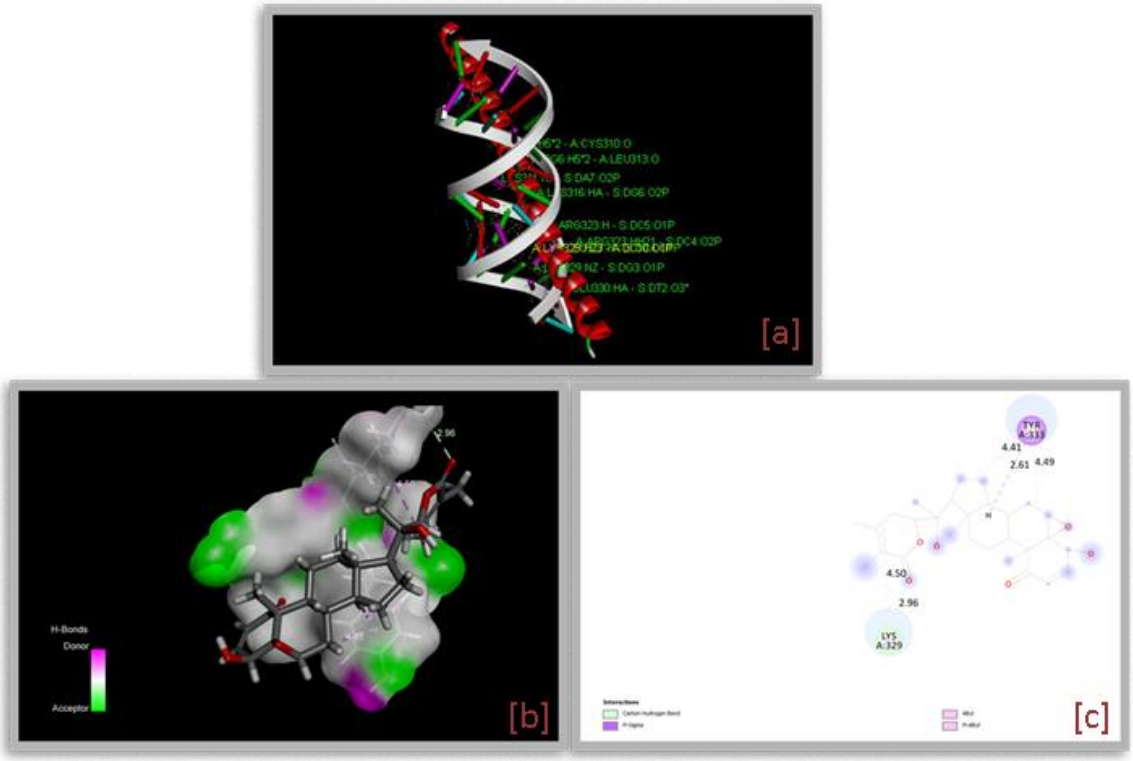
RESULTS:

Protein-ligand preparation:
Molecular docking is a critical stage during the virtual screening that identifies potential hits based on receptor-ligand interactions. Specifically, 2BKF, 1CI6, and 1H9D - these proteins were chosen from the PDB database based on their resolution and x-ray crystallography structure, and their 3D structures were downloaded from the database. The Hex tool was

then used to dock a randomly selected DNA sequence. The discovery studio visualizer identifies an active docking site for YASARA. The NAPCT database was utilized for the ligands, and the BIOVIA discovery studio visualizer was used to create a 2D structure for docking. Furthermore, the protein and ligand preparations were used in the docking procedure - loading the protein and ligand libraries into the YASARA software and docking them. Thus, it revealed binding energy, dissociation constant, and a hydrogen bond, along with the information regarding which ligand is better bound to the protein.

Molecular Docking

Analysis of prn DNA interaction had been done in figure 1. Specifically, the Protein 1CI6 has been selected as a receptor and a Random DNA sequence as a ligand for docking. The ligand name, binding energy, hydrogen bond, dissociation constant, and presence of interacting receptor residues are shown in Table 3 using YASARA docking. In Protein DNA docking using HEX, the Eshape value noted is -563.33.



(Figure 1a: 1CI6 protein and DNA Sequence; Figure 1b: 2D structure of complex 75 with 1CI6; Figure 1c: 3D structure of complex 75 with 1CI6)

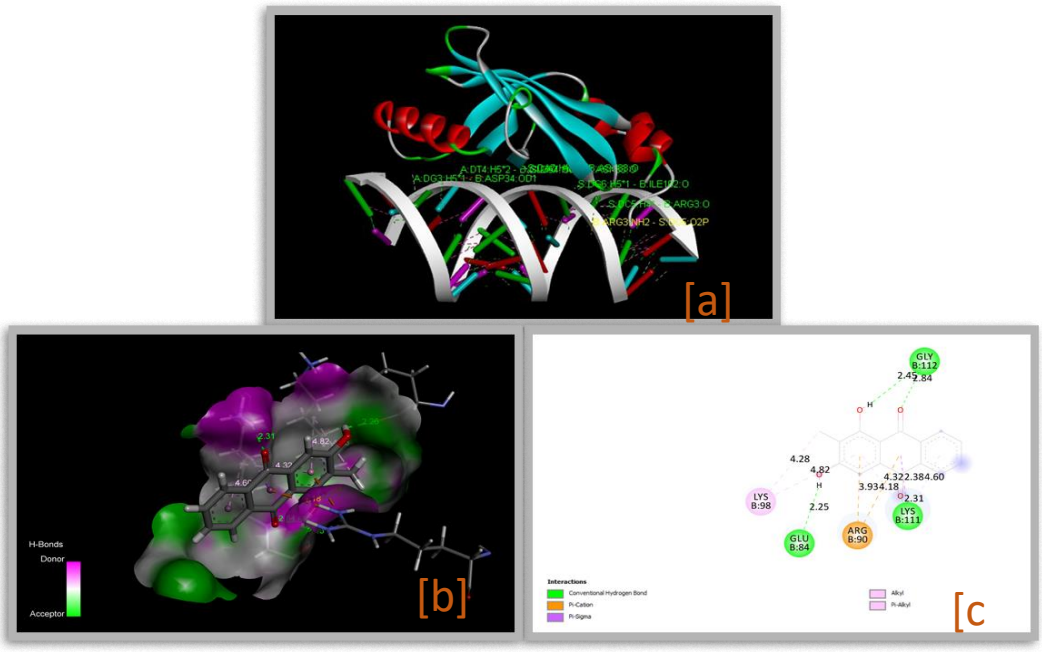
(Figure 1a) shows 1CI6 protein and random DNA sequence docking. Following the Protein-DNA Docking study, there were specific amino acid residues for future docking studies. Lys 329, Leu 313, Cys 310, Glu 330, Lys 311, Leu 327, Arg 23, Lys 316, Arg 323, and Lys 329 amino acids were chosen in the 1CI6 protein. (Figure 1b) and (Figure 1c) shows a 2D and 3D representation of docked complex 75, accordingly (Withanolide D). Having distances of 4.41, 4.49, 4.50, 2.61, and 2.96, respectively, the complete 2D complex reveals three alkyl bonds and one carbon-hydrogen bond with amino acids Try 333 and Lys 329. An inhibitory effect is observed with this compound. According to the Protein-Ligand Docking Results, the top three best hits were Withanolide D, Withaferin A, and Ursolic acid, with their Yasara Rank, ligand name, binding energy, hydrogen bond, dissociation constant, and interacting receptor residue (Table 3**)**.

(Table 3: 1CI6, 1H9D, 2BKF Protein with their details)

Protein ID	Sr No.	YASARA Rank	Ligand name	Binding energy[kcal/mol]	Hydrogen bond	Dissociation constant[pM]	Contacting receptor residues

1CI6	1	**75**	**Withanolide D**	**7.2240**	**1**	**5066847.00**	**Lys 329, Glu 330, Gln 332,Tyr 333, Leu 334, Asp 336**
	2	89	Withaferin A	6.9310	1	8308251.50	Lys 329, Glu 330, Gln 332, Tyr 333, Leu 334, Asp 336
	3	02	Ursolic Acid	6.5010	-	17167372.00	Lys 329, Glu 330, Tyr 333, Leu 334
1H9D	1	**16**	**Rubiadin**	**7.9720**	**2**	**1433661.12**	**Glu 24, Glu 84, Tyr 85, Asp 87, Arg 90, Tyr 96, Leu 97, Lys 98, Lys 111, Gly 112, Trp 113**
	2	14	Ginkgetin	7.9640	3	1453150.50	Glu 84, Tyr 85, Asp 87, Arg 90, Tyr 96, Leu 97, Lys 98, Ile 109, Lys 111,Gly 112,Glu 126,Phe 127,Asp 128,Glu 129,Glu 130
	3	06	Germacranolide	7.9210	1	1562536.00	Glu 24, Glu 84, Tyr 85, Arg 90, Tyr 96, Leu 97, Lys 98, Lys 111, Gly 112, Trp 113, Gly 123, Cys 124

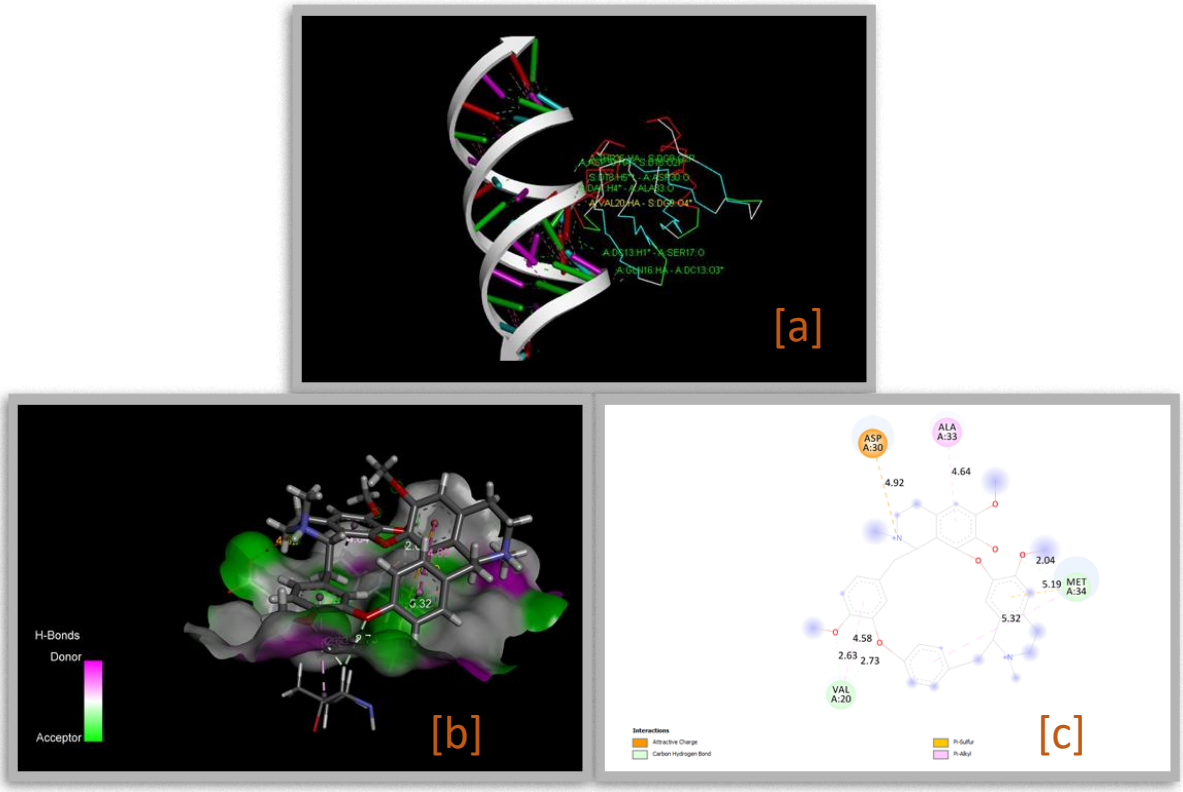
2BKF	1	**79**	**Fangchinoline**	**7.5530**	**-**	**2907887.50**	**Gln 16, Phe 18, Leu 19, Val 20, Ser 21, Asp 22, Thr 26, Asp 30, Ala 33, Met 34, Val 37, Ser 38**
	2	04	Theaflavin	7.3700	1	3960211.50	Ser 17, Phe 18, Leu 19, Val 20, Ser 21, Asp 22, Asn 25, Thr26, Asp 30, Ile 31, Ala 33, Met 34
	3	21	Protopine	6.8480	1	9557613.00	Phe18,Leu 19, Val 20, Ser 21, Asp 22, Thr 26, Asp 30, Ile 31, Ala 33, Met 34, Val 37



(Figure 2a: 1H9D Protein and DNA Sequence; Figure 2b: 2D structure of complex 16 with 1H9D; Figure 2c: 3D structure of complex 16 with 1H9D)

(Figure 2a) illustrates that for docking, the Protein 1H9D was selected as a receptor and a Random DNA sequence as a ligand. DNA interactions with proteins have been investigated. The Eshape value stated in Molecular Docking of Protein DNA Using HEX is -625.31. The amino acid residues are then selected for molecular docking: Asn 63, Ile 102, Asp 34, Glu 54, Arg 3, and Arg 63. (Figure 2b) and (Figure 2c) depict the docked complex 16 in 2D and 3D, respectively (Rubiadin). Three alkyl bonds and one pi alkyl bond are visible in the complete 2D complex. Two Pi-cation links, four traditional Hydrogen bonds with amino acids Gly 112, Lys 98, Glu 84, Arg 90, and Lys 111, respectively, with distances of 4.28, 4.82, 4.18, 2.38, 3.93, 4.32,2.25, 2.31, 2.45, 2.84. This compound can suppress activity.

The interaction of proteins with DNA has been studied. For docking, the Protein 2BKF was selected as a receptor, and a Random DNA sequence was chosen as a ligand. In (Figure 3a), the Eshape value mentioned in Protein DNA docking using HEX is -565.75. Furthermore, the residues Ala 33, Asp 30, Thr 26, Gln 16, Ser 17, Val 20and, Ser 21 were selected for molecular docking using Hex docking. This is the outcome of using the Discovery Studio Visualizer to locate an active YASARA Docking site.



(Figure 3a: 1H9D Protein and DNA Sequence; Figure 3b: 2D structure of complex 16 with 1H9D; Figure 3c: 3D structure of complex 16 with 1H9D)

It was determined that the three most significant hits in the docking process were Fangchinoline, Theaflavin, and Protopine based on their Yasara Rank, ligand name, binding energy, hydrogen bond, and dissociation constant as well as their interacting receptor residue (Table 3**)**. As well as their Contacting receptor residue, Withanolide D has maximum binding energy due to its hydrogen bond and dissociation constant of 5066847.00. For 1H9D protein, Rubiadin showed the highest binding energy, whereas, for 2BKF protein, Fangchinoline showed the highest binding energy, with dissociation constants of 1433661.12 and 2907887.50, respectively. Figures 3b and 3c depict representations of the docked complex 79 (Fangchinoline) in 2D and 3D, respectively. With distances of 4.58, 5.32, 4.64, 5.19, 2.04, and 4,93, the whole 2D structure of this complex consists of three Pi-alkyl bonds, one Pi-sulfur bond, one carbon-hydrogen bond, and one attractive charge. Complexes such as these are capable of suppressing activity.

Several transcription factor families aid the autonomous growth of cancer cells. The top three best hits in docking are Rubiadin, Ginkgetin, and Germacranolid, ligands for proteins with Yasara rank, binding energy, hydrogen bond strength, and dissociation constant (Table 3). The phytochemicals with the highest affinity for 1CI6 include Withanolide D, Withaferin A, and Ursolic acid.

ATF4 activation confers resistance to LDHA inhibition came from the observation that LDHA inhibition induced the expression of asparagine synthetase (ASNS) and glutamic-pyruvic transaminase 2 (GPT2; Figs 4I and EV5K), known transcriptional targets of ATF4, which are critical for de novo aspar-again (Asn) and alanine (Ala) biosynthesis, respectively.

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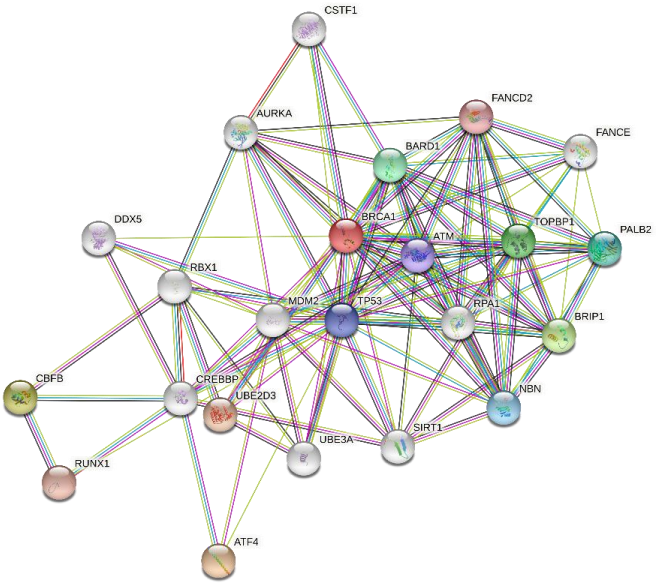

(Figure 4: String Interaction Network)

Each of them constructed a single hydrogen bond with the other. With binding energies of 7.2240 kcal/mol, 6.9310 kcal/mol, and 6.5010 kcal/mol, it interacted with the protein 1CI6. The hydrophobic bond engaging with the protein residue LYS 329 was seen in the protein-ligand complex of 1CI6 containing Withanolide D as the topmost ligand. Rubiadin, Ginkgetin, and Germacranolide ligands showed a greater affinity for 1H9D. They discovered binding energies of 7.9640 kcal/mol and 7.9720 kcal/mol for the protein 1H9D. Rubiadin (the highest ligand) has disclosed three hydrogen bonds: GLY 112, GLU 84, and LYS111. Several substances have been found to enhance 2BKF binding, including Fangchinoline, Theaflavin, and Protopine. A binding energy of 7.7530 kcal/mol was found for the protein 2BKF, followed by a value of 7.3700 kcal/mol and 6.8480 kcal/mol. Fangchinoline, the highest ligand, is involved in two hydrogen bond interactions: VAL 20 and MET 34. When Withanolide D binds to the protein 1CI6, 7.7170 kcal/mol when it binds to the protein 1H9D, and 6.7590 kcal/mol when it binds to the protein 2BKF. (Figure 4) reveals that the different protein-protein interactions network of the Transcription Factors ATF4, CBFB, and BRCA1 with the other proteins is shown in the above figures.

DISCUSSION:

The method of developing drugs based on a molecule's structure is known as molecular docking, and it predicts the binding mechanism and affinity of receptors and ligands. The most likely binding conformations must be identified in two steps: (i) accurate prediction of the interaction energy associated with each of the projected binding conformations; (ii) exploration of a vast conformational space reflecting numerous potential binding modes (Tanabe et al.). Activating transcription factor 4 (ATF4), linked to cisplatin resistance, is elevated in cisplatin-resistant cells. It has been demonstrated that cisplatin induces the expression of the transcription factor ATF4 and that overexpression of ATF4 induces cisplatin resistance in cells (Harding et al.). An additional significant finding was that glutathione levels were increased in these cell lines (Harding et al.). Results from a recent study indicated that ATF4–/– cells had lower glutathione production (Malik et al.). The CBFB gene mutation is associated with various human malignancies, including breast cancer (Cancer and Atlas). Cancers such as breast cancer, neuroblastoma, and osteoblasts overexpress ATF4, a protein that regulates tumor growth, autophagy, drug resistance, and metastasis. In pancreatic cancer, ATF4 has been implicated in regulating other genes. However, the precise functions of ATF4 in CAFs that promote pancreatic cancer growth and the mechanism of gemcitabine resistance have not yet been determined (Dai et al.).

CBFB has long been thought to act as a transcriptional cofactor for the RUNX1 and RUNX2 family proteins (Dai et al.). Specifically, CBFB enhances the chromatin binding of RUNX proteins by developing heterodimers to form a transcriptional complex because it regulates

the expression of genes with many functions in many cells and tissues (Stratton et al.). In breast cells, CBFB suppresses cancer by regulating both translation and transcription. CBFB improves hundreds of mRNAs, including RUNX1. As a result of the CBFB-RUNX1 transcriptional complex, NOTCH3, a breast cancer oncogene, is repressed in the nucleus. CBFB and RUNX1 mutations have been linked to a range of cancers, including breast, ovarian, and prostate cancer saying additional mechanisms mediate CBFB's tumour suppressive activity. It's also unclear whether the CBFB/RUNX1 axis works with other mechanisms to prevent breast cancer (Malik et al.). Several cancers have been linked to mutations in CBFB and RUNX1, including breast, ovarian, and prostate cancer (Miki et al.). The C-terminal region of BRCA1 contains a high proportion of negatively charged residues, suggesting that it may function in the transcriptional activation of future cancer cells (Monteiro et al.).

A possible approach to assessing the health risks associated with cancer-predisposing alleles of BRCA1 based on their response to transcriptional activation and DNA repair activity is to determine an anti-cancer treatment that can be established against the gene. We found that BRCA1 restoration reduced the expression of three genes associated with the basal-like phenotype in the mutant HCC1937 breast cell line: CDH3, KRT17, and KRT5. Furthermore, we discovered that siRNA knockdown of endogenous BRCA1 suppressed the expression of these genes in the luminal breast cancer cell line T47D (Laakso et al.). These findings are from previous immunohistochemistry studies showing that BRCA1-related tumors express genes indicative of basal-like epithelial phenotypes (Patel et al.). Using the search tool for retrieving interacting genes/proteins (STRING) database, PPIs for DEGs were visualized with a combined score of >0.7 to predict the interaction pattern between DEGs in brain and lung metastases. STRING contains 24.6 million proteins from 5090 different species. (Szklarczyk et al.).

CONCLUSION:

Based on our findings, three phytochemicals identified as hits using the YASARA screening method could be selective transcription factor receptor inhibitors. Hence, the YASARA molecular docking approach can be used to predict NPACT drug binding modes accurately. They were extracted from locally available fruits and vegetables and used as ingredients in traditional therapeutic formulations. The study identified three transcription factors as possible targets for cancer drugs. The Current approach was unique because it utilized DNA-TF binding followed by the docking of 96 natural compounds to the DNA binding pocket of the TF. The post-docking analysis ranked the compounds based on binding energy, number of hydrogen bonds, and dissociation constant. Withanolide D, its binding energy of 7.2240 kcal/mol, Rubiadin with a binding energy of 7.9720 kcal/mol, and Fangchinoline, its binding energy of 7.5530 kcal/mol, target more than one TF, and it can be further tested *in vitro* using different cancer cell lines.

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